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# Cardiorespiratory Fitness, Adiposity, and Heart Rate Variability: The CARDIA Study

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## Abstract

**Purpose:** The importance of cardiorespiratory fitness vs. adiposity in determining heart rate variability (HRV) is unclear.

**Methods:** From CARDIA, an observational cohort study, we included 2,316 participants (mean age 45.2±3.6 years at Year 20, 57% female, 43% black) with HRV measured in 2005-06 (Year 20), and graded exercise test duration (GXTd) and adiposity measures (BMI, waist circumference) obtained in 1985-86 (baseline) and 2005-06. HRV measures (standard deviation of all normal RR intervals [SDNN] and square root of the mean of the squares of differences between all successive RR intervals [RMSSD]) were obtained from resting 30-second 12-lead ECGs. Cross-sectional associations between GXTd, adiposity and HRV were assessed at Year 20. Longitudinal changes in GXTd and adiposity measures were categorized as ≥10% increase, <10% change (no change), or ≥10% decrease. We used multivariable logistic regression to assess associations of GXTd and adiposity measures with unfavorable vs. more favorable HRV (lower 25th percentile vs. upper 75$^{th}$ percentile).

**Results:** A 1-SD increment in GXTd was associated with 22% and 32% lower odds of unfavorable SDNN and RMSSD, respectively; associations remained significant after adjustment for adiposity. A 1-SD increment in adiposity measures was associated with 16-28% higher odds of unfavorable RMSSD; associations were not significant after adjustment for GXTd. Compared with no change/increase in GXTd, longitudinal decrease in GXTd was significantly associated with

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**CONFLICT OF INTEREST**

**None.** The results of the present study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. In addition, the results of the present study do not constitute endorsement by ACSM.

55% and 94% higher odds of unfavorable SDNN and RMSSD, respectively, at Year 20. These associations remained significant after adjusting for adiposity.

**Conclusion:** Cardiorespiratory fitness may be a stronger determinant of HRV than adiposity. Intervention studies are needed to better determine the differential effects of improved cardiorespiratory fitness vs. weight loss on HRV.

### Keywords

Heart rate variability; cardiorespiratory fitness; weight; adiposity

Heart rate variability (HRV) is a non-invasive marker of autonomic nervous system input to the heart (1). Increased sympathetic input decreases HRV, whereas increased parasympathetic input increases HRV. Cardiac arrhythmias are often initiated by or occur in patients with enhanced sympathetic and diminished parasympathetic tone. In post-myocardial infarction patients, low HRV is associated with greater risk of arrhythmic death (2) and total mortality (3). In the general population, low HRV is associated with a higher risk of coronary heart disease (4,5), atrial fibrillation (6), sudden cardiac death (7), and total mortality (5,8).

Although low HRV is a well-established predictor of adverse cardiovascular outcomes, data on the determinants of HRV remain sparse. Current literature suggests that modifiable factors such as physical activity or cardiorespiratory fitness and adiposity may be associated with HRV (9-16). Several studies have demonstrated an inverse association between weight gain and HRV (9,12,14). However, these studies reported only weight and body mass index (BMI), and did not consider other clinically relevant measures such as waist circumference (9,12,14). Studies showing a relationship between physical activity and HRV are limited by using self-reported physical activity as opposed to more objective measures of aerobic fitness such as the graded exercise test (12). Additionally, the cross-sectional design of most studies limits our ability to determine temporality (16-19). Moreover, very little is known about the relative importance of cardiorespiratory fitness vs. adiposity in determining HRV.

To address the aforementioned knowledge gaps, our study had two aims: (1) To evaluate the association of cardiorespiratory fitness and measures of adiposity with HRV in a community-based cohort of middle-aged individuals, and (2) To evaluate the association of antecedent 20-year change in cardiorespiratory fitness and measures of adiposity with HRV in midlife. For each of these aims, we also sought to determine the relative importance of cardiorespiratory fitness vs. measures of adiposity in determining HRV in midlife.

## METHODS

### Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal investigation of cardiovascular risk factor evolution in a population-based sample of 5,115 adults aged 18-30 years at baseline (1985-1986). Black and white men and women were recruited from Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Participants were reexamined 2, 5, 7, 10, 15, 20, 25, and 30 years after baseline; retention

rates across examinations were 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71% of the surviving cohort, respectively. All participants provided written informed consent. The study was approved by the Institutional Review Boards from each participating institution. A detailed description of study design and sampling protocol has been previously published (20).

The sample for the present investigation was drawn from participants who completed graded exercise treadmill testing (GXT) at baseline in 1985-86 and at Year 20 in 2005-06 and had complete data on waist circumference and BMI and model covariates (n=2,837). Of these, we excluded those who were missing HRV data at Year 20 (n=521), leaving an analytic sample comprising 2,316 participants.

## Graded Exercise Treadmill Testing

At baseline and at Year 20, participants underwent a symptom-limited GXT using a modified Balke protocol to measure cardiorespiratory fitness (21). The test protocol was designed to assess maximal, symptom-limited performance. After measurement of pulse, blood pressure and ECG, the participant started the protocol. The protocol consisted of 9 stages (2 min/stage, maximum 18 min/test) of progressively increasing difficulty, with the first 6 stages generally performed by walking. Stage 1 was 4.8 km/h at 2% grade (4.1 metabolic equivalents [METs]), progressing to stage 9 at 9.0 km/h at 25% grade (19.0 METs). The exercise test was terminated either due to fatigue (82.5%), shortness of breath (7.5%), abnormal ECG response (1%), medical reasons (5.3%), participant refusal (1.6%) or completion of the entire protocol (0.2%) (21). The exposure of interest was maximal exercise duration (seconds). Maximal exercise duration as assessed by the Balke protocol has been shown to be highly predictive (r= 0.94) of maximum oxygen uptake ($VO_2$ max) (22).

## Measures of Adiposity

Body weight with light clothing was measured to the nearest 0.2 kg, standing height without shoes was measured to the nearest 0.5 cm, and BMI was calculated from these measures in $kg/m^2$ (23). Waist circumference (to the nearest 0.5 cm) was measured laterally midway between the iliac crest and the lowest lateral portion of the rib cage and anteriorly midway between the xiphoid process of the sternum and the umbilicus. It was recorded as the average of two measurements.

## Measures of Heart Rate Variability

Year 20 resting ECGs were performed using GE MAC1200 and digitized at 500 Hz. HRV measures were obtained from 3 ×10 second resting ECGs and included SDNN (standard deviation of all normal RR intervals) and RMSSD (the square root of the mean value of the squares of differences between all successive RR intervals).

## Covariates

Covariates included age, sex, race (blacks and whites), field center, education (years), heart rate, diabetes, hypertension, smoking status (current, previous, and never), and use of β-

blockers, diltiazem, or verapamil. All covariates used in the regression models were assessed at Year 20 except for sex, race, and field center, which were assessed at Year 0 (1985-86).

### Statistical Analysis

We report means with standard deviations (SDs) or medians with interquartile range for continuous variables and counts with percentages for categorical variables. We conducted two analyses: a cross-sectional analysis and a longitudinal analysis.

For the cross-sectional analysis at Year 20, we used multivariable logistic regression to assess the association of GXT duration and measures of adiposity with the odds of lower 25th percentile of HRV vs upper 75$^{th}$ percentile of HRV. In Model 1, we adjusted for age, sex, race, field center, education, heart rate, diabetes, hypertension, smoking status, and use of β-blockers. For GXT duration, we additionally adjusted for measures of adiposity (Model 2a: adjustment for waist circumference, Model 2b: adjustment for BMI). For measures of adiposity, we additionally adjusted for GXT duration (Model 2c).

Longitudinal changes in GXT duration and measures of adiposity were categorized as ≥10% increase (longitudinal increase), <10% change (no change), or ≥10% decrease (longitudinal decrease). For GXT duration, we compared longitudinal decrease (unfavorable change) vs. no change/longitudinal increase (referent group). For measures of adiposity, we compared longitudinal increase (unfavorable change) vs. no change/longitudinal decrease (referent group). We used multivariable logistic regression to assess the association of longitudinal changes in GXT duration and measures of adiposity with the odds of an unfavorable HRV, the lower 25$^{th}$ percentile vs. those above the 25$^{th}$ percentile of HRV (upper 75th percentile). Model 1 covariates for the longitudinal analyses were similar to the cross-sectional analyses at Year 20. Next, we additionally adjusted for % change in waist circumference, BMI, or GXT duration as described for Models 2a, 2b and 2c in the cross-sectional analyses.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All *P* values reported were 2-sided, and Type I error was set at 5%.

## RESULTS

### Study Population

The analysis sample at Year 20 consisted of 2,316 participants (mean age 45.2 ± 3.6 years, 57% female, 43% black). During the 20-year period between Year 0 and Year 20, the mean BMI and waist circumference increased by 20% (from 24.1 kg/m$^2$ to 29.0 kg/m$^2$) and 18% (from 76.9 cm to 90.9 cm), respectively, and the GXT duration decreased by 28 % (from 595.2 to 426.0 seconds). Table 1 shows the characteristics of study participants at Year 0 and 20.

### Cross-Sectional Association of Cardiorespiratory Fitness and Measures of Adiposity with HRV at Year 20

Table 2 shows the cross-sectional association of GXT duration and measures of adiposity with SDNN and RMSSD at Year 20. In Model 1, a 1-SD increment in GXT duration was associated with 22% lower odds of unfavorable (low) SDNN and 32% lower odds of

unfavorable (low RMSSD. These associations were minimally attenuated and remained statistically significant after adjustment for waist circumference (Model 2a) or BMI (Model 2b). Higher waist circumference, but not BMI, was significantly associated with higher odds of unfavorable (low) SDNN. However, this association was no longer statistically significant after adjustment for cardiorespiratory fitness (Model 2c).

Notably, a 1-SD increment in waist circumference and BMI were significantly associated with 28% and 16% higher odds of unfavorable (low) RMSSD. These associations, however, were no longer statistically significant after adjustment for cardiorespiratory fitness. Multiplicative interactions of either adiposity or GXT duration with race or sex were not statistically significant for any of the analyses.

### Association of Longitudinal Change in Cardiorespiratory Fitness and Measures of Adiposity with HRV at Year 20

Table 3 shows the relationships of 20-year longitudinal change in cardiorespiratory fitness and measures of adiposity to HRV in midlife. Compared with no change/longitudinal increase in cardiorespiratory fitness, ≥10% longitudinal decrease in cardiorespiratory fitness was significantly associated with 55% higher odds of unfavorable (low) SDNN at Year 20. This association was minimally attenuated after adjustment for ≥10% increase in either waist circumference or BMI and remained statistically significant. This was also true for RMSSD, where a ≥10% longitudinal decrease in GXT was significantly associated with 94% higher odds of unfavorable (low) RMSSD at Year 20, which was minimally attenuated and remained statistically significant after controlling for ≥10% increase in either waist circumference or BMI.

Longitudinal changes in waist circumference and BMI were not significantly associated with SDNN at Year 20, either before or after controlling for ≥10% decrease in GXT duration. However, when we examined the association between ≥10% increase in waist circumference or BMI, these measures of adiposity were associated with 55% and 32% higher odds of unfavorable (low) RMSSD. After adjusting for decrease in GXT, the association with increase in BMI was no longer statistically significant; however, the association between ≥10% increase in waist circumference and unfavorable (low) RMSSD was 40% higher than with the reference group after controlling for decrease in GXT. As with the cross-sectional models, multiplicative interactions of either adiposity or GXT duration with race or sex were not statistically significant for any of the analyses.

## DISCUSSION

In a biracial population-based cohort study of young to middle-aged individuals, we observed that lower cardiorespiratory fitness and higher measures of adiposity were associated with lower HRV. The cross-sectional associations of lower cardiorespiratory fitness with lower HRV remained significant even after adjustment for measures of adiposity. By contrast, the associations of higher measures of adiposity with lower HRV were no longer significant after adjustment for cardiorespiratory fitness. In longitudinal analyses, a 20-year decrease in cardiorespiratory fitness was associated with lower SDNN and RMSSD in midlife; these associations remained statistically significant after controlling

for longitudinal increase in measures of adiposity. Longitudinal increase in both waist circumference and BMI was associated with lower RMSSD in midlife; however, only the waist circumference association was statistically significant after controlling for longitudinal decrease in cardiorespiratory fitness. Our findings were consistent in women and men, and blacks and whites. Collectively, our findings suggest that cardiorespiratory fitness may be more strongly associated with HRV than measures of adiposity. Our findings also suggest that the association between greater body fatness and low HRV can be largely explained by cardiorespiratory fitness.

Previous studies on the relationship of cardiorespiratory fitness and adiposity to HRV suffer from several methodologic limitations such as small sample sizes (9,10,14,15), cross-sectional design (16-19), highly-selected patient samples (9,14,15), subjective self-reported physical activity (12), and reliance on a single measure of adiposity such as weight or BMI (9,12,14). A critical knowledge gap also remains unaddressed—the relative importance of cardiorespiratory fitness and body fatness in determining HRV. A report from the SAPALDIA study (Swiss cohort Study on Air Pollution and Lung Diseases in Adults) partially addressed this question by evaluating whether regular exercise is associated with improved HRV, and whether the adverse effects of weight gain on HRV can be modified by regular exercise (12). The study reported that compared with sedentary obese subjects, SDNN was 19% higher in either normal weight or obese subjects exercising regularly. In addition, compared with sedentary subjects who gained weight, those who gained weight but exercised regularly had a 13% higher SDNN. The study, however, was limited by reliance on self-reported physical activity and a single measure of adiposity, BMI. A more recent study by Kiviniemi et al. (16) found that cardiorespiratory fitness was a stronger determinant of HRV than body fat percentage in middle-aged men and women. This study, however, was limited by its cross-sectional design and did not evaluate the effect of longitudinal change in cardiorespiratory fitness or adiposity.

Our study advances current knowledge on several fronts: (1) We demonstrated in a community-based sample of middle-aged individuals that lower cardiorespiratory fitness (measured objectively by GXT duration) and higher body fatness (indicated by two different measures) were associated with lower HRV, (2) The adiposity associations were no longer significant after adjustment for cardiorespiratory fitness whereas the latter’s association with HRV remained significant after accounting for adiposity, and (3) Importantly, over 20 years —throughout young and middle-aged adulthood—a longitudinal decrease in cardiorespiratory fitness was associated with lower SDNN and RMSSD in midlife. Of the two adiposity measures, only longitudinal increase in waist circumference was significantly associated with lower RMMSD in midlife after controlling for longitudinal decrease in cardiorespiratory fitness. In aggregate, our observations advance current knowledge by indicating that of the two modifiable lifestyle factors, cardiorespiratory fitness is more strongly related to HRV than adiposity.

In our study, HRV measures at Year 20 were obtained from short-term ECG recordings; hence, we could only examine time domain measures (SDNN and RMSSD) and not frequency domain measures. SDNN reflects total variability, while RMSSD estimates high-frequency variations in heart rate and primarily reflects parasympathetic activity (1). Of

note, the cross-sectional associations that we observed were consistent for both SDNN and RMSSD. However, in longitudinal analysis of changes in measures of adiposity, we observed a significant association with RMSSD but not with SDNN. Since RMSSD primarily reflects parasympathetic activity, our findings suggest a link between increase in adiposity and attenuated vagal tone. Furthermore, of the two adiposity measures, only longitudinal increase in waist circumference, but not BMI, was significantly associated with lower RMSSD after controlling for longitudinal decrease in cardiorespiratory fitness. This finding suggests that visceral adiposity may have a stronger association with HRV than total body fatness.

Our study has some clinical and public health implications. Although weight loss and maintaining an ideal body weight are associated with positive health outcomes, it is well established that it is extremely challenging to lose weight and prevent weight regain following initial weight loss (24,25). Given our data that suggest that higher cardiorespiratory fitness may have an independent role in predicting more favorable HRV than lower BMI, future clinical trials are warranted to determine both efficacy and effectiveness of exercise training vs. weight loss in improving HRV.

Some limitations of our study should be noted. First, HRV data were only obtained from 30-second ECG recordings. Short recordings may not encapsulate effects of the circadian rhythm and daily activity compared with long (24 hour) recordings. However, HRV measures derived from short and ultra-short (10 second) recordings are reliable (26-28). As such, short recordings have been employed in numerous epidemiological analyses as they pose a significant advantage over long recordings with respect to feasibility. In addition, the timing of the clinic exam would lead to measurement at approximately the same time of day, removing some concern about circadian rhythm. Second, approximately 18% of participants were excluded due to missing HRV data. The missing data resulted from logistical problems that were likely random in nature; thus, it would not have biased our results. Third, we evaluated change in adiposity between the Year 0 exam and Year 20 exam, and did not consider the effect of fluctuations in adiposity measures within shorter periods during this 20-year interval. Finally, we evaluated HRV at one time point and did not evaluate longitudinal change in HRV due to lack of available HRV data at baseline.

In conclusion, our report—based on a biracial population based-cohort study of young to middle-aged individuals—provides evidence that higher cardiorespiratory fitness and lower adiposity are associated with higher HRV. Notably, the cardiorespiratory fitness associations remained significant after adjusting for adiposity but the adiposity associations were no longer significant after adjusting for cardiorespiratory fitness, suggesting that cardiorespiratory fitness is the stronger determinant of HRV. Given the prognostic significance of HRV, further research is warranted to determine the effectiveness and feasibility of exercise training in improving HRV.

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**Table 1:**

Characteristics of Study Participants, CARDIA (2005-2006)

| Characteristic | 1985 | 2005-2006 |
|---|---|---|
| N | 2316 | |
| Age, years | 25.1 ± 3.5 | 45.2 ± 3.6 |
| Female | 1324 (57.2%) | |
| White | 1322 (57.1%) | |
| Center | | |
| Birmingham | 593 (25.6%) | |
| Chicago | 608 (26.3%) | |
| Minneapolis | 594 (25.7%) | |
| Oakland | 521 (22.5%) | |
| Education, years | 14.2 ± 2.3 | 15.2 ± 2.6 |
| Smoking | | |
| Never | 1422 (62%) | 1454 (63%) |
| Former | 326 (14%) | 452 (20%) |
| Current | 557 (24%) | 395 (17%) |
| Weight, kg | 69.9 ± 15.1 | 84.3 ± 20.4 |
| BMI, $kg/m^2$ | 24.1 ± 4.5 | 29.0 ± 6.5 |
| Waist circumference, cm | 76.9 ± 10.8 | 90.9 ± 15.0 |
| Hypertension | 53 (2.3%) | 442 (19.1%) |
| Diabetes | 8 (0.4%) | 145 (6.3%) |
| Graded Exercise Test duration, secs | 595.2 ± 177.5 | 426.0 ± 158.7 |
| SDNN, ms | NA | 26.6 (17.5, 41.4) |
| rMSSD, ms | NA | 27.7 (17.9, 42.3) |
| Heart rate, bpm | 62.7 ± 10.5 | 65.7 ± 10.0 |
| Beta-blocker use | 5 (0.2%) | 35 (1.5%) |
| Calcium channel blocker use | NA | 6 (0.26%) |

Data are presented as no. (%), mean ± SD, or median ($25^{th}$ percentile, $75^{th}$ percentile)

**Table 2.**

Cross-Sectional Association Between Cardiorespiratory Fitness and Measures of Adiposity with Heart Rate Variability at Year 20, CARDIA

| Independent variable | | OR per 1-SD increment in independent variable | 95% CI | P value |
|---|---|---|---|---|
| Lower 25th percentile of SDNN (ms) | | | | |
| Graded exercise test duration (s) SD: 159 s | Model 1 | 0.781 | 0.683, 0.894 | 0.0003 |
| | Model 2a: Model 1 + WC | 0.778 | 0.660, 0.918 | 0.0029 |
| | Model 2b: Model 1 + BMI | 0.755 | 0.641, 0.889 | 0.0007 |
| Waist circumference (cm) SD: 15 cm | Model 1 | 1.121 | 1.005, 1.250 | 0.0408 |
| | Model 2c: Model 1 + GXT duration | 0.995 | 0.870, 1.137 | 0.9358 |
| Body mass index (kg/m$^2$) SD: 6.4 kg/m$^2$ | Model 1 | 1.080 | 0.973, 1.199 | 0.1492 |
| | Model 2c: Model 1 + GXT duration | 0.953 | 0.840, 1.082 | 0.4616 |
| Lower 25th percentile of RMSSD (ms) | | | | |
| Graded exercise test duration (s) SD: 159 s | Model 1 | 0.675 | 0.588, 0.774 | <0.0001 |
| | Model 2a: Model 1 + WC | 0.720 | 0.610, 0.852 | 0.0001 |
| | Model 2b: Model 1 + BMI | 0.658 | 0.557, 0.777 | <0.0001 |
| Waist circumference (cm) SD: 15 cm | Model 1 | 1.280 | 1.148, 1.428 | <0.0001 |
| | Model 2c: Model 1 + GXT duration | 1.096 | 0.958, 1.253 | 0.1805 |
| Body mass index (kg/m$^2$) SD: 6.4 kg/m$^2$ | Model 1 | 1.164 | 1.048, 1.292 | 0.0044 |
| | Model 2c: Model 1 + GXT duration | 0.967 | 0.852, 1.098 | 0.6038 |

BMI, body mass index; CI, confidence interval; GXT, graded exercise test; OR, odds ratio; RMSSD, the square root of the mean value of the squares of differences between all successive RR intervals; SD, standard deviation; SDNN, standard deviation of all normal RR intervals; WC, waist circumference

Model 1: Adjusted for age, sex, race, study center, educational level, diabetes, hypertension, smoking status, use of β-blockers, and use of calcium channel blockers

Dependent variable: Lower 25th percentile of HRV vs. upper 75th percentile of HRV (referent)

**Table 3.**

Association Between Longitudinal Changes in Cardiorespiratory Fitness and Measures of Adiposity with Heart Rate Variability at Year 20, CARDIA

| Independent variable | | OR | 95% CI | P value |
|---|---|---|---|---|
| Lower 25th percentile of SDNN (ms) | | | | |
| Graded exercise test duration (s) * | Model 1 | 1.550 | 1.130, 2.126 | 0.0065 |
| | Model 2a: Model 1 + % increase in WC | 1.504 | 1.086, 2.083 | 0.0140 |
| | Model 2b: Model 1 + % increase in BMI | 1.523 | 1.102, 2.104 | 0.0108 |
| Waist circumference (cm) † | Model 1 | 1.193 | 0.952, 1.494 | 0.1247 |
| | Model 2c: Model 1 + % decrease in GXT duration | 1.104 | 0.873, 1.395 | 0.4087 |
| BMI (kg/m$^2$) † | Model 1 | 1.169 | 0.936, 1.460 | 0.1674 |
| | Model 2c: Model 1 + % decrease in GXT duration | 1.081 | 0.860, 1.359 | 0.5050 |
| Lower 25th percentile of RMSSD (ms) | | | | |
| Graded exercise test duration (s) * | Model 1 | 1.938 | 1.387, 2.709 | 0.0001 |
| | Model 2a: Model 1 + % increase in WC | 1.733 | 1.228, 2.445 | 0.0017 |
| | Model 2b: Model 1 + % increase in BMI | 1.851 | 1.315, 2.605 | 0.0004 |
| Waist circumference (cm) † | Model 1 | 1.554 | 1.230, 1.963 | 0.0002 |
| | Model 2c: Model 1 + % decrease in GXT duration | 1.401 | 1.099, 1.786 | 0.0065 |
| BMI (kg/m$^2$) † | Model 1 | 1.317 | 1.051, 1.651 | 0.0169 |
| | Model 2c: Model 1 + % decrease in GXT duration | 1.176 | 0.931, 1.484 | 0.1734 |

BMI, body mass index; CI, confidence interval; GXT, graded exercise test; OR, odds ratio; RMSSD, the square root of the mean value of the squares of differences between all successive RR intervals; SD, standard deviation; SDNN, standard deviation of all normal RR intervals; WC, waist circumference

Model 1: Adjusted for sex, race, study center and Year 20 covariates: age, educational level, diabetes, hypertension, smoking status, use of β-blockers and use of calcium channel blockers

* Percent change in GXT duration: ≥10% longitudinal decrease vs. no change or longitudinal increase

† Change in measures of adiposity: ≥10% longitudinal increase vs. no change or longitudinal decrease

Dependent variable: Lower 25th percentile HRV vs. higher 75th percentile HRV (referent)