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Resistance training, visceral obesity and inflammatory response: a review of the evidence

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Summary
Intra-abdominal obesity is an important risk factor for low-grade inflammation, which is associated with increased risk for diabetes mellitus and cardiovascular disease. For the most part, recommendations to treat or prevent overweight and obesity via physical activity have focused on aerobic endurance training as it is clear that aerobic training is associated with much greater energy expenditure during the exercise session than resistance training. However, due to the metabolic consequences of reduced muscle mass, it is understood that normal ageing and/or decreased physical activity may lead to a higher prevalence of metabolic disorders. Whether resistance training alters visceral fat and the levels of several pro-inflammatory cytokines produced in adipose tissue has not been addressed in earlier reviews. Because evidence suggests that resistance training may promote a negative energy balance and may change body fat distribution, it is possible that an increase in muscle mass after resistance training may be a key mediator leading to a better metabolic control. Considering the benefits of resistance training on visceral fat and inflammatory response, an important question is: how much resistance training is needed to confer such benefits? Therefore, the purpose of this review was to address the importance of resistance training on abdominal obesity, visceral fat and inflammatory response.

Keywords: Dose–response, inflammation, resistance training, visceral fat.

Introduction
Biological ageing is typically associated with a progressive increase in body fat mass and a loss of lean body mass, particularly skeletal muscle. Visceral fat increases by over 300% between the ages of 25 and 65 years, and this creates an increased risk for the development of type 2 diabetes mellitus (T2D) and cardiovascular disease (CVD) in adults with normal body mass index (BMI) (1). The underlying reasons are not well understood; however, it is likely that an age-related decrease in physical activity contributes to this problem (2). The distribution of excess fat in the abdominal region modifies the health risk profile. In contrast, excess adiposity in the periphery does not appear to increase the risk of developing CVD (3).

Visceral (intra-abdominal) adipose tissue (VAT) compared with total body fat correlates significantly better with triglycerides, systolic and diastolic blood pressure and is expected to decrease the sensitivity of target tissues to insulin (4,5). Furthermore, there is some evidence that visceral fat may also be associated with lower brain volume underlying the relationship of obesity and dementia (6). Intra-abdominal obesity is an important risk factor for low-grade inflammation, which is thought to partly explain the excess risk of CVD associated with obesity (7). It is proposed that hypertrophied adipocytes with large
triglyceride stores will have a high lipolytic rate; they will produce more leptin and less adiponectin, two important adipokines that influence inflammation and overall carbohydrate and lipid metabolism (8). Another important consequence of fat cell hypertrophy is the infiltration of VAT by macrophages. It is believed that crosstalk between adipocytes and macrophages contributes to the production of inflammatory cytokines (9). Several adipocytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), are produced in adipose tissue and induce hepatic production of C-reactive protein (CRP) (10). Elevated serum CRP level has been extensively reported as an independent predictor of CVD, and there is increasing evidence that CRP might play a role as a direct contributor to the atherosclerotic process (11).

Weight loss in obese individuals has been shown to improve or prevent many of the above-mentioned conditions (12). For the most part, recommendations to treat or prevent overweight and obesity via physical activity have focused on aerobic endurance training (AET) as it is clear that AET is associated with much greater energy expenditure during the exercise session than resistance training (RT). Although body weight does not change much with RT – it has been assumed that the main effect of RT on body composition is a shift from fat to muscle mass – the maintenance of a large muscle mass with RT may reduce obesity-related risk factors – namely dyslipidaemia, insulin resistance and T2D – associated with CVD (13–15). Concerning this, recent meta-analysis evidence confirms that RT may be an effective alternative for modifying metabolic abnormalities such as impaired glycaemic control (16). Due to the metabolic consequences of reduced muscle mass, it is understood that normal ageing and/or decreased physical activity may lead to a higher prevalence of metabolic disorders. Cross-sectional studies show that muscular strength is inversely related to both the metabolic syndrome and the all-cause mortality (17,18). An overview of how RT may influence atherosclerotic risk factors is presented graphically in Fig. 1. Thus, only RT has the power to increase muscle mass and strength. Based on the mitochondrial theory of ageing (19), RT may serve as a countermeasure of age-associated mitochondrial dysfunction by reducing potentially damaging compounds to mitochondria resulting from reactive oxygen species (20). This may have important implications for many disease processes, particularly T2D and the metabolic syndrome (21,22). Major health organizations such as the American College of Sports Medicine, American Heart Association and the American Diabetes Association have issued recommendations regarding RT for older or diabetic individuals (23–25). RT may reduce abdominal and visceral fat, which is known to increase with advancing age and influence glucose clearance. Possible mechanisms include increases in resting metabolic rate and sympathetic activity with RT as well as a reduction in hepatic lipogenesis (13). The anti-inflammatory effects of chronic RT may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and an induction of an anti-inflammatory environment with each bout of exercise. Nevertheless, the extent to which RT can alter several pro-inflammatory cytokines produced in adipose tissue is still unclear. Because it is well-established that exercise training has profound effects on obesity and T2D risk, the purpose of this review was to focus on the potential and unique effect of RT on VAT and specific biomarkers of inflammation such as adiponectin, leptin, CRP, IL-6 and TNF-α.

Implications of resistance training

A review of literature was conducted through MEDLINE databases to identify relevant studies from earliest record to September 2011. The following key words were used alone, or in various combinations, within the systematic search: obesity, abdominal obesity, exercise, RT, body composition, visceral fat, cytokine and inflammation. Reference lists from original and review articles were also reviewed in order to identify additional relevant studies. Only eligible full texts in English were considered for review. All randomized controlled trials (RCTs) comparing RT with an exercise or non-exercise control group in healthy or overweight/obese adults were examined. Exclusion criteria
for this review included (i) studies with single-bout RT interventions; (ii) studies where the intervention was less than 6 weeks in duration; (iii) studies with mere recommendations as intervention, without further detail; (iv) studies where the RT was not either directly supervised or well-documented; (v) studies with a dietary co-intervention in the experimental group that was not also applied to the control group and (vi) studies with concomitant AET in the experimental group that was not also applied to the control group. Two researchers (B.S. and M.A.) independently performed the literature search, quality assessment and data extraction. Any disagreements on inclusion of trials were resolved by discussion with the third author (U.S.).

The review comprises studies with both male and female subjects. RCTs with detailed RT prescriptions (relating to type, dose, intensity, frequency and duration of RT) were included in the review. Based on these criteria, 28 studies were included for review, involving the following four types of intervention (i) RT vs. non-exercise control (26–43); (ii) RT plus AET vs. AET (44–46); (iii) RT plus caloric restriction (CR) vs. CR alone (47–52) and (iv) RT plus CR vs. AET plus CR (53). The duration of interventions ranged from 6 to 12 weeks in 11 studies (26–29,31–34,38,40,42), 4 to 6 months in 13 studies (30,37,39,41,43,45,46,48–53), and 1 to 2 years in three studies (35,36,44). In one study, subjects were maintained on the intervention programme until a BMI < 25 was achieved (47). Most interventions involved two (35,36,41,44,48) or three (26,29–34,37–40,42,43,45–47,49–53) training sessions per week, with RT occurring on non-consecutive days. One study involved one session per week (27), while another study involved five sessions per week (28). The percentage of the one repetition maximum (1RM) or 8–15 repetition maximum (8–15RM) were scales used to define the intensity of RT. One set consisted of 8–15 repetitions without interruption, until severe fatigue occurred and completion of further repetitions was impossible. The training load was systematically adapted to keep the maximum possible repetition per set between 8 and 15. 8–15RM is equivalent to 70–80% 1RM for most exercises (15). The mean peak intensity of the interventions ranged from 40% 1RM (28) to 85% 1RM (41). The maximum number of sets for each muscle group per week (SMG/W) at the end of the intervention programme ranged from 2 SMG/W (44) to 27 SMG/W (38). The most common dose of RT at the end of the intervention was 6 SMG/W. RT on a weight machine was most commonly used for progressive RT. In most studies, the RT programme consisted of exercises for all major muscle groups. Exercises to strengthen the upper body included bench press (pectoralis), chest cross (horizontal flexion of the shoulder joint), shoulder press (trapezius), pull downs (latissimus dorsi), bicep curls, tricep extensions and exercises for abdominal muscles (sit-ups).

Lower body exercises included leg press (quadriceps femoris). Two studies performed RT using elastic bands (28,29), two studies prescribed leg exercises only (32,42) and one combined with plyometric jumps (32). Table 1 details the dose characteristics and main outcomes for the included studies.

Using resistance training as a treatment for visceral fat reduction

A recent meta-analysis aimed to evaluate the independent and synergistic effects of AET and progressive RT for beneficial VAT modulation (54). These data suggest that AET – even below current recommendations for obesity management – is effective in lowering VAT, while RT itself failed to induce significant reduction in VAT when compared with control. There are several possible reasons for this discrepancy. It has been suggested that AET has specific effects on decreasing VAT as it may lead to increased sympathetic tonus, thereby increasing lipolysis especially in abdominal fat (55). Furthermore, AET involves continuous activity of multiple large muscle groups, whereas RT involves isolated, brief activity of single muscle groups (37). Especially high-intensity AET can lead to chronic increases in 24-h growth hormone release, which acts to stimulate adipose tissue directly via hormone sensitive lipase and also indirectly by enhancing insulin sensitivity (54). In studies where AET and RT were directly compared, the effect size favoured AET but did not reach statistical significance. However, direct comparison between AET and RT is problematic due to differences in metabolic strain and appropriate dosage/volume. To do this, one in-house study tried to define comparable training units for both groups (56). A unit was defined as an organizational unit for both training groups. The authors took comparable training units of top athletes for each training group. A top weight-lift body builder, e.g. does 30U per muscle group per week, whereas a top endurance athlete trains for 10–12 h a week. For the latter study, we took 20% of these training units for each group. Combining RT with AET has been shown to be superior for visceral fat loss and to result in greater lean body mass when compared with AET alone (44–46).

In the present review, three additional studies were included in addition to papers used by Ismail et al. (26,27,47). Although the results show only a slight decrease in VAT with RT as the sole intervention, the clinical significance can be gauged by studying large prospective intervention studies examining the correlations between changes in VAT with exercise training and variables of metabolic risk. In STRRIDE (57), the data suggest that a reduction of as little as 11 cm² in VAT is significantly related to changes in low-density lipoprotein (LDL) particle number, LDL size and insulin sensitivity. In this context,
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Mean age/BMI (kg m$^{-2}$)</th>
<th>Study design</th>
<th>Frequency study length</th>
<th>Intervention</th>
<th>Main outcomes (RT group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallsworth et al. 2011 (26)</td>
<td>19 Obese adults with NAFLD 11 RT, 8 control</td>
<td>Not reported/32.3 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 8 weeks</td>
<td>RT: 8 Ex, 70% 1RM Dose: 9 S/MG/W</td>
<td>↓IHL ($P &lt; 0.05$) ↔VAT, SAT ↑IS ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Donges et al. 2010 (27)</td>
<td>102 sedentary adults 35 RT, 41 AET, 26 control</td>
<td>Not reported/27.8 kg m$^{-2}$</td>
<td>RT vs. AET vs. control</td>
<td>1 d week$^{-1}$ for 10 weeks</td>
<td>RT: 6 Ex, 75% 1RM Dose: 3 S/MG/W AET: 75% MHR 50 min week$^{-1}$</td>
<td>↓VAT ($P &lt; 0.05$) ↔CRP ($P &lt; 0.05$) ↓IL-6 (ns)</td>
</tr>
<tr>
<td>Fisher et al. 2010 (47)</td>
<td>126 overweight women 30.5 years/28.0 kg m$^{-2}$</td>
<td>RT+ CR vs. AET vs. CR 3 d week$^{-1}$ until a BMI &lt; 25</td>
<td>RT: 10 Ex, 80% 1RM CR: 800 kcal d$^{-1}$</td>
<td>2 d week$^{-1}$ for 16 weeks</td>
<td>RT: 7 Ex, 80% 1RM Dose: 6–10 S/MG/W</td>
<td>↓VAT, ↓ISAT ($P &lt; 0.001$) ↓IL-6 ($P &lt; 0.001$) ↔TNF-a ↓CRP ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Ibanez et al. 2010 (48)</td>
<td>34 obese women 48.6 years/35.0 kg m$^{-2}$</td>
<td>RT+ CR vs. CR vs. control 2 d week$^{-1}$</td>
<td>RT: 10 Ex (elastic band) Dose: 6–10 S/MG/W</td>
<td>5 d week$^{-1}$ for 12 weeks</td>
<td>RT: 10 Ex (elastic band) Dose: 15 S/MG/W</td>
<td>↓AD, ↓LP ($P &lt; 0.05$) ↑IS ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Ku et al. 2010 (28)</td>
<td>44 women with T2D 55.7 years/27.1 kg m$^{-2}$</td>
<td>RT+ CR vs. CR vs. control</td>
<td>RT: 10 Ex, 50–70% 1RM Dose: 15 S/MG/W</td>
<td>40–50% 1RM</td>
<td>2 d week$^{-1}$ for 16 weeks</td>
<td>↓VAT ($P &lt; 0.001$) ↔CRP ($P &lt; 0.001$) ↓IL-6 ($P &lt; 0.001$) ↓AD, ↓LP ($P &lt; 0.05$) ↓IS ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Kwon et al. 2010 (29)</td>
<td>28 women with T2D 56.4 years/27.4 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>RT: 10 Ex, 40–50% 1RM Dose: 9 S/MG/W</td>
<td>3 d week$^{-1}$ for 12 weeks</td>
<td>RT: 10 Ex, 40–50% 1RM Dose: 9 S/MG/W</td>
<td>↓VAT (ns) ↔AD, ↓LP ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Martins et al. 2010 (30)</td>
<td>45 adults with T2D 73.2 years/30.8 kg m$^{-2}$</td>
<td>RT vs. AET vs. control</td>
<td>RT: 8 Ex, 8–15RM 3–9 S/MG/W AET: 40–85% HRR 120 min week$^{-1}$</td>
<td>3 d week$^{-1}$ for 16 weeks</td>
<td>RT: 8 Ex, 8–15RM 3–9 S/MG/W AET: 40–85% HRR 120 min week$^{-1}$</td>
<td>↓CRP ($P &lt; 0.05$)</td>
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<tr>
<td>Phillips et al. 2010 (31)</td>
<td>35 elderly women 71.1 years/26.0 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>RT: 10 Ex, 80% 1RM Dose: 9 S/MG/W</td>
<td>3 d week$^{-1}$ for 10 weeks</td>
<td>RT: 10 Ex, 80% 1RM Dose: 9 S/MG/W</td>
<td>↓IL-6 ($P &lt; 0.05$) ↓TNF-a ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Bialucci et al. 2010 (44)</td>
<td>107 obese women 57.2 years/32.6 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>RT: 6 Ex, 70–80% 1RM Dose: 6–10 S/MG/W</td>
<td>3 d week$^{-1}$ for 24 weeks</td>
<td>RT: 7 Ex, 70–80% 1RM Dose: 6–10 S/MG/W</td>
<td>↓VAT, ↓ISAT ($P &lt; 0.0001$) ↓IL-6 ($P &lt; 0.001$) ↓TNF-a ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Brochu et al. 2009 (49)</td>
<td>(a) 23 healthy women 22.3 years/21.7 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>RT: 4 leg Ex Dose: 6–10 S/MG/W</td>
<td>3 d week$^{-1}$ for 24 weeks</td>
<td>RT: 4 leg Ex Dose: 6–10 S/MG/W</td>
<td>↓VAT, ↓ISAT ($P &lt; 0.0001$) ↓IL-6 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Guadalupe-Grau et al. 2009 (32)</td>
<td>107 obese women 57.2 years/32.6 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>RT: 4 leg Ex Dose: 6–10 S/MG/W</td>
<td>3 d week$^{-1}$ for 24 weeks</td>
<td>RT: 4 leg Ex Dose: 6–10 S/MG/W</td>
<td>↓VAT, ↓ISAT ($P &lt; 0.0001$) ↓IL-6 ($P &lt; 0.001$)</td>
</tr>
</tbody>
</table>

Table 1: Study characteristics and outcomes relative to baseline for reviewed resistance training interventions.
Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Mean age/BMI (kg m$^{-2}$)</th>
<th>Study design</th>
<th>Frequency study length</th>
<th>Intervention</th>
<th>Main outcomes (RT group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levinger et al. 2009 (33)</td>
<td>30 adults with HI-MR 15 RT, 15 control</td>
<td>50.8 years/not reported</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 10 weeks</td>
<td>RT: 7 Ex, 50–85% 1RM Dosage: 9 S/MG/W</td>
<td>↔CRP ↔IL-6 ↔TNF-α</td>
</tr>
<tr>
<td>Ahmadizad et al. 2007 (34)</td>
<td>24 overweight men 16 RT, 8 AET, 8 control</td>
<td>40.9 years/28.3 kg m$^{-2}$</td>
<td>RT vs. AET vs. control</td>
<td>3 d week$^{-1}$ for 12 weeks</td>
<td>RT: 11 Ex, 50–60% 1RM Dosage: 12 S/MG/W AET: 75–85% MHR 60–90 min week$^{-1}$</td>
<td>↔ AD</td>
</tr>
<tr>
<td>Olson et al. 2007 (35)</td>
<td>28 overweight women 16 RT, 12 control</td>
<td>39.0 years/26.9 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>2 d week$^{-1}$ for 52 weeks</td>
<td>RT: 9 Ex, 80% 1RM Dosage: 6 S/MG/W</td>
<td>↑AD (P &lt; 0.01) ↓CRP (P &lt; 0.01) ↔IL-6</td>
</tr>
<tr>
<td>Schmitz et al. 2007 (36)</td>
<td>133 overweight women 70 RT, 63 control</td>
<td>37.0 years/29.4 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>2 d week$^{-1}$ for 2 years</td>
<td>RT: 8–10 isotonic Ex 8–10 reps Dosage: 6:4 S/MG/W AET: 75–85% MHR 60–90 min week$^{-1}$</td>
<td>↑VAT, SAT</td>
</tr>
<tr>
<td>Sigal et al. 2007 (37)</td>
<td>251 T2D 60 RT, 60 AET, 60 RT + AET, 60 control</td>
<td>54.7 years/34.1 kg m$^{-2}$</td>
<td>RT vs. AET vs. RT + AET vs. control</td>
<td>3 d week$^{-1}$ for 22 weeks</td>
<td>RT: 7 Ex, 80% 1RM Dosage: 6–9 S/MG/W AET: 75–85% MHR 60–90 min week$^{-1}$</td>
<td>↓VAT, SAT</td>
</tr>
<tr>
<td>Ara et al. 2006 (38)</td>
<td>18 healthy men 12 RT, 6 control</td>
<td>22.7 years/24.9 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 6 weeks</td>
<td>RT: 5 Ex, 50–90% 1RM Dosage: 3–27 S/MG/W</td>
<td>↔LP</td>
</tr>
<tr>
<td>Brooks et al. 2006 (39)</td>
<td>62 obese T2D adults 31 RT, 31 control</td>
<td>66.0 years/30.9 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 16 weeks</td>
<td>RT: 5 Ex, 60–80% 1RM Dosage: 9 S/MG/W</td>
<td>↑AD (P &lt; 0.001) ↓CRP (P &lt; 0.05) ↓IS (P &lt; 0.05)</td>
</tr>
<tr>
<td>Binder et al. 2005 (40)</td>
<td>54 older adults 34 RT, 20 control</td>
<td>83.0 years/27.0 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 12 weeks</td>
<td>RT: 6 Ex, 65–85% 1RM Dosage: 6–9 S/MG/W</td>
<td>↑VAT, ↓ISAT (ns)</td>
</tr>
<tr>
<td>Fatouros et al. 2005 (41)</td>
<td>50 overweight men 14 HI-RT, 12 MI-RT, 14 LI-RT, 10 control</td>
<td>70.8 years/29.9 kg m$^{-2}$</td>
<td>RT vs. control</td>
<td>2 d week$^{-1}$ for 24 weeks</td>
<td>RT: 8 Ex, 50–85% 1RM HI-RT: 80–85% 1RM MI-RT: 50–65% 1RM LI-RT: 45–50% 1RM Dosage: 6 S/MG/W</td>
<td>↑AD (P &lt; 0.05) with HI-RT ↓LP (P &lt; 0.05) al RT groups ↓IS (P &lt; 0.05) al RT groups</td>
</tr>
<tr>
<td>Bruunsgaard et al. 2004 (42)</td>
<td>21 older adults 10 RT, 11 control</td>
<td>88.6 years/not reported</td>
<td>RT vs. control</td>
<td>3 d week$^{-1}$ for 12 weeks</td>
<td>RT: 2 leg Ex 50–80% 1RM Dosage: 9 S/MG/W</td>
<td>↓IL-6 (ns) ↓TNF-α (ns)</td>
</tr>
<tr>
<td>Cuff et al. 2003 (45)</td>
<td>28 obese T2D women 10 RT + AET, 9 AET, 9 control</td>
<td>63.4 years/33.3 kg m$^{-2}$</td>
<td>RT + AET vs. AET vs. control</td>
<td>3 d week$^{-1}$ for 16 weeks</td>
<td>RT: 5 Ex, 70% 1RM Dosage: 6 S/MG/W AET: 60–75% MHR 180 min week$^{-1}$</td>
<td>↓VAT, ↓ISAT (P &lt; 0.05) ↓IS (P &lt; 0.05)</td>
</tr>
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<td>Study</td>
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<tr>
<td>Park et al. 2003 (46)</td>
<td>30 overweight women</td>
<td>43.4 years/25.8 kg·m(^{-2})</td>
<td>RT + AET vs. AET vs. control</td>
<td>3 d week(^{-1}) for 24 weeks</td>
<td>RT: 10 Ex, 70% 1RM Dose: 3 S/MG/W AET: 60–70% HRR 180 min week(^{-1})</td>
<td>↓VAT, ↓SAT (P &lt; 0.01)</td>
</tr>
<tr>
<td>Janssen et al. 2002 (50)</td>
<td>38 obese women</td>
<td>34.8 years/31.6 kg·m(^{-2})</td>
<td>RT + CR vs. AET + CR vs. CR</td>
<td>3 d week(^{-1}) for 16 weeks CR: 1,000 kcal d(^{-1})</td>
<td>RT: 8 Ex, 70–80% 1RM Dose: 3 S/MG/W AET: 50–85% MHR 45–180 min week(^{-1})</td>
<td>↓VAT, ↓SAT (P &lt; 0.02) ↓Fasting insulin (P &lt; 0.02) ↓Insulin AUC (P &lt; 0.02)</td>
</tr>
<tr>
<td>Poehlman et al. 2000 (43)</td>
<td>51 younger women</td>
<td>28.0 years/22.0 kg·m(^{-2})</td>
<td>RT vs. AET vs. control</td>
<td>3 d week(^{-1}) for 28 weeks</td>
<td>RT: 9 Ex, 80% 1RM Dose: 9 S/MG/W AET: 75–90% MHR 75–120 min week(^{-1})</td>
<td>+→VAT, SAT ↑IS (ns)</td>
</tr>
<tr>
<td>Rice et al. 1999 (51)</td>
<td>29 obese men</td>
<td>39.8 years/33.8 kg·m(^{-2})</td>
<td>RT + CR vs. AET + CR vs. CR</td>
<td>3 d week(^{-1}) for 16 weeks CR: 1,000 kcal d(^{-1})</td>
<td>RT: 7 Ex, 70–80% 1RM Dose: 3 S/MG/W AET: 50–85% MHR 60–180 min week(^{-1})</td>
<td>↓VAT, ↓SAT (P &lt; 0.05) ↓Fasting insulin (P &lt; 0.05) ↓Insulin AUC (P &lt; 0.05)</td>
</tr>
<tr>
<td>Ross et al. 1996 (52)</td>
<td>33 obese men</td>
<td>39.0 years/33.0 kg·m(^{-2})</td>
<td>RT + CR vs. AET + CR vs. CR</td>
<td>3 d week(^{-1}) for 16 weeks CR: 1,000 kcal d(^{-1})</td>
<td>RT: 8 Ex, 70–80% 1RM Dose: 3 S/MG/W AET: 50–85% MHR 45–180 min week(^{-1})</td>
<td>↓VAT, ↓SAT (P &lt; 0.05) ↓Fasting insulin (P &lt; 0.05) ↓Insulin AUC (P &lt; 0.05)</td>
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<tr>
<td>Ross et al. 1994 (53)</td>
<td>24 obese women</td>
<td>35.5 years/31.8 kg·m(^{-2})</td>
<td>RT + CR vs. AET + CR vs. CR</td>
<td>3 d week(^{-1}) for 16 weeks CR: 1,000 kcal d(^{-1})</td>
<td>RT: 8 Ex, 70–80% 1RM Dose: 3 S/MG/W AET: 50–85% MHR 45–180 min week(^{-1})</td>
<td>↓VAT, ↓SAT (P &lt; 0.01)</td>
</tr>
</tbody>
</table>

↑, higher/more; ↓, lower/less; ↔, unchanged; 1RM, one-repetition maximum; AD, adiponectin; AET, aerobic endurance training; CR, caloric restriction; CRP, C-reactive protein; Ex, exercises; HI, high-intensity training; HRR, heart rate reserve; IHL, intrahepatic lipid; IL-6, interleukin-6; IS, insulin sensitivity; LI, low-intensity training; LP, leptin; MHR, maximum heart rate; MI, moderate-intensity training; MR, metabolic risk; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; ns, not significant; RT, resistance training; S/MG/W, sets for each muscle group per week; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-alpha; VAT, visceral adipose tissue; WL, weight loss.
Nieves et al. demonstrated that differences in visceral fat explain much of the atherogenic lipoprotein profile that is associated with obesity and insulin resistance (5). The aim of a Japanese prospective cohort study was to investigate whether reductions of visceral fat is associated with a decrease in the number of metabolic risk factors (58). The authors demonstrated that, irrespective of BMI, changes in VAT within 1 year correlated significantly with changes in the number of metabolic risk factors. Men who reduced their visceral fat by 30 cm² decreased their metabolic risk by approximately 25%. Key features associated with excess VAT, including insulin resistance, atherogenic dyslipidaemia, hypertension and inflammation, are often referred to collectively as the metabolic syndrome, which is linked to the development of CVD (59,60). RT has been shown to improve or prevent many of these metabolic features (13–16). It is unclear whether the improvement in metabolic health can be maintained in the longer term. A recently published study found that following a 15% (12 kg) diet-induced weight loss, RT prevented regain of VAT, while participants who did not train regained over 70% of their visceral fat lost (61). The major finding from another study was that RT is effective in maintaining diet- and aerobic exercise-induced improvements in metabolic features (i.e. insulin sensitivity, VAT) during an 8- to 12-week period of weight regain (62). However, this observation requires confirmation by additional studies though as this study has several limitations – the small sample size of only nine participants and the lack of a control group. It seems that RT has the potential to reduce VAT through both immediate effects (e.g. during weight loss or weight maintenance) and delayed effects (during weight regain). In this context, visceral fat increased by 21% over a 2-year period in overweight and obese premenopausal women in a standard care control group, but only 7% during the same time period in a RT group (36). It was concluded that RT attenuates visceral fat increases occurring over time in women.

Quantification of abdominal fat and its regional distribution has become increasingly important in assessing cardiovascular risk. Whether or not RT alone or combined with weight loss induces regional variation of visceral fat loss is a hypothesis that should be taken into consideration. The principal finding of one study was that VAT distribution after CR of 500 kcal d⁻¹ differs from that observed after the same dietary intervention plus RT (63). In obese women, CR plus RT reduces VAT volume in higher scans of this region (L2-L3), whereas after CR alone, the greatest relative VAT losses were located at L5-S1. Similarly, Ross et al. reported comparable reductions in VAT in the upper abdomen after a 16-week period of CR (1,000 kcal d⁻¹) in combination with AET or RT (53). Thus, the specific exercise programme (AET vs. RT), hypocaloric diet and/or combined interventions may alter adipose tissue metabolism and regional VAT depot loss, possibly by mobilizing free fatty acids from VAT at different regions of the abdomen. However, limitations still exist. Unfortunately, the differential effects on regional VAT loss of diet alone, RT alone and diet plus RT were not compared separately in these studies. Furthermore, VAT was measured at a number of levels, one of the most common is the L4-L5 space, but if other levels were used, the absolute areas would differ. Finally, no information is available about possible gender-specific responses on regional visceral fat changes in obese subjects. One study raised the possibility of gender specificity in visceral fat reduction response to RT (64). Hunter et al. studied older women and men after 25 weeks of RT (at 65–80% of 1RM). Results demonstrated that both genders significantly increased muscle mass and decreased whole-body fat mass. However, women also lost a significant amount of VAT (−11%), whereas the men did not. Additional studies are needed to clarify these possible gender-specific responses on regional VAT loss.

Impact on inflammatory risk modification: a meta-analysis

Several studies have documented significant associations between the amount of VAT and circulating levels of IL-6, TNF-α and CRP (65,66). Data from the Framingham Heart Study suggest that in women, an increase of 0.8 kg in VAT corresponds to an elevated CRP concentration of 1.8 mg L⁻¹ and a corresponding increase of 0.7 mg L⁻¹ in men (67). It seems paradox that women, who are generally at lower CVD risk than men, have higher CRP levels. This gender difference can be explained in terms of the greater accumulation of ‘healthy’ subcutaneous fat in women than in men (68). Taken together, elevated CRP levels may often be a good marker of a dysmetabolic state associated with ‘fat stored in the wrong place’. However, there is evidence that CRP may also be a biologically active protein that may play a causal role in atherothrombotic events (69–71). The data suggest that a 1-SD higher loge in CRP concentration (three-fold higher) represents a 23% increase in risk for coronary heart disease, a 32% increased risk for ischaemic stroke and a 34% increased risk for vascular mortality (72).

Although a recent systematic review conducted by De Salles et al. analyzed the effectiveness of RT in longitudinal clinical studies on cytokines on a limited number of studies and suggested some positive effects of RT programmes on inflammatory markers (73), of note is that the pooled effects of RT using meta-analysis has not yet been investigated. Therefore, we aimed to evaluate the effect of RT on specific biomarkers of inflammation such as adiponectin (AD), leptin (LP), CRP, IL-6 and TNF-α using meta-analysis. Our second goal was to investigate the potential of a dose–response relationship between duration, intensity and volume of RT exercise and assessed outcomes.
Data extraction
Eligible studies were reviewed independently by two of the authors to assess inclusion suitability and data extraction accuracy. A standardized data extraction form was developed in order to extract data from each study in the following areas: study population, intervention and outcome. The form included the following items: (i) general information including title, authors, source, setting, year of publication; (ii) trial characteristics, including study design and randomization; (iii) characteristics of participants, such as inclusion criteria, exclusion criteria, total number in intervention/control groups, gender distribution, mean age, diagnostic criteria, other baseline characteristics and dropouts; (iv) intervention type, dose, intensity, and frequency, as well as duration of the trial; (v) outcomes specified in the methods and (vi) results. For continuous variables, we extracted sample size as well as baseline and post-intervention means with standard deviation (SD) for the intervention and control groups. There were no dichotomous variable outcomes. Study characteristics were reported in evidence tables.

Quality assessment
The methodological qualities of RCTs included in this review were assessed according to JADAD score items (74). This 5-point quality scale includes points for randomization (described as randomized, 1 point; table of random numbers or computer generated randomization, additional 1 point), double blinding (described as double blind, 1 point; use of making such as identical placebo, additional 1 point) and follow-up (the numbers and reasons for withdrawal in each group are stated, 1 point) within the report of an RCT. An additional point was accepted if the analysis was by intention-to-treat. Final scores between 0 and 2 were considered as low quality, while final scores of 3 or more were regarded to represent studies of high quality as blinding of patients performing the exercise is not possible.

Statistical analysis
All data were analyzed with the software package REVIEW MANAGER 5.0.25 from the Cochrane Collaboration. Heterogeneity between trial results was tested with a standard chi-squared test ($\chi^2$). The $I^2$ parameter was used to quantify any inconsistency ($I^2 = |(\mathcal{Q} - \text{d.f.})/\mathcal{Q}| \times 100\%$, where $\mathcal{Q}$ is the chi-squared statistics and d.f. is its degrees of freedom). A value for $I^2$ greater than 50% has been considered to be substantial heterogeneity (75). For each outcome of interest, a meta-analysis was performed in order to determine the pooled effect of the intervention in terms of weighted mean differences (WMDs) between the post-intervention values of the intervention and control groups. To consider heterogeneity, the random-effects model was used to estimate WMD with 95% confidence intervals (CIs). Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. Funnel plots were used to assess potential publication bias (i.e. the tendency for studies that yield statistically significant positive results to be more likely to be submitted and accepted for publication). To determine the presence of publication bias, we assessed the symmetry of the funnel plots in which mean differences were plotted against their corresponding standard errors. In addition, we examined the potential of a dose–response relationship between RT variables (i.e. training duration, intensity and volume) and assessed the outcomes.

A random-effects meta-regression was performed to examine the association between duration, intensity (percentage of the one repetition maximum) and volume (sets per muscle group per week) of RT exercises with changes in inflammatory response. The $P$-values for differences in effects between RT variables were obtained using STATA 11.0 (Stata-Corp, College Station, TX, USA). Two-sided $P$-values < 0.05 were considered statistically significant.

Pooled effects of resistance training
There were no significant differences between the RT group and the control group in resting serum concentration of AD (WMD: 0.57 µg mL$^{-1}$, 95% CI: −0.82 to 1.96, $P = 0.42$), LP (WMD: −0.44 ng mL$^{-1}$, 95% CI: −1.71 to 0.82, $P = 0.49$), IL-6 (WMD: −0.23 pg mL$^{-1}$, 95% CI: −0.59 to 0.13, $P = 0.20$) and TNF-α (WMD: 0.12 pg mL$^{-1}$, 95% CI: −0.15 to 0.38, $P = 0.40$). Resting serum CRP was reduced by 0.23 mg L$^{-1}$ with RT, which was statistically significant (95% CI: −0.38 to −0.07, $P = 0.006$). Table 2 summarizes the pooled results for the intervention effects. Figure 2 shows the results from each study group for CRP change (WMD point estimate and 95% CI) in response to RT (graphically displayed as a forest plot).

Heterogeneity and dose–response relationship
We found heterogeneity across trials concerning some biomarkers of inflammation, i.e. AD ($I^2 = 54\%$) and LP ($I^2 = 78\%$). Heterogeneity may be explained by the range of different RT interventions used (and protocols used) across studies (76). Intervention differences included frequency, duration, intensity and dose of exercise; diversity in the initial strength and metabolic status of participating individuals.

Meta-regression revealed no statistically significant dose–response relationship between intensity of RT and changes in inflammatory response. Concerning the volume of RT, the only factor that explained part of the heterogeneity was for one outcome dose of RT at the end of the intervention programme with a significant positive impact on LP (rise in values) with increasing number of sets per week ($P = 0.02$). Figure 3 shows the dose–response relationship between volume of RT at the end of the intervention programme (SMG/W) and changes in effect size for LP (graphically displayed as a bubble plot).
Table 2: Pooled estimates of effect size (95% confidence intervals) expressed as weighted mean difference for the effect of resistance training on serum concentration of adiponectin (AD), leptin (LP), C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No studies</th>
<th>Sample size</th>
<th>WMD</th>
<th>95% CI</th>
<th>Pvalue</th>
<th>Inconsistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (μg mL⁻¹)</td>
<td>6</td>
<td>197</td>
<td>0.57</td>
<td>-0.82 to 1.96</td>
<td>0.42</td>
<td>54</td>
</tr>
<tr>
<td>LP (ng mL⁻¹)</td>
<td>6</td>
<td>175</td>
<td>-0.44</td>
<td>-1.71 to 0.82</td>
<td>0.49</td>
<td>78</td>
</tr>
<tr>
<td>CRP (mg L⁻¹)</td>
<td>8</td>
<td>440</td>
<td>-0.23</td>
<td>-0.38 to -0.07</td>
<td>0.006</td>
<td>3</td>
</tr>
<tr>
<td>IL-6 (pg mL⁻¹)</td>
<td>5</td>
<td>249</td>
<td>-0.23</td>
<td>-0.59 to 0.13</td>
<td>0.20</td>
<td>28</td>
</tr>
<tr>
<td>TNF-α (pg mL⁻¹)</td>
<td>5</td>
<td>204</td>
<td>0.12</td>
<td>-0.15 to 0.38</td>
<td>0.40</td>
<td>0</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Figure 2: Forest plot showing the results of a meta-analysis as pooled weighted mean difference (WMD) with 95% confidence intervals (CIs) in C-reactive protein (mg L⁻¹) for the eight included randomized controlled resistance training (RT) studies. For each RT study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The area of the shaded square reflects the relative weight of the study in the meta-analysis. The diamond at the bottom of the graph represents the pooled WMD.

Discussion

A RT intervention resulted in a significant lowering in circulating CRP by 0.23 mg L⁻¹ (eight trials) compared with the controls, but there was no significant difference between groups in AD (six trials), LP (six trials), IL-6 (five trials) and TNF-α (five trials). The mean change of 25% in CRP relative to baseline for reviewed RT interventions compares well with reported reductions achieved through medications. An intervention trial evaluating Rosuvastatin (JUPITER) has shown that statins can lower CRP levels by 37% compared with a placebo and can significantly reduce the incidence of major cardiovascular events (77). However, JUPITER included individuals who had lower-than-average LDL-cholesterol concentration and higher-than-average CRP concentration. Based on this review, the greatest improvements occurred when CRP was poor (>2.5 mg L⁻¹) at baseline. One meta-analysis aimed to evaluate the independent effect of AET on CRP in adults and reported that exercise was not effective at reducing CRP, as there is a non-significant 3% reduction in CRP overall (78). It seems that physical activity alone does not result in significant reductions in CRP and it is possible that changes in body mass (fat loss, lean body mass increase) may be an effective strategy for lowering CRP (79). The impact of a decrease of 0.23 mg L⁻¹ in CRP achieved in our review equates to an ~12.5% improvement towards a target value of 2 mg L⁻¹, and an ~8% improvement towards a normal value of 1 mg L⁻¹, for a person diagnosed with a threefold higher than the usual CRP concentration.

The specific mechanism, how RT reduces inflammation and suppresses CRP levels, is not well defined. It is likely that RT reduces CRP directly by reducing cytokine production in adipose tissue, muscle and mononuclear cells, or indirectly by increasing insulin sensitivity and improving endothelial function (80). Indeed, certain cytokine including AD, IL-6 and TNF-α can alter insulin sensitivity by triggering different key steps in the insulin signalling pathway (81). Specifically, increased concentrations of plasma AD are positively correlated with insulin sensitivity.
Studies included Ara et al. (38), Balducci et al. (44), Fatouros et al. (41), Guadalupe-Grau et al. (a, b) (32) and Ibanez et al. (48).

RT has been shown to improve insulin sensitivity and glucose uptake by the muscle in patients with T2D (39,56). The decrease in CRP levels observed in the studies included in our review suggests that the reduction in the inflammatory state per se, independent of weight loss, may be an important factor leading to improved insulin sensitivity and better metabolic control (39,44). It is possible that an increase in muscle mass after RT may be a key mediator. However, increased muscle mass was not associated with improvement in glycemic control in one in-house study (83). This supports the work of Holten et al. that changes in insulin sensitivity are more the consequence of intrinsic alterations in the muscle involving central proteins in the insulin signalling cascade (i.e. GLUT4 content) than explained by increases in muscle mass (84). Additionally, an up-regulation of adipose tissue lipolysis due to RT may have a direct influence on the AD response and may be attributed to an enhancement of insulin sensitivity (39,41). A recent systematic review suggests that AD indirectly decreases the level of CRP through a dose-dependent reciprocal inhibition of TNF-α (85). Furthermore, it is speculated that exercise training could decrease resting levels of TNF-α and, ultimately, CRP production, by reducing LP levels while increasing AD and insulin sensitivity (8,80).

The data show that RT is effective in increasing serum concentration of AD (35,41,44) while reducing LP levels (32,41,44) even without changes in body compositions. Thus, these cytokines seem to be inter-related and previous findings support the presence of a direct relationship between muscle mass and cytokine levels (86). Paradoxically, it has been suggested that exercise produces an increase in the release of IL-6 from active muscles, which, in turn, can suppress other pro-inflammatory markers, such as TNF-α (33,87). However, it is TNF-α from adipose tissue that stimulates the release of IL-6 which – chronically elevated – has been associated with VAT and insulin resistance (88). Therefore, TNF-α is proposed as the main driver of chronic low-grade inflammation and for glucose pathogenic metabolism (87,88). Hence, it is necessary to differentiate between the effects of chronically elevated IL-6 (secreted by adipocytes or infiltrated immune cells in the adipose tissue) from the acute several fold IL-6 increase (secreted by myocytes) that occurs with muscle contractions and appears to be anti-inflammatory (87–89). Additionally, muscle IL-6 has been identified as an essential regulator of satellite cell-mediated skeletal muscle hypertrophy both in vitro and in vivo studies (90). It is speculated that short-term RT inflammatory responses during successive training sessions may produce a long-term anti-inflammatory effect related to up-regulation of some cytokines (91). The above factors suggest that RT has the possibility of reducing expression of TNF-α, supporting the hypothesis of local anti-inflammatory effects due to RT intervention (92). However, the studies included in this review did not statistically support this hypothesis, even though two of the studies demonstrated a clinically relevant TNF-α reduction (31,44).

**Dose–response: how much resistance training is needed?**

Considering the benefits of RT on visceral fat and specific biomarkers of inflammation, an important question is: how much RT (duration, intensity and volume) is needed to confer such benefits? Significant improvements in VAT were achieved over a range of exercise intensities and volumes. For example, improvements in VAT were observed following moderate to high exercise intensities at 70% to 80% 1RM (27,43,45–53), low volume (3 S/MG/W) (27), moderate volume (6 S/MG/W) (47) and high volume (9 S/MG/W) (48) of RT. However, on the basis of the recent meta-analysis by Ismail et al. (54), RT itself failed to induce significant reduction in VAT when compared with the control group. Furthermore, there was no evidence to suggest a relationship between total exercise volume or mean intensity and VAT reduction. In contrast, data from STRRIDE revealed very well that a higher amount of AET resulted in greater reductions in measures of central obesity but there was no dose–response relationship between intensity of exercise and changes in visceral fat (93). Similarly, a 2007 review by Ohkawara et al. found that there is a dose–response relationship between the amount of exercise and changes...
in VAT in obese subjects without metabolic-related disorders (55). A significant VAT reduction was observed from about 10 metabolic equivalents (METs) × hour per week and, if obese subjects without metabolic dysfunction practiced AET, the degree of VAT loss could be directly attributed to the aerobic exercise amount (i.e. to reduce 10% of VAT in 10 weeks, 27 METs × h week⁻¹ is required) (55).

A recent review published by De Salles et al. analyzed the effectiveness of RT studies on resting levels of serum cytokines including AD, CRP and TNF-α (73). The authors concluded that training duration and intensity may affect the response of AD and CRP with greater responses shown with interventions of 16 weeks or longer with intensities equal or greater than 80% of 1RM. Based on this analysis, meta-regression revealed no statistically significant dose–response relationship between duration and intensity of RT and changes in inflammatory responses. Although meta-regression suggests no apparent association between RT intensity and inflammatory response, there was a tendency towards a low positive impact of intensity on resting serum AD. The possibility of a dose–response effect was raised by one study in which high-intensity RT (85% 1RM) was associated with an increase in AD of 4.3 μg mL⁻¹ (41), whereas low-intensity RT (60% 1RM) did not significantly augment AD levels (34,41). Furthermore, an increase in AD after RT was associated with improvements in insulin sensitivity (39,41,44). On the other hand, small to moderate improvements were produced by most aerobic exercise interventions regardless of training intensity (94,95), suggesting that perhaps changes in body composition associated with RT may be required for large effects on AD (85). Concerning the volume of RT, there is a tendency towards a positive impact on resting serum LP with increasing number of sets per muscle group per week at the end of the intervention programme. However, interpretative caution is urged on the fact that one included study of high volume was also of short duration and reported no effect on resting serum LP (38). This is in accordance with a number of studies that have investigated the effects of short-term training on LP concentrations and documented no effect on resting LP levels (96), with the exception of patients with T2D (97). Patients with T2D show reduced LP levels with long-term training and appear to be more sensitive to training-induced LP adaptations than other populations (44).

**Conclusion**

Limitations of the present review should be acknowledged, including the limited number of study groups and the heterogeneity in results of trials for some outcomes. The studies included in this review had a broad array of populations: men and/or women; adult and older individuals; overweight and obese; and people with metabolic risk and T2D. Thus, it is difficult to extrapolate conclusions or generalize the effects of RT with this diversity of studies, particularly when gender may result in different cytokine response to exercise, or age that is associated with increases in basal body fat and cytokine levels (98).

Inspection of funnel plots suggests that publication bias cannot be excluded to affect the results on the current meta-analysis. It appears that smaller studies with null results and larger standard errors have not been published. However, the interpretation of funnel plots can be very subjective (99). Furthermore, the fact that only studies published in English were included raises also the possibility of language bias (100). Most studies did not provide information on the quality of the intervention such as randomization method, allocation concealment and blinding of the study assignments to the persons performing the outcome measurements. For example, the intervals in time for sampling may have a profound effect on the inflammatory response. To measure training effects at rest, samples should be taken at least 72 h after the last RT bout. In addition, exercise training could be pro- or anti-inflammatory depending on the degree to which recovery occurs between exercise bouts (101). However, all of the exercise protocols presented in this review include non-consecutive training sessions to assure recovery. Finally, because studies are not randomly assigned to predictors, meta-regression analyses with predictors are considered to be observational in nature. Consequently, such analyses do not support causal inferences. Rather, the validity of these findings would need to be tested in large, well-designed RCTs.

In conclusion, although some reports show statistically significant reductions in visceral fat, it is unclear if the magnitude of these changes are physiologically meaningful and if they are independent of dietary influence. While the aerobic component of exercise therapy is central to exercised-induced VAT modulation, the present review highlights the need for more research examining the efficacy of combined AET and RT modalities, as it has been shown to be superior for visceral fat loss. Furthermore, there is now good evidence that RT attenuates visceral fat increases occurring over time. Based on this review, RT has the power to significantly reduce resting levels of serum CRP independent of weight loss in sedentary healthy or overweight/obese adults and tends to improve AD and LP profile with intensities equal or greater than 80% of 1RM, but the specific effects on the inflammatory cytokine are not clear, requiring further research. Hence, long-term RT could be an effective way to prevent or delay abdominal obesity and inflammatory chronic diseases.
Conflict of Interest Statement
No conflict of interest was declared.

References
Resistance training in obesity


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