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

Ahtiainen, Juha P.; Sallinen, Janne; Häkkinen, Keijo; Sillanpää, Elina

Accepted version (Final draft)

© The Authors, 2020. 

Rights: CC BY 4.0

Rights url: https://creativecommons.org/licenses/by/4.0/

Please cite the original version:

Ahtiainen, Juha P.; Sallinen, Janne; Häkkinen, Keijo; Sillanpää, Elina (2020). Inter-individual variation in responses to resistance training in cardiometabolic health indicators. Scandinavian Journal of Medicine and Science in Sports, Early online. DOI: 10.1111/sms.13650
INTER-INIVIDUAL VARIATION IN RESPONSES TO RESISTANCE TRAINING IN CARDIOMETABOLIC HEALTH INDICATORS

Running title: Individual resistance training responses

Juha P. Ahtiainen,1* Janne Sallinen,¹ Keijo Häkkinen,¹ Elina Sillanpää²,³

¹ Neuromuscular Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
² Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
³ Institute for Molecular Medicine Finland, Helsinki, Finland.

* Corresponding author: Juha Ahtiainen, PhD  http://orcid.org/0000-0003-2305-4741

Neuromuscular Research Center
Faculty of Sport and Health Sciences
University of Jyväskylä

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/SMS.13650

This article is protected by copyright. All rights reserved
P.O. Box 35
FIN-40014 University of Jyväskylä
Finland
Email: juha.ahtiainen@jyu.fi
Telephone: (358) 04-805374
Acknowledgments

The authors acknowledge the financial contributions of Peurunka Medical Rehabilitation Centre, Finland; the Ministry of Education, Finland; and the Central Finland Health Care District, Jyväskylä, Finland. The authors thank the dedicated group of study participants for their time and effort, which made this study possible.
ABSTRACT

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 responses 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 (i.e., 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 four-day food diaries.

Results: Metabolic responses to RT seemed to be highly individual, and both beneficial and unfavourable 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 personalised preventative health care.

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

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 favourable changes in commonly recognised risk factors for these conditions. However, the majority of studies on exercise training and cardiometabolic health have used middle-aged participants as subjects. Moreover, most studies have utilised 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. However, accumulating evidence indicates that RT is beneficial, especially in improving blood lipid profile, glycaemic control in T2D patients and reducing systolic and diastolic blood pressure in healthy subjects, pre-hypertensive and hypertensive subjects and people with metabolic syndrome.

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 has been acknowledged as one of the most important issues in experimental research. However, attempts to quantify individual responses are rare as proper quantification of individual variations requires randomised 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. Some subjects experience significant health benefits in a given trait, while minimal or even the opposite responses can occur in their peer trainers. However, although individual training responses as reflected in physical performance following 20- to 24-week RT are acknowledged, 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. Therefore, the present study examined inter-individual variations in responses 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 responses to RT compared with non-training
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 (i.e., 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 Supplemental Tables 1 and 2. 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 (e.g., 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 one or two-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 analysed before and after the 21-week intervention period. The study design is presented in Figure 1.

2.3 Resistance training programme
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. The detailed RT programme has been described previously. The RT programme was based on physical activity recommendations for public health. Briefly, the programme was a whole-body programme 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 seven 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%).

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, Outokumpu, Finland). 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 kilograms) 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, Germany) 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 metres (kg/m²).

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., Seoul, Korea) or a single frequency (50 kHz) device (Bodystat 1500, Bodystat, Ltd., Isle of Man, UK) Body composition measurements were always performed in a postabsorptive state after a 12-hour overnight fast.
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 minimise 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 mid-way 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 a.m. The day before the
measurements was a rest day from any strenuous physical activity, and the participants were
instructed to sleep at least eight hours during the previous night. All blood samples were drawn
from the antecubital vein and handled according to standardised 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, USA)\textsuperscript{16,17} or by enzymatic assays (Shimadzu CL-720 Micro-Flow
Spectrophotometer, Shimadzu Corp., Kyoto, Japan) and kits from Roche Diagnostics GmbH
(Mannheim, Germany).\textsuperscript{18,19} The sensitivities of the assays for serum total cholesterol and HDL-C
and for triglycerides were reportedly 0.08 mmol/L 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 (LDL-C = total cholesterol - HDL-C –
[triglycerides/2.2]).\textsuperscript{23}

2.6.2 Glucose metabolism. Blood glucose samples were analysed with a HemoCue glucose
analysers (B-Glucose Photometer, HemoCue AB, Ängelholm, Sweden). Serum insulin
concentrations were assayed using time-resolved immuno-Xuorometric assays (TR-IFMA), B080-
101 and an AutoDELFIA Xuorometer (Wallac, Turku, Finland)\textsuperscript{16,17} or radioimmunoassay kits
from Pharmacia & Upjohn Diagnostics AB (Uppsala, Sweden).\textsuperscript{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%.\textsuperscript{18,19} The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated
according to the following formula: fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5.\textsuperscript{24}

2.7 Resting blood pressure
Systolic and diastolic blood pressure were taken as the lower of two measurements in the supine position after a rest of 5 minutes\textsuperscript{16,17} or 15 minutes\textsuperscript{18,19} using an automatic sphygmomanometer (Omron, model HEM-705C, Omron Corporation, Hamburg, Germany). Blood pressure was measured before obtaining a blood sample (see 2.6 above). The test-retest variations for values of resting systolic and diastolic blood pressure were 4.1% and 4.3%, respectively\textsuperscript{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 analysed using nutrient analysis software (Nutrica ® 3.11, The Social Insurance Institution of Finland). The results of the dietary analyses are presented in Supplemental Table 3. The study designs included nutrition counselling according to the general Nordic Nutrition recommendations, including both verbal and written instructions, to provide guidance on a healthy diet sufficient for exercise requirements (i.e., to obtain sufficient energy and protein intake as well as recommended levels of fat and fibre). Subjects did not use any supplements, and they were instructed not to gain or lose weight. The dietary intake data is 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., Chicago, IL). The Kolmogorov–Smirnov test was used to test normality, and the Levene’s test was used to analyse 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 modelling. 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. TEM was calculated using the following formula: $TEM = \sqrt{\frac{\sum d^2}{2N}}$, 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 two-week non-training control period in the present study (Sallinen et al. unpublished data). 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/L and for HOMA-IR as 0.2 units.

‘Negative response’ was defined as a change beyond 1xTEM in a direction indicating a worsening of the trait, ‘non-response’ as a change within ±1xTEM, and ‘positive response’ as a change beyond 1xTEM 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 (i.e., the incidence of responses), a chi-square test ($\chi^2$) 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 $p \leq 0.05$.

3. RESULTS

3.1 Mean changes during the intervention

At baseline, fasting serum insulin concentrations were significantly greater ($F [1, 145] = 4.405, p = 0.038$) 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 ($F [1, 202] = 7.981, p = 0.005$), total body fat mass ($F [1, 192] = 4.904, p = 0.028$) and fasting blood glucose ($F [1, 145] = 6.780, p = 0.010$), which all declined in the RT group. Concurrently, the changes in fasting HDL-C ($F [1, 193] = 5.309, p = 0.022$), total body fat-free mass ($F [1, 192] = \ldots$)

This article is protected by copyright. All rights reserved
9.802, \( p = 0.002 \) and maximal muscle strength (normalised to body mass) \( (F [1, 195] = 124.744, p < 0.001) \) 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 of men and women separately are presented in Supplemental Tables 1 and 2.

Insert Table 1 here

### 3.2 Responsiveness to resistance training

The clinically relevant positive response over 0.38 mmol/L in HDL-C\(^{26} \) was observed in 33 subjects in the RT group and 4 subjects in the control group. When analysing changes between the responder groups (i.e. responses beyond TEM), positive responders in the RT group showed a greater response in HDL-C than the controls \( (t[72.132] = 3.714, p < 0.001) \) (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 \( (p < 0.001) \), indicating a greater responsiveness in older women, while a trend was observed in the training-induced changes in BMI \( (p = 0.084) \); \( F(4, 124) = 15.79, p < 0.001, R^2 = 0.581 \).

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).

Insert Figure 2 here

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.

Insert Table 2 here

### 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 4 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-definitionof-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 < 0.001) but not in the controls (p = 0.388) (Figure 4).

3.5 Nutrition

Protein intake normalised to body mass increased significantly (from 1.17 [0.29] to 1.25 [0.36] g/kg, p<0.05), but no other statistically significant changes were observed in dietary intake (total energy intake, carbohydrate and fat intake normalised to body mass, relative proportion of carbohydrates, proteins and fats of total energy intake, relative dietary fibre intake, and polyunsaturated to saturated fatty acid ratio) determined by the four-day diet diaries pre- and post-RT in 120 subjects in the RT group (women, n=75, men, n=45) (Supplemental Table 3).

4. DISCUSSION

In the present study, prominent inter-individual variations were observed in the responses 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.

This study revealed significant mean improvements in HDL-C levels following RT. A difference of 0.38 mmol/L has previously been shown to be associated with a 22% reduction in coronary heart disease risk. According to that categorisation, a clinically relevant response was reached by 26% of the trained subjects (see Figure 2A). Presently, understanding of the effects of RT on lipoprotein levels is inconsistent. The majority of published studies has indicated that RT does not significantly affect blood HDL-C and mainly lowers LDL-C levels. In the present study, significant improvements in HDL-C were observed, especially in older women, although in all the subjects exposed to a similar RT stimulus. This finding is in line with the observations of a recent research project on a similar study population. It is possible that the energy expenditure threshold for inducing lipoprotein changes was attained only in previously untrained older women, while others may need a greater training effort (i.e., greater intensity, volume and/or frequency of RT) and/or a longer training period to attain beneficial training responses.

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. 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. 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, could lead to increased fat metabolism. Thus, favourable body composition
changes with reductions in adipose tissue may be responsible for increases in plasma HDL-C, whether it is from aerobic training\textsuperscript{12,36,37} or RT.\textsuperscript{38}

The present study showed large intra-individual variations in responses in 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 unfavourable 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 unfavourable 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 generalise that RT based on physical activity guidelines for general health and fitness\textsuperscript{22} can be considered beneficial to all people, including patients with cardiometabolic disorders.\textsuperscript{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.\textsuperscript{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 generalised 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 responses of 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 appears 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 personalised preventive medicine.
Conflict of Interest

Authors declare that they have no conflict of interest.

Contributions

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.
References


This article is protected by copyright. All rights reserved


The study design and measurements

A. Individual changes (black bars are men, 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 grey 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 cut-off value of 0.38 mmol/L, which has been shown to be associated with a 22% reduction in coronary heart disease risk.

B. Individual changes (black bars are men, 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 grey shaded area illustrates the magnitude of technical errors of measurement.

Individual patterns of response following intervention. Positive responses (dark grey box), non-responses (light grey 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.
Individual patterns of increased metabolic risks (black box) in body mass index (BMI), waist circumference (waist), systolic blood pressure (SysBP), fasting high-density lipoprotein cholesterol (HDL-C), triglycerides (Trigly) and plasma glucose (Gluc) before and after the intervention period in A) resistance-trained and B) non-resistance-trained subjects. The ‘X’ sign indicates those subjects who were defined as having metabolic syndrome (MetSynd) according to the definition of the International Diabetes Federation. White stars in black boxes indicate medication affecting the corresponding risk factor. The ‘F’ sign above the individuals indicates women’s data. A grey box indicates that data were unavailable for a given variable.

**Supplemental Digital Content (SDC)**

- Supplemental Data File: Supplemental Table 1.docx
- Supplemental Data File: Supplemental Table 2.docx
- Supplemental Data File: Supplemental Table 3.docx
Table 1. Characteristics of the resistance-trained and non-resistance-trained (control) groups before and after intervention periods

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>n</th>
<th>Before 1-2-week control period</th>
<th>Baseline</th>
<th>Post 21-week Intervention</th>
<th>Change* from Baseline to Post (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (kg)</td>
<td>Trained</td>
<td>135</td>
<td>71.8 (10.5)</td>
<td>71.7 (10.4)</td>
<td>71.4 (10.5)</td>
<td>-0.3 (-0.6 to 0.0)</td>
<td>0.302</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>73</td>
<td>72.7 (9.9)</td>
<td>72.6 (9.6)</td>
<td>72.0 (9.4)</td>
<td>-0.6 (-1.0 to -0.2)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Trained</td>
<td>135</td>
<td>25.2 (3.7)</td>
<td>25.1 (3.7)</td>
<td>25.0 (3.7)</td>
<td>-0.1 (-0.2 to 0.0)</td>
<td>0.302</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>73</td>
<td>25.5 (3.5)</td>
<td>25.4 (3.4)</td>
<td>25.2 (3.3)</td>
<td>-0.2 (-0.4 to -0.1)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>Trained</td>
<td>134</td>
<td>90.3 (9.1)</td>
<td>89.9 (9.0)</td>
<td>88.0 (8.8)</td>
<td>-1.9 (-2.3 to -1.4)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>73</td>
<td>89.0 (9.1)</td>
<td>89.1 (8.9)</td>
<td>88.4 (8.5)</td>
<td>-0.7 (-1.4 to -0.1)</td>
<td></td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>Trained</td>
<td>128</td>
<td>19.4 (5.8)</td>
<td>19.3 (5.8)</td>
<td>18.6 (5.8)</td>
<td>-0.7 (-1.1 to -0.4)</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>n.a.</td>
<td>20.7 (6.8)</td>
<td>20.4 (6.9)</td>
<td>-0.1 (-0.6 to 0.3)</td>
<td></td>
</tr>
<tr>
<td>Fat-Free Mass (kg)</td>
<td>Trained</td>
<td>128</td>
<td>52.9 (8.3)</td>
<td>52.8 (8.1)</td>
<td>53.2 (8.5)</td>
<td>0.4 (0.1 to 0.6)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>n.a.</td>
<td>51.8 (10.1)</td>
<td>51.6 (10.4)</td>
<td>-0.3 (-0.6 to 0.1)</td>
<td></td>
</tr>
<tr>
<td>Leg press 1RM (kg) / Body mass (kg)</td>
<td>Trained</td>
<td>133</td>
<td>1.64 (0.35)</td>
<td>1.70 (0.37)</td>
<td>2.03 (0.44)</td>
<td>0.33 (0.31 to 0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>67</td>
<td>1.67 (0.33)</td>
<td>1.67 (0.33)</td>
<td>1.74 (0.37)</td>
<td>0.08 (0.04 to 0.11)</td>
<td></td>
</tr>
<tr>
<td>SysBP (mmHg)</td>
<td>Trained</td>
<td>122</td>
<td>132.9 (17.0)</td>
<td>129.4 (15.9)</td>
<td>125.8 (16.7)</td>
<td>-3.8 (-5.6 to -1.9)</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>66</td>
<td>133.3 (14.5)</td>
<td>130.6 (13.2)</td>
<td>128.4 (13.9)</td>
<td>-1.9 (-4.4 to 0.7)</td>
<td></td>
</tr>
<tr>
<td>DiasBP (mmHg)</td>
<td>Trained</td>
<td>122</td>
<td>81.2 (10.0)</td>
<td>79.4 (9.3)</td>
<td>77.3 (9.4)</td>
<td>-2.2 (-3.4 to -1.1)</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>66</td>
<td>82.4 (7.7)</td>
<td>80.2 (8.2)</td>
<td>79.5 (8.7)</td>
<td>-0.5 (-2.1 to 1.0)</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>Trained</td>
<td>129</td>
<td>1.41 (0.39)</td>
<td>1.33 (0.37)</td>
<td>1.48 (0.49)</td>
<td>0.14 (0.10 to 0.18)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>1.36 (0.43)</td>
<td>1.32 (0.42)</td>
<td>1.37 (0.43)</td>
<td>0.05 (-0.01 to 0.11)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>Trained</td>
<td>129</td>
<td>5.59 (0.92)</td>
<td>5.47 (0.88)</td>
<td>5.37 (0.82)</td>
<td>-0.10 (-0.19 to 0.00)</td>
<td>0.792</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>5.51 (0.90)</td>
<td>5.43 (0.89)</td>
<td>5.37 (0.88)</td>
<td>-0.07 (-0.21 to 0.06)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>Trained</td>
<td>129</td>
<td>1.06 (0.42)</td>
<td>1.07 (0.47)</td>
<td>1.07 (0.45)</td>
<td>-0.01 (-0.08 to 0.06)</td>
<td>0.915</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>1.16 (0.54)</td>
<td>1.18 (0.67)</td>
<td>1.13 (0.50)</td>
<td>0.03 (-0.07 to 0.12)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides to HDL-C ratio</td>
<td>Trained</td>
<td>129</td>
<td>0.84 (0.52)</td>
<td>0.91 (0.60)</td>
<td>0.92 (0.60)</td>
<td>-0.08 (-0.16 to 0.00)</td>
<td>0.958</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69</td>
<td>0.99 (0.71)</td>
<td>1.06 (0.90)</td>
<td>0.88 (0.61)</td>
<td>-0.09 (-0.20 to 0.02)</td>
<td></td>
</tr>
<tr>
<td>Fasting Insulin (mU/l)</td>
<td>Trained</td>
<td>122</td>
<td>n.a.</td>
<td>5.1 (3.0)</td>
<td>#</td>
<td>4.8 (3.0)</td>
<td>-0.3 (-0.6 to 0.0)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>27</td>
<td>n.a.</td>
<td>3.8 (2.0)</td>
<td>3.9 (2.2)</td>
<td>-0.1 (-0.7 to 0.6)</td>
<td></td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>Trained</td>
<td>123</td>
<td>n.a.</td>
<td>4.6 (0.7)</td>
<td>4.5 (0.7)</td>
<td>-0.2 (-0.2 to -0.1)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>27</td>
<td>n.a.</td>
<td>4.9 (0.9)</td>
<td>4.9 (0.9)</td>
<td>0.1 (-0.1 to 0.2)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR (units)</td>
<td>Trained</td>
<td>121</td>
<td>n.a.</td>
<td>1.1 (0.7)</td>
<td>1.0 (0.7)</td>
<td>-0.1 (-0.2 to 0.0)</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>27</td>
<td>n.a.</td>
<td>0.8 (0.5)</td>
<td>0.9 (0.5)</td>
<td>0.0 (-0.1 to 0.2)</td>
<td></td>
</tr>
</tbody>
</table>

BMI, Body Mass Index; 1RM, one repetition maximum; SysBP, Systolic Blood Pressure; DiasBP, Diastolic Blood Pressure; HDL-C, High-Density Lipoprotein Cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance. # = Statistically significant difference between the groups at baseline (adjusted by age and sex); n.a. = data not available. * Age, sex and the corresponding baseline value as covariate.
Table 2. Selective associations observed between the variables in the resistance-training group during the 21-week training intervention.

<table>
<thead>
<tr>
<th>Changes in HLD-C</th>
<th>Age ( r = .196 )</th>
<th>Baseline levels of triglycerides ( r = .176 )</th>
<th>Changes in BMI ( r = -.224 )</th>
<th>Changes in triglycerides ( r = -.279 )</th>
<th>Changes in fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 129 )</td>
<td>( n = 128 )</td>
<td>( n = 129 )</td>
<td>( n = 128 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p = .026 )</td>
<td>( p = .047 )</td>
<td>( p = .011 )</td>
<td>( p = .001 )</td>
<td></td>
</tr>
<tr>
<td>Changes in BMI</td>
<td></td>
<td></td>
<td>( r = .190 )</td>
<td></td>
<td>( r = .752 )</td>
</tr>
<tr>
<td></td>
<td>( n = 128 )</td>
<td></td>
<td>( n = 128 )</td>
<td>( n = 128 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p = .032 )</td>
<td></td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Changes in triglyceride / HDL-C -ratio</td>
<td></td>
<td></td>
<td></td>
<td>( r = .188 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( n = 121 )</td>
<td></td>
<td></td>
<td>( n = 121 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p = 0.039 )</td>
<td></td>
<td></td>
<td>( p = 0.039 )</td>
<td></td>
</tr>
</tbody>
</table>

HDL-C, High-Density Lipoprotein Cholesterol; BMI, Body Mass Index
CONTROL PERIOD (1-2 wk)  

All Subjects  
(n = 208)  

INTERVENTION PERIOD (21 wk)  

Resistance-trained (n = 135)  

Non-resistance-trained controls (n = 73)  

MEASUREMENTS:  

- Fasting blood sample:  
  - Cholesterol, HDL-C, LDL-C and triglycerides  
- Resting blood pressure  
- Waist circumference  
- Body composition  
- Maximal leg press strength  

Analyses of Technical Error of Measurement (TEM)  

- Fasting blood sample:  
  - Insulin and glucose  
- Dietary intake (food diary, 4 d)  
  (only strength trained)
Δ Systolic Blood Pressure (mmHg)

Resistance training group (n = 122):
mean response -3.6 (SD: 11.6)

Control group (n = 66):
mean response -2.2 (SD: 9.2)

Δ Cholesterol (mmol/L)

Resistance training group (n = 129):
mean response -0.10 (SD: 0.51)

Control group (n = 69):
mean response -0.05 (SD: 0.62)

Δ Triglycerides (mmol/L)

Resistance training group (n = 129):
mean response 0.001 (SD: 0.385)

Control group (n = 69):
mean response -0.022 (SD: 0.624)

Δ HDL-C (mmol/L)

Resistance training group (n = 129):
mean response 0.14 (SD: 0.31)

Control group (n = 69):
mean response 0.04 (SD: 0.22)
## RESISTANCE-TRAINED

<table>
<thead>
<tr>
<th></th>
<th>SysBP</th>
<th>HDL-C</th>
<th>Chol</th>
<th>Trigly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n=135</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## CONTROLS

<table>
<thead>
<tr>
<th></th>
<th>SysBP</th>
<th>HDL-C</th>
<th>Chol</th>
<th>Trigly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n=73</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- □ Positive response
- □ Un-changed
- ■ Negative response
| Pre | BMI | Waist | SysBP | HDL-C | Trigly | Gluc 
|-----|-----|-------|-------|-------|--------|------
|     | FFF |       |       |       |        |      |
|     |     |       |       |       |        |      |
|     | FFF |       |       |       |        |      |
|     |     |       |       |       |        |      |
|     |     |       |       |       |        |      |

**MetSynd**

```
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
```

| Post | BMI | Waist | SysBP | HDL-C | Trigly | Gluc 
|------|-----|-------|-------|-------|--------|------
|      | FFF |       |       |       |        |      |
|      |     |       |       |       |        |      |
|      | FFF |       |       |       |        |      |
|      |     |       |       |       |        |      |
|      |     |       |       |       |        |      |

**MetSynd**

```
xx x x x x x x x x x x x x x x x x
```

Subjects, n=135
Controls

Subjects, n=73

Pre
- BMI
- Waist
- SysBP
- HDL-C
- Trigly
- Gluc

MetSynd

Post
- BMI
- Waist
- SysBP
- HDL-C
- Trigly
- Gluc

MetSynd

Desirable levels of metabolic risk factors:
- BMI < 30 kg/m²
- Waist circumference: M < 94 cm, F < 88 cm
- SysBP < 130 mmHg
- HDL-C: M > 1.03 mmol/L (40 mg/dL), F > 1.29 mmol/L (50 mg/dL)
- Triglycerides < 1.7 mmol/L (150 mg/dL)
- Plasma Glucose: < 5.6 mmol/L (100 mg/dL)

Increased risk