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Exercise Physiology

Dose-response of capsiate on autonomic response in obese and normal weight young adult men: a randomized, crossover, double-blind placebo-controlled study

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Abstract - Objectives: To investigate the acute effects of different doses of capsiate on heart rate variability (HRV) and stress-related autonomic indices in overweight/obese and normal weight young adult men. **Methods:** Nineteen men (25.6 ± 4.6 years; 98.7 ± 26.0 kg) were classified as overweight/obese (OW/OB, n = 12; BMI > 25 kg/m^2) or normal weight (NW, n = 7; BMI < 24.9 kg/m^2), completed five non-consecutive laboratory visits, receiving placebo or capsiate at 12, 24, or 36 mg in capsules. Resting HRV was recorded for 30 min in the supine position and analyzed in the time domain (SDNN, RMSSD, TINN) and through stress-related indices (stress index, SNS and PNS indices). **Results:** As expected, the OW/OB group presented higher body weight, BMI, waist circumference, body fat percentage, and android and gynoid fat, and lower VO_2peak compared with the NW group ($p < 0.05$). No significant main effects of dose or group × dose interactions were found for HRV or stress-related indices. A non-significant trend toward higher SNS index at 36 mg in OW/OB compared with NW was observed ($p = 0.083$; Hedges's $g = 0.93$). **Conclusion:** Acute capsiate supplementation at doses of 12, 24, and 36 mg did not promote significant changes in resting HRV or stress-related autonomic indices in overweight/obese or normal weight young men, although a trend toward increased sympathetic activity was observed at 36 mg in OW/OB. Larger trials and higher or chronic doses are warranted to clarify the autonomic impact of capsiate across different body composition profiles.

Keywords: capsiate, heart rate variability, autonomic nervous system, obesity, TRPV1.

Introduction

Heart rate variability (HRV) is a noninvasive index of cardiac autonomic modulation, capturing the dynamic balance between sympathetic and parasympathetic input[1]. Higher vagal-related indices - RMSSD (root mean square of successive differences) and high-frequency (HF) power - or a lower LF/HF ratio indicate a

favorable autonomic profile[1]. Conversely, a shift toward sympathetic predominance, reflected by an elevated LF/HF ratio, signals altered autonomic control[1,2]. Because HRV integrates central and peripheral autonomic activity, resting HRV sensitively detects the acute neuromodulator effects of nutritional and ergogenic interventions; however, valid interpretation requires rigorous control of contextual and signal-acquisition factors in line with established guidelines[1].

In this context, modulation of the transient receptor potential vanilloid 1 (TRPV1) has been extensively investigated for its role in autonomic regulation, energy metabolism, and thermogenesis[3]. Capsaicin, the main pungent compound in peppers, is the most well-known agonist of this receptor. However, its non-pungent analog, capsiate - naturally found in the sweet pepper CH-19 Sweet (Capsicum annuum) - emerges as a promising alternative for nutritional supplementation due to its excellent gastrointestinal tolerability, as it does not cause discomfort associated with pungency[3].

Studies demonstrate that capsiate also acts as an agonist of TRPV1 similarly to capsaicin, which can promote increased lipid oxidation and sympathetic nervous system activity, with potential applications in obesity strategies[3,4]. Clinical data suggest that capsaicin and capsiate can increase energy expenditure and fat oxidation and may exert dose-dependent thermogenic effects[5], while acute capsinoid ingestion activates brown adipose tissue thermogenesis and whole-body energy expenditure in BAT-positive adults[6].

Emerging evidence, however, suggests that HRV responses to these bioactive compounds may depend on the administered dose and individual characteristics, such as body composition[2,3,7]. This observation reinforces the need to characterize dose-response relationships under controlled conditions, using a comprehensive set of HRV metrics such as RMSSD, SDNN (standard deviation of NN intervals), TINN (triangular interpolation of NN interval histogram), and stress-related indices like the SNS index (sympathetic nervous system activity)[1]. In addition, several studies indicate that overweight and obesity are associated with reduced HRV and a shift toward sympathetic dominance, even in young adults considered otherwise healthy, supporting HRV as an early marker of adiposity-related autonomic imbalance[8,9].

Therefore, the aim of this study was to investigate acute autonomic responses following different doses of capsiate in obese and normal weight young adults. By focusing on HRV (indices in the time and frequency domains) after a single dose in resting conditions, this work seeks to elucidate the dose dependence and consistency of autonomic effects, providing detailed evidence to guide future applications of these compounds in autonomic modulation.

Methods

Experimental design and ethical approval

This study employed a randomized, double-blind, placebo-controlled crossover design and was conducted in accordance with the principles outlined in the 2013 revision of the Declaration of Helsinki. All participants were informed about the potential risks and benefits of the study, and written informed consent was obtained prior to participation. The study protocol was approved by the Research Ethics Committee (approval number: 08100819.1.0000.5414). There was no direct involvement of patients or members of the public in the design, conduct, data analysis, or writing of this study.

Eligible participants were adults aged 18 to 35 years, free from musculoskeletal or cardiovascular conditions that could interfere with study procedures and had abstained from consuming ergogenic or stimulant substances throughout the study period. Each participant attended five non-consecutive laboratory visits, separated by a minimum of 48 h at the Laboratory of Cellular Exercise Physiology - LaFICE, at the São Paulo State University "Júlio de Mesquita Filho" (UNESP), Presidente Prudente, São Paulo, Brazil.

During the first visit, anthropometric assessments and body composition analysis were conducted using dual-energy X-ray absorptiometry (DXA). Participants were randomly assigned to five experimental conditions using an online randomization tool (https://www.random.org) managed by an independent researcher who did not participate the study.

The conditions included a placebo (PLA - 12 mg of Potato Starch) and three different doses of capsiate (12, 24, or 36 mg), the capsules were identical and without flavor, provided by Campos Manipulação (Presidente Prudente, Brazil). Capsules were administered 45 min before assessing resting metabolic rate and autonomic function to coincide with the peak plasma concentration of capsiate. Following ingestion, participants remained in a supine position for 30 min, where heart rate variability (HRV) was measured. No changes were made to outcomes.

Participants

The flow of participants through the trial is depicted in the CONSORT diagram (Figure 1). Participants were recruited from university announcements and social media between February and December 2022. Initially, 27 volunteers were assessed for eligibility. Three candidates were excluded for not meeting inclusion criteria. Thus, 24 young adult men were enrolled and allocated into two groups according to their BMI:

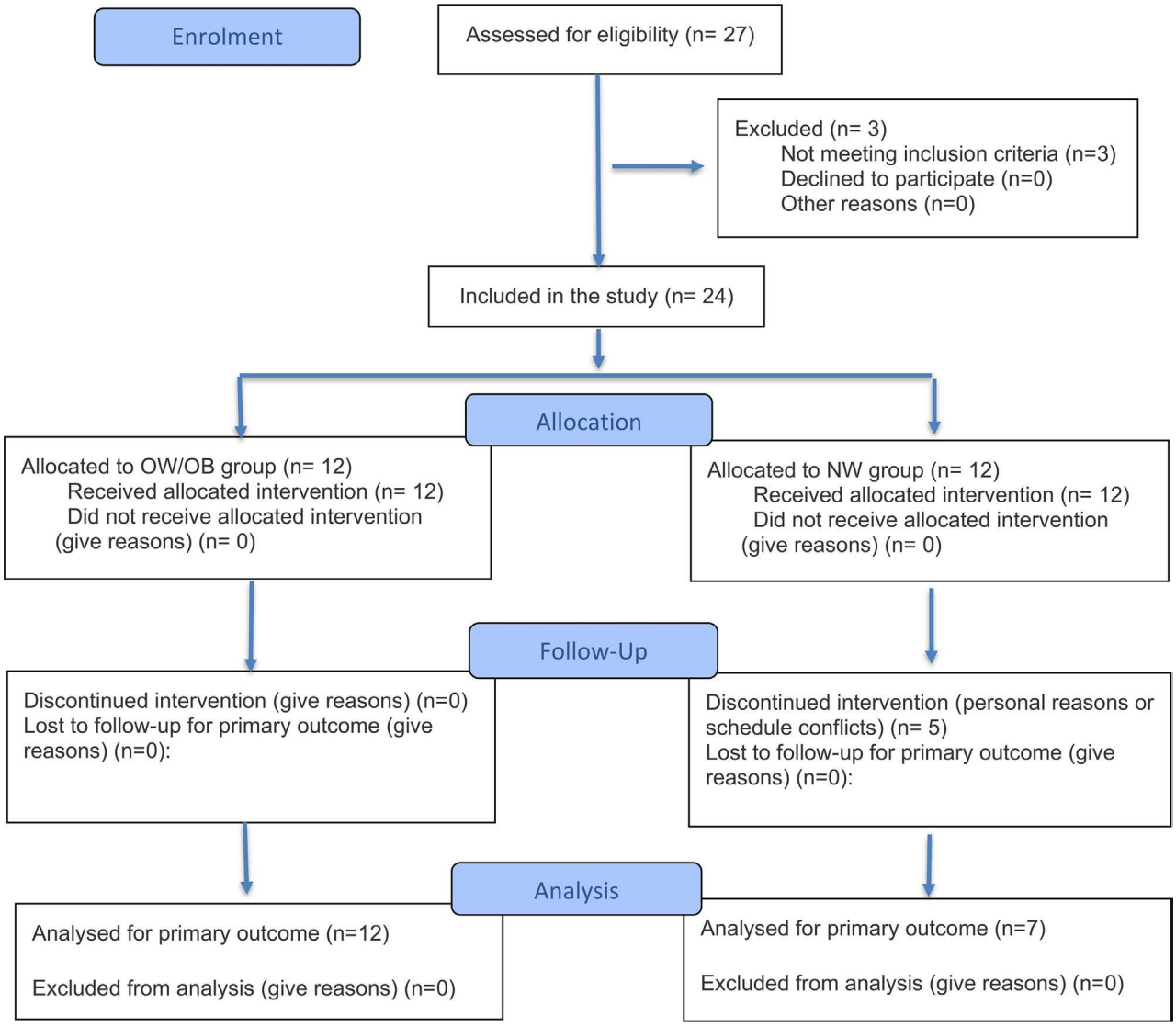

Figure 1 - CONSORT 2025 Flow Diagram. Flow diagram of the progress through the phases of a randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).

overweight/obese (OW/OB; n = 12) and normal weight (NW; n = 12). During the follow-up, 5 participants in the NW group discontinued the intervention due to personal reasons or inability to attend all laboratory visits. Consequently, 19 participants completed the study and were included in the final analysis: 12 in the OW/OB group (age: 27 ± 5 years; BMI: 36.4 ± 4.8 kg/m^2) and 7 in the NW group (age: 23 ± 4 years; BMI: 23.9 ± 3.3 kg/m^2).

Anthropometry, body composition, and physical activity status

The body weight was evaluated using an electronic scale (Filizola PL50 Ltd., Brazil) and the height was measured using a fixed stadiometer with an accuracy of 0.1 cm. The body mass index (BMI) was calculated using body mass in kilograms (kg) divided by height in meters (m) squared (kg/m^2). The fat-free mass and fat mass was assessed using DXA (DXA; Lunar DPX-NT scanner, General Electric Healthcare). The physical activity level was evaluated using a short version of the International Physical Activity Questionnaire (IPAQ).

Maximal incremental test

Participants performed the maximal incremental test on a treadmill (Inbramed MASTER CI, Inbrasport®, Porto Alegre, Brazil) in a temperature- and humidity-controlled environment. Expired gases were collected breath-by-breath with a silicone mask connected to a gas analyzer (Quark PFT - Cosmed®, Rome, Italy). Peak oxygen consumption (VO_2peak) was defined as

the highest average of the last 30 s of oxygen consumption when the difference was < 2.1 $mL.kg^{-1}.min^{-1}$ comparing the last two stages of the incremental test. Participants performed a 5-min warm-up by walking at 5 km/h before the test. The initial test speed was set at 6 km/h and increased by 1 km/h every 2 min. The treadmill incline was maintained at 1%, and the test ended when the participant reached voluntary exhaustion. Verbal encouragement was provided to ensure each volunteer ran to exhaustion. Additionally, a heart rate monitor (Polar Vantage NV, Electro Oy, Finland) and a subjective exertion scale (Borg scale 6-20) were used in parallel with the gas analyzer[10].

Heart rate variability

Heart rate variability (HRV) analysis was recorded beat-by-beat using a heart rate monitor (Polar V800, Polar Electro Oy, Kempele, Finland) during the 30-min resting at supine position[11]. Data were collected individually, with participants instructed to remain at rest and refrain from conversation during the procedure. Recorded data were then transferred to Polar Precision Performance software for analysis. Digital and manual filters were applied to eliminate premature ectopic beats and artifacts, and only series with more than 95% sinus beats were included in the study. HRV was analyzed in the time domain (SDNN; RMSSD and TINN) and through stress-related indices (Stress Index; SNS index - sympathetic nervous system activity; PNS index - parasympathetic nervous system activity), computed with Kubios HRV software.

Statistical analysis

Data are presented as mean and standard deviations (SD). The data distribution was verified by Shapiro-Wilk test. Two-way analysis (ANOVA) for repeated measures followed by Tukey's post hoc test was used to compare the effects of different capsiate doses on HRV. The homogeneity of variances was analyzed using Levene's test. Sphericity was assessed using the Mauchly W test, with the Greenhouse-Geisser correction applied where necessary. In cases where a significant dose × group interaction was observed, Tukey post-hoc analysis was conducted to identify differences, with adjustments made for multiple comparisons. Data was analyzed using Jeffreys's Amazing Statistics Program (JASP) software, and the figure was made using GraphPad Prism 10 software.

Results

Subjects

General characteristics of participants and their body composition are presented in Table 1. As expected, OW/OB group showed significant higher body weight (p-value < 0.001, Hedges's *g*: 2.34), BMI (p-value < 0.001, Hedges's *g*: 2.38), waist circumference (p-value < 0.001, Hedges's *g*: 2.30) compared to NW group, and the OW/OB group showed significant lower VO_2peak (p < 0.001, Hedges's *g*: 2.10) compared to NW group. Also, OW/OB group showed higher bone mineral density (p-value 0.021, Hedges's *g*: 1.24), percentage of body fat (p-value < 0.001, Hedges's *g*: 3.48), as well as the android fat (p-

Table 1 - General characteristics and body composition of young adult men participants classified overweight/obese (OW/OB) and normal weight (NW).

Variables	N	OW/OB (n=12)	N	NW (n=7)	p-value
General characteristics					
Age (years)	12	27 ± 5	7	23 ± 4	0.081
Body weight (kg)	12	113.56 ± 19.18	7	73. 28 ± 12.63	< **0.001**
BMI (kg/m^2)	12	36.46 ± 4.80	7	23.95 ± 3.32	< **0.001**
VO_2peak ($mL/kg.min^{-1}$)	12	41.86 ± 7.18	7	55.01 ± 4.02	< **0.001**
Waist circumference (cm)	12	104.42 ± 12.04	7	79.94 ± 7.33	< **0.001**
MVPA (min/day)	12	96.25 ± 61.98	7	125.00 ± 74.77	0.378
Body composition - DXA					
Bone mineral density (g/cm^2)	12	1.43 ± 0.12	7	0.94 ± 0.64	**0.021**
Lean soft mass (kg)	12	68.23 ± 9.96	7	41.82 ± 29.79	**0.011**
Body fat (%)	12	36.83 ± 5	7	12.88 ± 9.40	< **0.001**
Android body fat (%)	12	45.42 ± 5.84	7	11.77 ± 10.01	< **0.001**
Gynoid body fat (%)	12	37.05 ± 6.15	7	12.97 ± 9.90	< **0.001**

Note: Data are presented as mean ± standard deviation (SD). BMI: body mass index, MVPA: moderate-to-vigorous physical activity. DXA: dual-energy X ray densitometry. Bold p-values < 0.05.

value < 0.001, Hedges's *g*: 4.44) and gynoid fat (p-value < 0.001, Hedges's *g*: 3.13), and lower intracellular water (p-value < 0.001, Hedges's *g*: −1.05) compared to NW group. Thus, these results highlight key body composition and cardiorespiratory fitness differences between OW/OB and NW individuals.

Heart rate variability response in different dosages of capsiate

There was no significant response of different dosages of capsiate on heart rate variability (Figure 2). Based on our initial question whether different doses of capsiate would benefit the heart rate variability, we observed a trend of higher sympathetic nervous system (SNS) index in OW/OB group (p-value 0.083, Hedges's *g*: 0.93) at the maximum dose (36 mg) of capsiate compared to NW group (Figure 2B). This finding highlights that 36 mg of capsiate may increase the sympathetic nervous system, however, OW/OB individuals tend to show a lower parasympathetic (vagal) activity, leading to imbalanced autonomic control.

Discussion

In this study, we tested three doses of capsiate - a non-pungent capsaicin analogue and TRPV1 agonist - to assess dose-response effects on time-domain and stress-related HRV metrics in young men across a range of body compositions. We observed no significant main effects of dose and no group × dose interactions for any outcome. Accordingly, our findings do not support a meaningful acute effect of capsiate on global HRV, aligning with prior evidence of small, context-dependent autonomic shifts and modest metabolic responsiveness to TRPV1 agonists in individuals with excess adiposity.

Zsiborás et al. conducted a meta-analysis showing that both capsaicin and capsiate slightly increase energy expenditure (EE) and reduce respiratory quotient (RQ), indicating greater lipid oxidation[3]. However, the authors emphasized that these effects were more consistent in overweight/obese individuals (BMI > 25 kg/m^2), whereas normal-weight participants showed less evident responses, suggesting an influence of body composition on the magnitude of autonomic and metabolic responses[3]. This finding complements our observations, as overweight/obese individuals in the present study exhibited a tendency toward increased SNS index when supplemented with the highest dose of capsiate (36 mg), although this difference did not reach statistical significance.

In addition, chronic supplementation with 6 mg/day capsinoids for 12 weeks in adults with overweight/obesity was associated with reductions in abdominal fat and a near-significant increase in fat oxidation[12], whereas 3-9 mg/day dihydrocapsiate for 28 days induced only a small thermogenic effect of approximately 50 kcal/day without changes in fat oxidation[13]. These metabolic findings reinforce the notion that capsinoid-induced adaptations are of small magnitude, which may partly explain the absence of clear autonomic changes in our acute HRV outcomes.

A clinical trial conducted by our research group adds relevant data about acute capsiate supplementation in young men: in that study, capsiate did not promote significant changes in energy expenditure, substrate oxidation, or food intake, but it did modify resting HRV parameters, with an increase in the LF/HF ratio[7]. This finding suggests that, although the metabolic effects may not be significant under acute conditions, changes in autonomic balance can occur at rest after ingestion of the compound[5]. To address gaps in the literature, we administered an initial 12-mg capsiate dose and scheduled measurements at ~45 min, coinciding with its peak plasma concentration, and stratified participants by BMI.

Osuna-Prieto et al. also observed that acute ingestion of 12 mg dihydrocapsiate before a 60-min cycling bout at FATmax in sedentary men with overweight/obesity did not increase energy expenditure, fat oxidation, or heart rate during exercise compared with placebo[14]. When taken together with our findings, these results support the view that a single acute dose of capsinoids around 12 mg may be insufficient to elicit robust metabolic or autonomic responses in individuals with higher adiposity.

A previous study showed that obese young women had lower sympathetic responsiveness, as assessed by spectral analysis of HRV, after ingestion of a meal containing capsaicin compared with lean women[2]. The lack of a significant increase in diet-induced thermogenesis in the obese group was attributed to attenuated sympathetic activation, leading to the hypothesis that obesity may be associated with reduced autonomic plasticity in response to thermogenic intake and may interact with sex-related differences[2].

More recently, Zaleski et al. reported that dietary capsaicin intake elicited sex-specific parasympathetic responses, with RMSSD increasing in men and decreasing in women compared with placebo, highlighting a sexual dimorphism in cardiac autonomic responses to TRPV1 agonists[15]. In parallel, a recent narrative review synthesized evidence that excess adiposity and poor dietary profiles are consistently associated with reduced HRV, higher sympathetic predominance, and increased cardiometabolic risk, whereas weight loss and lifestyle interventions tend to improve HRV indices[9]. In this context, it is plausible

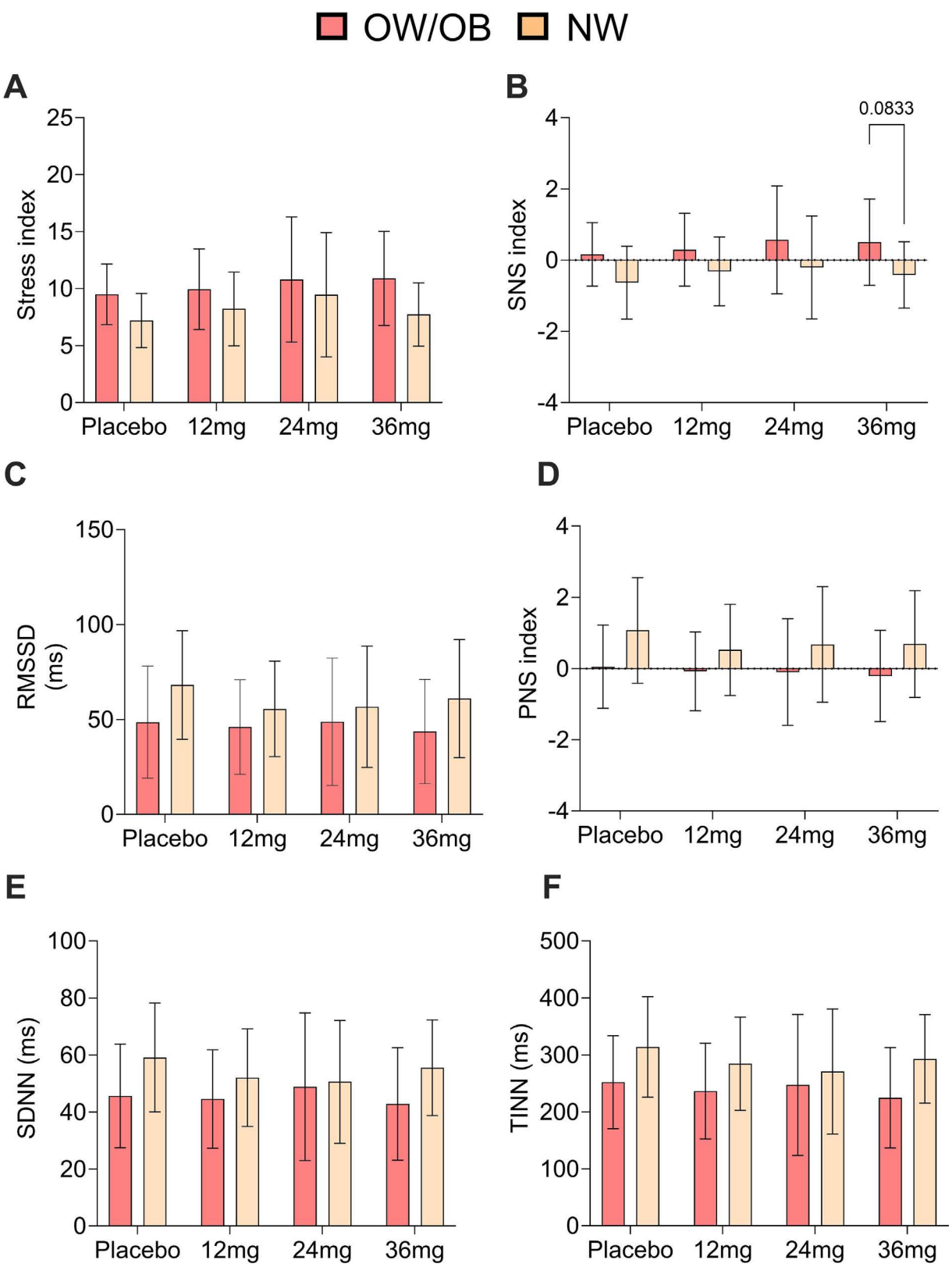

Figure 2 - Acute effects of capsiate supplementation (12, 24, and 36 mg) on HRV of young adult men participants classified overweight/obese (OW/OB) and normal weight (NW). Note: normal-weight (NW, beige bars) and overweight/obese (OW/OB, red bars) individuals. (A) Stress Index; (B) SNS index; (C) RMSSD; (D) PNS index; (E) SDNN; (F) TINN. Values are expressed as mean ± standard deviation (SD). Analysis performed using a mixed-model repeated measures design (two factors: group × condition).

that both adiposity and sex modulate autonomic responsiveness to capsaicin and capsinoids, such that obese and/or female participants may exhibit blunted or even opposite HRV responses compared with lean or male participants.

Taken together, these findings suggest that capsiate has no meaningful acute effect on HRV at the doses tested; any detectable autonomic response may require doses > 36 mg. Given its non-pungent profile, no adverse events were reported, and higher dosing is likely well tolerated. Differences in body composition did not affect the outcomes.

This study has methodological strengths and limitations that should be acknowledged. Key strengths include the randomized, double-blind, placebo-controlled crossover design, which minimizes inter-individual variability, and strict standardization protocols that enhance internal validity. Additionally, the inclusion of multiple doses (12, 24, and 36 mg) enabled dose-response evaluation within the same individuals. However, several limitations warrant consideration: the small sample size, particularly in the normal-weight group (n = 7), may have limited statistical power to detect smaller effects or subtle dose-response relationships; consequently, findings should be interpreted as hypothesis-generating rather than conclusive. Second, the acute, single-dose protocol prevents extrapolation to chronic adaptations. Third, the study included only young men (18-35 years) and assessed HRV exclusively at rest, which prevented the analysis of autonomic responses to physiological stress (e.g., exercise), thus limiting generalizability to women and older adults. Regarding future directions, adequately powered trials with larger sample sizes are needed to confirm these preliminary observations. Critically, longitudinal protocols (e.g., 8-12 weeks) should investigate whether sustained capsiate supplementation produces cumulative autonomic adaptations beyond acute responses, potentially in combination with exercise interventions to assess synergistic effects on autonomic and metabolic outcomes across diverse populations.

Conclusion

In conclusion, acute capsiate supplementation with different doses (12, 24, 36 mg) did not elicit significant changes in resting HRV or stress-related indices in either overweight/obese or normal weight young men. A non-significant trend toward a higher SNS index was observed at 36 mg in the overweight/obese subgroup, suggesting that autonomic responsiveness to capsiate may be dose dependent. Future trials should investigate higher doses driven by autonomic outcomes and incorporating complementary nonlinear HRV metrics specifically in the overweight/obese population to determine whether capsiate can produce clinically meaningful autonomic modulation.

AI use statement

No AI was used in this research.

Author contributions

Pedro EM Oliveira: conceptualisation, methodology, formal analysis, writing - original draft, writing - review and editing. **Valéria LG Panissa:** writing - review and editing. **Vinicius AM Soares:** writing - review and editing. **Fabrício E Rossi:** writing - review and editing. **Fabio S Lira:** conceptualisation, methodology, writing - review and editing. **Camila S Padilha:** conceptualisation, methodology, formal analysis, writing - original draft, writing - review and editing, final approval.

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Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

Conflict of interest statement

Authors declare no conflict of interest.

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