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Are There Interindividual Responses of Cardiovascular Disease Risk Markers to Acute Exercise? A Replicate Crossover Trial

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ABSTRACT

SHEN, T., A. E. THACKRAY, J. A. KING, T. F. ALOTAIBI, T. M. ALANAZI, S. A. WILLIS, M. J. ROBERTS, L. LOLLI, G. ATKINSON, and D. J. STENSEL. Are There Interindividual Responses of Cardiovascular Disease Risk Markers to Acute Exercise? A Replicate Crossover Trial. *Med. Sci. Sports Exerc.*, Vol. 56, No. 1, pp. 63–72, 2024. **Purpose:** Using a replicated crossover design, we quantified the response heterogeneity of postprandial cardiovascular disease risk marker responses to acute exercise. **Methods:** Twenty men (mean (SD) age, 26 (6) yr; body mass index, 23.9 (2.4) $kg \cdot m^{-2}$) completed four 2-d conditions (two control, two exercise) in randomized orders. On days 1 and 2, participants rested and consumed two high-fat meals over 9 h. Participants ran for 60 min (61 (7)% of peak oxygen uptake) on day 1 (6.5 to 7.5 h) of both exercise conditions. Time-averaged total area under the curve (TAUC) for triacylglycerol, glucose, and insulin were calculated from 11 venous blood samples on day 2. Arterial stiffness and blood pressure responses were calculated from measurements at baseline on day 1 and at 2.5 h on day 2. Consistency of individual differences was explored by correlating the two replicates of control-adjusted exercise responses for each outcome. Within-participant covariate-adjusted linear mixed models quantified participant-by-condition interactions and individual response SDs. **Results:** Acute exercise reduced mean TAUC-triacylglycerol (−0.27 $mmol \cdot L^{-1} \cdot h$; Cohen's $d = 0.29$, $P = 0.017$) and TAUC-insulin (−25 $pmol \cdot L^{-1} \cdot h$; Cohen's $d = 0.35$, $P = 0.022$) versus control, but led to negligible changes in TAUC-glucose and the vascular outcomes (Cohen's $d \leq 0.36$, $P \geq 0.106$). Small-to-moderate, but nonsignificant, correlations were observed between the two response replicates ($r = -0.42$ to 0.15, $P \geq 0.066$). We did not detect any individual response heterogeneity. All participant-by-condition interactions were $P \geq 0.137$, and all individual response SDs were small with wide 95% confidence intervals overlapping zero. **Conclusions:** Large trial-to-trial within-subject variability inhibited detection of consistent interindividual variability in postprandial metabolic and vascular responses to acute exercise. **Key Words:** EXERCISE, TRIACYLGLYCEROL, GLUCOSE, INSULIN, ARTERIAL STIFFNESS, INDIVIDUAL VARIABILITY

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Cardiovascular disease (CVD) is a major cause of premature mortality globally (1). Many studies have shown that regular exercise is inversely associated with all-cause and cardiovascular mortality (2). Alongside "training"-related adaptations, the cardiometabolic benefits of exercise are related to the acute effect of each bout on mediators of CVD risk (3–5). Specifically, several studies have shown that acute exercise reduces concentrations of triacylglycerol (TAG) (4,6), glucose (3), and insulin (7) in the postprandial state, which is more reflective of the usual metabolic state than fasted concentrations. The maximal postprandial TAG lowering effect of single exercise bouts typically emerges 12 to 20 h after exercise cessation (4), which coincides with the peak in lipoprotein lipase activity that has been implicated mechanistically in promoting TAG clearance from the circulation (4,8). Furthermore,

single bouts of exercise have also been shown to elicit improvements in vascular outcomes such as blood pressure (BP) (9) and arterial stiffness (10). Without an exercise stimulus, evidence suggests TAG, glucose, insulin, and BP responses to a single meal exhibit good reproducibility (11–15). Although the repeatability of postprandial metabolic and vascular responses to single exercise bouts has not been widely investigated, initial insights suggest the reproducibility of postprandial lipemic responses in the 4 h immediately after two repeated exercise bouts is poor (12).

Understanding of the acute effects of exercise on CVD risk markers is predominantly based on average (mean) responses to an exercise stimulus within study samples. However, variability exists within an individuals' response to any given intervention, a concept that underpins the discipline of "precision medicine" (16). The relevance of identifying and quantifying interindividual differences in biomedical research has been highlighted recently (17–19). Moreover, the importance of accounting for random within-subject variability over repeated measurements and experimental conditions when making judgments about interindividual variation has been emphasized (16,20–23). We have previously adopted a replicated crossover study design and associated documented analysis approaches (16,24–27) to identify the presence of interindividual variability in appetite responses to acute exercise (18) and standardized meal intake (17). Importantly, these studies incorporated replicated exercise and control study arms enabling the participant-by-condition interaction to be quantified appropriately (16,25). A similar design and analysis approach, including the between-replicate correlation analysis reported by Senn et al. (16,25), has also been adopted recently to demonstrate interindividual variability in BP responses to antihypertensive medications (27). With a conventional parallel-arm or crossover design, it is impossible to derive the participant-by-treatment interaction term and make robust inferences concerning response heterogeneity as there is no repeated implementation of the experimental conditions (16). Whether individual variability exists in postprandial metabolic and vascular responses to acute exercise bouts after accounting for random within-subject variability over time is not known.

The present study adopted a replicated crossover design to investigate whether "true" and consistent interindividual variability exists in postprandial CVD risk marker responses to acute exercise bouts. Within this research design, we also examined the consistency of postprandial responses to exercise performed on repeated occasions. This was achieved by adopting a statistical framework involving the between-replicate correlation coefficients and participant-by-condition interaction terms reported by Senn et al. (16,25) and the variance comparison approach reported by others (21,28,29). The primary outcome in this study was postprandial TAG concentrations with several other postprandial CVD risk markers assessed as secondary outcomes (glucose, insulin, BP, and pulse wave velocity (PWV)). We hypothesized that postprandial metabolic and vascular responses to single exercise bouts would be consistent on two occasions, and individual response heterogeneity would be evident in the magnitude of response in healthy young men.

METHODS

Ethical approval and participants. All study procedures were approved by the Loughborough University Ethics Advisory Committee. Twenty healthy men (aged 18 to 37 yr) provided written informed consent to participate in this study. Participants were nonsmokers, body mass stable (defined as ≤3 kg change in previous 3 months), not currently dieting or taking any medications, had no history of medical conditions that may impact the study outcomes, and could tolerate all foods provided. This study was registered at ClinicalTrials.gov as NCT05022498. Participant characteristics are presented in Table 1.

Pre-assessments. Before the main experimental conditions, participants completed questionnaires assessing current health status, medical history, and physical activity habits (30), anthropometric measurements, and two treadmill (RUN RACE; Technogym, Gambettola, Italy) running tests in the laboratory. Stature was measured using a stadiometer (285; Seca GmbH & Co. KG, Hamburg, Germany), whereas body mass and body fat percentage were determined using an integrated bioelectrical impedance analyzer (Seca mBCA 515; Seca GmbH & Co. KG). Waist circumference was measured at the narrowest point between the lowest rib and the iliac crest.

Participants were familiarized with walking and running on the treadmill before completing two exercise tests. The relationship between running speed and oxygen consumption was determined via a 4 × 4-min incremental submaximal test. Participants began running at a speed between 5 and 9 $km \cdot h^{-1}$ (depending on their fitness level), which was increased by 1 to 1.5 $km \cdot h^{-1}$ at the start of each subsequent stage, whereas the treadmill gradient remained fixed at 1% throughout. After 30 min of recovery, participants completed a ramped (+1% incline each minute) peak oxygen uptake ($\dot{V}O_2$ peak) test at a fixed individual speed until they reached volitional exhaustion. During both tests, expired air samples were monitored continuously using an online breath-by-breath gas analysis system (MetaMax® 3B; Cortex, Leipzig, Germany), and heart rate was recorded continuously using short-range telemetry (Polar T31; Polar Electro, Kempele, Finland). The Borg CR-10® rating scale was used for assessing the rating of perceived exertion (RPE) in the last 10 s of each stage, where 0 represents "nothing at all" and 10 "maximal" (31). Peak oxygen uptake was determined as the highest 30-s rolling average. Data from these tests were used to determine the treadmill speed for the main experimental conditions.

Experimental design. In a replicated, crossover experimental design, each participant completed four 2-d conditions

TABLE 1. Participant characteristics.

Parameter	Mean (SD)
Age (yr)	26 (6)
Body mass (kg)	75.7 (8.9)
Body mass index ($kg \cdot m^{-2}$)	23.9 (2.4)
Waist circumference (cm)	82.8 (8.1)
Body fat percentage (%)	19.8 (7.0)
Peak oxygen uptake ($L \cdot min^{-1}$)	3.4 (0.7)
Peak oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$)	45.1 (10.4)

Data presented for $n = 20$.

(two exercise and two control), each separated by a washout of at least 5 d. Figure 1 provides a schematic overview of the procedures completed within the main conditions. An online software application was used to generate the randomization sequence of main conditions (http://www.sealedenvelope.com/). Before each condition, participants refrained from strenuous physical activity, alcohol, and caffeine for 24 h. Dietary intake was recorded in the 48 h before the first experimental condition and replicated in the same period before the subsequent conditions, which was facilitated by a weighed diet record.

Main experimental trials—day 1. Before arrival, the laboratory temperature was set to 21°C. Participants arrived at the laboratory at 08:00 after a 10-h overnight fast. Participants rested on a bed in a semisupine position (30-degree angle) for 30 min, after which measurements of arterial BP and arterial stiffness (brachial-to-ankle PWV (ba-PWV) and carotid-to-femoral PWV (cf-PWV)) were taken (Vicorder; Skidmore Medical, Bristol, UK). All measurements were taken on the left-hand side of the body, and the average of three measurements was calculated. A fasted blood sample was subsequently taken from an antecubital vein. Biochemical and vascular CVD risk markers at baseline on day 1 are presented in Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/MSS/C906.

Participants then consumed a standardized breakfast meal (see below), after which a clock was started (0 h, ~08:45). A standardized lunch meal (see below) was provided 4 h later (~12:45). Participants rested in the laboratory throughout day 1 of the exercise and control conditions, except that 60 min of treadmill running (1% incline, 60% $\dot{V}O_2$ peak) was performed at 6.5 h (~15:15) in the two exercise conditions. Oxygen consumption and carbon dioxide production were measured continuously during exercise, whereas heart rate and RPE were assessed at 10-min intervals. The treadmill speed was adjusted if necessary during both exercise conditions to ensure the target exercise intensity was achieved. The exercise energy expenditure and substrate utilization were subsequently estimated using the equations of Frayn (32).

At ~8 h (16:45), participants were free to leave the laboratory and were provided with a standardized evening meal (margherita pizza, 290 g, 2511 kJ, 32% fat, 52% carbohydrate, 16% protein) to consume before 22:00. Other than this meal, participants only consumed plain water before returning to the laboratory the next morning. Participants were also instructed to minimize physical activity during this time.

Main experimental trials—day 2. Participants arrived at 08:00 after a 10-h overnight fast. A cannula (BD Venflon; Becton-Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein, and a fasting blood sample was collected. Subsequent blood samples were collected at 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, and 8 h. Arterial stiffness and BP were measured at 2.5 h (~11:15). A standardized breakfast (see below) was consumed at 0 h (~08:45) and a standardized lunch (see below) at 4 h (~12:45). In both exercise and control conditions, participants rested in the laboratory throughout the day until the final blood sample was taken at 8 h (~16:45).

Laboratory test meals. On both experimental days, breakfast consisted of plain croissants, milk chocolate spread, double cream, and chocolate milkshake, providing 60 kJ per kilogram of body mass (57% fat, 35% carbohydrate, 8% protein). Lunch consisted of white bread, cheddar cheese, butter, double cream, and chocolate milkshake, which provided 60 kJ of energy intake per kilogram of body mass (60% fat, 28% carbohydrate, 12% protein). Both meals were consumed within 10 min, and plain water was provided *ad libitum* during the laboratory visits.

Blood sampling and biochemical analysis. Venous blood samples were collected into precooled potassium ethylenediaminetetraacetic acid (EDTA) Monovettes (Sarstedt, Leicester, UK) and centrifuged at 1165*g* for 10 min at 4°C (Labofuge 400R; Thermo Scientific, Langenselbold, Germany). The plasma supernatant was aliquoted and stored at −80°C. Plasma concentrations of TAG, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and high-sensitivity C-reactive protein were measured in duplicate using a benchtop analyzer (Pentra 400; HORIBA Medical, Montpellier, France), whereas insulin concentrations were measured in duplicate using an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). The within-batch coefficient of variation for each assay was as follows: 1.0% for TAG, 0.4% for total cholesterol, 0.6% for high-density lipoprotein cholesterol, 0.6% for low-density lipoprotein cholesterol, 0.4% for glucose, 3.3% for insulin, and 1.6% for high-sensitivity C-reactive protein.

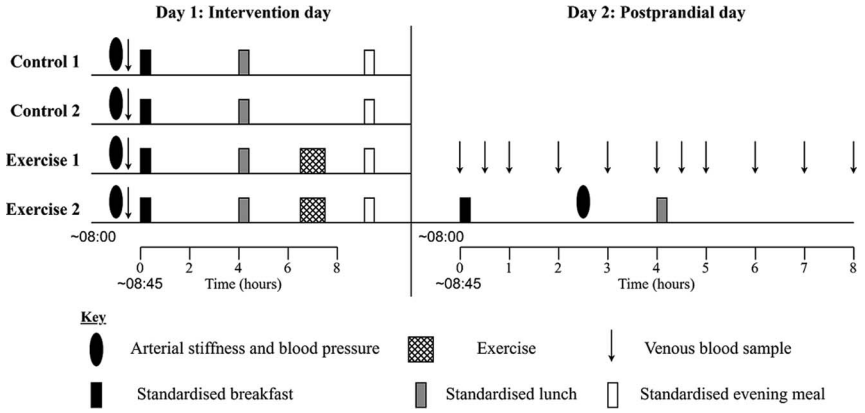

FIGURE 1—Schematic of the study design. Participants completed the four conditions in a randomized order.

Arterial stiffness and BP measurements. PWV, as the gold standard measure of arterial stiffness (33), and BP were measured using a Vicorder system (Skidmore Medical). In accordance with the manufacturer instructions, participants rested for 30 min before measurements were performed with participants lying supine at a 30-degree angle. Arterial stiffness was determined by measuring 1) ba-PWV between the brachial and ankle arteries and 2) cf-PWV between the carotid and femoral arteries. For ba-PWV, the brachial cuff was attached to the mid of the brachial artery on the left arm and the ankle cuff was attached above the left ankle. For cf-PWV, the carotid cuff was attached over the left carotid palpation and the femoral cuff was placed around the upper left thigh. The distance between ba-PWV and cf-PWV cuffs was integrated into the Vicorder system, and the arterial BP measurements were obtained from the brachial cuff. Three ba-PWV (including arterial BP) and three cf-PWV measurements were taken, and the average value was calculated. Each ba-PWV and cf-PWV measurement was obtained consecutively separated by a 1-min interval, and a 5-min interval separated the three measurements.

Statistical analyses. The sample size of 20 participants was determined primarily by the onerous nature of the study design involving four time-consuming trials and multiple measurements of outcomes derived from blood samples and vascular assessments. The value of this pragmatic approach to sample size justification has been highlighted previously (34,35). Although the replicated nature of both intervention and control trials should increase statistical power for detection of overall mean intervention effect, the estimation of required sample size for detection of intervention response heterogeneity is more complicated. One of the primary analyses reported by Senn et al. (16,25) for quantifying individual consistency of response is the correlation coefficient between the two replicates of control trial-adjusted exercise responses. This component of our suite of analyses has been reported in several previous studies (17,18,27,36), the idea being that consistent individual differences in treatment response would be indicated by a moderate-to-high correlation between study design replicates (16,25). We hypothesized that consistent individual responses would be indicated by a "moderate" correlation coefficient of at least 0.4 (36). Using the GPower 3.1 software, it can be estimated that a sample size of 20 participants would enable a "moderate" target correlation of 0.44 to be detected as statistically significant. The 95% confidence interval (CI) of this target correlation coefficient of 0.44 would be 0.00 to 0.74 for a sample size of 20 participants.

Data were analyzed using the IBM SPSS Statistics software for Windows version 25.0 (IBM Corporation, Armonk, NY) in addition to the PROC MIXED procedure in SAS OnDemand for Academics (SAS Institute, Cary, NC) (37), which formulated within-participant linear mixed models for quantifying any participant-by-condition interactions. The primary outcome in this study was time-averaged total area under the curve (TAUC) for TAG, and the secondary end points were glucose, insulin, ba-PWV, cf-PWV, systolic BP (SBP), and diastolic BP (DBP). Primary and secondary outcomes were identified *a priori* before data collection for the study commenced. The trapezium rule was used to calculate the time-averaged TAUC on day 2 for TAG (TAUC-TAG), glucose (TAUC-glucose), and insulin (TAUC-insulin). For arterial stiffness and BP, delta responses (pre-to-post change scores) were calculated as the difference between the postprandial measurement on day 2 (2.5 h) and the fasting assessment at baseline on day 1.

The analysis approach was designed to explore consistency of interindividual differences in the exercise effect in three stages as outlined previously (17,18). First, each participant's first exercise condition was paired to the first control condition in their individual sequence, and the control-adjusted treatment effect was computed for response 1 (exercise 1 minus control 1). This process was repeated for the second condition pairs to calculate response 2 (exercise 2 minus control 2). As reported by Senn et al. (16,25), Pearson's correlation coefficients were quantified between the first and second response replicates for each outcome to determine the consistency of the replicated control-adjusted exercise effect. Thresholds of 0.1, 0.3, and 0.5 were used to define small, moderate, and large correlation coefficients, respectively (38).

Second, an overall estimate of the true individual difference SD for the treatment response was calculated using the following equation:

$$SD_{IR} = \sqrt{SD_E^2 - SD_C^2}$$

where SD_{IR} is the SD of the true individual differences in exercise (treatment) response adjusted for variance in the control conditions, and SD_E and SD_C are the SDs of the TAUC (biochemical outcomes) or pre-to-post change (vascular outcomes) in exercise and control conditions, respectively (21,28,29). A positive SD_{IR} indicates the variability in treatment response is greater than any random within-subject variability. Third, this naïve estimation was supplemented with a modeling approach involving a separate within-participant linear mixed model to quantify the participant-by-condition interaction for each outcome (16,25). Condition, period (condition sequence), and the period-by-condition interaction were modeled as fixed effects, with participant and the participant-by-condition interaction modeled as random effects (refer to the SAS base code supplied in the Supplemental Digital Content). Models were also repeated to include the fasted baseline value (0 h) of the dependent variable on day 1 as a covariate. Residual diagnostics procedures were undertaken to assess the influence of a potential set of observations on the adequacy and the stability of the modeled covariance parameter estimates (39,40). Inspection of the biochemical data revealed unusually high fasting insulin and/or glucose concentrations in five experimental conditions spanning four participants. Although confirmation that all participants arrived at the laboratory fasted on day 1 and day 2 was acquired verbally, noncompliance with this requirement cannot be ruled out in these trials. Therefore, we performed a sensitivity analysis for all biochemical outcomes that excluded the trials with irregular fasting concentrations to ensure the data were interpreted appropriately.

All data are summarized as mean (SD). Student's paired *t*-tests were used to compare treadmill exercise responses. In

line with the Difference Elicitation in TriAls ($DELTA^2$) group recommendations (41), standardized effect sizes (ES, Cohen's *d*) were calculated due to the absence of a clinical anchor to identify meaningful between-condition differences for the outcomes in this study. Thresholds of 0.2, 0.5, and 0.8 were considered small, moderate, and large effects, respectively (38). Although this "fall-back" approach is not the preferred method of defining a (clinically) important difference, alternative methods were not appropriate for the outcomes studied in the present analysis because the influence of a given change in outcomes on overall morbidity or mortality has not been well defined (41). The minimal clinically important difference (MCID) of individual responses was calculated to indicate the smallest worthwhile impact of exercise on each outcome (42). The threshold of 0.2 for interpreting standardized mean changes (38) was halved (0.1) and multiplied by the baseline between-subject SD (21,29). Statistical significance was accepted as $P < 0.05$, and two-sided statistical tests and estimations were selected.

RESULTS

Exercise responses. There were no statistically significant differences in any of the mean exercise responses between the two exercise bouts ($P > 0.105$), and the standardized ESs were trivial apart from the small ES for fat oxidation and net energy expenditure (Table 2).

Circulating TAG, glucose, and insulin. Pearson's correlation coefficients between the two replicates of control-adjusted exercise responses were small to moderate in magnitude but were not statistically significant for the TAUC-TAG ($r = -0.42$ (95% CI, −0.73 to 0.03), $P = 0.066$; Fig. 2A), TAUC-glucose ($r = -0.28$ (95% CI, −0.64 to 0.19); $P = 0.235$; Fig. 2C), and TAUC-insulin ($r = 0.11$ (95% CI, −0.35 to 0.52); $P = 0.657$; Fig. 2E). The period-adjusted mean TAUC values were lower in the exercise than control condition for TAG (−0.27 $mmol \cdot L^{-1} \cdot h$, $P = 0.017$) and insulin (−25 $pmol \cdot L^{-1} \cdot h$, $P = 0.022$), but between-condition differences for mean TAUC-glucose were trivial (0.09 $mmol \cdot L^{-1} \cdot h$, $P = 0.126$) (main effect of condition; Table 3). No statistically significant participant-by-condition interactions were identified for the biochemical outcomes (all $P \geq 0.137$), and the SD_{IR} values for estimates 1 (naïve approach) and 2 (modeling approach) were relatively small with wide 95% CI (Table 3). The SD_{IR} values for TAG and glucose were negative, indicating greater variability in the control than exercise conditions (estimate 2; Table 3). Additional adjustment for fasted baseline values on day 2 revealed similar findings to unadjusted models (Supplemental Table 2, Supplemental Digital Content, Estimated marginal means and SEs of the TAUC values for day 2 baseline-adjusted biochemical outcomes in the exercise and control conditions with the true individual differences SD, http://links.lww.com/MSS/C906). Examination of the individual data plots revealed that 70% and 15% of participants exhibited average responses below and above the MCID, respectively, for TAUC-TAG (Fig. 2B). Corresponding values for TAUC-glucose were 30% below and 65% above (Fig. 2D), and for TAUC-insulin, the values were 85% below and 15% above (Fig. 2F). The plasma TAG, glucose, and insulin concentrations over the postprandial period across each condition are presented at the group and individual level in Supplemental Figures 1–3, Supplemental Digital Content, Plasma TAG, glucose, and insulin concentrations during the replicated control and exercise conditions, http://links.lww.com/MSS/C906.

Sensitivity analysis for biochemical outcomes. Sensitivity analysis that removed trials with unusually high fasting insulin and/or glucose concentrations revealed similar small-to-moderate but nonsignificant correlations between the two sets of control-adjusted exercise responses for TAUC-TAG ($r = -0.47$ (95% CI, −0.78 to 0.03), $P = 0.065$), TAUC-glucose ($r = -0.31$ (95% CI, −0.70 to 0.22), $P = 0.247$), and TAUC-insulin ($r = -0.08$ (95% CI, −0.56 to 0.43), $P = 0.764$). Exclusion of this data did not influence the significance of the participant-by-condition interactions (all $P \geq 0.137$) or substantially alter the SD_{IR} for estimate 1 or estimate 2 (Table 3). Additional adjustment for fasted baseline values on day 2 did not alter interpretation of the models (Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/MSS/C906).

Arterial BP and pulse wave velocity responses. Pearson's correlation coefficients between the two replicates of control-adjusted exercise responses were small and not statistically significant for ba-PWV ($r = 0.01$ (95% CI, −0.43 to 0.45), $P = 0.97$; Fig. 3A), cf-PWV ($r = -0.03$ (95% CI, −0.46 to 0.42), $P = 0.909$; Fig. 3C), SBP ($r = 0.15$ (95% CI, −0.31 to 0.56), $P = 0.529$; Fig. 3E), and DBP ($r = -0.06$ (95% CI, −0.49 to 0.39), $P = 0.799$; Fig. 3G). The 95% CI for the period-adjusted mean difference between exercise and control conditions overlapped zero, and standardized ESs were trivial apart from the small ES for cf-PWV (main effect of condition; Table 4). No statistically significant participant-by-

TABLE 2. Responses during the treadmill exercise bouts on the two occasions.

Variable	Exercise Condition 1	Exercise Condition 2	Mean Difference (95% CI)[a]	ES	*P*
Oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$)	29.4 (5.4)	29.6 (5.0)	−0.2 (−1.0 to 0.6)	0.04	0.602
% Peak oxygen uptake	61 (7)	62 (7)	−1 (−2 to 1)	0.08	0.542
Respiratory exchange ratio	0.96 (0.04)	0.96 (0.06)	0.00 (−0.02 to 0.02)	0.04	0.857
Heart rate (bpm)	155 (12)	155 (12)	0 (−6 to 6)	0.01	0.982
RPE	6 (1)	6 (1)	0.1 (−0.5 to 0.6)	0.06	0.847
Fat oxidation (g)	9.9 (6.2)	11.9 (7.1)	−2.0 (−4.4 to 0.5)	0.30	0.105
Carbohydrate oxidation (g)	153.4 (34.6)	155.6 (44.2)	−2.2 (−15.5 to 11.0)	0.06	0.730
Net energy expenditure (kJ)	2840 (521)	2952 (584)	−112 (−260 to 36)	0.20	0.130

Values are presented as mean (SD) for $n = 20$. Data were analyzed using Student's paired *t*-tests.
[a]Values represent the mean absolute difference (95% CI of the mean difference between the two exercise conditions).

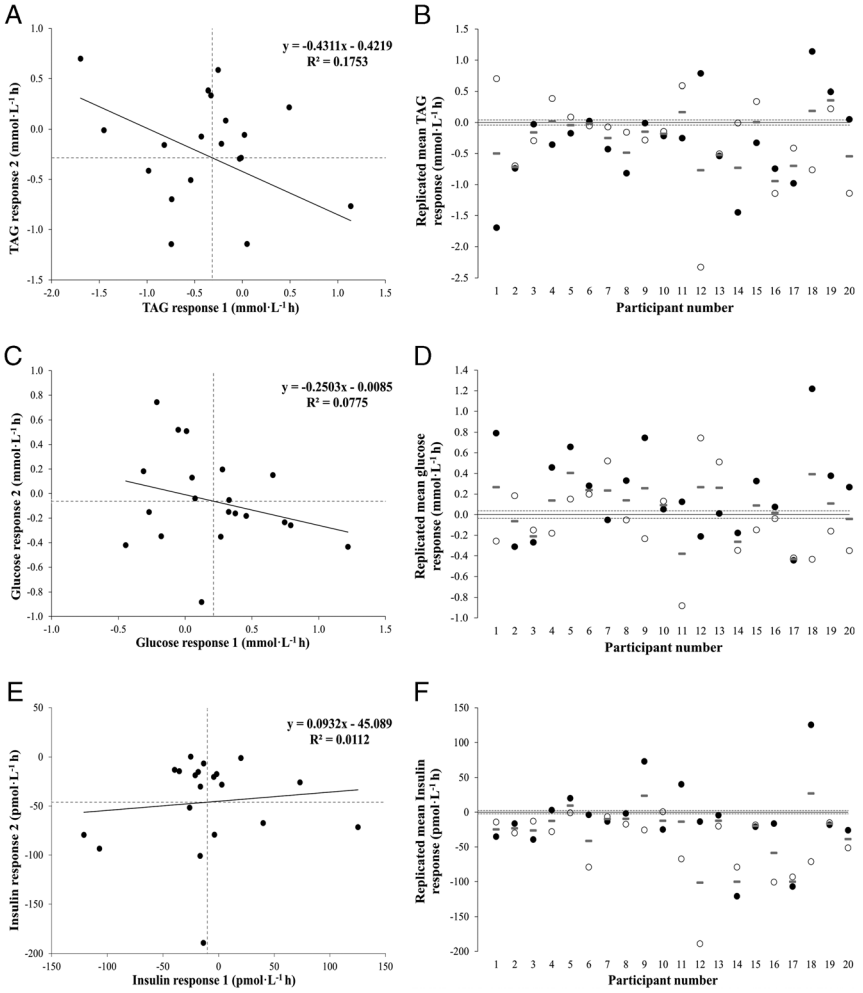

FIGURE 2—Panels A, C, and E, Relationship between exercise and control TAUC on the two occasions for TAG (panel A), glucose (panel C), and insulin (panel E). "Response 1" corresponds to the first pair of conditions (exercise 1 minus control 1) and "response 2" corresponds to the second pair of conditions (exercise 2 minus control 2). The *dotted vertical and horizontal lines* represent the mean responses. Panel B, D, and F, Individual changes in the TAUC for TAG (panel B), glucose (panel D), and insulin (panel F) between the exercise and control conditions (exercise minus control). For each participant, the *black circles* represent the TAUC value for "response 1," *white circles* represent "response 2," and *gray lines* represent each participant's replicated mean response. *Dashed lines* indicate the standardized MCID calculated as 0.1 multiplied by the day 2 baseline between-subject SD (21).

condition interactions were identified for the vascular outcomes (all $P \geq 0.140$), and the SD_{IR} for estimates 1 and 2 were small with 95% CI that overlapped zero considerably (Table 4). Inconsistency in the direction of SD_{IR} between estimate 1 and estimate 2 was noted for all outcomes (Table 4). Adjustment of models for fasted baseline values on day 2 revealed similar

TABLE 3. Estimated marginal means and SEs of the TAUC values for biochemical outcomes in the exercise and control conditions with the true individual differences SD.

	Mean (SE)		Main Effect of Condition[a]			Estimate 1[b]	Estimate 2[c]	
Outcome	Exercise	Control	Mean Difference (95% CI)	ES	*P*	Individual Differences SD	Individual Differences SD (95% CI)	*P* (Int)
TAUC-TAG (mmol·L^{-1}·h)								
Main analysis	1.76 (0.20)	2.03 (0.20)	−0.27 (−0.49 to −0.05)	0.29	0.017	−0.53	−0.27 (−0.48 to 0.29)	0.349
Sensitivity analysis	1.70 (0.20)	1.95 (0.19)	−0.25 (−0.47 to −0.04)	0.26	0.025	−0.63	−0.31 (−0.51 to 0.24)	0.219
TAUC-glucose (mmol·L^{-1}·h)								
Main analysis	5.03 (0.12)	4.94 (0.12)	0.09 (−0.03 to 0.20)	0.16	0.126	0.15	−0.19 (−0.29 to 0.11)	0.137
Sensitivity analysis	5.06 (0.13)	4.96 (0.13)	0.10 (−0.02 to 0.22)	0.18	0.103	−0.14	−0.19 (−0.31 to 0.15)	0.220
TAUC-insulin (pmol·L^{-1}·h)								
Main analysis	164 (14)	189 (15)	−25 (−45 to −4)	0.35	0.022	−53	25 (−25 to 43)	0.327
Sensitivity analysis	163 (13)	186 (15)	−23 (−45 to −1)	0.33	0.043	−47	34 (−19 to 52)	0.137

Data for the main analysis involved 80 experimental conditions in $n = 20$ men. Data for the sensitivity analysis involved 75 experimental conditions in $n = 16$ men.

[a]Estimated from a within-participant random effects linear mixed model.

[b]Estimate 1: individual differences SD estimated using $SD_{IR} = \sqrt{SD_E^2 - SD_C^2}$, where SD_{IR} is the SD of the true individual response, and SD_E and SD_C are the SDs of the TAUC in exercise and control conditions, respectively (21,28,29).

[c]Estimate 2: individual differences SD estimated using a random effects statistical model based on Senn et al. (25). The SD was calculated from the participant-by-condition interaction term modeled as a random effect, and the *P* value is for this interaction term.

SE, standard error; SD, standard deviation; int, participant-by-condition interaction.

findings to unadjusted models (Supplemental Table 3, Supplemental Digital Content, http://links.lww.com/MSS/C906). Examination of the individual data plots revealed that 50% and 40% of participants exhibited average responses below and above the MCID, respectively, for ba-PWV (Fig. 3B). Corresponding values for cf-PWV were 65% below and 30% above (Fig. 3D), for SBP, values were 45% below and 30% above (Fig. 3F), and for DBP, values were 35% below and 55% above (Fig. 3H).

DISCUSSION

This study investigated the consistency of postprandial CVD risk marker responses to acute exercise and sought to determine whether "true" interindividual variability in responses was meaningful between participants using a robust study design and statistical approaches (16,21,25,28,29). Our findings demonstrate that postprandial CVD risk marker responses to acute exercise were inconsistent across the replicated conditions and could not be distinguished from the relatively large

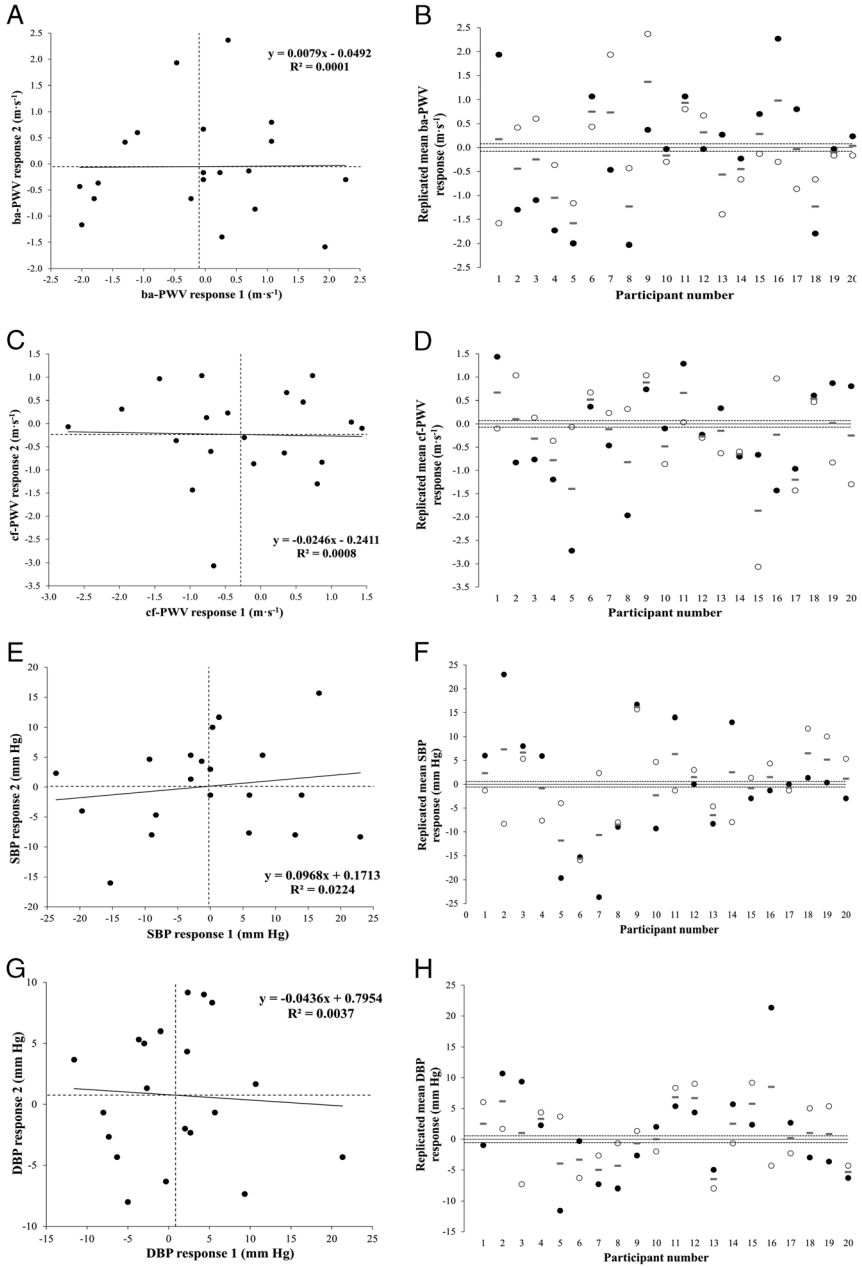

FIGURE 3—Panels A, C, E, and G: Relationship between exercise and control delta response on the two occasions for ba-PWV (panel A), cf-PWV (panel C), SBP (panel E), and DBP (panel G). "Response 1" corresponds to the first pair of conditions (exercise 1 minus control 1) and "response 2" corresponds to the second pair of conditions (exercise 2 minus control 2). The *dotted vertical and horizontal lines* represent the mean responses. Panel B, D, F, and H: Individual changes in the delta response for ba-PWV (panel B), cf-PWV (panel D), SBP (panel F), and DBP (panel H) between the exercise and control conditions (exercise minus control). For each participant, the *black circles* represent the delta response for "response 1," *white circles* represent "response 2," and *gray lines* represent each participant's replicated mean response. *Dashed lines* indicate the standardized MCID calculated as 0.1 multiplied by the day 2 baseline between-subject SD (21). Delta response: calculated as day 2 time 2.5 h minus day 1 time 0 h.

TABLE 4. Estimated marginal means and SE of pre-to-post change scores for vascular outcomes in the exercise and control conditions with the true individual differences SD.

Outcome (Delta Response, $n = 20$)[a]	Mean (SE)		Main Effect of Condition[b]			Estimate 1[c]	Estimate 2[d]	
	Exercise	Control	Mean Difference (95% CI)	ES	P	Individual Differences SD	Individual Differences SD (95% CI)	P (Int)
ba-PWV ($m \cdot s^{-1}$)	–0.01 (0.14)	0.14 (0.13)	–0.15 (–0.51 to 0.22)	0.17	0.417	0.59	–0.23 (–0.58 to 0.49)	0.704
cf-PWV ($m \cdot s^{-1}$)	–0.08 (0.13)	0.21 (0.16)	–0.29 (–0.64 to 0.07)	0.36	0.106	–0.30	0.38 (–0.41 to 0.67)	0.366
SBP (mm Hg)	3.54 (1.34)	3.98 (1.59)	–0.45 (–3.90 to 3.00)	0.06	0.793	–4.26	3.73 (–3.94 to 6.59)	0.354
DBP (mm Hg)	–0.04 (1.09)	–0.50 (0.90)	0.46 (–1.60 to 2.52)	0.08	0.651	3.57	–2.82 (–4.30 to 1.61)	0.140

[a]Delta response: calculated as day 2 time 2.5 h minus day 1 time 0 h.
[b]Estimated from a within-participant random effects linear mixed model.
[c]Estimate 1: individual differences SD estimated using $SD_{IR} = \sqrt{SD_E^2 - SD_C^2}$, where SD_{IR} is the SD of the true individual response, and SD_E and SD_C are the SDs of delta response of exercise and control conditions, respectively (21,28,29).
[d]Estimate 2: individual differences SD estimated using a random effects statistical model based on Senn et al. (25). The SD was calculated from the participant-by-condition interaction term modeled as a random effect, and the *P* value is for this interaction term.
SE, standard error; SD, standard deviation; int, participant-by-condition interaction.

random within-subject variability for each metabolic and vascular outcome investigated.

The impact of single bouts of exercise on short-term CVD risk marker responses has been investigated in many studies (3–5,43). This evidence base includes studies involving healthy individuals, as well as those with, or at high-risk of, cardiometabolic disease. The mean responses seen in this study are consistent with prior findings, with exercise reducing circulating concentrations of postprandial TAG and insulin when measured 12 to 36 h after exercise (44–46). The exercise-induced reduction in circulating TAG is likely mediated by the secretion of TAG-richer very low-density lipoproteins from the liver that have a higher affinity for lipoprotein lipase clearance, whereas the insulin response is likely due to a transitory increase in skeletal muscle insulin sensitivity (4,47,48). Moreover, although acute exercise may lower BP, PWV, and circulating glucose concentrations in populations with obesity and obesity-related risk factors, the lack of response identified in this study when considering the mean data is consistent with data derived from studies in healthy individuals and with outcomes measured closer to the cessation of exercise (10,46,49).

In line with Senn et al. (16,25), we examined the consistency of postprandial CVD risk marker responses to acute exercise by quantifying the correlation coefficient between pairs of control-adjusted exercise responses. Our data show that no clear associations exist between paired responses in any of the outcomes, indicating a lack of consistency in response to exercise performed on repeated occasions. Indeed, across each of the outcomes examined, there were several instances where a participant's control-adjusted exercise response on one occasion was lower, but an opposite direction of response was apparent for the second replicate. This test–retest variability can be attributed to random biological variation (meal and exercise responses) (50,51).

Previous research has sought to quantify the reproducibility of postprandial CVD risk marker responses to single meals and/or acute exercise exposures (11–15,52,53). Specifically, these studies provide evidence that meal-stimulated responses are reproducible when postprandial assessments are repeated on at least two occasions for TAG (11,12,14,15) and BP (13). Notably, O'Doherty et al. (12) reported a Spearman's ranked correlation coefficient of 0.90 for postprandial TAG between replicated 4-h oral fat tolerance tests at rest. However, greater variation in the postprandial TAG response emerged when an identical bout of exercise was undertaken immediately before meal ingestion (Spearmen's ranked correlation coefficient, 0.42) (12). Similarly, poor reproducibility has also been described for postprandial glucose responses to three identical bouts of cycling (52), along with brachial artery PWV in response to two identical cycling tests (53). Unfortunately, a limitation of previous studies when exploring exercise-specific responses is the failure to account for random within-subject variability of the measurement, which can be determined by measuring outcomes in repeated control and intervention condition arms, and subsequently adjusting the intervention response for the natural fluctuations that occur over time (16,21,25). Importantly, the present study advances the existing evidence base with the adoption of a research design that accounts for within-subject random variation over repeated experimental trials when deriving the participant-by-condition interaction (16,21,25,51). It is also worth noting that the standardization procedures, including the control of dietary intake, implemented in the days before capturing postprandial responses may introduce a source of variability in the exercise and/or meal response. In this study, dietary intake was replicated within participants in the 48 h before day 1 of each condition, and carefully standardized meals were provided on day 1 and 2 of each experimental condition. Such meticulous standardization of dietary intake is not always apparent in the literature but is a vital consideration for any investigation of reproducibility and interindividual variability.

We adopted a replicated crossover study design to quantify interindividual differences in exercise response by comparing the SDs of the TAUC values (biochemical outcomes) or change scores (vascular outcomes) between intervention and control arms (21,28,29). We identified relatively small SDs for individual responses in all outcomes, which were negative for TAG, glucose, ba-PWV, and DBP (based on estimate 2) indicative of greater variability in the control than in the exercise arms. Furthermore, there was some disparity in the individual differences SD estimated using the naïve and modeling approaches with both a negative and positive SD_{IR} apparent for estimate 1 and estimate 2 for many outcomes. Collectively, these findings are not consistent with the presence of exercise response heterogeneity for postprandial CVD risk markers but imply a high level of random condition-to-condition variability is present in the outcome measurements that makes it challenging to detect any individual differences in exercise response.

This study is the first to explore the reproducibility and interindividual variability of postprandial CVD risk markers in response to acute exercise within a replicated crossover study design using robust statistical approaches. The 2-d approach elicits a realistic reflection of the delayed effects of acute aerobic exercise on postprandial CVD risk markers. To mitigate any potential confounding effects, we implemented careful standardization procedures for diet and physical activity and required participants to rest in the laboratory throughout day 1 of all experimental conditions. However, we suspect some participants did not follow the fasting requirements across all experimental conditions as unusually high fasting insulin and/or glucose concentrations were identified in a few conditions. Although the sensitivity analysis excluding the problematic data did not alter the interpretation of the main analysis, we recognize this may be a limitation of the study. Furthermore, the study is limited by the relatively small sample size, which is reflective of the onerous nature of the replicated crossover design requiring rigorous standardization, replicated exercise protocols, and multiple outcome assessments (54). Finally, our study is also restricted to young, healthy men, so future extension of this work to women, older individuals, and clinically relevant populations such as those who have overweight/obesity or are at elevated CVD risk is required to determine the generalizability of the present findings.

CONCLUSIONS

In conclusion, this study has shown that postprandial CVD risk marker responses to acute exercise are not consistent on repeated occasions. Furthermore, high levels of random within-subject variation and measurement error prohibit the identification of genuine interindividual response heterogeneity. These findings may help to explain inconsistencies in postprandial outcomes between conditions and should be considered when designing new experiments.

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