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Author(s): Ahtiainen, Juha P.; Sallinen, Janne; Häkkinen, Keijo; Sillanpää, Elina

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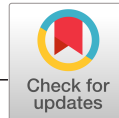
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Inter-individual variation in response to resistance training in cardiometabolic health indicators

Juha P. Ahtiainen¹ | Janne Sallinen¹ | Keijo Häkkinen¹ | Elina Sillanpää^{2,3}

¹Faculty of Sport and Health Sciences, Neuromuscular Research Center, University of Jyväskylä, Jyväskylä, Finland

²Faculty of Sport and Health Sciences, Gerontology Research Center, University of Jyväskylä, Jyväskylä, Finland

³Institute for Molecular Medicine Finland, Helsinki, Finland

Correspondence

Juha P. Ahtiainen, Faculty of Sport and Health Sciences, Neuromuscular Research Center, University of Jyväskylä, P.O. Box 35, FIN-40014 Jyväskylä, Finland.
Email: juha.ahtiainen@jyu.fi

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Resistance training (RT) may improve metabolic health; however, the extent of its effectiveness is constantly evaluated to assess improvements in the group means, thus obscuring the heterogeneous individual effects. This study investigated inter-individual variation in response to RT as reflected in metabolic health indicators and how age, sex, nutrition, and pre-training phenotypes are associated with such variabilities.

Methods: Previously collected data of men and women (39-73 years, 135 trained, 73 non-trained controls) were pooled for analysis. Measurements were taken twice before training to estimate individual day-to-day variations and measurement errors (n = 208). The individual responsiveness to the 21-week RT in cardiometabolic health indicators (ie, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), cholesterol and triglycerides) was determined. Body composition was estimated by bioimpedance and dietary intake according to 4-day food diaries.

Results: Metabolic responses to RT seemed to be highly individual, and both beneficial and unfavorable changes were observed. Large inter-individual variations in training response were not explained by a subject's age, sex, body composition, or nutritional status, with the exception of improvements in HDL-C, which were associated with simultaneous decreases in body fat in older women. The incidence of metabolic syndrome diminished following RT.

Conclusion: This study showed that RT could improve some specific metabolic health indicators beyond normal day-to-day variations, especially in blood lipid profile. Further studies are needed to elucidate genetic and other mechanisms underlying the heterogeneity of RT responses. This knowledge may be useful in providing individually tailored exercise prescriptions as part of personalized preventative health care.

KEYWORDS

blood pressure, body composition, glucose, insulin, lipid profile

1 | INTRODUCTION

It is well known that cardiovascular diseases and diabetes are major causes of morbidity and mortality worldwide. On the other hand, it is also well established that exercise training can produce favorable changes in commonly recognized risk factors for these conditions.¹ However, the majority of studies on exercise training and cardiometabolic health have used middle-aged participants as subjects.^{2,3} Moreover, most studies have utilized aerobic training, while the effects of resistance training (RT) on metabolic health indicators, such as blood pressure, plasma glucose, and blood lipid profile, are less well understood.³ However, accumulating evidence indicates that RT is beneficial, especially in improving blood lipid profile,^{4,5} glycemic control in T2D patients⁶ and reducing systolic and diastolic blood pressure in healthy subjects,⁷ pre-hypertensive and hypertensive subjects,⁸ and people with metabolic syndrome.⁹

To date, physical activity recommendations let us assume that exercise training has a similar beneficial effect on metabolic risk factors across the population. Almost all studies have evaluated the effectiveness of interventions on improving the mean values of these risk indicators in the population, thus obscuring the heterogeneous individual effects. Individual responses to treatments have been acknowledged as one of the most important issues in experimental research.¹⁰ However, attempts to quantify individual responses are rare as proper quantification of individual variations requires randomized controlled designs reinforced with repeated measures (control period) to determine measurement errors, individual day-to-day variations, and other random variations.

There are considerable inter-individual variabilities in the potential to improve cardiorespiratory fitness and metabolic risk factors in response to aerobic training in apparently healthy adults.¹¹⁻¹³ Some subjects experience significant health benefits in a given trait, while minimal or even the opposite responses can occur in their peer trainers.^{13,14} However, although individual training responses as reflected in physical performance following 20- to 24-week RT are acknowledged,¹⁵ individual responses as reflected in metabolic health indicators are presently largely unknown. In general, RT can be highlighted as an important strategy for the prevention of cardiometabolic risk factors and diseases as it is suitable for improving physical performance and functioning in older and obese subjects and also has a great deal of potential for disease prevention.^{16,17} Therefore, the present study examined inter-individual variations in response to RT as reflected in cardiometabolic health indicators in middle-aged and older men and women. The individual variations in the training responses are evaluated against those of their non-trained peers. The issue is addressed based on data from previously published studies in our laboratory.

2 | MATERIALS AND METHODS

2.1 | Subjects

Two extensive research projects conducted in our laboratory from 2002 to 2006 were included in a retrospective analysis to reveal heterogeneity in response to RT compared with non-training subjects using a large data set.¹⁶⁻¹⁹ The present investigation used the data of 208 volunteers (age 56 ± 7 years, from 39 to 73 years; height 169.6 ± 9.3 cm; weight 72.1 ± 10.3 kg; BMI 25.3 ± 3.6 kg/m²) who were randomly divided within the research projects to resistance-trained (men, $n = 56$; women, $n = 79$) or non-resistance-trained (ie, control) groups (men, $n = 34$; women, $n = 39$). All subjects whose data were available in the original cohort were included in the present study. The physiological characteristics of the subjects are presented in Table 1 and separately for men and women in Tables S1 and S2. The subjects were all Caucasians living in the Jyväskylä region of Finland and were recruited for the study using newspaper advertisements. A physician's examination of each participant was conducted before the study began. Exclusion criteria included pronounced obesity and any systemic disease (eg, diabetes, cancer, cardiovascular diseases, malfunctions of the thyroid gland, rheumatoid arthritis). The subjects were not previously experienced in RT. The subjects were instructed to continue their current lifestyles throughout the study period. Thirteen subjects from the RT and six from the control group used medication for high blood pressure, and they were excluded from the analyses of blood pressure responses. Six subjects from the RT and four from the control group used statin medication, and they were excluded from the blood lipids analyses.

Informed consent was obtained from all participants. All procedures performed in the study involving human participants were conducted in accordance with the ethical standards of the Ethics Committee of the Central Finland Health Care District or the Ethical Committee of the University of Jyväskylä, Finland and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.2 | Study design

The first 1- or 2-week period was a control period with no RT for all the subjects. Thereafter, 21 weeks of RT intervention was carried out with the RT group while the control group refrained from RT. The measurements for all subjects took place before and after the control period and after the intervention. Measurements for fasting glucose and insulin and the dietary diaries were collected and analyzed before and after the 21-week intervention period. The study design is presented in Figure 1.

TABLE 1 Characteristics of the resistance-trained and non-resistance-trained (control) groups before and after intervention periods

Group	n	Before 1- to 2-week control period	Baseline	Post-21-week intervention	Change ^a from baseline to post (95% CI)	P-value
		Mean (SD)	Mean (SD)	Mean (SD)		
Body mass (kg)						
Trained	135	71.8 (10.5)	71.7 (10.4)	71.4 (10.5)	-0.3 (-0.6 to 0.0)	.302
Controls	73	72.7 (9.9)	72.6 (9.6)	72.0 (9.4)	-0.6 (-1.0 to -0.2)	
BMI						
Trained	135	25.2 (3.7)	25.1 (3.7)	25.0 (3.7)	-0.1 (-0.2 to 0.0)	.302
Controls	73	25.5 (3.5)	25.4 (3.4)	25.2 (3.3)	-0.2 (-0.4 to -0.1)	
Waist circumference (cm)						
Trained	134	90.3 (9.1)	89.9 (9.0)	88.0 (8.8)	-1.9 (-2.3 to -1.4)	.005
Controls	73	89.0 (9.1)	89.1 (8.9)	88.4 (8.5)	-0.7 (-1.4 to -0.1)	
Fat mass (kg)						
Trained	128	19.4 (5.8)	19.3 (5.8)	18.6 (5.8)	-0.7 (-1.1 to -0.4)	.028
Controls	69	n.a.	20.7 (6.8)	20.4 (6.9)	-0.1 (-0.6 to 0.3)	
Fat-free mass (kg)						
Trained	128	52.9 (8.3)	52.8 (8.1)	53.2 (8.5)	0.4 (0.1 to 0.6)	.002
Controls	69	n.a.	51.8 (10.1)	51.6 (10.4)	-0.3 (-0.6 to 0.1)	
Leg press 1RM (kg)/body mass (kg)						
Trained	133	1.64 (0.35)	1.70 (0.37)	2.03 (0.44)	0.33 (0.31 to 0.36)	<.001
Controls	67	1.67 (0.33)	1.67 (0.33)	1.74 (0.37)	0.08 (0.04 to 0.11)	
SysBP (mm Hg)						
Trained	122	132.9 (17.0)	129.4 (15.9)	125.8 (16.7)	-3.8 (-5.6 to -1.9)	.224
Controls	66	133.3 (14.5)	130.6 (13.2)	128.4 (13.9)	-1.9 (-4.4 to 0.7)	
DiasBP (mm Hg)						
Trained	122	81.2 (10.0)	79.4 (9.3)	77.3 (9.4)	-2.2 (-3.4 to -1.1)	.080
Controls	66	82.4 (7.7)	80.2 (8.2)	79.5 (8.7)	-0.5 (-2.1 to 1.0)	
HDL-C (mmol/L)						
Trained	129	1.41 (0.39)	1.33 (0.37)	1.48 (0.49)	0.14 (0.10 to 0.18)	.022
Controls	69	1.36 (0.43)	1.32 (0.42)	1.37 (0.43)	0.05 (-0.01 to 0.11)	
Cholesterol (mmol/L)						
Trained	129	5.59 (0.92)	5.47 (0.88)	5.37 (0.82)	-0.10 (-0.19 to 0.00)	.792
Controls	69	5.51 (0.90)	5.43 (0.89)	5.37 (0.88)	-0.07 (-0.21 to 0.06)	
Triglycerides (mmol/L)						
Trained	129	1.06 (0.42)	1.07 (0.47)	1.07 (0.45)	-0.01 (-0.08 to 0.06)	.915
Controls	69	1.16 (0.54)	1.18 (0.67)	1.13 (0.50)	0.03 (-0.07 to 0.12)	
Triglycerides to HDL-C ratio						
Trained	129	0.84 (0.52)	0.91 (0.60)	0.92 (0.60)	-0.08 (-0.16 to 0.00)	.958
Controls	69	0.99 (0.71)	1.06 (0.90)	0.88 (0.61)	-0.09 (-0.20 to 0.02)	
Fasting insulin (mU/l)						
Trained	122	n.a.	5.1 (3.0) [#]	4.8 (3.0)	-0.3 (-0.6 to 0.0)	.878
Controls	27	n.a.	3.8 (2.0)	3.9 (2.2)	-0.1 (-0.7 to 0.6)	
Fasting glucose (mmol/L)						
Trained	123	n.a.	4.6 (0.7)	4.5 (0.7)	-0.2 (-0.2 to -0.1)	.010
Controls	27	n.a.	4.9 (0.9)	4.9 (0.9)	0.1 (-0.1 to 0.2)	

(Continues)

TABLE 1 (Continued)

Group	n	Before 1- to 2-week control period	Baseline	Post-21-week intervention	Change ^a from baseline to post (95% CI)	P-value
		Mean (SD)	Mean (SD)	Mean (SD)		
HOMA-IR (units)						
Trained	121	n.a.	1.1 (0.7)	1.0 (0.7)	-0.1 (-0.2 to 0.0)	.432
Controls	27	n.a.	0.8 (0.5)	0.9 (0.5)	0.0 (-0.1 to 0.2)	

Abbreviations: 1RM, one-repetition maximum; BMI, body mass index; DiasBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; n.a., data not available; SysBP, systolic blood pressure.

^aAge, sex, and the corresponding baseline value as covariate.

[#]Statistically significant difference between the groups at baseline (adjusted by age and sex).

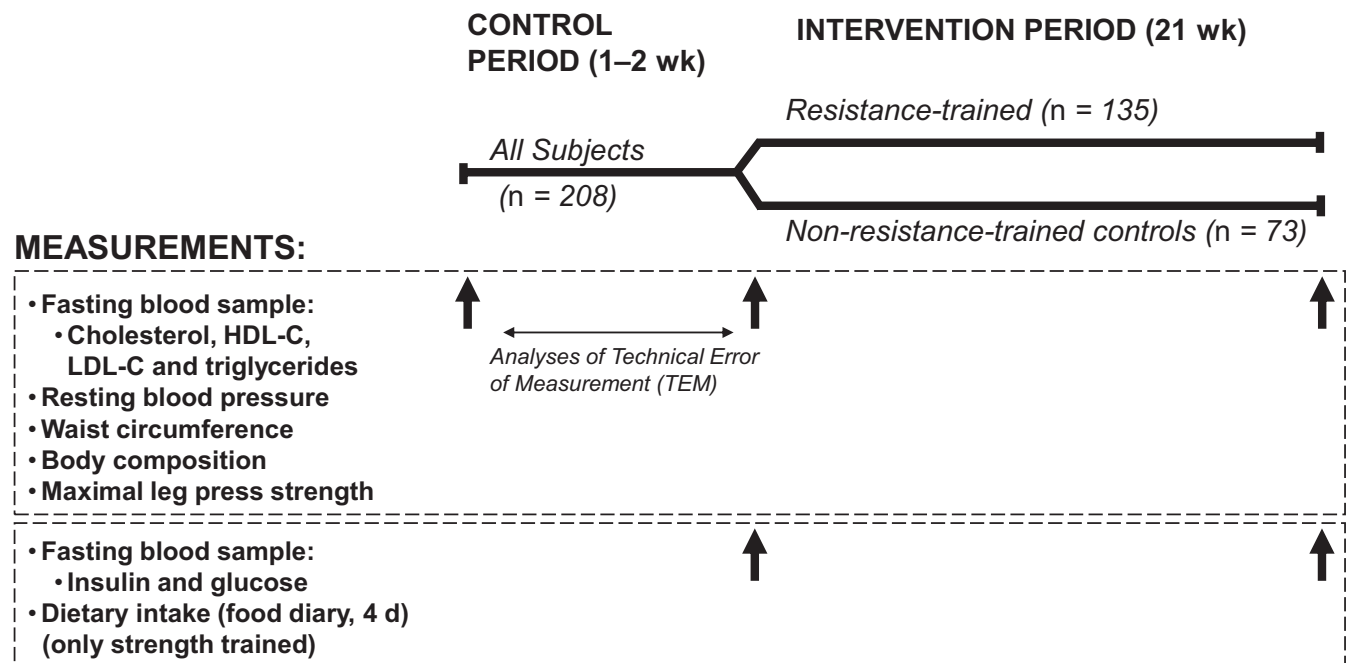


FIGURE 1 The study design and measurements

2.3 | Resistance-training program

All the subjects in the RT group participated in a similar 21-week RT intervention. We previously showed with the larger sample size (including some of the present subjects) that the RT regimen used in the present study induced muscle strength and size gains, but considerable inter-individual variation occurred in the training responses.¹⁵ The detailed RT program has been described previously.^{20,21} The RT program was based on physical activity recommendations for public health.²² Briefly, the program was a whole-body program with supervised training sessions twice a week. Each training session consisted of six to eight exercises for the lower and upper extremities and trunk with three to six sets per exercise and one- to two-minute recovery periods between the sets. The training load increased progressively during three specific training cycles of 7 weeks,

while the number of repetitions (reps) per set decreased from 10 to 20 to 8 to 12 and finally 5 to 8. The training adherence was reported to be very high (>95%).^{16–18}

2.4 | Muscle strength

Maximal bilateral concentric strength of the leg extensors (hip, knee, and ankle extensors) was assessed in a horizontal leg press device starting at a knee angle of 70 degrees to a full extension of 180 degrees (David 210 Dynamometer, David Fitness and Medical). The one-repetition maximum (1RM) was determined by three to five separate attempts against the resistance determined by the loads chosen on the weight stack (accuracy of 2.5 kg) with at least one-minute rest periods between the attempts. After each attempt, the load was increased until the subject was unable to extend their legs to the required

position. The last acceptable extension with the highest possible load was determined to be 1RM. The 1RM test results were expressed relative to the subject's current body mass.

2.5 | Anthropometry

2.5.1 | Body height, weight, and body mass index (BMI)

Body weight (Model 708 [$d = 0.1$ kg], Seca) and height were measured with participants barefoot and in light clothing. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2).

2.5.2 | Body composition

The percentage of body fat (fat %), total body fat mass, and total body fat-free mass were estimated according to the eight-polar bioimpedance method using a multifrequency current device (InBody 3.0, Biospace Co.)^{16,17} or a single frequency (50 kHz) device (Bodystat 1500, Bodystat, Ltd.)^{18,19} Body composition measurements were always performed in a post-absorptive state after a 12-hour overnight fast. The day preceding the measurement day was a rest day from exercise. Subjects were also instructed to avoid hot saunas, to drink normally the day before the measurements, and to minimize physical activity in the morning prior to the bioimpedance measurement.

2.5.3 | Waist circumference

Waist circumference was measured by body composition measurement using an inelastic plastic tape measure midway between the lateral lower ribs and the iliac crest. An average of two or three measurements was used in calculations.

2.6 | Blood metabolic health indicators

Blood samples were taken after a 12-hour fast between 7:00 and 9:00 AM. The day before the measurements was a rest day from any strenuous physical activity, and the participants were instructed to sleep at least 8 hours during the previous night. All blood samples were drawn from the antecubital vein and handled according to standardized laboratory practice.

2.6.1 | Blood lipids and lipoproteins

Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using a Vitros

DT60 dry chemistry system (Ortho Clinical Diagnostics)^{16,17} or by enzymatic assays (Shimadzu CL-720 Micro-Flow Spectrophotometer, Shimadzu Corp.) and kits from Roche Diagnostics GmbH.^{18,19} The sensitivities of the assays for serum total cholesterol and HDL-C and for triglycerides were reportedly 0.08 and 0.05 mmol/L, respectively, and the inter-assay variations were 1.7% and 1.8%, respectively. LDL cholesterol (LDL-C) concentration (mmol/L) was estimated using the Friedewald formula ($\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} - [\text{triglycerides}/2.2]$).²³

2.6.2 | Glucose metabolism

Blood glucose samples were analyzed with a HemoCue glucose analyzer (B-Glucose Photometer, HemoCue AB). Serum insulin concentrations were assayed using time-resolved immuno-Xuorometric assays (TR-IFMA), B080-101 and an AutoDELFIA Xuorometer (Wallac)^{16,17} or radio-immunoassay kits from Pharmacia & Upjohn Diagnostics AB.^{18,19} The sensitivity of the assay was below 2.5 mU/L, the intra-assay variation was 5.3%, and the inter-assay variation was 7.6%.^{18,19} The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according to the following formula: $\text{fasting insulin (mU/L)} \times \text{fasting glucose (mmol/L)} / 22.5$.²⁴

2.7 | Resting blood pressure

Systolic blood pressure and diastolic blood pressure were taken as the lower of two measurements in the supine position after a rest of 5 minutes^{16,17} or 15 minutes^{18,19} using an automatic sphygmomanometer (Omron, model HEM-705C, Omron Corporation). Blood pressure was measured before obtaining a blood sample (see Section 2.6 above). The test-retest variations for values of resting systolic and diastolic blood pressure were 4.1% and 4.3%, respectively.¹⁸

2.8 | Nutrition

The dietary intake was assessed with the use of food diaries for three workdays and one weekend day at the beginning and at the end of the study period. Both verbal and written instructions were given to the subjects to record all the foods and drinks they consumed, including portion size as household measures, preparation technique, and brand names. The food diaries were analyzed using nutrient analysis software (Nutrica[®] 3.11, The Social Insurance Institution of Finland). The results of the dietary analyses are presented in Table S3. The study designs included nutrition counseling according to the general Nordic Nutrition recommendations, including

both verbal and written instructions, to provide guidance on a healthy diet sufficient for exercise requirements (ie, to obtain sufficient energy and protein intake as well as recommended levels of fat and fiber). Subjects did not use any supplements, and they were instructed not to gain or lose weight. The dietary intake data are available for 120 subjects of the RT group.

2.9 | Statistical analyses

All data are presented as mean and standard deviation (SD). Statistical analyses were carried out using SPSS 24.0 software for Windows (SPSS, Inc). The Kolmogorov-Smirnov test was used to test normality, and the Levene's test was used to analyze the homogeneity of variances. Due to random violations in the normal distribution assumption, the data on blood glucose, insulin, and triglycerides were natural-log-transformed before the statistical modeling. However, the untransformed data are presented throughout the report. A univariate analysis of variance (ANOVA) adjusted by age and sex was used to assess the differences between the RT and control groups at baseline. The differences in changes between the RT and control groups following intervention were assessed using the univariate ANOVA with age, sex, and corresponding baseline values as covariates. A Bonferroni post-hoc test was used to confirm differences between the groups. Linear regression analysis was conducted to assess the causes of the changes in the metabolic health indicators. Age, sex, and baseline values as well as changes following intervention in body composition (fat percentage, total body fat, and fat-free mass) and nutritional variables were investigated as potential predictors. Moreover, a Pearson product-moment correlation coefficient was used to determine the associations between the variables. The values obtained before and after the non-training control period in the whole group of subjects in systolic blood pressure, cholesterol, triglycerides, and HDL-C were used to calculate the technical error of measurement (TEM), which considers the measurement error and the normal day-to-day biological variation of the trait.¹³ TEM was calculated using the following formula: $TEM = \sqrt{(\sum d^2)/2N}$, where D is the difference between measurements and N is the number of

subjects measured. The TEM was 8.7 mm Hg for systolic blood pressure, 0.25 mmol/L for plasma triglycerides, 0.34 mmol/L for cholesterol, and 0.12 mmol/L for HDL-C. For fasting blood glucose (0.40 mmol/L), TEM was defined by the data (men and women, $n = 91$) collected over a 2-week non-training control period in the present study.^{18,19} Because repeated measures over the control period were not available for fasting insulin, TEM was defined according to previously published threshold criteria as 1.73 mU/L¹³ and for HOMA-IR as 0.2 units.²⁵ “Negative response” was defined as a change beyond $1 \times TEM$ in a direction indicating a worsening of the trait, “non-response” as a change within $\pm 1 \times TEM$, and “positive response” as a change beyond $1 \times TEM$ in a beneficial direction. The differences between the RT and control groups in negative and positive responses were determined by an independent samples t test. To determine differences in categorical variables (ie, the incidence of responses), a chi-square test (χ^2) was used to determine differences between the groups and a McNemar's test was used to determine differences between baseline and post-intervention. Statistical significance was accepted when $P \leq .05$.

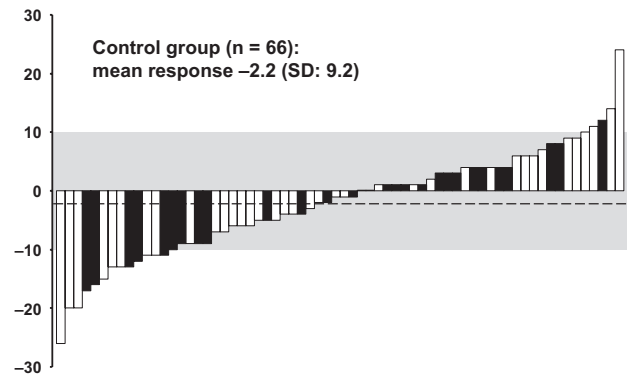
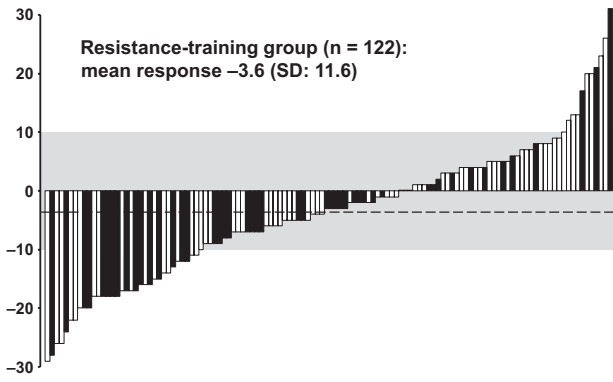
3 | RESULTS

3.1 | Mean changes during the intervention

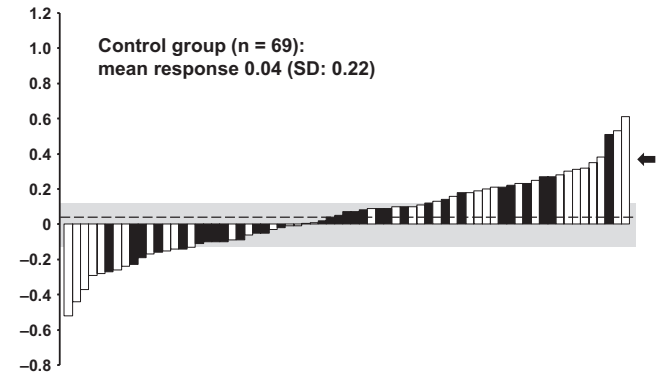
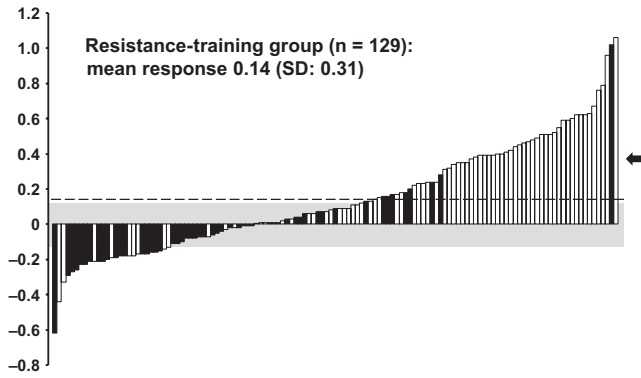
At baseline, fasting serum insulin concentrations were significantly greater ($F [1, 145] = 4.405, P = .038$) in the RT group than in the control group (Table 1). In other variables, there were no differences between groups before training. There was a significant difference over time between the RT and control groups during the 21-week intervention period in waist circumference ($F [1, 202] = 7.981, P = .005$), total body fat mass ($F [1, 192] = 4.904, P = .028$), and fasting blood glucose ($F [1, 145] = 6.780, P = .010$), which all declined in the RT group. Concurrently, the changes in fasting HDL-C ($F [1, 193] = 5.309, P = .022$), total body fat-free mass ($F [1, 192] = 9.802, P = .002$), and maximal muscle strength (normalized to body mass) ($F [1, 195] = 124.744, P < .001$) also differed between the training and control groups over time, with the RT group showing training-related improvements (Table 1). The data for the responses

FIGURE 2 A, Individual changes (black bars are men, and white bars are women) during intervention in systolic blood pressure, cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) in the resistance-trained and non-resistance-trained groups. The gray-shaded area illustrates the magnitude of technical errors of measurement. The dashed horizontal line represents the mean change. The arrows at right in HDL-C denote the cutoff value of 0.38 mmol/L, which has been shown to be associated with a 22% reduction in coronary heart disease risk.²⁶ B, Individual changes (black bars are men, and white bars are women) in fasting serum insulin, blood glucose, and homeostatic model assessment of insulin resistance (HOMA-IR) during intervention in the RT group. The dashed horizontal line represents the mean change. The gray-shaded area illustrates the magnitude of technical errors of measurement

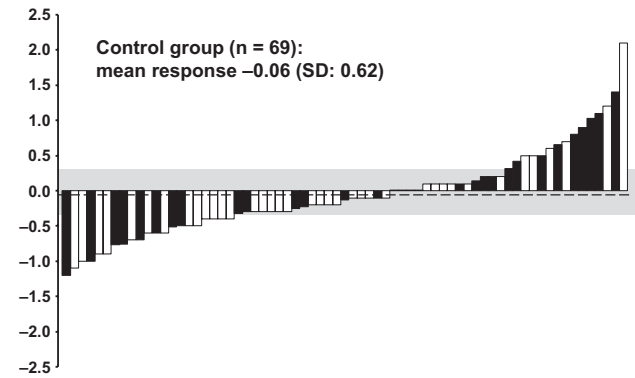
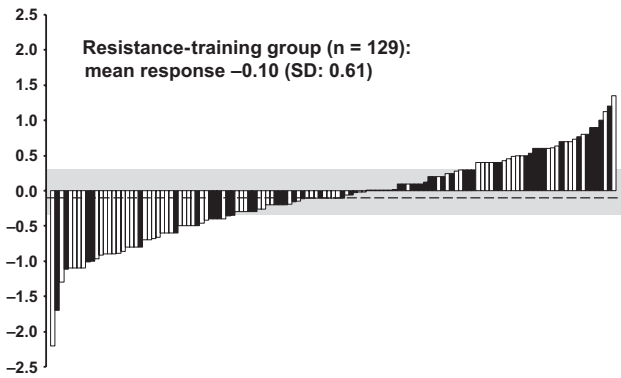
Δ Systolic Blood Pressure (mmHg)



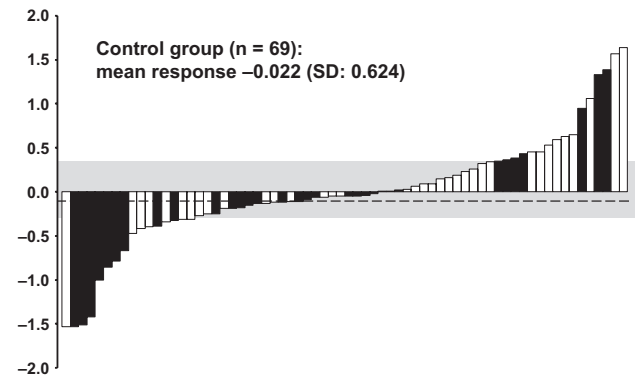
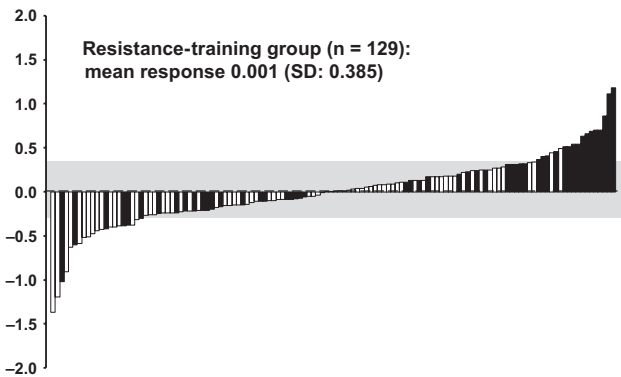
Δ HDL-C (mmol/L)



Δ Cholesterol (mmol/L)



Δ Triglycerides (mmol/L)



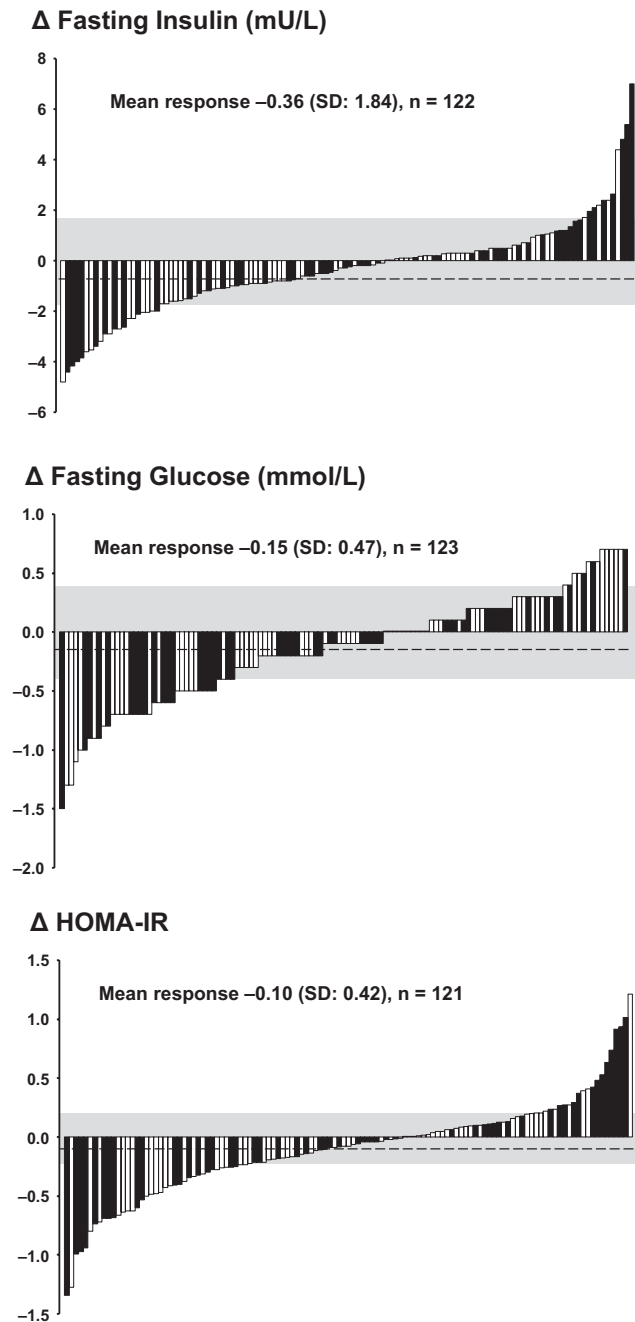


FIGURE 2 (Continued)

of men and women separately are presented in Tables S1 and S2.

3.2 | Responsiveness to resistance training

The clinically relevant positive response over 0.38 mmol/L in HDL-C²⁶ was observed in 33 subjects in the RT group and four subjects in the control group. When analyzing changes between the responder groups (ie, responses beyond TEM), positive responders in the RT group showed a greater response in HDL-C than the controls ($t[72.132] = 3.714$,

$P < .001$) (Figure 2A). In further analyses, the response in HDL-C in the RT group, but not in the controls, was most strongly associated with age and sex ($P < .001$), indicating a greater responsiveness in older women, while a trend was observed in the training-induced changes in BMI ($P = .084$); $F(4, 124) = 15.79$, $P < .001$, $R^2 = .581$.

In the RT group, positive responses in fasting serum insulin, blood glucose, and HOMA-IR were observed in 16 (13%), 20 (16%), and 43 (36%) of the subjects, respectively, while negative responses were observed in 13 (11%), 12 (10%), and 21 (17%) of the subjects, respectively (Figure 2B).

TABLE 2 Selective associations observed between the variables in the resistance-training group during the 21-week training intervention

	Age	Baseline levels of triglycerides	Changes in BMI	Changes in triglycerides	Changes in fat mass
Changes in HLD-C	$r = .196$ $n = 129$ $P = .026$	$r = .176$ $n = 128$ $P = .047$	$r = -.224$ $n = 129$ $P = .011$	$r = -.279$ $n = 128$ $P = .001$	
Changes in BMI				$r = .190$ $n = 128$ $P = .032$	$r = .752$ $n = 128$ $P < .001$
Changes in triglyceride/ HDL-C-ratio					$r = .188$ $n = 121$ $P = .039$

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

The results of the selective correlation analysis of the RT group are presented in Table 2 to highlight relevant associations observed between the changes in metabolic health indicators and body composition. These correlations were not observed in the control group.

3.3 | Intra-individual responsiveness

None of the subjects in the RT or the control group showed a negative or positive response in all risk factors specifically examined here (Figure 3; systolic blood pressure, HDL-C, cholesterol and triglycerides). In the RT group, 39 subjects (29%) showed no positive responses in any variables, while in 63 subjects (47%), no negative responses were observed. In the controls, the corresponding values were 27% and 42%, respectively. In the RT group, 15 subjects (11%) showed no responses in all four variables, and 95 subjects (70%) showed positive responses in at least one variable. In controls, the corresponding values were 8% and 73%, respectively. A Pearson's chi-square test determined that there were no statistically significant associations between the training and control groups and the proportions of positive, negative, and non-responses in systolic blood pressure, HDL-C, cholesterol, and triglycerides.

3.4 | Occurrence of metabolic syndrome

To assess the clinical relevance of changes in risk factors, occurrence of metabolic syndrome before and after the intervention was determined according to the definition of the International Diabetes Federation (<https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definition-of-the-metabolic-syndrome.html>). There were no statistically significant associations between the RT and control groups in the prevalence of increased metabolic health risks at baseline or post-intervention or in their changes over

the intervention period. However, a statistically significant decrease was observed in the proportion of subjects with metabolic syndrome from baseline to post-intervention in the RT group ($P < .001$) but not in the controls ($P = .388$) (Figure 4).

3.5 | Nutrition

Protein intake normalized to body mass increased significantly (from 1.17 [0.29] to 1.25 [0.36] g/kg, $P < .05$), but no other statistically significant changes were observed in dietary intake (total energy intake, carbohydrate and fat intake normalized to body mass, relative proportion of carbohydrates, proteins, and fats of total energy intake, relative dietary fiber intake, and polyunsaturated to saturated fatty acid ratio) determined by the 4-day diet diaries pre- and post-RT in 120 subjects in the RT group (women, $n = 75$, men, $n = 45$) (Table S3).

4 | DISCUSSION

In the present study, prominent inter-individual variations were observed in response to RT as reflected in cardiometabolic health indicators in middle-aged and older men and women who had no previous experience of RT. It should be noted that a great magnitude of inter-individual variability also occurred in untrained control subjects, suggesting that the training stimulus, whether negative or positive, may exceed normal diurnal fluctuations in these health indicators only in a small portion of the subjects. However, HDL-C levels appeared to improve significantly with RT in some subjects. Considerable intra-individual variation was observed between cardiometabolic health indicators, and positive and negative responses appeared to cumulate only in a small portion of the subjects. Notably, in the present study, RT seemed to improve health status by decreasing the proportion of the subjects determined as having metabolic syndrome.

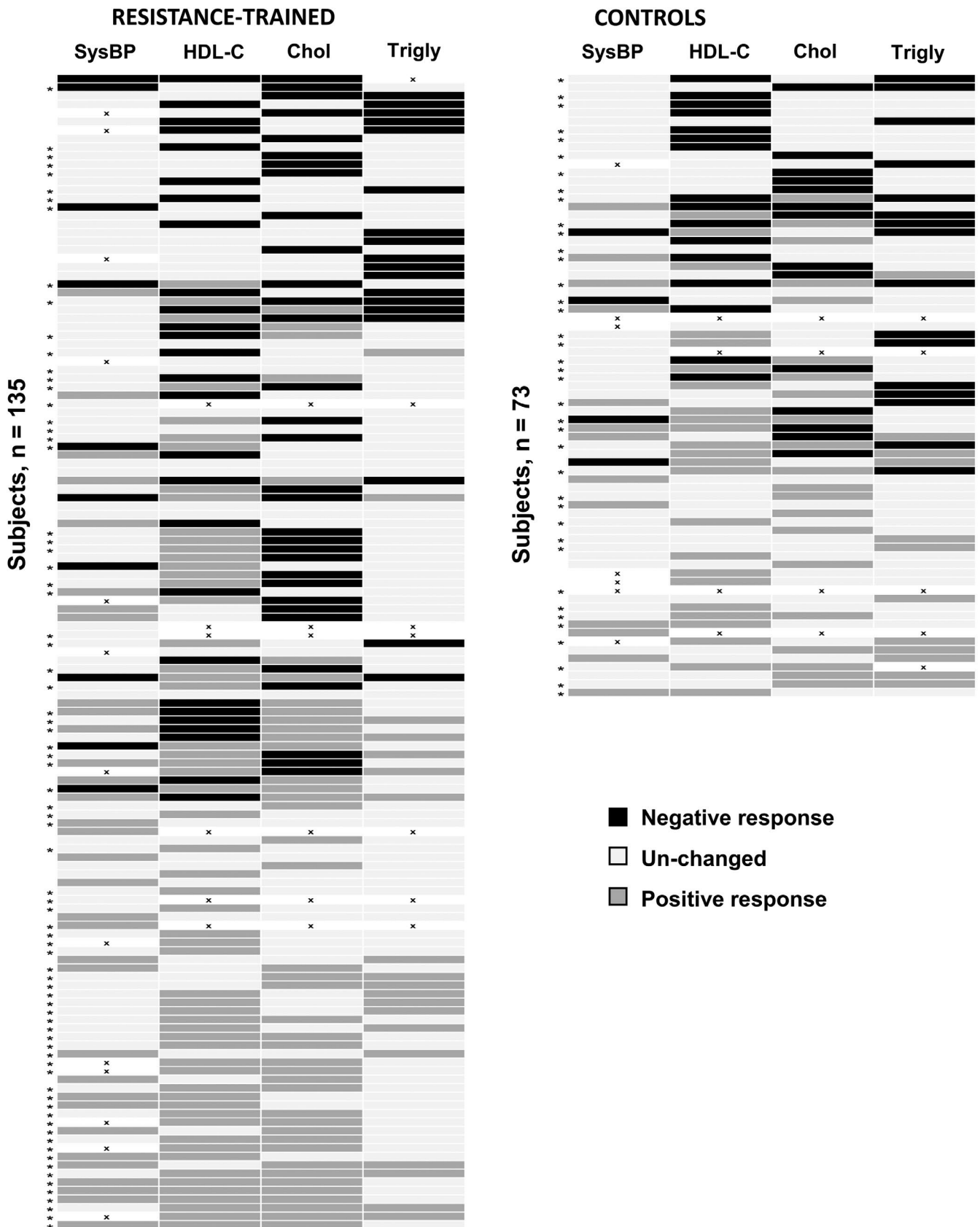


FIGURE 3 Individual patterns of response following intervention. Positive responses (dark gray box), non-responses (light gray box), and negative responses (black box) are shown for all participants across systolic blood pressure (SysBP), high-density lipoprotein cholesterol (HDL-C), cholesterol (Chol), and triglycerides (Trigly). A cross in the box indicates that data were unavailable for a given variable or excluded from the analyses due to medication's effect on the corresponding variable. The stars on the left side indicate the data for women

volume and/or frequency of RT) and/or a longer training period to attain beneficial training responses.^{28,29}

The changes in HDL-C following RT appeared to be associated with the changes in body composition and especially with the concomitant decreases in total body fat mass. We found significant increases in mean muscle strength and fat-free mass and concurrent decreases in waist circumference and fat mass, although total body mass and nutritional status remained virtually unchanged. Only modest increments in energy expenditure could be observed during the RT sessions, but increases in muscle mass with chronic RT can reduce body fat by increasing the resting metabolic rate.³⁰⁻³³ Similarly, as with aerobic exercise training, increased energy expenditure through RT may elicit increases in HDL-C through increases in enzyme activity such as lecithin-cholesterol acyltransferase, which is responsible for ester transfer to HDL cholesterol.³⁴ In addition, a higher resting metabolic rate due to increases in skeletal muscle mass and qualitative adaptations of muscles, such as enhanced glucose transport and mitochondrial oxidative capacity,³⁵ could lead to increased fat metabolism. Thus, favorable body composition changes with reductions in adipose tissue may be responsible for increases in plasma HDL-C, whether it is from aerobic training^{12,36,37} or RT.³⁸

The present study showed large intra-individual variations in response to systolic blood pressure, HDL-C, cholesterol, and triglycerides as most of the subjects had positive and/or negative changes in these risk factors following the intervention period (see Figure 3). The proportions of positive, negative, and non-responses did not differ between the resistance and control groups. Generally, the present RT intervention did not induce overall responses in the direction of health benefits in these health indicators, but it did not show harmful effects, either. As indicated by the control group's data, the levels of cardiometabolic health indicators may fluctuate considerably over time. Thus, it remains elusive whether in some individuals in the RT group the actual responses to training itself were beneficial or unfavorable for their health status.

When the incidence of metabolic syndrome was examined in the present experimental groups before and after the intervention (see Figure 4), the proportion of subjects defined as having metabolic syndrome decreased only in the RT group. This finding indicates that RT may have some beneficial effects on the prevalence of metabolic syndrome. However, the evidence is not strong, since the prevalence of unfavorable values in metabolic risk factors did not differ between the groups or the change during the intervention. Nonetheless, this study showed that some individuals may benefit from RT while the opposite effects may occur in others. Although negative responses were observed in the present risk factors in some subjects, the effects of the present RT intervention

cannot be simply interpreted as detrimental to the subjects' overall health status and well-being. We can still generalize that RT based on physical activity guidelines for general health and fitness²² can be considered beneficial to all people, including patients with cardiometabolic disorders.³⁹

By combining the previously collected data, the present investigation studied a large group of resistance-trained subjects, allowing the examination of a wide spectrum of individual responsiveness to RT. The study also included a large group of non-resistance-trained control subjects to examine the effects of RT on various cardiometabolic health indicators. In addition, repetitive measurements were carried out at baseline, enabling calculations of technical error of measurement to determine individual training responsiveness. Unfortunately, it was not possible to obtain data on fasting insulin and glucose from controls to gain further information about their RT responses. Moreover, RT may increase resting metabolic rates, which could consequently reduce visceral fat, which is known to increase with advancing age.⁴⁰ Resting metabolic rates were not determined in the present studies, and the present methods did not provide accurate estimations of abdominal or visceral fat content. Thus, their possible roles in the present findings of HDL-C responses could not be investigated. The present results could be generalized to a previously untrained middle-aged and older population without diagnosed diseases. It is not known whether the training responses would be similar if individuals were exposed to different exercise doses or modalities or a longer training period.

5 | PERSPECTIVES

The present investigation provides novel information about individual differences in metabolic health indicators in response to RT. This study showed that RT might increase HDL-C concentrations, especially in older women, which could be explained by RT-induced decreases in fat mass. However, it appears that inter-individual variations in response to the present cardiometabolic health indicators, at least during the first 21 weeks of RT, cannot be explained by age, sex, body composition, nutritional status, or the baseline values of the health indicators. Large ranges in positive and negative responses were observed in all the present health indicators in both resistance-trained and non-resistance-trained subjects with no prominent differences between the groups. This finding suggests that the overall effects of the RT on the cardiometabolic health indicators appear to be minor. Monitoring individual responses to training interventions is crucial to better understand heterogeneity in training benefits and, on the other hand, adverse effects if they occur. Future studies should investigate the underlying determinants of individuality in training responsiveness so that individually

tailored exercise training regimens can finally be offered in the context of personalized preventive medicine.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTION

JPA, JS, KH, and ES made substantial contributions to the conception and design of the study, and/or the acquisition of data, and/or the analysis and interpretation of data. JPA, JS, KH, and ES were involved in drafting the manuscript, and/or revising it critically for important intellectual content. JPA, JS, KH, and ES have agreed to be accountable for all aspects of the work and have given final approval of the version to be published.

ORCID

Juha P. Ahtiainen  <https://orcid.org/0000-0003-2305-4741>

Elina Sillanpää  0000-0001-6375-959X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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