MAYO CLINIC

ORIGINAL ARTICLE

Effect of Exercise and Pharmacological Interventions on Visceral Adiposity: A Systematic Review and Meta-analysis of Long-term Randomized Controlled Trials

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Abstract

Objective: To assess the effectiveness of exercise and pharmacotherapy interventions in reducing visceral adipose tissue (VAT).

Patients and Methods: A systematic search of Ovid MEDLINE, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov, New York Academy of Science Grey Literature Report, and OpenGrey was combined with hand searches of existing literature. A total of 2515 titles and abstracts were reviewed. Only randomized controlled trials evaluating the effectiveness of monitored exercise or pharmacological interventions in reducing VAT by using computed tomography or magnetic resonance imaging during a sustained intervention period (≥6 months) were included. Data were independently extracted by reviewers according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and assessed for quality and risk of bias. Separate analyses for each intervention were performed using random effect models, with pooled estimates of the change in VAT area (in centimeters squared) from baseline to follow-up reported as standardized mean difference (SMD; with 95% CI).

Results: A total of 3602 participants from 17 randomized controlled trials were included in the final analysis. Both exercise and pharmacological interventions were associated with significant reductions in VAT: small reduction with pharmacological interventions (SMD, −0.27; 95% CI, −0.47 to −0.07; P=.02) and more substantial reductions with exercise interventions (SMD, −0.54; 95% CI, −0.63 to −0.46; P<.001). The mean absolute VAT reduction was greater in pharmacological trials than in exercise trials. Meta-regression exhibited a linear correlation between VAT and weight loss (R^2=0.52 for exercise and R^2=0.88 for pharmacological interventions), but VAT reduction relative to weight loss differed by intervention type.

Conclusion: Exercise interventions resulted in greater reduction in VAT relative to weight loss than did pharmacological interventions. A preferential reduction in VAT may be clinically meaningful when monitoring success of interventions because weight loss alone may underestimate benefits.

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The adverse cardiometabolic effects of obesity are well described, with a growing recognition that visceral adipose tissue (VAT) is a key contributor to the pathogenesis of the metabolic syndrome.[1] Accumulation of VAT is also associated with an increased risk of cardiovascular disease,[2] type 2 diabetes,[3] and cancer.[4]

Interventions aimed at achieving weight loss include lifestyle modification (diet and exercise), pharmacological therapies, and bariatric surgery. Reductions in body weight in general, and in VAT in particular, have the potential to substantially reduce the risk of cardiometabolic disease. For example, exercise has been suggested to produce

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selective reduction in VAT, even in the absence of overall body weight loss[5,6]; however, studies are of modest size and significant heterogeneity and therefore have limited generalizability across interventions. Furthermore, currently there are no published guidelines on recommended therapeutic approaches to reduce VAT because large-scale, sustained duration randomized controlled intervention trials are lacking.

In this study, we conducted a systematic review and meta-analysis of randomized controlled trials to assess the relative effectiveness of sustained (≥6 months) exercise and pharmacological interventions in VAT reduction in adults. We hypothesized that monitored exercise interventions would result in a greater and more consistent reduction in VAT relative to overall weight loss when compared with pharmacological therapies, given previous reports that short-term aerobic exercise[7] and high-intensity interval training[8] reduce VAT even in the absence of a hypocaloric diet or body mass index (BMI, calculated as the weight in kilograms divided by the height in meters squared) change.

PATIENTS AND METHODS

Data Sources and Search Strategy

A comprehensive computerized search of Ovid MEDLINE, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov, New York Academy of Science Grey Literature Report, and OpenGrey was conducted for human studies in adults older than 18 years published in English from the date of inception to September 30, 2015 with the expertise of a medical librarian. This was supplemented by hand searching additional relevant articles identified through March 31, 2016 and review of reference lists of the selected articles. The online searches contained 1 or more subject headings or keywords for visceral adiposity (eg, *visceral fat*) and desired interventions (eg, *exercise*). The initial search included surgical and dietary interventions for weight loss, though these were later excluded from the analysis because of lack of sufficient trial data (surgery) or excessive trial heterogeneity (diet). Efforts were made to contact relevant authors to acquire missing information. The search strategy, study selection, and analysis were performed in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for systematic reviews.[9] The systematic review protocol and search strategy (Registration No. 91187) is publicly available in https://s3-us-west-2.amazonaws.com/utsw-patientcare-web-production/documents/Systematic_Review_Protocol_-_PROSPERO-sm.pdf.

Study Selection

Studies included in this analysis were required to have (1) a randomized, placebo-controlled trial design; (2) VAT area (in centimeters squared) as an outcome, directly measured by computed tomography or magnetic resonance imaging; (3) sustained intervention for at least 6 months (because shorter-term interventions, especially ≤3 months, may not reflect routine clinical practice); (4) monitored exercise interventions (for exercise studies); and (5) current US Food and Drug Administration (FDA)—approved or previously considered weight loss agents or agents commonly used for the treatment of weight loss or components of the metabolic syndrome including those used in the treatment of diabetes and cardiovascular disease (for pharmacological studies). Studies of specific comorbid conditions associated with weight gain, such as polycystic ovarian syndrome and growth hormone deficiency, were excluded because these results were not believed to be generalizable to the general population. Studies with an active control arm (interventions that are not placebo-controlled) and studies that measured VAT in variables other than area (eg, volume) were excluded to maintain homogeneity and interpretability between studies. Titles and abstracts were independently screened by 2 authors (S.R. and B.P.) for potential inclusion.

Data Extraction and Quality Assessment

For each study, data were extracted for baseline characteristics of the study population,

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including mean age, sex, weight (in kilograms), BMI (in kilograms per meters squared), race/ethnicity, waist circumference (in centimeters), and the prevalence of comorbid diabetes. Study methodology including duration and modality of intervention with associated measures of variance was also extracted. For studies not reporting outcomes as a mean difference between baseline and end point measurements, outcomes were calculated using reported baseline and end point data. Quality of the included studies was evaluated for risk of bias quantitatively by using the Jadad scale[10] and qualitatively by using the Cochrane risk of bias assessment tool.[11-13] Studies were given positive indicators in the Cochrane tool for randomized controlled study design and for providing clear descriptions of blinding processes and allocation concealment. Studies were awarded positive indicators for reporting of loss to follow-up and for providing available data on those not included in end point analysis. The Jadad score rated studies on the presence of 5 characteristics: (1) randomization, (2) appropriateness of randomization scheme, (3) double-blind design, (4) appropriateness of blinding scheme, and (5) description of dropouts and withdrawals.

Outcomes

The primary end point was change in VAT area (in centimeters squared), measured as the SMD change between the intervention and control groups, from baseline to follow-up. Secondary end points included change in weight, change in BMI, and change in subcutaneous adipose tissue (SAT) area (in centimeters squared). Outcomes were based on the longest follow-up period available for each study.

Data Syntheses and Statistical Analyses

Individual patient-level data were not available for the studies in this analysis; thus, tabular data were used. The results of the quantitative meta-analysis of the outcomes of VAT change from baseline to follow-up were summarized as standardized mean difference (SMD) with 95% CI at last follow-up between the intervention and control groups. The SMD was used instead of weighted mean difference, given the inclusion of both computed tomography and magnetic resonance imaging methods, to account for potential variation in scale between these 2 modalities. Groups were compared using random effect models, given considerable heterogeneity in study populations and execution of interventions among the included studies. The pooled SDs for the net change in all outcomes were obtained or imputed (when not available) assuming a correlation coefficient of 0.90 between baseline and final measurements. For studies comparing different exercise protocols or multiple weight loss agents, each intervention was assessed independently against the control.

Analyses of each intervention were also stratified by exercise regimen and sex. Sensitivity analyses were performed, with each study sequentially removed on the basis of the study's performance on qualitative and quantitative quality assessment and sample size. Heterogeneity was assessed among studies using the I^2 statistic within each study group and within subgroups. I^2 values of less than 25% and 50% or greater were considered to be minimal and substantial, respectively. Funnel plots were developed and examined to identify publication bias, and the Egger test was performed to assess relationships between effect size and sample size.[14]

All P values were 2-sided, with statistical significance specified at $P<.05$. A meta-analysis of the outcomes was conducted using metan and metareg functions available in Stata version 12.1 (StataCorp LP).[15] The risk of bias analysis was performed using the Cochrane Collaboration's assessment tool in RevMan version 5.2.[11] This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16,17]

Role of the Funding Source

This study was funded by the National Institutes of Health (grant no. K23 DK106520).

The funder had no role in the study's design, conduct, or reporting.

RESULTS

From the 2515 titles screened for inclusion, 80 were assessed by full-text review and 17 were included in the final meta-analysis[18-36] (Figure 1). In addition, 2 pharmacological studies that met all inclusion criteria except borderline follow-up time (~5 months) were included in sensitivity analyses only. The study group consisted of 12 exercise trials contributing 2094 individuals as well as 6 pharmacological trials contributing 1508 individuals (Table). The mean follow-up time was 9±2.9 months for exercise interventions and 8±2.1 months for pharmacological interventions. Most exercise trials were performed in the United States and Canada, while pharmacological trials included 3 from the United States or Canada, 4 multinational cohorts, 1 Swedish trial, and 1 Japanese trial.

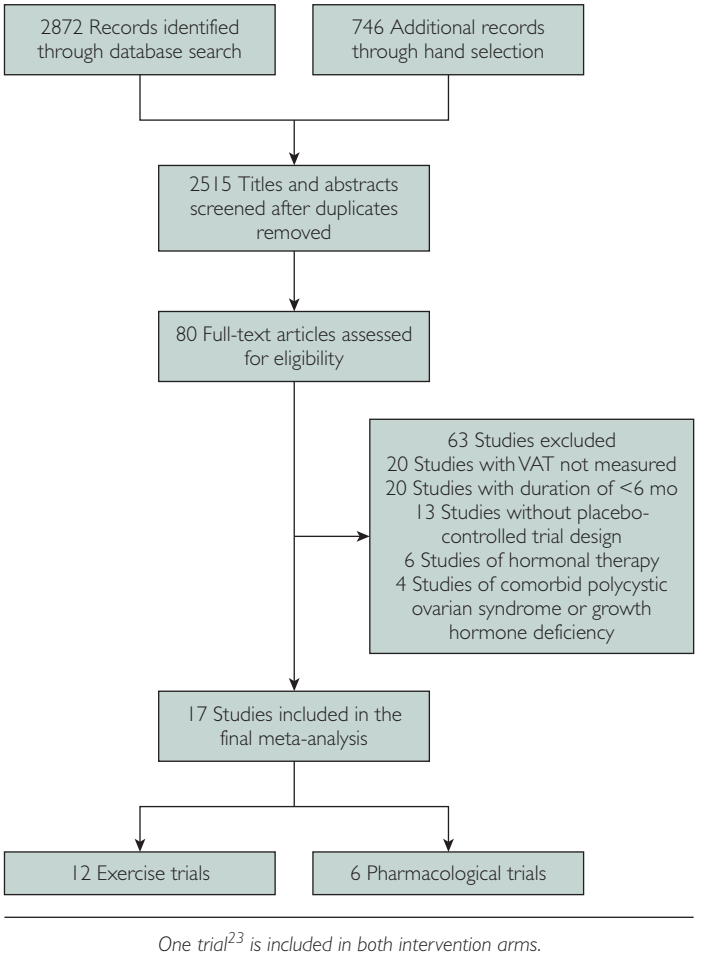

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram describing the process of study identification and selection. VAT = visceral adipose tissue.

Participants enrolled in exercise cohorts were predominantly women (65.1%) with a mean age of 54±7.3 years and a mean BMI at enrollment of 31±5.4 kg/m^2. Patients with diabetes were excluded from all but 2 exercise trials,[20,27] which included only patients with diabetes. The mean dropout rate in exercise trials was 17.9%. Pharmacological trials included studies of rimonabant, gemfibrozil, metformin, rosuvastatin, orlistat, and ezetimibe. Additional studies of liraglutide and empagliflozin were included in sensitivity analyses. Participants in pharmacological trials were also predominantly women (52.7%) with a mean age of 51±11.0 years and a mean BMI at enrollment of 34±5.6 kg/m^2. Dropout rates were lower at 12%. Similar to exercise trials, patients with diabetes were excluded from most trials but were included in trials of orlistat[33] and rimonabant.[31]

Quality Assessment

Among all trials, 8 exercise trials and 4 pharmacological trials received a "high-"quality Jadad score, corresponding to a Jadad score of 3 or more. Quality assessment using the Cochrane tool is presented in Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org). Low scores corresponded to studies that failed to describe attrition bias or provide information on the effect of loss to follow-up on subsequent analysis. Publication bias was assessed visually using a funnel plot and the Egger test for bias (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). The summary estimate of the included studies is represented by the solid vertical line, with smaller studies represented by open circles gathered at the base of the plot and larger studies at the peak. The symmetry of the funnel plot and a nonsignificant

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TABLE. Characteristics of Interventions and Populations at Baseline in Included Randomized Controlled Trials[a,b]

	Study characteristic						Intervention arm baseline data			Quality assessment		
Reference, year	Treatment	Control	N	Setting	Follow-up time (mo)	Men	Mean age (y)	Baseline BMI (kg/m^2)	Diabetes	Jadad score	Dropout rate (%)[c]	Quality range
Barone et al,[18] 2009	Exercise	Placebo	104	United States	6	51 (49.0)	64.6±5.7	29.4±3.8	Excluded	−1	10	Low
Brochu et al,[19] 2009	Exercise with caloric restriction	Caloric restriction	107	Canada	6	0 (0)	57.2±5	32.6±4.9	Excluded	4	22	High
Dobrosielski et al,[20] 2012	Exercise	Placebo	140	Baltimore, USA	6	81 (58.0)	57±6	33.0±0.6	Included (100%)	4	19	High
Donnelly et al,[21] 2003	Exercise	Placebo	74	Nebraska and Kansas, USA	16	31 (41.3)	W: 24±5 M: 22±4	W: 28.7±3.2 M: 29.7±2.9	Excluded	4	44	High
Friedenreich et al,[22] 2011	Exercise	Placebo	320	2 centers in Alberta, Canada	12	0 (0)	61.2±5.4	29.1±4.5	Excluded	4	2.8	High
Fujimoto et al,[23] 2007	Exercise	Placebo	497	Diabetes prevention program: 27 centers in the United States	12	163 (32.8)	W: 51.2±10.4 M: 57.3±10.9	W: 33.2±5.3 M: 31.8±4.7	Excluded	1	2.4	Low
Hunter et al,[24] 2010	Aerobic exercise Resistance exercise	Placebo	69[d]	Alabama, USA	12	0 (0)	34.7±8.4 34.1±7.2	23.5±1 23.9±1	Excluded	1	Not reported	Low
McTiernan et al,[25] 2007	Exercise	Placebo	202	Gastroenterology practices: United States	12	102 (69.4)	W: 54.4±7.1 M: 56.6±7.6	W: 28.5±4.8 M: 30.1±4.8	Excluded	3	7[e]	High
Poehlman et al,[26] 2000	Endurance exercise Resistance exercise	Placebo	51	Vermont, USA	6	0 (0)	29±5 28±3	22±2 22±2	Excluded	4	36	High
Sigal et al,[27] 2007	Combined exercise Aerobic exercise Resistance exercise	Placebo	251	8 community-based facilities in Ottawa, Canada	6	160 (63.7)	53.5±7.3 53.9±6.6 54.7±7.5	35.0±9.6 35.6±10.1 34.1±9.6	Included (100%)	4	12	High
Slentz et al,[28] 2005	Low/moderate exercise Low/vigorous exercise High/vigorous exercise	Placebo	175	North Carolina, USA	8	91 (52.0)	54±5.4 53±7 51.5±5.3	29.8±3.2 29.7±3.1 29.1±2.4	Excluded	3	32	High
Stewart et al,[29] 2005	Exercise	Placebo	104	Baltimore, Maryland, USA	6	51 (49.0)	W: 64.3±5.8 M: 61.7±4.5	W: 29.1±4.4 M: 29.7±3	Excluded	2	10	Low
Astrup et al,[30] 2012[f,g]	Liraglutide: 1.2 mg Liraglutide: 1.8 mg Liraglutide: 2.4 mg Liraglutide: 3.0 mg Orlistat	Placebo	84	19 research sites in 8 European countries	5	156 (28.0)	47.2±9.7 45.5±10.9 45.0±11.1 45.9±10.7 45.9±9.1	34.8±2.6 35.0±2.6 35.0±2.8 34.8±2.8 34.1±2.6	Excluded	4	30	High

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TABLE. Continued

Reference, year	Study characteristic						Intervention arm baseline data			Quality assessment		
	Treatment	Control	N	Setting	Follow-up time (mo)	Men	Mean age (y)	Baseline BMI (kg/m^2)	Diabetes	Jadad score	Dropout rate (%)[c]	Quality range
Després et al,[31] 2009	Rimonabant	Placebo	799	53 centers in 14 countries	12	370 (46.3)	49.9±12.3	36.3±6.4	Included	3	20	High
Dumont et al,[32] 2001	Gemfibrozil	Placebo	64	Quebec, Canada	6	64 (100.0)	46±6	31.6±2.7	Excluded	−1	Not reported	Low
Fujimoto et al,[23] 2007	Metformin	Placebo	474	Diabetes prevention program: 27 centers in the United States	12	176 (34.9)	W: 51.3±9.2 M: 52.6±11.0	W: 32.9±5.6 M: 31.7±4.4	Excluded	0	2	Low
Jansson et al,[36] 2011[h]	Rosuvastatin	Placebo	54	Gothenburg, Sweden	6	54 (100)	54±5.2	Not reported	Excluded	3	7	Low
Kelley et al,[33] 2004	Orlistat	Placebo	39	Pittsburgh, Pennsylvania, USA	6	13 (33.3)	50.3±1.9	34.0±1.0	Included (100%)	3	25	High
Ridderstrale et al,[34] 2014[g]	Empagliflozin and metformin	Glimepiride and metformin	91	173 sites in 23 countries	26	40 (44.0)	57.6±8.6	31.5±4.6	Included (100%)	4	16[i]	High
Takase et al,[35] 2012	Ezetimibe	Placebo	78	Hamamatsu, Japan	6	50 (64.1)	63.8±11.4	27.8±2.3	Included	2	0	Low

[a]BMI = body mass index; M = men; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; W = women.
[b]Data are presented as mean ± SD or as No. (percentage) unless otherwise indicated.
[c]Reported for the entire study population.
[d]Not the entire sample: excludes nonadherers.
[e]For the intervention group only, dropout rates in controls not reported.
[f]All data except VAT and SAT data are for the entire sample of participants for which n was 95, 90, 93, 93, 95, 98, respectively. VAT and SAT were measured in a subset of patients for whom n is presented in this table.
[g]Included in sensitivity analyses only.
[h]Unpublished data, available through ClinicalTrials.gov.
[i]Dropout rate for the entire study, not reported for the VAT substudy.

P value in the Egger test together suggest that there was no significant publication bias (*P*=.32).

Primary Outcome: VAT Reduction

In pooled analyses, exercise intervention was associated with a medium reduction in VAT (SMD, −0.54; 95% CI, −0.63 to −0.46) compared with a small reduction seen with pharmacological interventions (SMD, −0.27; 95% CI, −0.47 to −0.07) (Figure 2A). Both results reached statistical significance. Although exercise interventions more effectively reduced VAT as compared to controls, the mean absolute VAT reduction was greater in pharmacological trials, which produced a VAT reduction of 23.9±37.8 cm^2 as compared with a reduction of 15.3±40.4 cm^2 with exercise. This discrepancy can be attributed to greater VAT reductions seen in control groups in pharmacological trials. Among exercise trials, aerobic regimens reduced VAT the most, producing an absolute reduction of 16.4±37.8 cm^2, followed by combined aerobic/resistance regimens (14.0±23.6 cm^2) and resistance-only regimens (12.2±46.5 cm^2) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Among pharmacological trials, the greatest reduction in VAT was seen in the cohort given orlistat 120 mg thrice daily, with a mean absolute VAT reduction of 67 cm^2, followed by rimonabant and gemfibrozil. Consistent reductions in VAT were found with both liraglutide and the combination of empagliflozin and metformin (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). We found substantial heterogeneity among studies for both exercise (I^2=73%) and pharmacological (I^2=62%) interventions. Given that loss of VAT in response to diet, exercise, or pharmacotherapy is correlated with baseline VAT (more likely to have greater VAT loss with higher baseline VAT) and that baseline VAT is related to sex (higher in men than in women), we evaluated the effects of the interventions stratified by sex and found similar effects of exercise and pharmacological interventions on VAT loss in both sexes. Given the small number of patients with diabetes included in the studies, we were unable to evaluate any differential effects of exercise or medications on VAT loss between those with and without diabetes.

Secondary Outcomes: Weight, BMI, and SAT Reduction

Both exercise and pharmacological interventions resulted in a medium and statistically significant reduction in weight (SMD, −0.66, 95% CI, −0.92 to −0.40 for exercise interventions and SMD, −0.56; 95% CI, −0.66 to −0.45 for pharmacological interventions) (Figure 2B). Meta-regression exhibited a linear correlation between change in weight and change in VAT for both exercise and pharmacological interventions (R^2=0.52 for exercise and R^2=0.88 for pharmacological interventions). However, the reduction in VAT relative to weight loss for each intervention type differed (on the basis of the slope of the best fit regression line), with greater VAT loss relative to weight at smaller achieved weight reductions with pharmacological interventions in contrast to greater VAT loss relative to weight at greater achieved weight reductions with exercise interventions (Figure 3A). For example, using meta-regression, for an approximately 7 kg reduction in weight with exercise, the expected VAT reduction would be 0.5 cm^2 as compared with the same VAT reduction achieved with only approximately 2 kg of weight loss with pharmacological therapy (Figure 3B). In contrast, to achieve −3 cm^2 reduction in VAT with medication, approximately 18 kg of weight loss would be required as compared with only approximately 14 kg of weight loss with exercise. Body mass index and SAT exhibited modest reductions with exercise interventions (SMD, −0.61; 95% CI, −0.70 to −0.53 and SMD, −0.61; 95% CI, −0.69 to −0.52, respectively) and small effects with pharmacological studies in pooled analyses (SMD, −0.34; 95% CI, −0.44 to −0.24 and SMD, −0.34, 95% CI, −0.54 to −0.14, respectively) (Supplemental Figure 3, available online at http://www.

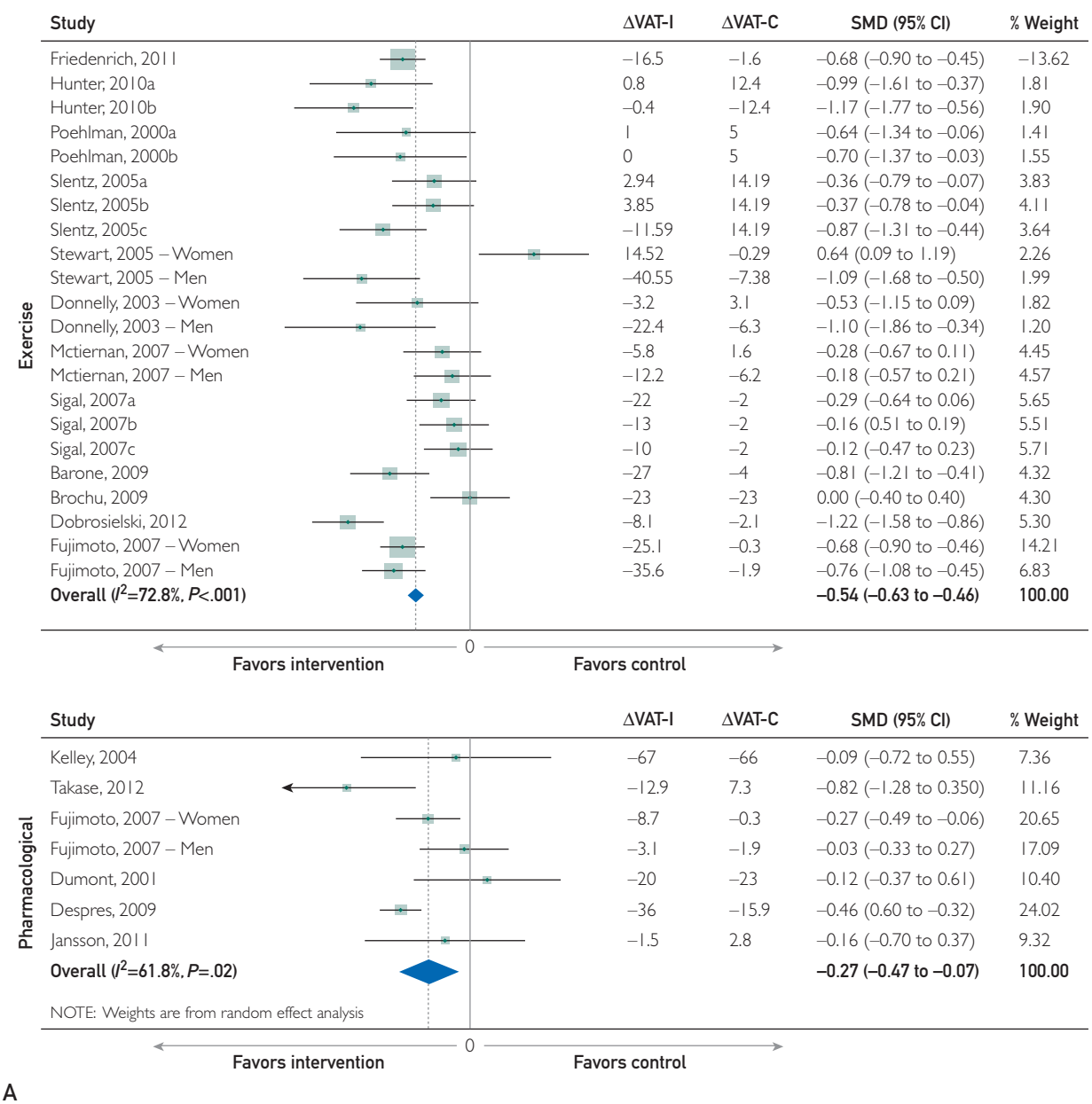

FIGURE 2. Pooled (A) changes in visceral adiposity and (B) changes in weight by intervention type. VAT change is measured in centimeters squared and weight change in kilograms. % Weight refers to the individual contribution of each study to the overall pooled estimate. SMD = standardized mean difference; VAT = visceral adipose tissue; -I = intervention group; -C = control group.

mayoclinicproceedings.org), and they were correlated with reductions in VAT.

DISCUSSION

Accumulation of visceral fat has been linked to the development of the metabolic syndrome and has been hypothesized to be the driver of an unfavorable metabolic profile in obesity.[37-40] Both lifestyle and pharmacological interventions have the potential to reduce VAT to improve cardiometabolic outcomes. We report that in overweight and obese adults, both long-term, sustained monitored exercise and pharmacological

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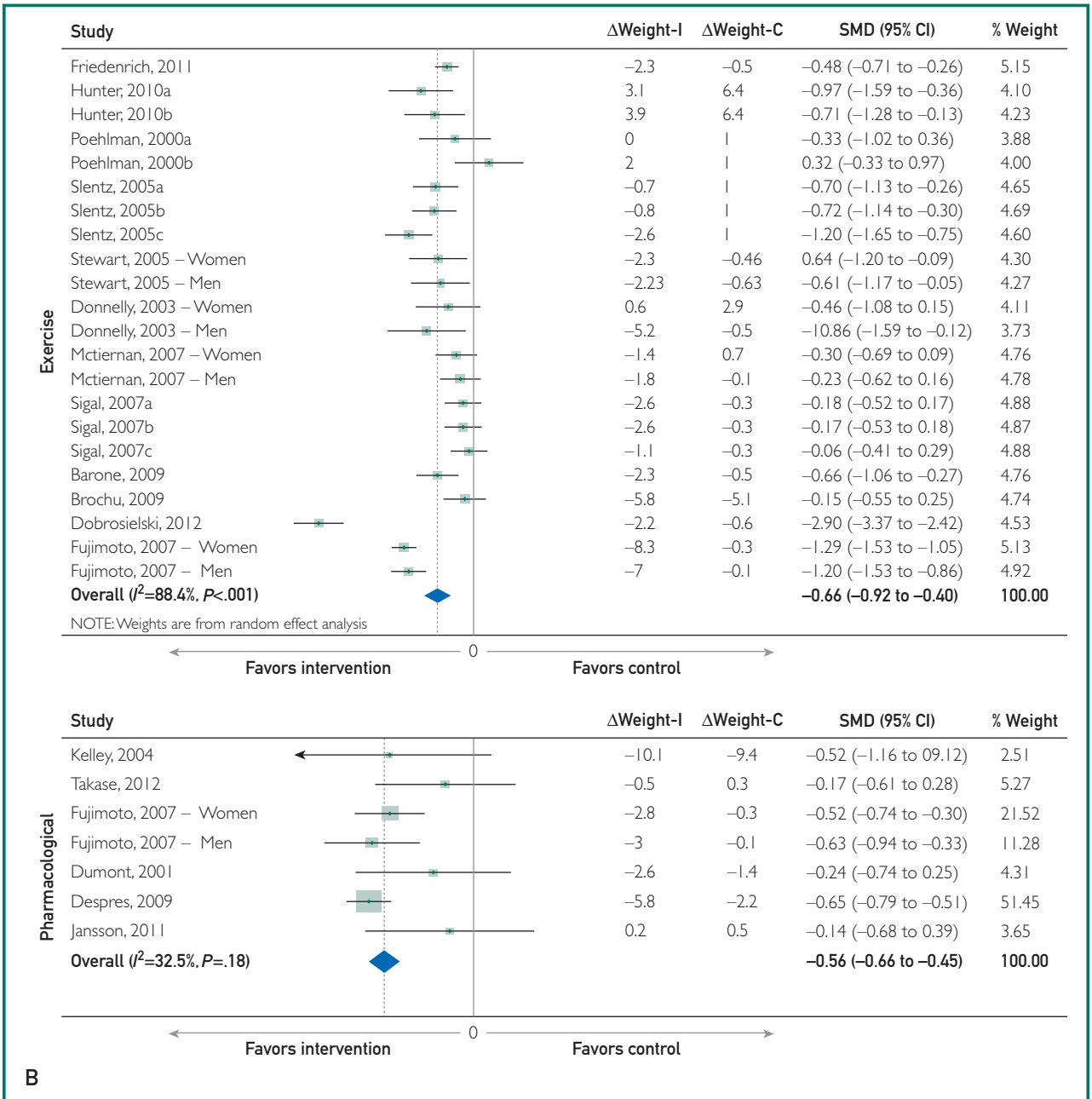

FIGURE 2. (*continued*).

interventions reduce VAT, as well as SAT, weight, and BMI. Although neither intervention preferentially targeted VAT over SAT, exercise interventions produced a modest and sustained reduction and appeared to reduce VAT more than pharmacological regimens relative to controls. Moreover, the degree of VAT reduction relative to weight loss differed by intervention type, suggesting that monitoring success in exercise and pharmacological interventions using weight loss alone may underestimate benefits. Indeed, emerging evidence supports the notion that a lifestyle modification program characterized by an increase in physical activity and a balanced diet can reduce the

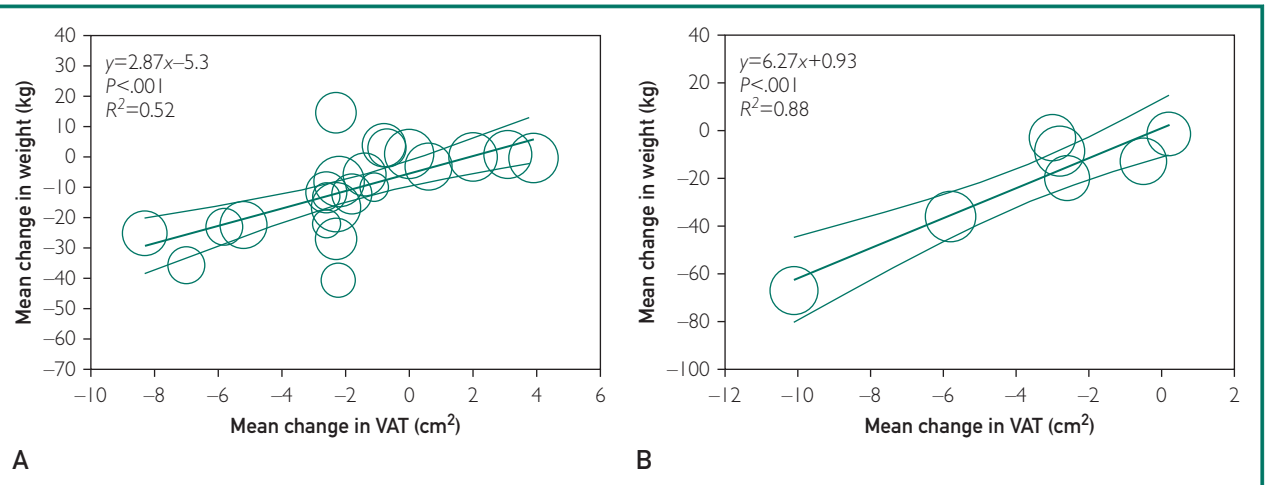

FIGURE 3. Relationship between weight loss and visceral adipose tissue (VAT) reduction in (A) exercise trials and (B) pharmacological trials. Data represent the mean change (95% CI) in weight by VAT reduction in a random effect model.

risk of obesity-related comorbid conditions despite minimal or no weight loss. The benefits of such an approach may include reductions in visceral fat and cardiometabolic risk factors and increases in both skeletal muscle mass and cardiorespiratory fitness.[5,41] Differences in VAT loss relative to changes in weight between intervention types may reflect concomitant loss of lean mass in pharmacological trials not present in exercise interventions that can maintain or increase lean mass. Overall, these findings suggest that both exercise and pharmacological therapies effectively affect VAT reduction compared with placebo, while also resulting in modest reductions in both SAT and weight.

Previous studies have assessed the effect of exercise interventions on weight and body fat distribution.[7,42-50] However, many previous studies comparing different modalities for weight and VAT reduction have not examined these outcomes with long-term follow-up, randomized controlled study design, or assessment of other adipose depots. Our study addresses many of these limitations in the literature and confirms findings of the meta-analyses by Ismail et al[44] and Vissers et al[7] that exercise alone can produce reductions in VAT in overweight and obese individuals and provides further evidence to support the role of aerobic exercise and combined aerobic and resistance regimens in VAT reduction. Aerobic exercise in particular may improve cardiorespiratory fitness and multiple metabolic biomarkers. Furthermore, although it is evident from our study and others that aerobic exercise compared with resistance training results in greater VAT reduction, alternative exercise variables such as the volume (ie, amount of exercise per unit time) and intensity (ie, aerobic level of a given exercise type during training) of an exercise program may also affect VAT.[51] Our study also goes beyond the findings of those previous studies in reporting reductions in SAT as well as VAT and in correlating changes in these adipose depots with overall weight loss. These findings suggest that specific markers of VAT loss are likely important when monitoring the success of weight loss interventions. Initiatives designed to better assess lifestyle and pharmacological interventions for weight loss using direct imaging-based assessments of VAT or alternative surrogate markers such as hypertriglyceridemic waist,[52] rather than weight or BMI in isolation, are likely to report that preferential VAT loss beyond BMI is clinically meaningful.

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To our knowledge, this study is the first systematic review and meta-analysis of sustained pharmacological and exercise interventions on changes in VAT and weight. Two previous meta-analyses have aimed to assess different modalities for reduction in VAT.[42,45] Our study differs in 2 key aspects: (1) we limited our inclusion to randomized controlled trials only and (2) we assessed studies with a follow-up time of 6 months or more to test our hypothesis for sustained weight loss. A more recent analysis by Merlotti et al[45] extends these findings to surgical interventions as well and supports our finding that reductions in VAT are correlated with reductions in SAT regardless of intervention type. That analysis is also limited by inclusion of nonrandomized data as well as studies with relatively short follow-up.

Previous studies have proposed mechanisms for the modulation of visceral adiposity and its effect on cardiovascular risk. Early hypotheses associated excess VAT with cardiovascular risk by means of impaired liver metabolism, which in turn contributes to impaired glucose tolerance and hypertriglyceridemia. However, more recent studies suggest that an overactive hypothalamic-pituitary-adrenal axis may be the primary driver of an unfavorable cardiometabolic profile resulting in increased VAT and cardiovascular disease risk.[53] Accumulation of VAT is believed to result in increased circulating blood volume and systemic proatherogenic inflammatory factors and adipokines, which together translate to an increased risk of developing heart failure and atherosclerotic cardiac disease.[54]

Our finding that absolute VAT reduction was greater in pharmacological trials than in exercise studies may potentially be attributed to greater VAT reductions seen in control groups in pharmacological trials. Pharmacological trials uniformly include caloric restriction protocols/counseling in both the experimental and control arms because medications are considered for approval as adjunctive therapies to diet. The presence of caloric restriction leading to greater VAT reduction in both arms of pharmacological studies may therefore underlie this finding. The mechanisms of action of the pharmacological agents included in this study vary substantially and are summarized in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org). Although rimonabant, a cannabinoid receptor (CB1) blocker, was not approved by the FDA and was suspended worldwide in the late 2000s owing to adverse effects, other agents targeting CB1 remain in the pipeline, suggesting value in continued investigation of this pathway.[55] Although orlistat and glucagon-like peptide 1 analogs including liraglutide remain the mainstays of FDA-approved weight loss therapy in the United States, there has been increased interest in the newer sodium-glucose cotransporter 2 inhibitors given their demonstrable benefits in the treatment of diabetes and cardiovascular disease. Individually, however, only rimonabant, ezetimibe (unproven weight loss mechanism, but may be related to reduction in intestinal fat absorption), and empagliflozin/metformin reached statistical significance for VAT reduction or weight loss.

Strengths and Limitations

The strengths of the present study include the inclusion of only randomized controlled trials and a large sample size with a diverse population of overweight and obese adults that allows for generalization to the general population. Furthermore, we evaluated multiple weight loss modalities over long-term follow-up, with potentially greater clinical relevance than studies of short-term interventions. Several limitations merit comment. We were able to access aggregate data only rather than patient-level data, which may influence the effect estimates. Furthermore, many randomized controlled trials of weight loss interventions do not include body fat distribution outcomes, so we were unable to assess the effect of other FDA-approved agents for weight loss on VAT reduction. In addition, many trials lacked data on the effect of weight and VAT loss on other metabolic risk factors and biomarkers and thus we cannot draw direct conclusions about improvements in cardiovascular health as a result of these interventions. Finally, as

with all meta-analyses, selection bias cannot be completely ruled out because articles were retrieved only from published trials.

Clinical Implications

In pooled analyses, exercise interventions resulted in a medium improvement in visceral adiposity, subcutaneous adiposity, and weight whereas pharmacological interventions for weight loss resulted in smaller overall effects. Importantly, change in weight was found to be an overall predictor of VAT change but may underestimate the effect on VAT reduction in exercise studies. Previous work has reported that the regional distribution of body fat is more important than excess adiposity per se in driving the cardiovascular disease risk associated with excess of body weight.[53] Because the relationship between reduction in visceral fat and weight is variable, body weight in isolation may be an inadequate clinical marker and prognostic indicator of cardiovascular risk in obesity. Our findings support the use of more specific markers of VAT when monitoring the success of weight loss interventions. In addition, future studies of weight loss interventions should embed assessments of body fat distribution, such as VAT, to determine clinical benefits. Interventions that result in substantial VAT loss with less effect on overall weight may still be clinically meaningful.

More information is needed on the effects of newer agents for cardiometabolic disease, such as sodium-glucose cotransporter 2 inhibitors, in modulating visceral fat, as they are likely to play an increasingly important role in the management of complications of obesity, such as type 2 diabetes. Although the present findings support the use of exercise over pharmacotherapy in achieving weight loss and VAT reductions, the potential synergistic effects of both therapies combined compared with either therapy alone could not be determined in our study and will require further investigation.

CONCLUSION

Exercise interventions resulted in greater reduction in VAT relative to weight loss than did pharmacological interventions. A preferential reduction in VAT may be clinically meaningful and is important when monitoring success of interventions because weight loss alone may underestimate benefits. The reduction in VAT seen with both pharmacotherapy and exercise, in addition to empirical improvements in VAT with a calorie-restricted diet, suggests a role for a multimodality approach to the treatment of overweight/obesity using a combination of strategies to help guide therapy and lower cardiovascular risk.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **FDA** = US Food and Drug Administration; **SAT** = subcutaneous adipose tissue; **SMD** = standardized mean difference; **VAT** = visceral adipose tissue

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