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A bout of endurance and resistance exercise transiently decreases plasma levels of bile acids in young, sedentary adults

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Circulating bile acids (BA) are signaling molecules that control glucose and lipid metabolism. However, the effects of acute exercise on plasma levels of BA in humans remain poorly understood. Here, we evaluate the effects of a bout of maximal endurance exercise (EE) and resistance exercise (RE) on plasma levels of BA in young, sedentary adults. Concentration of eight plasma BA was measured by liquid chromatography–tandem mass spectrometry before and 3, 30, 60, and 120 min after each exercise bout. Cardiorespiratory fitness (CRF) was assessed in 14 young adults (21.8 ± 2.5 yo, 12 women); muscle strength was assessed in 17 young adults (22.4 ± 2.5 yo, 11 women). EE transiently decreased plasma levels

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of total, primary, and secondary BA at 3 and 30 min after exercise. RE exerted a prolonged reduction in plasma levels of secondary BA ($p < 0.001$) that lasted until 120 min. Primary BA levels of cholic acid (CA) and chenodeoxycholic acid (CDCA) were different across individuals with low/high CRF levels after EE ($p \leq 0.044$); CA levels were different across individuals with low/high handgrip strength levels. High CRF individuals presented higher levels of CA and CDCA 120 min after exercise vs baseline (+77% and +65%) vs the low CRF group (−5% and −39%). High handgrip strength levels individuals presented higher levels of CA 120 min after exercise versus baseline (+63%) versus the low handgrip strength group (+6%). The study findings indicate that an individual's level of physical fitness can influence how circulating BA respond to both endurance and resistance exercise. Additionally, the study suggests that changes in plasma BA levels after exercising could be related to the control of glucose homeostasis in humans.

KEYWORDS

Chenodeoxycholic acid, cholic acid, exerkines, lipidomics, physical fitness

1 | INTRODUCTION

It is well known that exercise training induces multiple beneficial effects on metabolism.[1] However, the molecular mechanisms underlying these health benefits are poorly understood.[2] Exercise acutely elicits a complex metabolic response that involves organ and cellular communications through changes in the concentration of a myriad of molecules.[3] A better understanding of this response is needed to unravel the mechanisms by which cellular and biochemical pathways are affected by exercise. For these reasons, the implementation of new molecular techniques, such as metabolomics in the exercise physiology field, is providing new insights into the metabolic and molecular pathways involved in the health-related benefits of exercise.[4,5]

The liver is a central organ in the regulation of energy metabolism. Among many other metabolic functions, the liver produces bile acids (BA) from cholesterol.[6] Hepatocytes synthesize the primary BA cholic (CA) and chenodeoxycholic (CDCA) and conjugate them with either glycine (~75%) or taurine (~25%).[7] These BA are then stored in the gallbladder and secreted along with the bile into the duodenum, where they support the absorption of dietary lipids and fat-soluble vitamins.[8] When the primary BA reach the colon, they undergo metabolic conversions by certain gut bacteria that express enzymes involved in BA metabolism to be converted into secondary BA, including deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) and its glycine and taurine conjugates.[7] Approximately 90% of the BA undergo enterohepatic circulation for reuse in the liver and 5% are excreted in feces, whereas only a small fraction (>5%) reaches the systemic circulation.[9,10] Circulating BA notably exert signaling actions in several peripheral tissues and organs.[11,12] The endocrine effects associated with circulating BA are driven by the activation of Takeda-G-protein-receptor-5 (TGR5) and the farnesoid X receptor (FXR), which are expressed in tissues such as adipose tissue, skeletal muscle, and pancreas.[13] In fact, preclinical studies have revealed that the activation of TGR5 by BA leads to an increase in energy expenditure and improves glucose and lipid metabolism (3–5).

During exercise, sustained muscle activity is supported by a fine-tuned and coordinated liver response that mobilizes energy stores and metabolites.[14] Only a scarce number of studies have examined the effects of endurance exercise (EE)[15–17] and resistance exercise (RE)[15] on circulating BA levels, all of them in trained individuals.[15–17] However, none of these studies were conducted in young, sedentary adults or investigated whether the effect of exercise on circulating BA depends on the individual's physical fitness such as cardiorespiratory fitness (CRF) or muscle strength levels of the individuals, which are well-recognized markers of health status.[18,19]

This study aimed to investigate the acute effect (i.e., up to 120 min after the exercise bout) of EE and RE on plasma levels of BA in young, sedentary adults. As a secondary aim, we investigated whether these effects were related to the individual's CRF and muscle strength levels.

2 | MATERIALS AND METHODS

2.1 | Individuals and study design

This study has been conducted before starting the exercise intervention program of the ACTIBATE study (ACTivating Brown Adipose Tissue through Exercise; ClinicalTrials.gov ID: NCT02365129).[20] A total of 14 individuals (21.8 ± 2.5 yo; 86% women) underwent the EE trials, whereas 17 individuals (22.4 ± 2.5 yo; 64% women) underwent the RE trials. Of individuals, 12 individuals underwent both trials. Inclusion criteria included, among others: (i) report to be sedentary (i.e., <20 min/day of moderate-to-vigorous physical activity on <3 days/week); (ii) to be a nonsmoker; (iii) no medication, and (iv) have a stable body weight over the last 3 months (≤3 kg change). Exclusion criteria included (i) diagnosis of diabetes, hypertension, or other medical conditions that could be life-threatening or that can interfere with/be aggravated by exercise; (ii) pregnancy; (iii) use of medication that could affect energy metabolism; and (iv) having frequent exposures to cold temperatures.

The study was approved by the Ethics Committee on Human Research of the University of Granada (no. 924) and by the Servicio Andaluz de Salud (Centro de Granada, CEI-Granada). All individuals signed informed consent. The study protocol and experimental design were applied following the last revised ethical guidelines of the Declaration of Helsinki.

2.2 | Acute exercise trials

Both EE and RE trials were performed in a fasted state (i.e., 3–5 h fasting), after avoiding stimulants (e.g., caffeine) and any moderate- and vigorous-intensity exercise (24 and 48 h, respectively) on separate days (≥72 h separation between the EE and RE trials). Acute exercise trials took place between 11:00 and 20:00 h.

The EE consisted of a maximum effort test on a treadmill (Pulsar treadmill, H/P/Cosmos Sports & Medical GmbH, Nussdorf-Traunstein, Germany) following the modified Balke protocol.[21] Briefly, individuals walked at 3 km/h for 1 min and at 4 km/h for 2 min as warming up (0% grade).[21] Then, the test started by walking at 5.3 km/h with a 0% grade. From that moment on, the treadmill grade was increased by 1% every min, until volitional exhaustion reached.[21] At this point, individuals started a 5-min recovery walking at 4 km/h and 0% grade.[21] During the whole test, individuals were equipped with a heart rate monitor (Polar RS800CX, Polar Electro Öy, Kempele, Finland), 10 electrodes for electrocardiogram monitoring, and a Hans–Rudolph plastic mask (model 7400; Hans Rudolph Inc., Kansas City, MO, USA) connected to a preVent™ metabolic flow sensor (Medical graphics Corp, St Paul, MN, USA) for respiratory gas exchange analysis using a CPX Ultima CardioO2 gas exchange analysis system (Medical Graphics Corp, St Paul, MN, USA). During the test, respiratory gas exchange (oxygen consumption [VO_2] and carbon dioxide production [VCO_2]) was recorded and the VO_2peak was determined as the highest observed VO_2 value, after excluding artifacts if needed.

The RE consisted of a combination of four different strength tests: (i) a maximum isometric strength test with leg press, (ii) a maximum isometric handgrip strength test, as well as (iii) and (iv) two 1-repetition maximum (1-RM) tests with bench and leg press, respectively.[22] Individuals first completed the maximum isometric strength test with leg press. After being positioned into the leg press machine (A300 Leg Press, Model 2531, Keiser Corporation, Fresno CA, USA), individuals performed two 3-s repetitions, 2 min apart, for which they were instructed and encouraged to push as hard as they could for the entire duration of the set. Afterward, individuals performed the handgrip strength test by completing two repetitions with each hand, 1 min apart, using a Takei 5401 digital Grip-D hand dynamometer (Takei, Tokyo, Japan).[23] For the handgrip strength test, individuals remained in a standing position, with the exercising arm parallel and slightly separated from the trunk. The individuals were asked to squeeze the grip gradually and continuously, and as hard as possible. Men executed the test with the grip span of the dynamometer fixed at 5.5 cm, while it was adjusted to the hand size for women, according to a validated equation.[23] The highest strength recorded in each hand was selected, and the average between both hands was used for the analyses.

Then, individuals performed the leg press 1-RM test with the same leg press machine. After performing 1 set of 10 repetitions with a self-selected lightweight for warming-up, they were instructed to perform one set of eight repetitions selecting the resistance for which they could perform at least 15 repetitions. After a 1-min recovery, the resistance load was increased by the study personnel, aiming to set a load with which the individual could perform <10 repetitions, and individuals were instructed to do as many repetitions as possible. The individuals were instructed to stop exercising after 3–4 repetitions if they felt they could perform more than 10 repetitions with the resistance load. If they performed more than 10 repetitions, they rested for 5 min and repeated the test with a higher load. The maximum number of attempts for assessing the RM (in a set of <10

repetitions) was 3. Lastly, individuals performed the bench press 1-RM test following the same procedure described for the leg press, on a bench within a pneumatic power rack (Power rack, Model 3111, Keiser Corporation, Fresno CA, USA). The 1-RM of both exercises was estimated by the Wathen equation mentioned.[24]

2.3 | Blood samples collection

For the baseline characteristics of the individuals, fasting blood samples were drawn from the antecubital vein in the morning (8.00–9.00 A.M) after overnight fasting (>10 h). Blood samples were collected in Vacutainer Tubes® and centrifuged, to obtain serum (in Vacutainer® SST™ II Advance tubes) and plasma (in Vacutainer® Hemogard™ tubes, containing potassium salt of ethylenediaminetetraacetic acid as an anticoagulant) aliquots that were stored at −80°C until analyses. For the acute exercise trials, blood samples were collected before, and 3, 30, 60, and 120 min after the end of each exercise session. Analysis of BA was carried out in plasma samples.

2.4 | Determination of plasma bile acids levels

Plasma levels of BA were determined by a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) method.[25] Briefly, BA were extracted from plasma using liquid–liquid extraction and analyzed with a Shimadzu LC system (Shimadzu Corporation, Kyoto, Japan) connected to a QTRAP 6500+ mass spectrometer (SCIEX, Framingham, MA, USA). The protocol enabled the relative quantification of primary (i.e., CA, CDCA, glycocholic acid [GCA], and glycochenodeoxycholic acid [GCDCA]) and secondary (i.e., DCA, glycodeoxycholic acid [GDCA], glycolithocholic acid [GLCA], glycoursodeoxycholic acid [GUDCA]) BA. The area peak ratio (peak are of analytes divided by peak area of respective internal standard) of primary and secondary BA measured was summed from the individual data, and the newly computed variables were expressed as total BA, primary BA, and secondary BA.

The BA detected by this method are listed in Table S1, whereas the isotopically labeled internal standards used are shown in Table S2. Relative standard deviations (RSDs) were calculated for each analyte present in the quality control (QC) samples (Table S1). All analytes showed RSD values in QC samples below 10%, ensuring high data quality. An extensive description of the sample preparation, profiling of BA, and data preprocessing is available in Supplementary Material.

2.5 | Anthropometric and body composition

Weight and height were measured barefoot and wearing light clothing, using a SECA scale and stadiometer (model 799; Electronic Column Scale, Hamburg, Germany). Body mass index (BMI) was calculated from weight and height (kg/m^2). Waist circumference (WC) was measured at the minimum perimeter, at the end of a normal expiration, with the arms relaxed on both sides of the body. Waist circumference was measured twice with a plastic tape measure; the two measures were averaged for further analyses. Lean, fat, and visceral adipose tissue (VAT) masses were measured by dual-energy X-ray absorptiometry using a Discovery Wi device (Hologic Inc., Bedford, MA, USA) equipped with the analysis software APEX (version 4.0.2). Fat mass was also expressed as a percentage of body weight and lean and fat mass indices as kg/m^2, respectively.

2.6 | Cardiometabolic risk factors

The serum levels of cardiometabolic risk parameters were measured following standardized procedures, and the homeostasis model assessment (HOMA index), and fatty liver index (FLI) were calculated.[26] Glucose serum concentration was measured using an AU5832 analyzer (Beckman Coulter, Brea, CA, USA) with a Beckman Coulter reagent (OSR6521). Insulin concentration was measured by chemiluminescence immunoassays using the UniCel DxI 800 analyzer (Beckman Coulter) with Beckman Coulter chemiluminescent reagent (33410). The circulating concentrations of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), glutamic pyruvic transaminase (GTP), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and creatinine were measured using an AU5832 spectrophotometer (Beckman Coulter) with Beckman Coulter reagents (OSR6116, OSR60118, OSR6187, OSR6507, OSR6520, OSR6204, and OSR6678, respectively). Low-density lipoprotein-cholesterol (LDL-C concentration) (mM) was calculated from the Friedewald formula[27]. The concentration of C-reactive protein, C3 protein, and C4 protein was measured by immunoturbidimetric assays (OSR6299, OSR6159, and OSR6160, respectively) using an AU5832 spectrophotometer. Leptin and adiponectin concentrations were measured in plasma using the MILLIPLEX MAG Human Adipokine Magnetic Bead Panel 2 (Catalogue # HADK2MAG-61 K) and a MILLIPLEX MAP Human Adipokine Magnetic Bead Panel 1 (Catalogue # HADK1MAG-61 K), respectively (Luminex Corporation, Austin, TX, USA).

Systolic and diastolic blood pressure were measured on three separate days using an automatic Omron M2 (Omron Healthcare, Kyoto, Japan).

2.7 | Statistical analyses

Descriptive data are expressed as mean ± standard deviation unless otherwise stated. First, data normality was checked using the Shapiro–Wilk test, visual histograms, and Q-Q plots. None of the BA followed a normal distribution, thereby all values were log2-transformed for the analyses. The effects of EE and RE on plasma levels of BA were analyzed by one-way repeated-measures analysis of variance (ANOVA), with the time when blood was collected (i.e., baseline, 3, 30, 60, and 120 min) as a factor. The fold changes, relative to the baseline of BA concentrations, were calculated with the log2-transformed outcomes. Next, the function "Visual Binning" of SPSS (Statistical Package for the Social Sciences v.26.0; IBM Corporation, Chicago, IL, USA) was used to divide the EE cohort into individuals with low/high CRF relative to body weight based on the median levels of the VO_2peak. The same function was used to divide the RE cohort into individuals with low/high lower body muscle strength based on the median levels of RM leg press relative to body weight, and into individuals with low/high upper body muscle strength based on the median levels of RM bench press and handgrip relative to body weight, respectively. Then, two-factor repeated measures ANOVAs were performed to investigate whether the acute effects of the EE and RE were different depending on the CRF, muscle strength levels, and type of exercise (Factor 1 "time" [baseline, 3, 30, 60, and 120 min] and Factor 2 "CRF, muscle strength levels, and type of exercise" [low/high CRF levels, low/high muscle strength levels, or endurance/resistance exercise]). The differences in specific time points between low/high CRF individuals were assessed by *t*-tests for independent samples. We performed *t*-tests for independent samples to compare parameters between individuals with low/high CRF and low/high handgrip levels (i.e., differences at baseline in body composition, cardiometabolic risk factors, and CRF levels). All analyses were performed using the Statistical Package for the Social Sciences v.26.0 (IBM Corporation, Chicago, IL, USA) and figures were built with GraphPad Prism software v.9 (GraphPad Software, San Diego, CA, USA). The statistical significance was set at $p < 0.05$.

3 | RESULTS

The characteristics of the study participants for both EE and RE interventions are shown in Table 1.

TABLE 1 Baseline characteristics of the study participants.

	Endurance ($n = 14$)		Resistance ($n = 17$)	
	Mean	SD	Mean	SD
Demographics				
Age (years old)	21.8	2.5	22.4	2.5
Male (%)	2	14%	6	35%
Female (%)	12	86%	11	64%
Body composition				
BMI (kg/m^2)	24.2	4.0	25.3	4.2
Lean mass (kg)	39.6	7.2	41.8	9.0
Fat mass (kg)	24.1	9.5	26.2	6.7
Fat mass (%)	35.9	10.0	37.1	6.3
VAT mass (g)	326	173	378	160
Physical Fitness				
RM leg press (kg)	205.2	54.8	210.3	69.6
VO_2peak (mL/kg/min)	40.7	7.2	40.0	9.6
Time to exhaustion (s)	806	236	872	219

Note: Data are presented as mean and standard deviation (SD), unless otherwise stated.

Abbreviations: BMI, body mass index; RM, repetition maximum; VAT, visceral adipose tissue; VO_2, oxygen consumption.

3.1 | Plasma levels of bile acids transiently decrease after a bout of both endurance and resistance exercise

After the exercise bout, EE decreased plasma levels of total and secondary BA at 3 and 30 min after exercise (−52% and −45%, respectively), whereas primary BA decreased only at 3 min after exercise (−59%; Figure 1A; all $p \leq 0.014$, $\eta^2 \geq 0.272$). After this time point, plasma levels of total and secondary BA gradually increased, while primary BA returned nearly to baseline levels at 120 min (−18%). The analysis of the response of each BA revealed that EE lowered plasma levels of the conjugated primary BA GCA and GCDCA 30 min after exercise (−79% and −28%, respectively), while the unconjugated primary BA CA decreased only 3 min after exercise (−42%; Figure 1B; all $p \leq 0.010$, $\eta^2 \geq 0.292$). After the 30-min time point, plasma levels of GCA and GCDCA remained stable, while CA levels continued to increase until surpassing their baseline levels 120 min after exercise (+40%; Figure 1B; all $p \leq 0.010$, $\eta^2 \geq 0.292$). The secondary BA DCA, GDCA, GLCA, and GUDCA displayed a decreased concentration until 30 min after EE (−20%, −94%, −61%, and −34%, respectively), which did not change upon the subsequent time points (Figure 1C; all $p \leq 0.020$, $\eta^2 \geq 0.264$).

On the contrary, RE reduced plasma levels of secondary BA, reaching the lowest levels at 120-min postexercise

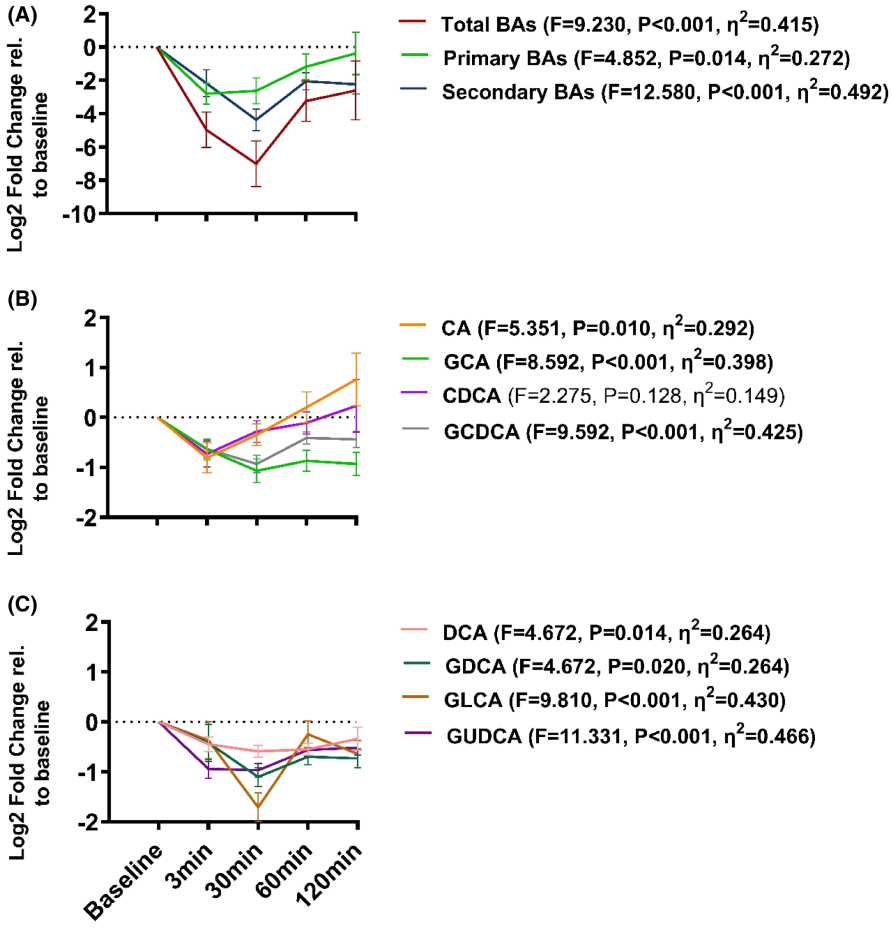

FIGURE 1 Acute endurance exercise transiently reduces the plasma levels of total, primary, and secondary bile acids ($n = 14$). Changes in total bile acid groups (A), and specific changes in primary bile acids (B) and secondary bile acids (C) after acute endurance exercise. Each curve represents the mean log2 fold-change in plasma levels relative to the baseline levels of each group of bile acids or specific bile acid. F, P, and η^2 values were obtained from repeated measures analyses of variance (ANOVA). Error bars show the standard error of the mean. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDC, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid.

(−26%; Figure 2A; $p < 0.001$, $\eta^2 = 0.270$). Specifically, RE reduced the concentration of the primary BA GCA and GCDCA and remained under baseline levels at time point 120 min (−68% and −17%) (Figure 2B; all $p \leq 0.005$, $\eta^2 \geq 0.205$). Similar effects were also observed for the plasma levels of the secondary BA GDCA, GLCA, and (−101%, −39%, and −17%; Figure 2C; all $p \leq 0.020$, $\eta^2 \geq 0.187$).

3.2 | Individuals with different cardiorespiratory fitness and handgrip strength levels display a different response of plasma bile acids after acute bouts of exercise

The EE cohort was divided into two groups, that is, individuals with low versus high CRF levels. We found that the response of plasma levels of primary BA after EE was different between high versus low CRF levels (Figure 3B; $p_{interaction} = 0.044$). Indeed, while primary BA levels acutely decreased 3 min after exercise in both low and high CRF levels groups (−64% and −65%), the plasma levels of primary BA increased beyond the baseline values only in individuals with high CRF levels after 120 min (+37%; Figure 3B). On the Contrary, the plasma levels of primary BA remained under baseline levels for the whole period in participants with low CRF levels (−53%; Figure 3B). Specifically, the trajectories on the whole primary BA levels might be driven by the primary BA species CA (Figure 3D; high CRF = +77% vs. low CRF = −5%, $p_{interaction} = 0.028$) and CDCA (Figure 3F; high CRF = +65% vs. low CRF = −39%, $p_{interaction} = 0.029$). Except for DCA (Figure 3H; $p_{interaction} = 0.048$), no other differences were observed for total, secondary, or the rest of the BA species (Figure 3A, C, E, G, I–K; all $p_{interaction} \geq 0.105$).

Similarly, the RE cohort was divided into individuals with low and high forearm muscular strength (handgrip) levels. Since muscular strength is strongly affected by the weight of this individual, we performed this division expressing handgrip relative to the body weight. Interestingly, we found that the trajectories of plasma levels of primary BA after RE were different between individuals with low and high handgrip strength levels (Figure 4B; $p_{interaction} = 0.034$). Participants with high handgrip strength levels showed an increase in plasma levels of primary BA after 120 min (+24%; Figure 4B), whereas in participants with low handgrip strength levels, the plasma levels of primary BA remained stable

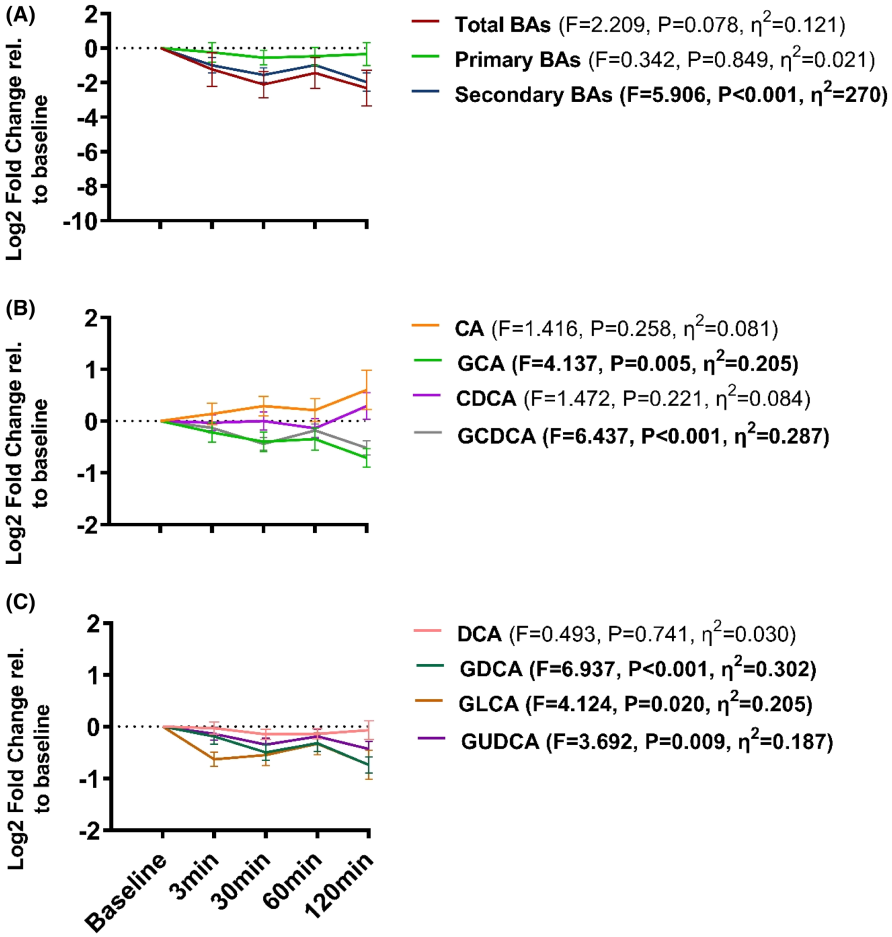

FIGURE 2 Acute resistance exercise exerts a prolonged reduction of plasma levels of secondary bile acids ($n = 17$). Changes in total bile acid groups (A), and specific changes in primary bile acids (B) and secondary bile acids (C) after acute resistance exercise. Each line represents the mean log2 fold change relative to the baseline of each group of bile acids or individual bile acids. F, P, and η^2 values were obtained from repeated measures analyses of variance (ANOVA). Error bars show the standard error of the mean. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDC, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid.

(+4%; Figure 4B). Furthermore, the plasma levels of the unconjugated primary BA CA increased beyond baseline values in the group of high handgrip strength (Figure 4D; high handgrip strength levels = +63% vs., low handgrip strength levels = +6%, $p_{interaction} = 0.028$). No other differences were detected for total, secondary, or the rest of the BA species (Figure 4A, C, E–K; all $p_{interaction} \geq 0.226$). Nevertheless, no differences were observed in the trajectories of plasma levels of BA after RE when the division between groups was performed with leg press (Figure S1A–K; $p_{interaction} \geq 0.568$) or bench press strength levels (Figure S2A–K; $p_{interaction} \geq 0.140$).

3.3 | Endurance and resistance exercises induce a different response of plasma levels of bile acids

The analyses comparing the response of plasma levels of BA to EE and RE revealed that there was a significant time × exercise interaction in six of 11 BA analyses, (Figure S3A). Specifically, there were significant time × exercise interactions when analyzing total, primary, and secondary BA (Figure S3B–D; $p_{interaction} \geq 0.039$) that were explained by differences in the conjugated primary BA GCDCA (Figure S3E; $p_{interaction} \geq 0.012$) and the conjugated secondary BA GLCA and GUDCA (Figure S3F–G; $p_{interaction} \geq 0.002$).

3.4 | Phenotypical differences between individuals with low versus high fitness level

As expected, individuals with high CRF levels presented higher VO_2peak (+38%) in comparison with their low CRF levels counterparts (Table 2; $p = <0.001$), yet the time spent in completing the maximal waking effort test was similar between both groups (Table 2; $p = 0.263$). Individuals with high CRF levels presented lower BMI (−21%), adiposity levels (−34% fat mass percentage; −47% VAT mass), insulin resistance profile (−45% insulin levels; −49% HOMA index), and immunometabolic profile (−77% serum leptin; −58% C-reactive protein; −15% creatinine, and −16% C3 levels) in comparison with their low CRF levels counterparts (Table 2; all $p \leq 0.024$). However, no differences were observed in hepatic enzymes, fatty liver index, or blood pressure levels. (Table 2; all $p > 0.05$). The differences in glucose and immunometabolic parameters persisted after adjusting for fat mass % (Table 2; all $p \leq 0.045$).

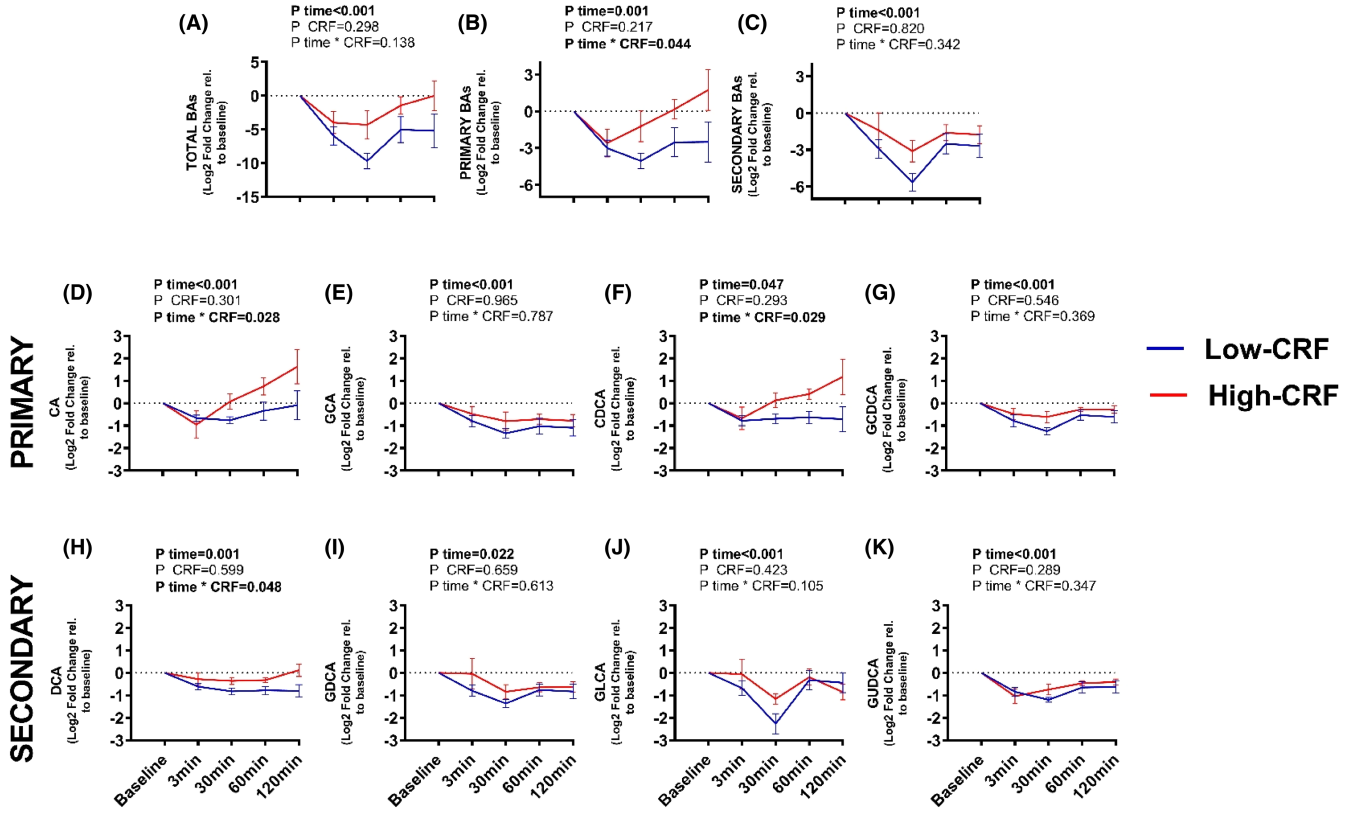

FIGURE 3 Response in plasma levels of bile acids after acute endurance exercise is different between young adults with low and high cardiorespiratory fitness levels. Changes in total bile acids (A), primary bile acids (B), secondary bile acids (C), CA (D), GCA (E), CDCA (F), GCDCA (G), DCA (H), GDCA (I), GLCA (J) and GUDCA (K) levels after acute endurance exercise. Each line represents the mean log2 fold change relative to the baseline of each group of bile acids or individual bile acids. P values were obtained from two-factor (low/high CRF and time) repeated measures analyses of variance (ANOVA). Error bars show the standard error of the mean. CA, cholic acid; CDCA, chenodeoxycholic acid; CRF, cardiorespiratory fitness; DCA, deoxycholic acid; GCA, glycocholic acid; GCDC, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid.

On the contrary, individuals with high handgrip strength levels also presented lower fat mass % (−18%), insulin resistance profile (−30% insulin levels; −32% HOMA index), and HOMA index (−32%), but higher LDL-C levels (+31%) than individuals with low handgrip strength levels (Table 3; all $p \leq 0.034$). Only the differences in LDL-C levels persisted after adjusting for fat mass % (Table 3; $p = 0.006$).

4 | DISCUSSION

Overall, EE acutely decreased plasma levels of total, primary, and secondary BA, which remained low for 30 min and either increased or remained stable for 90 more minutes. On the contrary, RE reduced the plasma levels of secondary BA, and they did not return to baseline levels. Interestingly, the response of the plasma levels of the primary BA CA and CDCA after EE and the plasma levels of CA after RE were different across individuals with low and high physical fitness levels. Those participants with higher levels of physical fitness—CRF or handgrip strength levels—showed unconjugated primary BA values in response to exercise that increased beyond baseline levels, whereas participants with low levels did not show this increase. There were no differences in plasma levels of BA after RE between individuals with low and high lower- and upper-body strength levels.

4.1 | A bout of endurance exercise transiently reduces plasma levels of bile acids

Our findings are congruent with a prior study in which running 21 km significantly reduced the serum concentration of total BA by −46%, specifically CA, DCA, and GUDCA, in 30 middle-aged (nine women) recreational runners just after finishing the exercise.[16] Similarly, another study found a reduction in plasma levels of GCA and DCA immediately after finishing a long-running session (80.5 km, treadmill) in nine trained middle-aged male runners.[17]

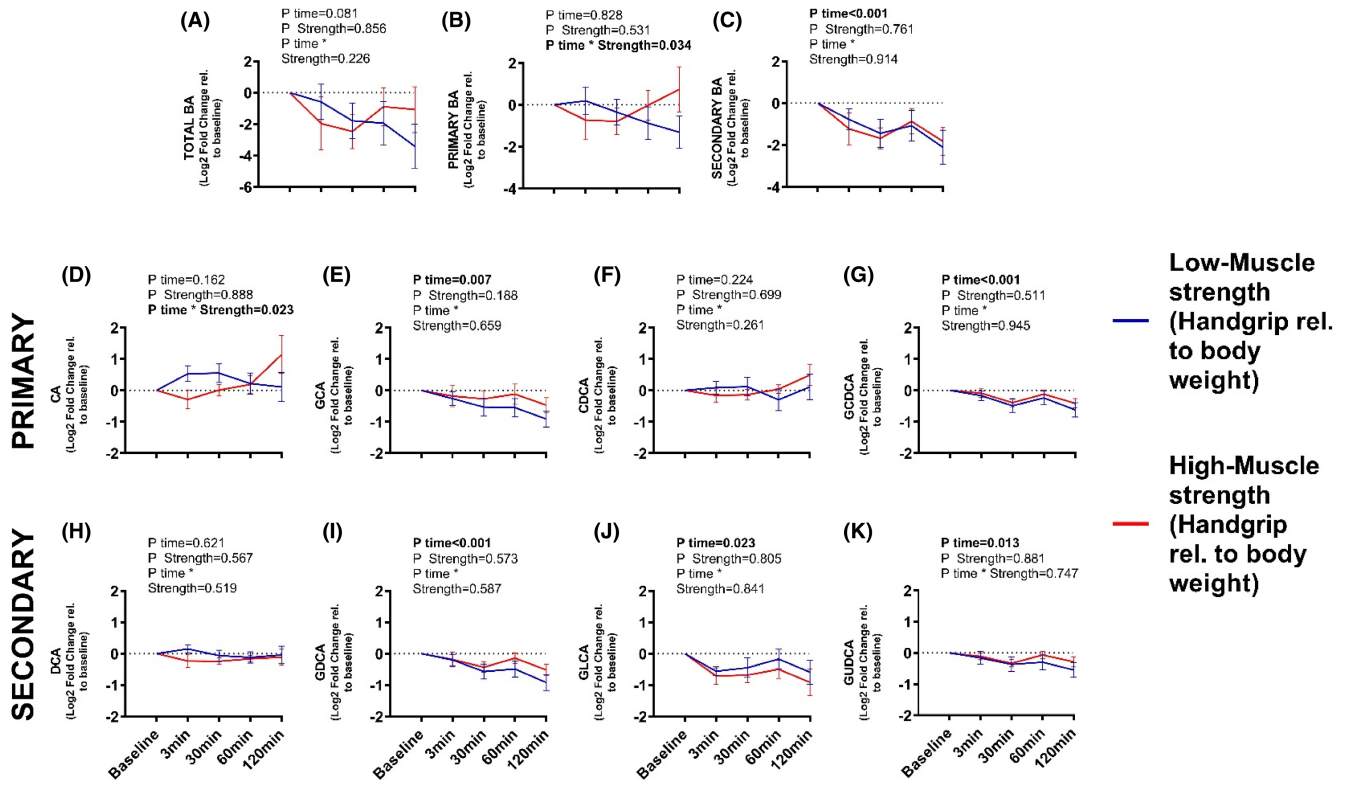

FIGURE 4 Response in plasma levels of bile acids in response to a bout of resistance exercise is different between young adults with low and high handgrip strength levels. Changes in total bile acids (A), primary bile acids (B), secondary bile acids (C), CA (D), GCA (E), CDCA (F), GCDCA (G), DCA (H), GDCA (I), GLCA (J) and GUDCA (K) levels after acute resistance exercise. Each line represents the mean log2 fold change relative to the baseline of each group of bile acids or individual bile acids. *p* Values were obtained from two-factor (low/high handgrip strength levels and time) repeated measures analyses of variance (ANOVA). Error bars show the standard error of the mean. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDC, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid.

However, in a study by Morville et al.,[15] they observed that plasma levels of total, primary, and secondary BA did not change after 60 min of EE on a cyclergometer at a 70% VO_2 peak in recreationally active men .[15] This absence of a decrease in circulating BA after exercise might be explained by the type of EE (i.e., cycling vs. walking), duration, and intensity of their EE protocol, which resulted in a less extenuating bout of exercise in comparison with our maximum walking effort test. However, at the individual level, they reported an increase in LCA levels,[15] which was not measured in our study. We measured the conjugated form of LCA with glycine, GLCA, yet we found that both RE and EE decreased GLCA levels. Unfortunately, Morville et al.[15] did not measure GLCA, which precludes us to conduct any comparison or withdraw any firm conclusions. Furthermore, the time points of blood collection used in the running studies (i.e., just after exercise)[16,17] significantly differ from our EE protocol, precluding us to conduct comparisons during the recovery phase. Of note is that the aforementioned studies[15–17] included active individuals with higher CRF levels than the sedentary individuals enrolled in our cohort. This is a fact to consider since CRF is a key factor influencing the response to exercise in terms of circulating molecules involved in energy metabolism, during both the early – 2 to 15 min – and late – 30 to 60 min after exercise—phase of the recovery,[5] and thereby could be modulating the BA response as well. Altogether, the current level of evidence suggests that extenuating EE, either in the case of our study (maximum walking effort test) or running long distances – 21 km,[16] or 80.5 km[17] – acutely reduces the circulating levels of BA during the first 30 min after exercise in humans.

4.2 | A bout of resistance exercise exerts a prolonged reduction of plasma levels of bile acids

The same 10 individuals in the study of Morville et al. performed a RE session on a separate day consisting of five resistance drills (i.e., five sets of 10 repetitions with 90 s of resting between sets; total duration of the session 60 min).[15] Oppositely to our findings, they found that RE reduced total plasma levels of BA 60 and 180 min after

TABLE 2 Baseline characteristics of the individuals who performed acute aerobic exercise with low ($n = 7$) and high ($n = 7$) levels of cardiorespiratory fitness (CRF).

	Low CRF ($n = 7$)		High CRF ($n = 7$)		p	P_1
	Mean	SD	Mean	SD		
Sex (*n*. %)					0.127	—
Men	0	0	2	29		
Women	7	100	5	71		
Age (years)	22.9	2.4	20.7	2.3	0.112	0.167
Body composition						
BMI (kg/m^2)	27.0	3.7	21.3	1.6	**0.006**	**0.012**
WC (cm)	82.0	9.7	76.0	8.7	0.24	0.498
Lean mass (kg)	39.7	5.2	39.5	9.2	0.969	**0.009**
LMI (kg/m^2)	14.3	1.6	14.2	2.3	0.94	0.074
Fat mass (kg)	31.9	5.6	16.2	4.7	**<0.001**	—
FMI (kg/m^2)	11.5	2.2	6.0	2.1	**<0.001**	—
Fat mass (%)	43.2	3.1	28.7	9.1	**0.002**	—
VAT (g)	426.2	178.5	224.9	95.1	**0.022**	—
Cardiometabolic risk factors						
Glucose (mg/dL)	89.9	4.5	85.1	6.2	0.125	0.316
Insulin (μIU/mL)	10.9	5.5	6.0	1.1	**0.015**	**0.045**
HOMA index	2.5	1.4	1.3	0.2	**0.012**	**0.039**
Creatinine (mg/dL)	0.7	0.1	0.8	0.1	0.05	**0.012**
GTP (IU/L)	18.9	13.9	17.1	11.9	0.774	0.902
GGT (IU/L)	23.9	24.7	14.6	3735.0	0.552	0.669
ALP (IU/L)	63.1	16.5	56.7	16.9	0.447	0.383
Fatty liver index	14.4	10.9	5.8	2.9	0.113	0.124
Total cholesterol (mg/dL)	169.1	48.6	175.0	35.9	0.722	0.264
HDL-C (mg/dL)	49.7	6.6	56.0	10.9	0.214	0.369
LDL-C (mg/dL)	103.7	41.9	106.0	31.2	0.79	0.293
Triglycerides (mg/dL)	78.4	44.1	65.1	18.8	0.591	0.654
C-reactive protein (mg/L)	2.9	2.1	1.2	1.7	**0.033**	**0.023**
C3 (mg/dL)	152.7	14.3	127.5	22.5	**0.024**	**0.025**
C4 (mg/dL)	33.9	10.2	25.3	9.3	0.086	0.224
Leptin (μg/L)	11.6	4.6	2.7	2.2	**0.006**	**<0.001**
Adiponectin (mg/L)	10.9	6.3	15.7	10.3	0.316	0.524
Systolic blood pressure (mmHg)	116.9	9.1	116.7	15.8	0.977	0.178
Diastolic blood pressure (mmHg)	72.5	4.8	70.1	6.6	0.451	0.502
Cardiorespiratory fitness						
VO_2peak rel. to body weight (mL/min/kg)	34.0	5.9	46.8	4.6	**<0.001**	**0.010**
Time until exhaustion (s)	794.3	106.3	888.0	299.0	0.268	0.263

Note: Data are presented as mean and standard deviation (SD), otherwise stated. p Values are derived from Student's t-test for independent samples. P_1 values are derived from the analyses of covariance adjusting for fat mass percentage. Boldfaced values mean $p < 0.05$. For statistical analyses, serum levels of cardiometabolic risk factors were log10-transformed.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; C3, complement component 3; C4, complement component 4; FMI, fat mass index; GGT, gamma-glutamyl transferase; GTP, glutamic pyruvic transaminase; HDL-c, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; LMI, lean mass index; RM, repetition maximum; SUV, standardized uptake value; VAT, visceral adipose tissue; VO_2, oxygen consumption; WC, waist circumference.

TABLE 3 Baseline characteristics of the individuals who performed acute resistance exercise with low ($n=9$) and high ($n=8$) levels of muscle strength.

	Low handgrip strength ($n=9$)		High handgrip strength ($n=8$)		p	P_1
	Mean	SD	Mean	SD		
Sex (*n*. %)					0.259	—
Men	2	22	4	50		
Women	7	73	4	50		
Age (years)	21.9	2.2	23.0	2.8	0.393	0.083
Body composition						
BMI (kg/m^2)	25.5	2.7	25.0	5.7	0.808	0.538
WC (cm)	81.1	9.2	85.5	14.6	0.463	0.468
Lean mass (kg)	39.4	7.0	44.5	10.6	0.256	0.726
LMI (kg/m^2)	14.0	1.5	15.3	3.0	0.285	0.562
Fat mass (kg)	28.2	3.7	23.9	8.8	0.240	—
FMI (kg/m^2)	10.1	1.8	8.2	2.7	0.099	—
Fat mass (%)	40.5	4.5	33.3	6.1	**0.014**	—
VAT (g)	374.2	123.1	383.0	202.4	0.915	—
Cardiometabolic risk factors						
Glucose (mg/dL)	87.2	4.2	85.6	7.0	0.534	0.206
Insulin (μIU/mL)	8.8	2.3	6.2	1.6	**0.017**	0.180
HOMA index	1.9	0.5	1.3	0.3	**0.014**	0.119
Creatinine (mg/dL)	0.7	0.1	0.8	0.1	0.072	0.394
GTP (IU/L)	14.7	5.5	20.0	12.4	0.401	0.908
GGT (IU/L)	16.8	9.1	17.9	12.2	0.860	0.868
ALP (IU/L)	76.8	28.9	68.1	21.3	0.508	0.276
Fatty liver index	14.0	12.7	24.5	32.2	0.413	0.346
Total cholesterol (mg/dL)	147.6	18.8	177.0	36.8	0.060	**0.027**
HDL-C (mg/dL)	50.7	7.7	52.3	14.4	0.936	0.653
LDL-C (mg/dL)	82.8	18.8	108.8	27.5	**0.034**	**0.006**
Triglycerides (mg/dL)	70.3	21.8	79.0	40.9	0.729	0.485
C-reactive protein (mg/L)	1.7	1.2	2.0	1.7	0.891	0.282
C3 (mg/dL)	140.9	19.3	142.3	19.7	0.888	0.583
C4 (mg/dL)	25.7	8.9	30.5	12.1	0.368	0.421
Leptin (μg/L)	6.5	4.8	4.6	4.0	0.206	0.867
Adiponectin (mg/L)	9.1	3.6	10.5	8.1	0.992	0.572
Systolic blood pressure (mmHg)	115.3	10.9	115.1	13.6	0.979	0.336
Diastolic blood pressure (mmHg)	68.1	9.1	71.6	7.7	0.414	0.093

Note: Data are presented as mean and standard deviation (SD), otherwise stated. p Values are derived from Student's t-test for independent samples. P_1 values are derived from the analyses of covariance adjusting for fat mass percentage. Boldfaced values mean $p<0.05$. For statistical analyses, serum levels of cardiometabolic risk factors were log10-transformed.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; C3, complement component 3; C4, complement component 4; FMI, fat mass index; GGT, gamma-glutamyl transferase; GTP, glutamic pyruvic transaminase; HDL-c, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; LMI, lean mass index; RM, repetition maximum; SUV, standardized uptake value; VAT, visceral adipose tissue; WC, waist circumference.

finishing the exercise (−35% and −41%, respectively). Specifically, RE reduced plasma levels of CA (−69% at 60 and 180 min), CDCA (−55% at 120 min and −52% at 180 min), and GUDCA (−58% immediately after, and −83% at 60 and 180 min).[15] The differences between RE protocols might explain the discrepancies with our

results since they conducted a more extenuating protocol in terms of intensity and duration. For this reason, future studies implementing different degrees of durations and intensity are needed to understand the impact of RE on circulating levels of BA in humans.

Additionally, it is well known that EE and RE engage different types of muscle groups and types of fibers[28] that result in an exercise-type-specific metabolite fingerprint.[29] We observed that EE exerted a greater and prolonged decrease in total, primary, and secondary BA in comparison with RE. Nonetheless, the qualitative and quantitative comparisons between the effects of EE and RE on plasma levels of BA must be conducted with caution since the design of our study and the study by Morville et al.[15] implemented EE and RE protocols that differed in intensity and duration, thereby preventing to withdraw any firm conclusions.

4.3 | Impact of individuals' physical fitness status on plasma levels of bile acids after a bout of endurance and resistance exercise

Recent evidence has shown that an exercise and diet-induced weight loss intervention improves insulin sensitivity and fitness along with a reduction in total fasting serum BA levels in sedentary, insulin-resistant women,[30] thus contributing to the notion that plasma levels of BA—either after acute or exercise training—are linked to glucose metabolism and homeostasis in humans. This hypothesis is further supported by evidence from preclinical studies in which the activation of the TGR5 in muscle and pancreas was linked to an improved glucose tolerance[31–33] and experiments in diabetic mice where TGR5 agonism ameliorated insulin resistance and restored systemic glucose homeostasis.[34] Unfortunately, our study design and reduced power size preclude us to establish any causal relationship between the increases in primary BA levels and the better glucose metabolism status of individuals with high CRF and high strength handgrip levels. Studies assessing glucose metabolism parameters during and after exercise along with circulating levels of BA are warranted to confirm this. It is worth mentioning that athletes, which present higher CRF levels in comparison with sedentary individuals, present a different gut microbiota composition [35,36] and that it could constitute a critical component of their physical performance.[37] Moreover, it seems that BA profiles in response to different dietary challenges are not influenced by the fecal microbiota composition and diversity of individuals, but by variants in small intestinal BA transporter encoding genes.[38] Based on that, it might be possible that not only genes related to BA synthesis but also genes involved in small intestinal BA transporter synthesis, could be explaining the specific BA signature associated with a better metabolic phenotype in our cohort. Further research is warranted to unveil if gut microbiota composition might influence the acute exercise response of circulating BA in humans.

5 | STRENGTHS AND LIMITATIONS

Our study is not exempt from limitations. First, our findings may not be extrapolatable to trained and/or older individuals, individuals with metabolic complications that affect glucose metabolism (e.g., type 2 diabetes). We did neither measure taurine-conjugated BA nor the unconjugated form of LCA and UCDCA. Moreover, we cannot eliminate a possible diurnal variation effect of exercise on plasma levels of BA. Finally, the sex heterogeneity of our cohort precludes us to evaluate to what extent the response of plasma levels of BA to acute exercise could be sex-dependent since most of our cohort was composed mostly of women. On the contrary, our study also presents strengths. For instance, we provided a well-phenotyped cohort (e.g., body composition, cardiometabolic risk factors) and we measured BA at four different time points after the bout of exercise. Furthermore, this study is the first in shedding light on the role of physical fitness on the response in the response of circulating levels of BA to acute exercise.

6 | CONCLUSION

Our study reveals that EE and RE transiently decrease plasma levels of BA in young, sedentary adults. Individuals with higher levels of CRF and handgrip strength display a different response of primary plasma BA after EE and RE, suggesting that the individual's physical fitness modulates the response of circulating BA to exercise in humans. Further studies investigating the biological meaning of these observations are warranted.

7 | PERSPECTIVE

It is well known that exercise constitutes a powerful therapeutic tool for obesity and its associated cardiometabolic diseases.[39] However, scientific progress has only begun to explain the complex molecular mechanisms by which exercise exerts its beneficial effects,[2,5] and how this knowledge can be used to design personalized exercise interventions for improving human health. For this reason, the emergence of circulating BA as signaling molecules

that regulate energy expenditure and glucose and lipid metabolism has aroused considerable interest. Although it seems clear that both acute and exercise training decrease circulating BA, there is a big gap in knowledge on the mechanisms governing these responses and their physiological relevance. For this reason, it is of clinical interest that future exercise trials elucidate how individuals' body composition (i.e., lean body mass), metabolic parameters (i.e., insulin sensitivity glucose tolerance), and/or cardiorespiratory fitness parameters (i.e., VO_2max, VO_2peak) influence the BA response to different exercise types and interventions. These advantages will help to optimize future exercise interventions aiming to treat obesity and improve cardiometabolic health.

AUTHOR CONTRIBUTIONS

FJOP contributed to the material preparation and data collection, study conception/design, statistical analyses, and drafted the manuscript. LJF contributed to the material preparation and data collection and statistical analyses. APF contributed to the material preparation and data collection. WY contributed to the material preparation and data collection. IK contributed to the material preparation and data collection. XD contributed to the material preparation and data collection. JRL contributed to the material preparation and data collection. GSD contributed to the material preparation and data collection. PCNR contributed to the material preparation and data collection. JRR contributed to the material preparation and data collection, study conception/design, and drafted the manuscript. BMT contributed to the material preparation and data collection, study conception/design, and drafted the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Any additional data information is available upon reasonable request.

CLINICAL TRIAL REGISTRATION

This study has been conducted under the framework of the ACTIBATE study (ACTivating Brown Adipose Tissue through Exercise; ClinicalTrials.gov ID: NCT02365129).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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