Review

A systematic review and meta-analysis for effects of exercise interventions on accumulation of subcutaneous, visceral, and ectopic fat in overweight and obese adults: a randomized controlled trial

Junga Lee 1,*

- ¹ Sports Medicine and Science, Kyung Hee University, Gyeonggi-do, 17104, Korea
- * Author to whom correspondence should be addressed.

Abstract: (1) Background: Overweight and obese adults seek effective exercise interventions to reduce accumulated fat, but the effectiveness of these interventions vary across studies. The purpose of this meta-analysis was to investigate the effectiveness of exercise interventions in overweight and obese adults based on measurement of accumulated fat distributions. (2) Methods: Databases were used to select eligible studies for this meta-analysis. Randomized controlled trials with a control and experimental group were included. Degrees of effectiveness of exercise interventions were computed to assess the benefits on reducing weight and subcutaneous, visceral, and ectopic fat accumulation. (3) Results: A total of twenty-one studies were included in this meta-analysis. Participation in exercise interventions showed beneficial effects in reducing weight and subcutaneous and visceral fat. The effectiveness of exercise interventions on ectopic fat accumulation could not be assessed due to the limited number of studies measuring ectopic fat. Additionally, effectiveness of exercise interventions that depended on measurements of accumulated fat varied. The average exercise intervention for overweight and obese individuals was moderate to vigorous intensity, 4 times per week, 50 minutes per session, and 22 weeks duration. (4) Conclusions: Participating in exercise interventions has favorable effects on reducing weight and accumulation of subcutaneous and visceral fat.

Keywords: fat; obesity; randomized controlled trials; meta-analysis

1. Introduction

There are two billion overweight or obese individuals worldwide, and more than 25% of these are over 18 years old [1]. Obesity in this population rose from about 4.5% in 1975 to about 13% in 2016, while the number of those overweight increased from about 22% to about 39% [1]. An accumulation of fat is a crucial factor that increases morbidity and mortality. Overweight and obese adults had a higher rate of chronic diseases. A previous meta-analysis reported that being overweight and obese were associated with a higher rate of disease-specific and all-cause mortality [2]. Additionally, ectopic fat, which accumulates in all organs or tissues including skeletal muscle, liver, pericardium, perirenal tissues, and perivascular areas, may also be a cause of chronic disease including cardiorenal metabolic risks [3]. Ectopic fat deposited in skeletal muscle and the liver may influence systemic metabolic energy, and pericardial fat is associated with coronary atherosclerosis [4]. Also, pericardial, perivascular, and renal sinus fat may affect adjacent anatomic organs leading to direct lipotoxicity resulting in cytokine secretion [5,6]. Decreasing accumulation of fat is preventive healthy behavior.

Participation in exercise or dietary interventions leads to reduced accumulations of fat and improvement in the cardiorenal metabolic risks. A recent meta-analysis among obese children and adolescents demonstrated that exercise or diet had favorable effects on accumulation of fats including ectopic fat [7]. However, the effects of exercise for overweight and obese adults may be different than

children and adolescents. Also, outcomes of exercise interventions on changes in accumulated fat may be different. This can be ascertained through measuring methods of fat: computed tomography (CT), magnetic resonance imaging (MRI), volume-localized 1H-magnetic resonance spectroscopy (MRS), and dual-energy X-ray absorptiometry (DAX) that identify accumulations of fat in different organs. Also, depending on the different methods, clinically useful measurements of accumulated fat need to be defined. Therefore, the purpose of this meta-analysis was to understand the effects of exercise intervention on overweight and obese adults and to investigate fat distribution differences and ectopic fat measurements.

2. Materials and Methods

2.1. Searching processes

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis statements (PRISMA) [8] and used the MEDLINE and EMBASE databases to identify relevant studies from January 1990 to July 2019 for this meta-analysis. Search terms for eligible articles were accumulated fat; ectopic fat (liver, hepatic, visceral, abdominal, intrahepatic, intramyocellular, myocardial, cardiac, pancreatic); obesity (overweight, adipose tissues); and exercise (aerobic, endurance, strength, resistance). Inclusion criteria were: reporting results of the effects of pre- and post-exercise interventions; recruiting overweight or obesity adults; randomized controlled trials; indicating determination methods for being overweight and obese; and describing measurement technologies including CT, MRI, MRS, and DAX. Exclusion criteria were being a pilot study, systematic review, or meta-analysis review. Missing results for ectopic fat deposits was another exclusion criterion. We also manually searched references cited in review articles to identify further relevant studies. The Cochrane Collaboration's Risk of Bias Tool was used to assess the quality of the selected studies [9].

2.2. Statistical analysis

We used Comprehensive Meta-analysis 2nd version software (Biostat, Englewood, USA). The standardized mean difference statistic, which is the difference in treatment and control group means divided by the pooled standard deviation, was used to calculate the effect size. Heterogeneity between study results was tested with the Q test. If p-values were less than 0.10, we considered the results to be homogeneous. Based on the values of I2, we determined inconsistency; <50% of I2 for small inconsistency, and $\geq50\%$ of I2 for large inconsistency. Risk of bias across studies was assessed by visual inspection of the funnel plot.

3. Results

We described the selection process in Figure 1. A total of 21,400 studies from the initial search were found; 21,322 of these were initially excluded due to not being related to our topic of exercise intervention and ectopic fat. Finally, a total twenty-one studies were selected for meta-analysis [10-30]. The basic characteristics of the selected studies including the first author's name, country in which the study was conducted, design of the study, numbers of participants, levels of body mass index (BMI), sex, contents of exercise interventions, and major findings are presented in Table 1. All participants had to be older than 18 years. Exercise types in selected studies consisted of 12 studies using aerobic exercise; 3 studies using resistance exercise; one study using interval exercise; and 5 studies using combined exercise including aerobic exercise such as jogging, walking, and cycling, and resistance exercise such as squats, leg extensions, leg curls, elbow flexions, triceps extensions, lateral pull-downs, bench presses, military presses, lower back extensions, and bent leg sit-ups. The average duration of participating in exercise interventions was 22 weeks, 4 times per week for about 50 minutes. The average number of participants for each exercise intervention was 35. The average intensity of exercise was from moderate to vigorous intensity exercise.

3.1. Effects of exercise interventions on weight

Overweight and obese individuals who participated in exercise interventions had significantly decreased weight (d=-0.61 [95% confidence interval, -0.82-0.41; p=0.00; k=14]). The degree of effectiveness included all exercise interventions.

3.2. Effects of exercise interventions on subcutaneous fat as measured with CT and MRI

Subcutaneous adipose tissues were measured by CT and MRI. Participants engaging in exercise intervention had significantly decreased subcutaneous fat (d=-0.34 [95% CI, -0.55–0.13; p < 0.001; k=13]) when the measure of effectiveness included all measurements of subcutaneous fat, including those obtained from CT and MRI. Subgroup analysis of CT measurements showed a significant decrease in subcutaneous fat (d=-0.30 [95% CI, -0.55–0.04; p = 0.02; k=8]), but MRI measurements (d=-0.05 [95% CI, -0.78–0.68; k=8]) did not show a significant decrease in subcutaneous fat.

3.3. Effects of exercise interventions on visceral fat as measured from CT and MRI

Visceral fat was measured by CT and MRI. Exercise interventions were effective in reducing visceral fat (d=-0.65 [95% CI, -0.90–0.40; p = 0.001; k=11]). Subgroup analysis demonstrated decreased visceral fat measured by both CT (d=-0.83 [95% CI, -1.18–0.48; p =0.001; k=14]), and MRI (d=-0.43 [95% CI, -0.80–0.05; p = 0.001; k=4]). This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.

3.2. Figures, and Tables

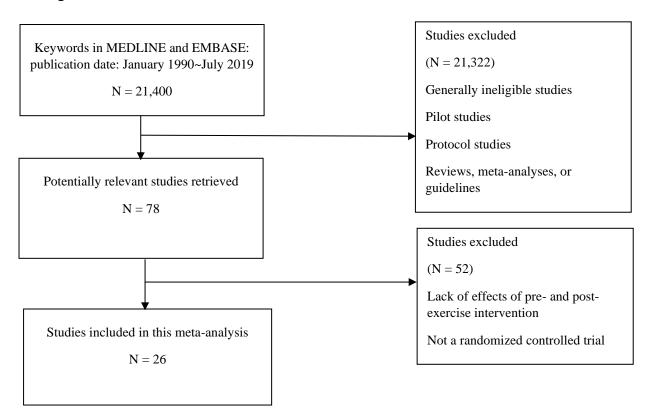
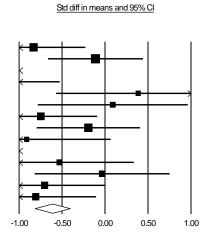


Figure 1. Selection process for the systematic review and meta-analysis

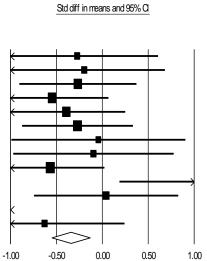
<u>Study name</u>	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ross (2004) weight loss	-0.83	0.31	0.09	-1.43	-0.23	-2.71	0.01
Ross (2004) no weight loss	-0.11	0.28	0.08	-0.66	0.44	-0.40	0.69
Park (2003) aerobic exercise	-2.92	0.64	0.41	-4.18	-1.66	-4.54	0.00
Park (2015) combined	-1.52	0.51	0.26	-2.52	-0.53	-3.00	0.00
Irving (2008) low	0.39	0.49	0.24	-0.57	1.34	0.79	0.43
Irving (2008) high	0.09	0.45	0.20	-0.78	0.96	0.20	0.84
Hunter (2010) aerobic	-0.75	0.33	0.11	-1.40	-0.09	-2.23	0.03
Hunter (2010) resistnace	-0.19	0.31	0.09	-0.80	0.41	-0.63	0.53
Johnson (2009)	-0.91	0.50	0.25	-1.89	0.06	-1.83	0.07
Larson-Meyer (2006)	-2.86	0.59	0.35	-4.02	-1.69	-4.82	0.00
Ibanez (2010)	-0.53	0.44	0.19	-1.39	0.33	-1.20	0.23
Idoate (2011)	-0.03	0.40	0.16	-0.82	0.75	-0.08	0.93
Batrakoulis (2018) 20weeks	-0.70	0.36	0.13	-1.40	-0.01	-1.98	0.05
Batrakoulis (2018) 40weeks	-0.81	0.36	0.13	-1.51	-0.10	-2.25	0.02
	-0.61	0.10	0.01	-0.82	-0.41	-5.88	0.00
				2			



Test for heterogeneity: $(Q = 45.62, P < 0.001, I^2 = 71.50\%)$

Weight

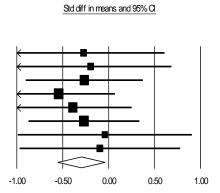
Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Park (2003) aerobic exercise	-0.27	0.45	0.20	-1.15	0.61	-0.61	0.54
Park (2015) combined	-0.20	0.45	0.20	-1.07	0.68	-0.44	0.66
Hunter (2010) aerobic deep	-0.27	0.33	0.11	-0.90	0.37	-0.82	0.41
Hunter (2010) resistance deep	-0.54	0.31	0.10	-1.16	0.07	-1.74	0.08
Hunter (2010) aerobic superfical	-0.39	0.33	0.11	-1.03	0.25	-1.20	0.23
Hunter (2010) resistance superfical	-0.27	0.31	0.09	-0.87	0.33	-0.88	0.38
Irving (2008) low intensity	-0.04	0.48	0.23	-0.99	0.91	-0.09	0.93
Irving (2008) high intensity	-0.10	0.45	0.20	-0.97	0.78	-0.22	0.83
Ross (2004)	-0.57	0.30	0.09	-1.16	0.02	-1.88	0.06
Johnson (2009)	1.19	0.51	0.26	0.19	2.20	2.32	0.02
lbanez (2010)	0.04	0.40	0.16	-0.74	0.83	0.11	0.92
Larson-Meyer (2006)	-2.39	0.55	0.30	-3.46	-1.32	-4.37	0.00
Idoate (2011)	-0.63	0.44	0.20	-1.50	0.24	-1.41	0.16
	-0.34	0.11	0.01	-0.55	-0.13	-3.22	0.00



Test for heterogeneity: (Q = 26.23, P < 0.001, $\overset{2}{I}$ = 54.25%)

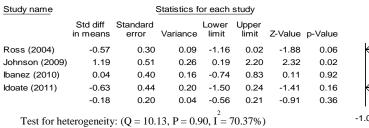
Subcutaneous fat: all measurements

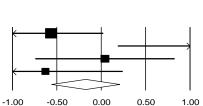
Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Park (2003) aerobic exercise	-0.27	0.45	0.20	-1.15	0.61	-0.61	0.54
Park (2015) combined	-0.20	0.45	0.20	-1.07	0.68	-0.44	0.66
Hunter (2010) aerobic deep	-0.27	0.33	0.11	-0.90	0.37	-0.82	0.41
Hunter (2010) resistance deep	-0.54	0.31	0.10	-1.16	0.07	-1.74	0.08
Hunter (2010) aerobic superfical	-0.39	0.33	0.11	-1.03	0.25	-1.20	0.23
Hunter (2010) resistance superfica	l -0.27	0.31	0.09	-0.87	0.33	-0.88	0.38
Irving (2008) low intensity	-0.04	0.48	0.23	-0.99	0.91	-0.09	0.93
Irving (2008) high intensity	-0.10	0.45	0.20	-0.97	0.78	-0.22	0.83
	-0.30	0.13	0.02	-0.55	-0.04	-2.29	0.02



Test for heterogeneity: $(Q = 1.26, P = 0.02, I^2 = 00\%)$

Subcutaneous fat: CT

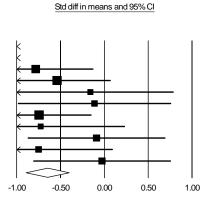




Std diff in means and 95% CI

Subcutaneous fat: MRI

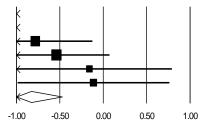
Studyname	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Park (2003) aerobic exercise	-5.83	1.02	1.05	-7.84	-3.82	-5.69	0.00
Park (2015) combined	-4.86	0.89	0.79	-6.60	-3.12	-5.47	0.00
Hunter (2010) aerobic	-0.78	0.34	0.11	-1.44	-0.12	-2.33	0.02
Hunter (2010) resistance	-0.54	0.31	0.10	-1.15	0.07	-1.73	80.0
Irving (2008) low intensity	-0.16	0.48	0.23	-1.11	0.79	-0.33	0.74
Irving (2008) high intensity	-0.11	0.45	0.20	-0.99	0.76	-0.25	0.80
Ross (2004)	-0.74	0.30	0.09	-1.34	-0.15	-2.44	0.01
Johnson (2009)	-0.73	0.49	0.24	-1.69	0.24	-1.48	0.14
lbanez (2010)	-0.09	0.40	0.16	-0.87	0.70	-0.22	0.82
Larson-Meyer (2006)	-0.75	0.43	0.19	-1.60	0.10	-1.74	80.0
Idoate (2011)	-0.03	0.40	0.16	-0.81	0.76	-0.07	0.95
	-0.65	0.13	0.02	-0.90	-0.40	-5.17	0.00



Test for heterogeneity: (Q = 55.31, P < 0.001, I = 81.92%)

Visceral fat: all measurements

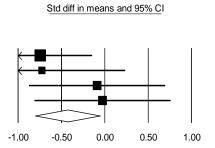
<u>Study name</u>	Statistics for each study							
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Park (2003) aerobic exercise	-5.83	1.02	1.05	-7.84	-3.82	-5.69	0.00	
Park (2015) combined	-4.86	0.89	0.79	-6.60	-3.12	-5.47	0.00	
Hunter (2010) aerobic	-0.78	0.34	0.11	-1.44	-0.12	-2.33	0.02	
Hunter (2010) resistance	-0.54	0.31	0.10	-1.15	0.07	-1.73	80.0	
Irving (2008) low intensity	-0.16	0.48	0.23	-1.11	0.79	-0.33	0.74	
Irving (2008) high intensity	-0.11	0.45	0.20	-0.99	0.76	-0.25	0.80	
	-0.83	0.18	0.03	-1.18	-0.48	-4.59	0.00	
Test for heterogeneity: $(Q = 49.77, P < 0.001, I = 89.95\%)$								



Std diff in means and 95% CI

Visceral fat: CT

Study name	Statistics for each study							
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Ross (2004)	-0.74	0.30	0.09	-1.34	-0.15	-2.44	0.01	
Johnson (2009)	-0.73	0.49	0.24	-1.69	0.24	-1.48	0.14	
lbanez (2010)	-0.09	0.40	0.16	-0.87	0.70	-0.22	0.82	
Idoate (2011)	-0.03	0.40	0.16	-0.81	0.76	-0.07	0.95	
	-0.43	0.19	0.04	-0.80	-0.05	-2.24	0.02	
Test for heterogeneity: $(O = 3.17, P = 0.37, I = 5.28\%)$								



Visceral fat: MRI

Figure 2. Exercise intervention effects on overweight and obese adults

Table 1. Exercise Intervention Characteristics of Selected Studies								
First author (ye ar), Country	Design	Participants	Exercise intervention	Major Findings				
Batrakoulis, (2018), Greece	RCT: control (n=21), exercise (n=14), exercise-detraining (n=14)	Overweight or obese (25.1-34.9 kg/m²), average 36 years old	40 weeks, 3 times/week, combined exercises including aerobic exercise, resistance exercise, and neuromotor exercise, moderate intensity	A whole-body dual-energy X-ray absorptiometry scanner				
Besnier (2015), U.S.A.	RCT: moderate intensity (n=46), re sistance training (n=46), 60% aero bic exercise (n=45), home exercise (45)	Obese older adults (27-40 kg/m ²), average 20-40 years old	RT: moderate intensity (cycle-ergometers, 60% VO ₂ max, 4 days/week, 55 minutes)	Dual X-ray absorptiometry (DXA)				
Blue (2018), U.S.A.	RCT: short interval training (n=1 8), long interval training (n=16), a nd control (n=9)	Obese adults (25-45 kg/m²), 18-50 years old	8 weeks, short interval training (10 repetition of 1-minute bouts, 90% peak power output), long interval training (5 repetition of 2-minute bouts, 80-100% peak power output)	Muscle cross-sectional area and thigh fat thicknes s (ultrasound), lean mass and fat mass of legs (DXA)				
Brochu (2009), Canada	RCT: caloric restriction (n=71) vs. caloric restriction and resistance ex ercise (n=36)	Overweight (> 27 kg/m²), averag e 58 years old	6 months, resistance exercise (phase 1: 3 weeks, 15 repetitions or ~65% of maximum, and 2~3 sets, p hase 2: 5 weeks, 12 repetitions or ~70% of maximum, and 2~3 sets, phase 3: 9 weeks, 8~10 repetitions or ~75%-80% of maximum, and 2~4 sets and p hase 4: 8 weeks, 10~12 repetitions, ~70-75% of maximum, 3~4 sets)	Visceral fat (CT), abdominal fat area (CT)				
Coker (2009), UK	RCT: moderate intensity exercise (n=6), high intensity exercise (n=6), and control (n=6)	Overweight or obese $(26 \le BMI < 37 \text{ kg/m}^2)$, 65-90 years old	12 weeks, 1000 kcal energy expend: cycle-ergomete rs, 50% of VO_{2peak} , or 75% of VO_{2peak}	Fat mass and lean tissue: X-ray, abdominal subcutaneous adipose tissues and abdominal muscle wall: CT				
Gepner (2018), U.S.A.	RCT: exercise (n=139), control (n= 139)	Overweight and obese older adult s (27-41 kg/m ²), \geq 55 years old	18 months, 60 minutes, 65% MHR of aerobic training, 80% of MHR of resistance training (2 sets, leg extension, leg curl, elbow flexion, triceps extension, lateral pull-down, lower back extension, bent leg situps)	Visceral adipose tissue, intrahepatic fat, pancreatic fat, intrapericardial fat, superficial subcutaneous adipose tissue, deep subcutaneous adipose tissue, renal sinus fat, and femur intermuscular adipose tissue (MRI)				
Goodpaster, (2 010), U.S.A.	RCT: physical activity (n=67), and control (n=63)	Obesity (> 30 kg/m²), 30-55 years old	12 months, moderate intensity physical activity, bris k walking, 60 minutes, 5days/week, 10,000 steps/da y	Abdominal adipose tissues and hepatic fat content s (CT)				
Hunter (2010), U.S.A.	RCT: control (n=26), aerobic exerc ise (n=15), resistance exercise (n=18)	Overweight women $(27 \le BMI \le 30 \text{ kg/m}^2)$, 21-46 years old	1 year, aerobic exercise (week 1: 20 minutes, 67% maximum heart rate, and then continues duration a nd intensity increased, week 8: 80 minutes, 80% of maximum heart rate), resistance exercise (squats, 1 eg extension, leg curl, elbow flexion, triceps extension, lateral pull-down, bench press, military press, 1 ower back extension, and bent leg sit-ups, 10 repetitions and 80% of 1RM)	Whole body lean and fat tissue (X-ray), intra- abdominal adipose tissue, deep subcutaneous adipose tissue, subcutaneous adipose tissue (CT)				
Ibanez (2010), Spain	RCT: diet (n=12), diet + resistance exercise (n=13), and control (stret ching, n=9)	Obese women (30-40 kg/m²), aver age 40-60 years old	16 weeks, leg extensor muscles, arm extensor muscle, 4-5 muscle group exercise, 70-80% of 1RM	Volumes of visceral and subcutaneous adipose tis sue and muscle volume: MRI				
Idoate (2011), Spain	RCT: diet (n=12), diet + resistance exercise (n=13), and control (n=9)	Obesity (30-40 kg/m²), 40-60 year s old	16 weeks, 50-70% 1RM, leg extensor, bench press, cardiovascular and whole-body conditioning exercis e, 20~60 min, 3 time/week,	Abdominal adipose tissue (CT), SAT (MRI)				
Irving (2008), U.S.A.	RCT: control (n=7), low intensity exercise (n=11), and high intensity	Obese women, average 51 years old	16 weeks, walking/running, low intensity RPE ~10-12, week 1-2 (300 kcal, 1-2 days/week), week 3-4	Body fat, fat free mass, fat mass, abdominal fat, subcutaneous fat, abdominal visceral fat, mid-thigh				

	exercise (n=9)		(350 kcal, 4 days/week), week 5-16 (400 kcal, 5-1 6 days/week), high intensity RPE ~15-17	fat area, mid-thigh skeletal muscle: CT
Irwin (2003), U.S.A.	RCT: aerobic and resistance exerci se (n=87), and control (stretching, n=86)	Overweight or obese postmenopa usal women (≥35 kg/m²), 50-75 years old	7 weeks, aerobic exercise (60-75% MHR, 45 minut es), resistance exercise (10 repetitions/2sets, leg ext ension, leg curls, leg press, chest press, and seated dumbbell row)	Total body fat, intra-abdominal fat, subcutaneous abdominal fat (CT)
Janssen (2002), Canada	RCT: diet (n=13), diet + aerobic e xercise (n=11), diet + resistance ex ercise (n=14)	Obese women (>27 kg/m²), avera ge 37 years old	16 weeks, aerobic exercise (50-85% MHR, 60 minu tes, 5days/week), resistance exercise (leg extension, leg flexion, super pullover, bench press, shoulder press, triceps extension, biceps curl), 8-12 repetitions, 3 days/week	Total fat, abdominal subcutaneous fat at L4-L5, s keletal muscle, intramuscular fat: MRI
Johnson (200 9), Australia	RCT: control (n=8), and exercise (n=12)	Obesity (≥ 35kg/m²)	4 weeks, a supervised, progressive aerobic exercise, cycle ergometer, total 30~34 minutes (15 minutes s essions and 5 minutes rest), 3 times/week, 50% V O2peak for week1, 60% for week 2, and 70% for week 3 and 4, 15 minutes sessions and 5 minutes rest	Hepatic triglyceride concentration and vastus later alis intramyocellular triglyceride concentration (poi nt-resolved spectroscopy), subcutaneous adipose ti ssues area, hepatic lipid saturation index (HMRS), visceral adipose tissue area (MRI)
Ko (2016), Canada	RCT: combined exercise (n=59), a nd control (n=21)	Obese old adults, 60-80 years old	6 months, aerobic exercise (treadmill, 5 days/week, 60-70% VO _{2peak} , 30 minutes, resistance exercise (3 days/week, chest press, shoulder raise, shoulder flex ion, leg extension, biceps curl, abdominal crunches, modified push-ups)	Total, abdominal, abdominal subcutaneous, and vi sceral adipose tissue (MRI) above the L4-5 intervertebral space
Larson-Meyer, (2006), U.S.A.	RCT: calorie restriction (n=12), cal orie resistance exercise (n=12), low calorie (n=11), and control (n=11)	Overweight (25 ≤ BMI ≤ 30 kg/m ²), Caucasians, 15 African America ns, and 1 Asian, 25~50 years old for man, 25~45 years old for women	6 months, structured exercise (walking, running, or stationary cycling), 5 days/week	Visceral adipose tissue (CT), adipose tissue (X-ra y), fat cell size (Multisizer-3 counter), ectopic fat deposition in liver and muscle (point-resolved spe ctroscopy)
Nicklas (2009), U.S.A.	RCT: caloric restriction (n=29), cal oric restriction and moderate intens ity aerobic exercise (n=36), caloric restriction and vigorous intensity e xercise (n=30)	Overweight and obese postmenop ausal women ($25 \le BMI \le 40 \text{ k}$ g/m ²), average 58 years old	20 weeks, treadmill at intensity of 45-50% (moderate intensity) or 70-75% (vigorous intensity) of heart rate reserve	Whole body fat mass, lean mass, and percentage body fat (X-ray), visceral and subcutaneous adipose tissue volumes around abdomen (CT)
Park (2003), R epublic of Kor ea	RCT: aerobic training group (n=1 0), combined training group (n=1 0), control (n=10)	Overweight or obese (25-35 kg/m ²), average 40 years old	Aerobic training (60-70% HRmax, 60 minutes, 6 days/week), combined training groups (3 days/week for resistance exercise, 3 days/week for aerobic exercise)	Abdominal visceral fat, subcutaneous fat and visceral fat (CT)
Park (2015), Republic of Korea	RCT: combined exercise (n=10), a nd control (n=10)	Abdominal obese postmenopausal women (≥ 24 kg/m²), average 57 years old	12 weeks, resistance exercise (70% of 1RM, 10-12 repetitions, 3 days/week, 30 minutes), aerobic exerc ise (40-75% HRR, 40 minutes, 3 days/week)	Visceral fat (CT)
Christiansen (2009), Denmark	RCT: exercise (n=25), hypocaloric diet (n=29), hypocaloric diet + exe rcise (n=29)	Obese women (30-40 kg/m²), 18-45 years old	12 weeks, 3 times/week, 60-75 minutes, aerobic ex ercise, 70% HRR, 500-600 kcal energy expenditure	Adipose tissue, skeletal muscle: MRI
Quist (2018), Denmark	RCT: aerobic exercise (n=21), leis ure-time exercise (n=21), vigorous intensity (n=33), control (n=16)	Obese adults (25-35 kg/m²), 20-45 years old	6 months, bike exercise (320 kcal/day for women, 42 kcal/day for men), leisure-time exercise of mode rate (50-70% VO _{2peak}), vigorous intensity (50-70% VO _{2peak})	Body composition (DXA)
Ross (2004), C	RCT: control (n=23), diet weight 1	Overweight or obese (>27 kg/m	14 weeks, 500 kcal energy expend, daily exercise	Adipose tissue, skeletal muscle, fat-free skeletal

anada	oss (n=28), exercise weight loss (n=23), exercise without weight loss (n=28)	²), average 43 years old	(brisk walking or light jogging), ~80% MHR	muscle
Schmitz (200 7), U.S.A.	RCT: strength training (n=71 at ye ar 1, n=70 at year 2) and control (n=67 at year 1, n=63 at year 3)	Overweight or obese (25-35 kg/m ²), 25-44 years old	16 weeks, 2 days/week, 3 sets of 8-10 repetitions, quadriceps, hamstring, gluteal, pectoral, erector spinae, latissimus dorsi, rhomboid, deltoid, biceps, and triceps muscles	Body composition: DAX, abdominal fat areas (tot al, subcutaneous, and intraabdominal): CT at the L2-L3 interspace
Slentz (2005), U.S.A.	RCT: high amount/vigorous intensity (n=42), low amount/vigorous intensity (n=46), low amount/moderate intensity (n=40), and control (n=47)	Overweight and obese (25 ≤ BMI ≤ 35 kg/m²), 137 Caucasians, 2 9 African Americans, 49 Asians/ Hispanics, 40~65 years old	8 months, 1) high amount/vigorous intensity (joggin g 20 miles/week), 2) low amount/vigorous intensity (jogging 12 miles/week), and 3) low amount/moder ate intensity (walking 12 miles/week)	Visceral fat (CT), Subcutaneous fat, Total abdomi nal fat, body weight
Thong (2000), Canada	RCT: control (n=8), diet + weight loss (n=14), exercise + weight loss (n=14), and exercise + weight ma intain (n=16)	Obese men (≥30 kg/m²), average 44 years old	12 weeks, 700 kcal energy expend: 75% VO_{2max} (~ 80% MHR), walking or jogging	Total adipose tissue, subcutaneous adipose tissue, visceral adipose tissue: MRI
Verreijen (20 17), Netherland s	RCT: control (n=14), protein (n=1 3), resistance exercise (n=19), and protein and resistance exercise (n= 22)	Obese older adults (average 32.2 kg/m²), average 62.4 years old	10 weeks, resistance training (3 days/week, 1hour, squats, lunges, chest press, shoulder press, biceps c urls, triceps extensions, standing rows, step-ups, cru nches)	Body composition (air displacement plethysmography)

4. Discussion

Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted. This meta-analysis found that participating in exercise interventions had a positive influence on reducing weight and subcutaneous, visceral, and ectopic fat in overweight or obese individuals. Only a limited number of studies regarding the effects of exercise intervention on overweight or obese adults are available for review. Studies with ectopic fat measurements are particularly rare. We conducted a meta-analysis to find the effects of exercise intervention on overweight or obese adults as measured by accumulation of fat.

Exercise intervention had a beneficial effect on reducing weight and fat accumulation, including both subcutaneous and ectopic fat, among overweight or obese adults. Fat distributions accumulate as subcutaneous, visceral, and ectopic fat in other organs depending on their capacities for fat storage [31]. A recent meta-analysis of three studies reported that overweight or obese children and adolescents had beneficial effects from exercise intervention. These children and adolescents had reductions in subcutaneous, visceral, and ectopic fat accumulation after completing exercise interventions [7]. However, no meta-analysis study focusing on adults has been performed. This meta-analysis selected all studies that reported effects of exercise interventions on reducing weight and fat accumulation in overweight or obese adults. We found degrees of effectiveness on subcutaneous and visceral fat, but we were unable to ascertain the same effectiveness on ectopic fat due to the limited number of studies in which ectopic fat was measured. This should be addressed in future studies as a recent meta-analysis of three studies, two of which were conducted in the same laboratory, found that hepatic fat in obese children and adolescents who participated in exercise interventions was decreased.

While the exercise interventions were effective in reducing the accumulated fat in overweight or obese adults, the degrees of effectiveness varied according to method of measurement, either CT or MRI. CT and MRI were used to measure subcutaneous and visceral fat in all selected studies. Visceral fat as measured by CT demonstrated a substantial effect with large heterogeneity while subcutaneous fat measured by CT and visceral fat measure by MRI demonstrated less effectiveness and smaller heterogeneity. Subcutaneous fat reduction measured by MRI was not significantly effective due to a small sample size and large heterogeneity. Also, we were unable to compute the effectiveness of exercise intervention on ectopic fat deposition; no MRI studies on liver adipose tissues had been conducted in overweight or obese adults. Considering the differences in measurement methods, further studies are needed to delineate clinically meaningful measurements of accumulated fat. Exercise interventions consisted of moderate to vigorous intensity, 50 minutes per session, and 4 times per week for 22 weeks. Exercise types included aerobic, resistance, combined aerobic and resistance, and interval training. These are important for designing an evidence-based exercise intervention for overweight or obese adults. Current findings of exercise intensity and durations were higher than recommendations of the American College of Sports Medicine (ACSM) for long-term weight loss, which is 200-300 minutes per week of moderate intensity exercise. Maintaining weight loss and preventing weight regain after completing exercise interventions need to be addressed in future studies through long-term follow-up.

There are four potential mechanisms for the findings of this study. First, exercise helps to increase skeletal muscle including increased muscle mass and strength, skeletal muscle glucose uptake, and fatty acid oxidation [32]. Second, the effects of exercise on liver tissues may include increased hepatic uptake of fatty acids and decreased hepatic glucose production, cholesterol synthesis, and glycogen synthesis [33]. Third, in adipose tissue, exercise works to reduce fat mass and leptin and resistin production and increase lipolysis and adiponectin production [34]. Last, participating in exercise decreased chronic inflammation and increased growth factor production leading to endocrine changes that improve systemic mechanisms.

This study had some limitations. First, selected studies were still too limited for generalizing to all overweight or obese adults. Second, while reliability and validity were found, all measurements of each organ's adipose tissues were different in the selected study. Third, we suggested a guideline for exercise interventions in overweight or obese individuals based on descriptions of the selected studies, but the guideline requires improvement in detail. Last, this meta-analysis included all races, but an exercise guideline should be developed considering differences in race.

5. Conclusions

Overweight or obese adults who participated in exercise interventions demonstrated weight and subcutaneous and visceral fat reduction. All types of exercise including aerobic and resistance exercise were effective; and moderate to vigorous intensity exercise programs, 4 times per week, for 50 minutes, and 22 weeks duration may be the most effective based on the available evidence.

Author Contributions: Conceptualization, J.L.; methodology, J.L.; software, J.L.; validation, J.L.; formal analysis, J.L.; investigation, J.L.; resources, J.L.; data curation, J.L.; writing—original draft preparation, J.L.; writing—review and editing, J.L.; visualization, J.L.; supervision, J.L.; project administration, J.L.; funding acquisition, J.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: None

Conflicts of Interest: The authors declare no conflict of interest.

References

- 1. WHO. Obesity and overweight. Geneva, Switzerland, 2018; pp https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
- 2. Flegal, K.M.; Kit, B.K.; Orpana, H.; Graubard, B.I. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013, *309*, 71-82, doi:10.1001/jama.2012.113905.
- 3. Lim, S.; Meigs, J.B. Ectopic fat and cardiometabolic and vascular risk. *Int J Cardiol* 2013, *169*, 166-176, doi:10.1016/j.ijcard.2013.08.077.
- 4. Gastaldelli, A.; Basta, G. Ectopic fat and cardiovascular disease: what is the link? *Nutr Metab Cardiovasc Dis* 2010, *20*, 481-490, doi:10.1016/j.numecd.2010.05.005.
- 5. Siegel-Axel, D.I.; Haring, H.U. Perivascular adipose tissue: An unique fat compartment relevant for the cardiometabolic syndrome. *Rev Endocr Metab Disord* 2016, *17*, 51-60, doi:10.1007/s11154-016-9346-3.
- 6. Lim, S. Ectopic fat assessment focusing on cardiometabolic and renal risk. *Endocrinol Metab* (Seoul) 2014, 29, 1-4, doi:10.3803/EnM.2014.29.1.1.
- 7. Hens, W.; Vissers, D.; Hansen, D.; Peeters, S.; Gielen, J.; Van Gaal, L.; Taeymans, J. The effect of diet or exercise on ectopic adiposity in children and adolescents with obesity: a systematic review and meta-analysis. *Obes Rev* 2017, *18*, 1310-1322, doi:10.1111/obr.12577.
- 8. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009, 151, W65-94, doi:10.7326/0003-4819-151-4-200908180-00136.
- 9. Higgins, J.P.; Altman, D.G.; Gotzsche, P.C.; Juni, P.; Moher, D.; Oxman, A.D.; Savovic, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A., et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011, *343*, d5928, doi:10.1136/bmj.d5928.
- 10. Larson-Meyer, D.E.; Heilbronn, L.K.; Redman, L.M.; Newcomer, B.R.; Frisard, M.I.; Anton, S.; Smith, S.R.; Alfonso, A.; Ravussin, E. Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects.

- Diabetes Care 2006, 29, 1337-1344, doi:10.2337/dc05-2565.
- 11. Slentz, C.A.; Aiken, L.B.; Houmard, J.A.; Bales, C.W.; Johnson, J.L.; Tanner, C.J.; Duscha, B.D.; Kraus, W.E. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol (1985)* 2005, *99*, 1613-1618, doi:10.1152/japplphysiol.00124.2005.
- 12. Johnson, N.A.; Sachinwalla, T.; Walton, D.W.; Smith, K.; Armstrong, A.; Thompson, M.W.; George, J. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology* 2009, *50*, 1105-1112, doi:10.1002/hep.23129.
- 13. Brochu, M.; Malita, M.F.; Messier, V.; Doucet, E.; Strychar, I.; Lavoie, J.M.; Prud'homme, D.; Rabasa-Lhoret, R. Resistance training does not contribute to improving the metabolic profile after a 6-month weight loss program in overweight and obese postmenopausal women. *J Clin Endocrinol Metab* 2009, *94*, 3226-3233, doi:10.1210/jc.2008-2706.
- 14. Hunter, G.R.; Brock, D.W.; Byrne, N.M.; Chandler-Laney, P.C.; Del Corral, P.; Gower, B.A. Exercise training prevents regain of visceral fat for 1 year following weight loss. *Obesity (Silver Spring)* 2010, *18*, 690-695, doi:10.1038/oby.2009.316.
- 15. Nicklas, B.J.; Wang, X.; You, T.; Lyles, M.F.; Demons, J.; Easter, L.; Berry, M.J.; Lenchik, L.; Carr, J.J. Effect of exercise intensity on abdominal fat loss during calorie restriction in overweight and obese postmenopausal women: a randomized, controlled trial. *Am J Clin Nutr* 2009, *89*, 1043-1052, doi:10.3945/ajcn.2008.26938.
- 16. Irving, B.A.; Davis, C.K.; Brock, D.W.; Weltman, J.Y.; Swift, D.; Barrett, E.J.; Gaesser, G.A.; Weltman, A. Effect of exercise training intensity on abdominal visceral fat and body composition. *Med Sci Sports Exerc* 2008, *40*, 1863-1872, doi:10.1249/MSS.0b013e3181801d40.
- 17. Thong, F.S.; McLean, C.; Graham, T.E. Plasma leptin in female athletes: relationship with body fat, reproductive, nutritional, and endocrine factors. *J Appl Physiol (1985)* 2000, *88*, 2037-2044, doi:10.1152/jappl.2000.88.6.2037.
- 18. Ibanez, J.; Izquierdo, M.; Martinez-Labari, C.; Ortega, F.; Grijalba, A.; Forga, L.; Idoate, F.; Garcia-Unciti, M.; Fernandez-Real, J.M.; Gorostiaga, E.M. Resistance training improves cardiovascular risk factors in obese women despite a significative decrease in serum adiponectin levels.

 *Obesity (Silver Spring) 2010, 18, 535-541, doi:10.1038/oby.2009.277.
- 19. Janssen, I.; Fortier, A.; Hudson, R.; Ross, R. Effects of an energy-restrictive diet with or without exercise on abdominal fat, intermuscular fat, and metabolic risk factors in obese women. *Diabetes Care* 2002, *25*, 431-438, doi:10.2337/diacare.25.3.431.
- 20. Schmitz, K.H.; Hannan, P.J.; Stovitz, S.D.; Bryan, C.J.; Warren, M.; Jensen, M.D. Strength training and adiposity in premenopausal women: strong, healthy, and empowered study. *Am J Clin Nutr* 2007, *86*, 566-572, doi:10.1093/ajcn/86.3.566.
- 21. Park, S.K.; Park, J.H.; Kwon, Y.C.; Kim, H.S.; Yoon, M.S.; Park, H.T. The effect of combined aerobic and resistance exercise training on abdominal fat in obese middle-aged women. *J Physiol Anthropol Appl Human Sci* 2003, *22*, 129-135.
- 22. Ross, R.; Janssen, I.; Dawson, J.; Kungl, A.M.; Kuk, J.L.; Wong, S.L.; Nguyen-Duy, T.B.; Lee, S.; Kilpatrick, K.; Hudson, R. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. *Obes Res* 2004, *12*, 789-798, doi:10.1038/oby.2004.95.
- 23. Goodpaster, B.H.; Delany, J.P.; Otto, A.D.; Kuller, L.; Vockley, J.; South-Paul, J.E.; Thomas, S.B.; Brown, J.; McTigue, K.; Hames, K.C., et al. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. *JAMA* 2010, *304*, 1795-1802, doi:10.1001/jama.2010.1505.
- 24. Idoate, F.; Ibanez, J.; Gorostiaga, E.M.; Garcia-Unciti, M.; Martinez-Labari, C.; Izquierdo, M. Weight-loss diet alone or combined with resistance training induces different regional visceral fat changes in obese women. *Int J Obes (Lond)* 2011, *35*, 700-713, doi:10.1038/ijo.2010.190.
- 25. Blue, M.N.M.; Smith-Ryan, A.E.; Trexler, E.T.; Hirsch, K.R. The effects of high intensity interval training on muscle size and quality in overweight and obese adults. *J Sci Med Sport* 2018, *21*, 207-212, doi:10.1016/j.jsams.2017.06.001.
- 26. Quist, J.S.; Rosenkilde, M.; Petersen, M.B.; Gram, A.S.; Sjodin, A.; Stallknecht, B. Effects of active commuting and leisure-time exercise on fat loss in women and men with overweight and obesity: a randomized controlled trial. *Int J Obes (Lond)* 2018, *42*, 469-478,

- doi:10.1038/ijo.2017.253.
- 27. Besnier, F.; Lenclume, V.; Gerardin, P.; Fianu, A.; Martinez, J.; Naty, N.; Porcherat, S.; Boussaid, K.; Schneebeli, S.; Jarlet, E., et al. Individualized Exercise Training at Maximal Fat Oxidation Combined with Fruit and Vegetable-Rich Diet in Overweight or Obese Women: The LIPOXmax-Reunion Randomized Controlled Trial. *PLoS One* 2015, *10*, e0139246, doi:10.1371/journal.pone.0139246.
- 28. Batrakoulis, A.; Jamurtas, A.Z.; Georgakouli, K.; Draganidis, D.; Deli, C.K.; Papanikolaou, K.; Avloniti, A.; Chatzinikolaou, A.; Leontsini, D.; Tsimeas, P., et al. High intensity, circuit-type integrated neuromuscular training alters energy balance and reduces body mass and fat in obese women: A 10-month training-detraining randomized controlled trial. *PLoS One* 2018, *13*, e0202390. doi:10.1371/journal.pone.0202390.
- Park, S.M.; Kwak, Y.S.; Ji, J.G. The Effects of Combined Exercise on Health-Related Fitness, Endotoxin, and Immune Function of Postmenopausal Women with Abdominal Obesity. *J Immunol Res* 2015, *2015*, 830567, doi:10.1155/2015/830567.
- 30. Christiansen, T.; Paulsen, S.K.; Bruun, J.M.; Overgaard, K.; Ringgaard, S.; Pedersen, S.B.; Positano, V.; Richelsen, B. Comparable reduction of the visceral adipose tissue depot after a diet-induced weight loss with or without aerobic exercise in obese subjects: a 12-week randomized intervention study. *Eur J Endocrinol* 2009, *160*, 759-767, doi:10.1530/EJE-08-1009.
- 31. Zamboni, M.; Rossi, A.P.; Fantin, F.; Budui, S.L.; Zoico, E.; Zamboni, G.A.; Mazzali, G. Predictors of Ectopic Fat in Humans. *Curr Obes Rep* 2014, 3, 404-413, doi:10.1007/s13679-014-0126-7.
- 32. Pedersen, B.K.; Febbraio, M.A. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 2012, *8*, 457-465, doi:10.1038/nrendo.2012.49.
- 33. Zinker, B.A.; Mohr, T.; Kelly, P.; Namdaran, K.; Bracy, D.P.; Wasserman, D.H. Exercise-induced fall in insulin: mechanism of action at the liver and effects on muscle glucose metabolism. *Am J Physiol* 1994, *266*, E683-689, doi:10.1152/ajpendo.1994.266.5.E683.
- 34. Kramer, C.K.; Zinman, B.; Retnakaran, R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med* 2013, *159*, 758-769. doi:10.7326/0003-4819-159-11-201312030-00008.