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Obesity Comorbidity/Pathophysiology

Comparison of reducing epicardial fat by exercise, diet or bariatric surgery weight loss strategies: a systematic review and meta-analysis

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Summary

The objectives were to determine whether epicardial fat (EAT) is subject to modification, and whether various strategies accomplish this end point and the relationship between weight loss and EAT. A systematic review of the literature following meta-analysis guidelines was conducted using the search strategy 'epicardial fat' OR 'epicardial adipose tissue' AND 'diet' OR 'exercise' OR 'bariatric surgery (BS)' OR 'change in body weight' limited to humans. Eleven articles were identified with 12 intervention approaches of which eight studies showed a statistically significant reduction in EAT. A random-effects meta-analysis suggests an overall significant reduction of 1.12 standardized units (95% CI = [–1.71, –0.54], P value < 0.01). While there is a large amount of heterogeneity across study groups, a substantial amount of this variability can be accounted for by considering intervention type and change in body mass index (BMI). These variables were incorporated into a random-effects meta-regression model. Using this analysis, significant EAT reduction occurred with diet and BS but not with exercise. BMI reductions correlated significantly with EAT reductions for diet-based interventions, i.e. for some but not all interventions. In conclusion, EAT, a factor that is significantly associated with coronary artery disease, can be modified. The type of intervention, in addition to the amount of weight loss achieved, is predictive of the amount of EAT reduction.

Keywords: Bariatric surgery, diet, epicardial fat, exercise.

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Introduction

Epicardial adipose tissue (EAT) or epicardial fat is the adipose tissue depot located mainly around the epicardial coronary vessels and is also present on the myocardial surface from which it can extend into the heart to be interspersed with myocardial muscle fibres (1). Epicardial fat serves several important physiologic functions including buffering the coronary artery against the torsion induced by the arterial pulse wave and cardiac contraction, offsetting rapid changes in the width of the blood vessels with arterial pulse and allowing vessel expansion to permit coronary remodelling (1). Data indicate, however, that excess epicardial fat is associated with coronary artery atherosclerosis (2,3). A recent meta-analysis demonstrated that EAT is significantly thicker in patients with coronary artery disease (CAD) compared to those without CAD (4). The relationship of EAT to CAD has been attributed at least in part to the capacity of EAT to produce and secrete pro-atherosclerotic and pro-inflammatory hormones and cytokines as well as reactive oxygen species that may lead to the development of coronary atherosclerosis presumably by a paracrine mechanism (1,5–7).

A fundamental goal of preventive cardiology is the evaluation and implementation of successful strategies to minimize coronary atherosclerosis. Considering the link between epicardial fat and coronary atherosclerosis, the primary objective of this study was to determine whether EAT is subject to modification and the extent to which such modification is possible. The primary objective of this study was, by means of meta-analysis, to synthesize the evidence on whether EAT can be modified by means of weight loss interventions, in particular bariatric surgery, exercise and diet interventions. The secondary objective was to determine whether or not the means by which weight loss is achieved has any bearing on EAT reduction and its extent.

Methods

Literature review

A systematic review of the literature was conducted following meta-analysis guidelines and using preferred reporting system for systematic review and meta-analysis for observational studies (8,9). A systematic search was conducted until July 2014 to identify studies that examined the relationship between weight loss strategies and epicardial fat. The Medline and Embase databases were searched using the PubMed and OvidSP platforms. The full electronic search strategy used was 'epicardial fat' OR 'epicardial adipose tissue' AND 'diet' OR 'Exercise' OR 'bariatric surgery' OR 'change in body weight' limited to humans. Similar search terms were used when searching OvidSP Medline and OvidSP Embase.

Studies that met the following criteria were included (i) an original study published in a peer-review journal; (ii) measurement of epicardial fat and (iii) adults aged ≥18 years. The exclusion criteria included duplicate studies, abstracts from unpublished studies, reviews, case reports and letters. The absence of measurement of change in EAT or measurement of EAT before and after the intervention was also an exclusion criterion. No study was to be excluded on the basis of the study design. No studies were to be excluded on the basis of the nature of the study population (healthy vs. comorbid conditions). There were no exclusions on the basis of the clinical (disease) characteristics of the participants. The reason for this is mainly due to the absence of these kinds of clinical data in many of the studies. Furthermore, the criteria for the diagnosis of conditions such as diabetes mellitus are rarely provided so it is not possible to make between-study comparisons.

A predefined protocol was used in accordance with recommendations (8). From each eligible study, patient characteristics and the method of measurement of epicardial fat were systematically recorded. Patient characteristics included average age, sex, baseline body mass index (BMI) and body weight. In addition, the correlation of changes in BMI, body weight and epicardial fat was recorded. The principal summary outcome measure was the measurement of EAT before and after an intervention or over a specific time period of the study.

Statistical methods

The weighted means and standard deviations of the collected data were calculated by using the number of cases per study (N) as weights. A meta-analysis looking at change in epicardial fat (EAT) was conducted with a random-effects model using the 'metafor' package for the R statistical software environment (10). Meta-regression was performed with the same software package and utilized a mixed-effects model with modulators. Because complete information on standard deviations was reported in only three of the source publications, missing information was imputed based on the heuristic suggestions of Follman *et al.* (11). These imputations consisted of (i) substituting missing standard deviations for changes with estimates based on pre-intervention and post-intervention means and standard deviations and (ii) substituting missing correlation coefficients with estimates based on publications for which complete information was available (12,13) as well as the number of months of follow-up (i.e. observations measured across a shorter follow-up time will be more highly correlated than those measured across a lengthy period).

Because of the fact that change in epicardial fat was recorded in different scales (mm and mL), changes were standardized using change score standardization (14). As such, standardized change scores correspond approximately to the raw change observed divided by the standard deviation of the change (10). Statistical heterogeneity was assessed with the I^2 statistic and tested using Cochran's Q-test adjusted for moderators. The I^2 statistic represents the percentage of total variation across studies that is due to heterogeneity rather than chance (15).

Results

The systematic search identified 55 citations with six duplicates (Fig. 1). The abstracts from each citation were screened and 35 were removed, specifically 20 review articles, editorials or letters, as well as 15 abstracts from unpublished studies. The remaining 14 full-text articles were reviewed in full. Three studies, which did not measure change in epicardial thickness in humans, were removed so that 11 articles met the eligibility criteria. Considering all of the studies, there were 269 individuals of different ethnicity who were studied (Table 1). Because one of the studies used two different procedures (16), we considered the two components separately. Thus, there were 12 studies from 11 publications (12,13,16–24).

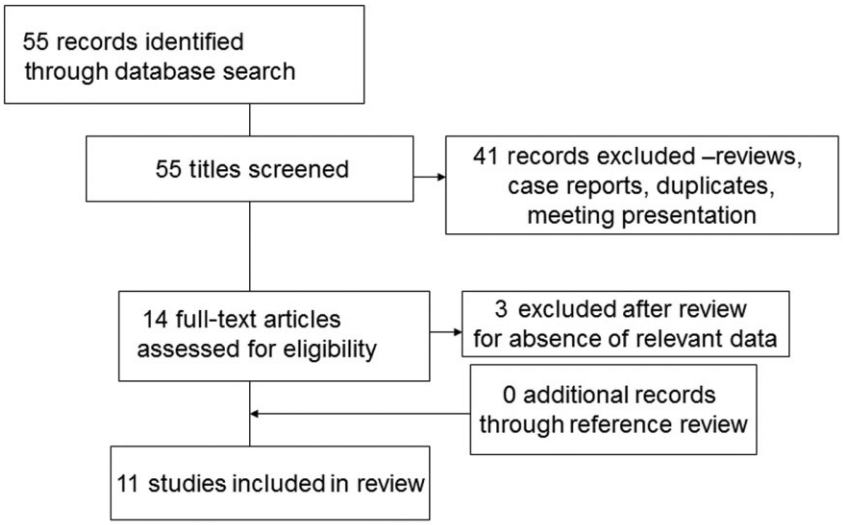

Figure 1 Flow diagram for selection of publications that were used in this analysis.

Table 1 Characteristics of the study population

Study	*N*	Intervention type	Details	Baseline BMI (kg m^{-2})	Mean change in BMI (kg m^{-2})	Change in epicardial fat
Iacobellis *et al.* 2008 (20)	20	Diet	900 kcal d^{-1} diet	44.95	–6.9	–4.00 mm
Fu *et al.* 2013 (22)	32	Diet	Combined a diet and exercise approach. 1,200 kcal d^{-1} diet. Biweekly 60-min fitness programme. Education on maintaining a healthy lifestyle.	33.6	–3.1	–0.81 mm
Kim *et al.* 2009a (21)	27	Diet	Achieved a 73% reduction in calorie consumption to an average of 1,547 kcal d^{-1} without a change in energy expenditure	30.5	–3.3	–1.23 mm
Kim *et al.* 2009b (19)	24	Exercise	Ergometer: 60 min d^{-1}, 3 days/week, gradually increasing to 60–70% of maximum heart rate by the fourth week	30.7	–1.4	–0.72 mm
Wilund *et al.* 2010 (18)	7	Exercise	Ergometer: 45 min d^{-1}, 3 days/week, moderate intensity	30.1	0.2	–0.60 mm
Jonkers *et al.* 2013 (17)	12	Exercise	6-month 'individualized training program' followed by 'a 12-day trekking expedition'	28.7	–1.4	0.00 mL
Foppa *et al.* 2013 (24)	13	Bariatric surgery	Laparoscopic adjustable gastric banding (25%) and Roux-en-Y gastric bypass (75%)	44.1	–7.0	–0.50 mm
Graziani *et al.* 2013 (13)	51	Bariatric surgery	Type of bariatric surgery not mentioned	47.9	–12.2	–3.10 mm
Kokkinos *et al.* 2013a (16)	14	Bariatric surgery	Roux-en-Y gastric bypass	47.9	–13.4	–0.23 mm
Kokkinos *et al.* 2013b (16)	23	Bariatric surgery	Sleeve gastrectomy	51.6	–13.3	–0.09 mm
Willens *et al.* 2007 (12)	23	Bariatric surgery	19 Roux-en-Y gastric bypass: two underwent laparoscopic vertical band gastroplasty and one underwent laparoscopic adjustable gastric banding	54.0	–14.0	–1.30 mm
Gaboritt *et al.* 2012 (23)	23	Bariatric surgery	19 sleeve gastrectomies: five Roux- en-Y gastric bypasses and one adjustable gastric banding (2 dropouts)	43.1	–10.8	–39 mL

Exercise

Three studies with a total of 43 subjects reported on participation in exercise programmes (17–19). One programme used a stationary ergometer for 45 min of cycling 3 days/week at a moderate intensity (18). Another with a more structured programme used a cycling ergometer, gradually increasing to 60–70% of maximum heart rate (~50% of peak VO_2) by the fourth week (19). In the third study, the exercise amounts were difficult to quantitate as

patients with diabetes mellitus received a 6-month 'individualized training program' followed by 'a 12-day trekking expedition consisted of moderate-intensity exercise (walks of approximately 4–7 hours daily), of which 4 days were spent above 3,000-m elevation' (17). Subjects participating in all three exercise programmes recorded elevated baseline BMI (average of 30 kg m^{-2}).

Diet

There were two studies that focused exclusively on weight loss following diet (20,21). A third study combined a diet and exercise approach (22). All three studies utilized a very low-calorie diet because the participants were significantly overweight (average baseline BMI of subjects 35.4 kg m^{-2}).

One study used a very low-calorie diet (900 kcal d^{-1}) (20). The second study achieved a 73% reduction in calorie consumption to an average of 1,547 kcal d^{-1} without a change in energy expenditure (21). The study that combined a diet and exercise approach consisted of a 1,200 kcal d^{-1} diet, a biweekly 60-min fitness programme and education component focused on maintaining a healthy lifestyle with diet and exercise (22). For the purposes of the meta-analysis, we will consider this intervention as diet based due to the fact that the exercise component of the programme was not nearly as intensive as in the other exercise-based interventions considered and the low-caloric diet regime resembled the other diet-based approaches.

Bariatric surgery

Five studies consisting of a total of 147 persons evaluated the change in EAT after bariatric surgery (12,13,16,23,24). As anticipated, the procedure was done in persons who were morbidly obese and the average BMI was 48.3 kg m^{-2}. The kinds of bariatric surgeries were mainly Roux-en-Y gastric bypass or sleeve gastrectomy (Table 1). One study reported their data according to the type of surgery which they concluded produced different effects on epicardial fat so the data were separately analysed from that study (16).

EAT reduction

Eight of the 12 intervention approaches resulted in a statistically significant reduction in EAT as reported in the original publication. Two studies found insufficient evidence of a reduction in EAT (17,24). One study (18) reported a statistically significant difference in the reduction in EAT for an exercise intervention ($n = 7$) compared to a control group ($n = 8$) despite the exercise group itself failing to show a statistically significant reduction.

A random-effects meta-analysis of all publications suggests an overall significant reduction of 1.12 standardized units (95% CI = [−1.71, −0.54], P value < 0.01) (Fig. 2). This analysis, while ignoring the substantial differences between studies (intervention type, baseline EAT, baseline BMI, etc.), suggests that EAT can be reduced by means of weight loss intervention. It should be noted that there was a large amount of heterogeneity across study groups, as the I^2 statistic that describes the percentage of variation across studies that is due to heterogeneity was 93%.

Relationship between weight loss and reduction in EAT

Three of the 12 studies reported the correlation observed between change in body weight and change in EAT. Additionally, one study provided patient level data that made calculating the correlation possible (20). Of these four studies, only one found a significant positive correlation ($r = 0.469$, P value < 0.01) (22). The three other studies found insufficient evidence of any correlation between the amount of weight lost post intervention and the amount of EAT reduction ($r = 0.05$, P value = 0.83 (20); $r = 0.22$, P value = 0.5 (24); $r = 0.14$, P value = 0.53 (23)).

A mixed-effects meta-regression adjusting for mean change in BMI did not account for any of the between-study heterogeneity. R^2, which represents the percentage of between-study variance explained by the covariates, was very low ($R^2 = 0\%$) and indicated that there was no significant association between mean change in BMI and mean change in EAT (P value = 0.26). This is shown in Fig. 3 where the grey diamonds represent the regression-adjusted study-level standardized mean changes and black boxes show the observed changes. Poor agreement between these suggests that change in BMI poorly predicts change in EAT.

We next sought to determine whether considering the type of intervention affected the relationship between the change in BMI and change in EAT. We found that including intervention type and interaction between intervention type and change in BMI to the random-effects meta-regression explained a substantial amount of between-study heterogeneity with $R^2 = 71\%$ (Fig. 4). This is evident by the grey boxes lining up quite well with the black boxes. The implication of this finding is that while the amount of change in BMI on its own is not necessarily indicative of the amount of change in EAT, considering the amount of change in BMI alongside the method by which this change is achieved can be predictive of the amount of change in EAT.

The meta-regression provides estimates of standardized mean changes in EAT for varying amounts of change in BMI and intervention type with 95% confidence intervals (Fig. 5). It is apparent that reductions in BMI are significantly associated with reductions in EAT for diet-based interventions: for each additional kg m^{-2} decrease in BMI

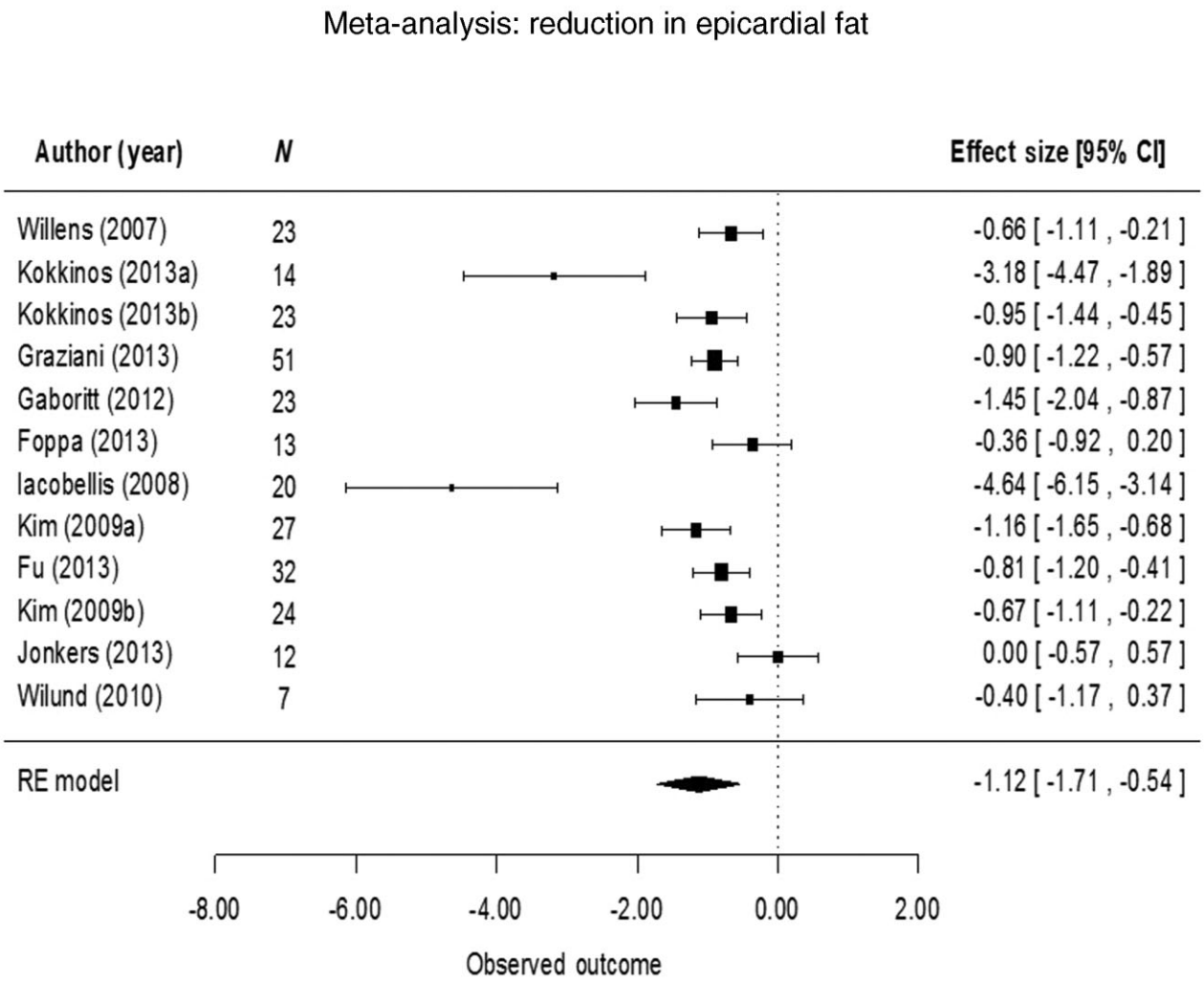

Figure 2 Mete-regression analysis for the standardized change in epicardial adipose tissue (EAT) suggests an overall significant reduction of 1.12 standardized units (($P < 0.01$).

achieved by diet, a reduction of about one standardized unit in EAT is expected (slope = 0.99, 95% CI = [0.45, 1.52]). Such a relationship between change in BMI and change in EAT is less apparent for bariatric surgery, (slope = 0.11, 95% CI = [–0.10, 0.31]). With respect to exercise, there is insufficient evidence to claim that such a relationship exists (slope = –0.03, 95% CI = [–0.99, 0.92]). It should be noted however that the three exercise interventions resulted in minimal changes in BMI (–1.4 kg m^{-2}, 0.2 kg m^{-2}). Consequently, one cannot rule out the possibility of a relationship between change in BMI and change in EAT, should more meaningful weight loss by exercise-based intervention be attained.

Discussion

To our knowledge, this is the first comprehensive structured review and meta-analysis focused on changes in EAT with intervention strategies aimed at weight loss. The absence of a single study that compares different modalities aimed at reduction of EAT underscores the necessity for and in turn the value of a comparative evaluation. The result of this evaluation, the assembly of evidence across all studies, is that a reduction in the amount of EAT is clearly feasible. This is an extremely important concept because of the significant positive relationship between the amount of EAT and the prevalence of coronary atherosclerotic disease (4). These data in turn support the contention that EAT may be a modifiable factor responsible for the increase in cardiovascular events in overweight individuals (25,26). The data in the present study suggest that not only is EAT a potentially modifiable risk factor for CAD but that EAT modification may be a target of programmes to modify CAD risk.

Weight loss following *dietary intervention* was significantly associated with reductions in EAT: the greater the

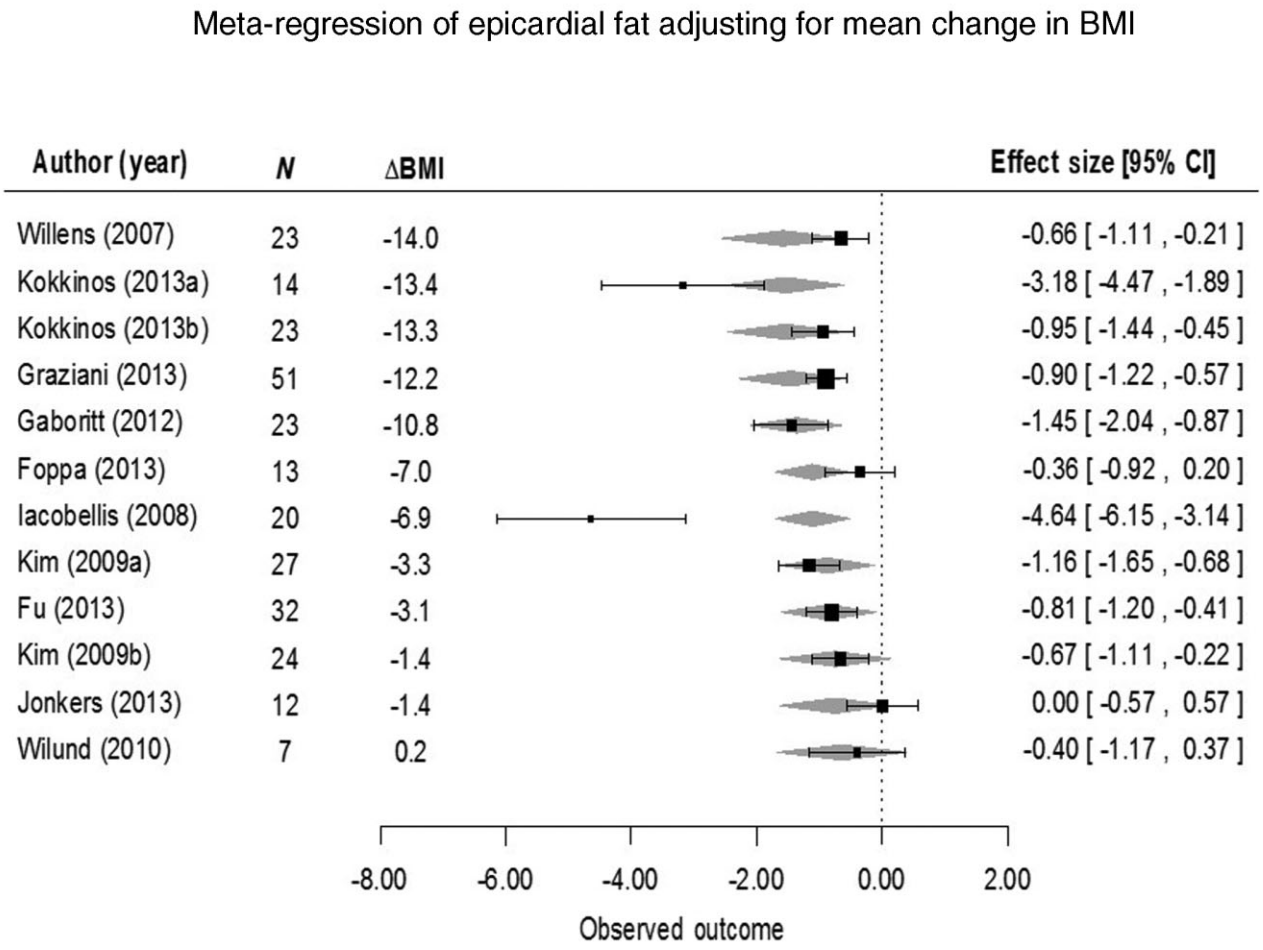

Figure 3 Meta-regression analysis for the change in body mass index (BMI) as a predictor of standardized change in epicardial adipose tissue (EAT). Overall effect is not significant ($P = 0.2$).

reduction in BMI, the greater the reduction in EAT. Furthermore, all three dietary intervention programmes significantly reduced EAT.

The ability of *exercise* to reduce EAT mass is less established: two of the three studies considered showed significant, albeit modest reductions in EAT (mean change of –0.72 mm (19), mean change of –0.60 mm (18)). The lack of a more substantial effect of exercise on EAT reduction may appear to conflict with the general consensus that exercise can reduce adiposity even while body weight is unchanged due to exercise-induced enhancement of lipolysis which has been attributed to elevated catecholamine concentrations and a small decrease in insulin concentration (27). There are distinct differences between EAT and other fat depots in their metabolism (1,28) as well as other factors (29). The effect of catecholamines to induce lipolysis is in part dependent on the adipose depot. Beta-adrenergic lipolytic sensitivity is 10–20 times greater in abdominal adipocytes from both men and women than in gluteal adipocytes (30). EAT likely does not respond in the exact same manner as other adipose depots. It is noteworthy, however, that the exercise programmes did not produce a meaningful reduction in body weight (the weighted average of change in BMI was only $-1.14\ kg\ m^{-2}$) so we can speculate that a certain amount of weight loss may be a biological requirement for a reduction in EAT.

Bariatric surgery was significantly associated with a reduction in EAT in all but one study. The issue of whether different types of bariatric surgery produce different effects on EAT reduction despite similar reductions in weight has been raised by Kokkinos *et al*., who reported that although weight loss or reduction in waist circumference was similar, there was a significant difference in terms of EAT reduction between Roux-en-Y and sleeve gastroplasty with a greater reduction in EAT with the Roux-en-Y procedure (16). The other studies considered during this analysis do not appear to support this contention. While Foppa *et al*. had most (75%) of their procedures using Roux-en-Y, their bariatric surgery study was the only one that failed to find a

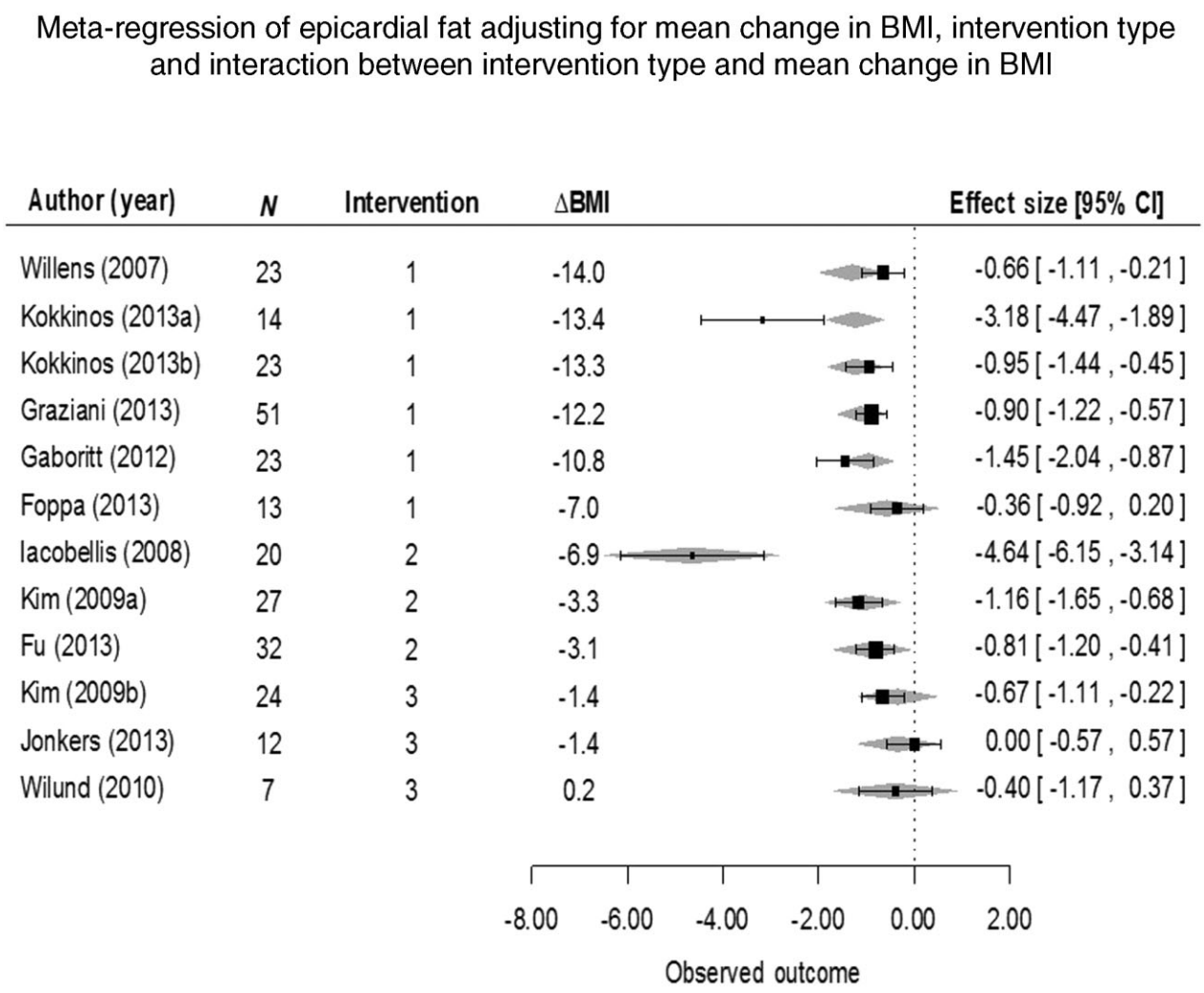

Figure 4 Meta-regression analysis of the standardized change in epicardial adipose tissue (EAT) adjusted for mean change in body mass index (BMI), the type of study intervention (bariatric surgery, diet, exercise), and the interaction of these two.

significant reduction in EAT (24). In contrast, Gaborit *et al.* 2012 had most of their procedures using sleeve gastroplasty (19 of 23) and reported a significant and substantial reduction in EAT (–39 mL, P value < 0.001) (23).

Data from *population studies* support the idea that weight loss can lead to reduction in EAT. In a free-living population without a known weight loss or exercise programme, a subset of the EISNER (Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research) registry which comprised asymptomatic healthy volunteers and patients who had coronary artery calcium scanning, EAT change was weakly correlated with weight change ($r = 0.37$, $P < 0.001$) (31). EAT decreased in the subjects with weight loss and increased progressively with weight gain (31). In multivariate analysis after adjusting for age, gender, hypercholesterolemia, family history of CAD and diabetes mellitus, the per cent change in weight or BMI was significantly associated with change in EAT over a 4-year observation period (31).

Another finding of our study was the absence of a significant overall relationship between the amount of weight loss and the amount of reduction in EAT. While the amount of weight loss is a determinant of the reduction in EAT, we contend that the means by which weight loss occurs is also an important factor. The most dramatic demonstration is the finding that while the greatest reduction in body weight occurred by means of bariatric surgery, the reductions in EAT were similar in the diet group. Such a concept supports the suggestion of Kim *et al.* that 'it is likely that different types of intervention program affect the change in the pattern of epicardial fat thickness' (19).

The absence of a correlation between change in BMI and change in EAT for bariatric surgery interventions was an unexpected result for some investigators. Gaborit *et al.*

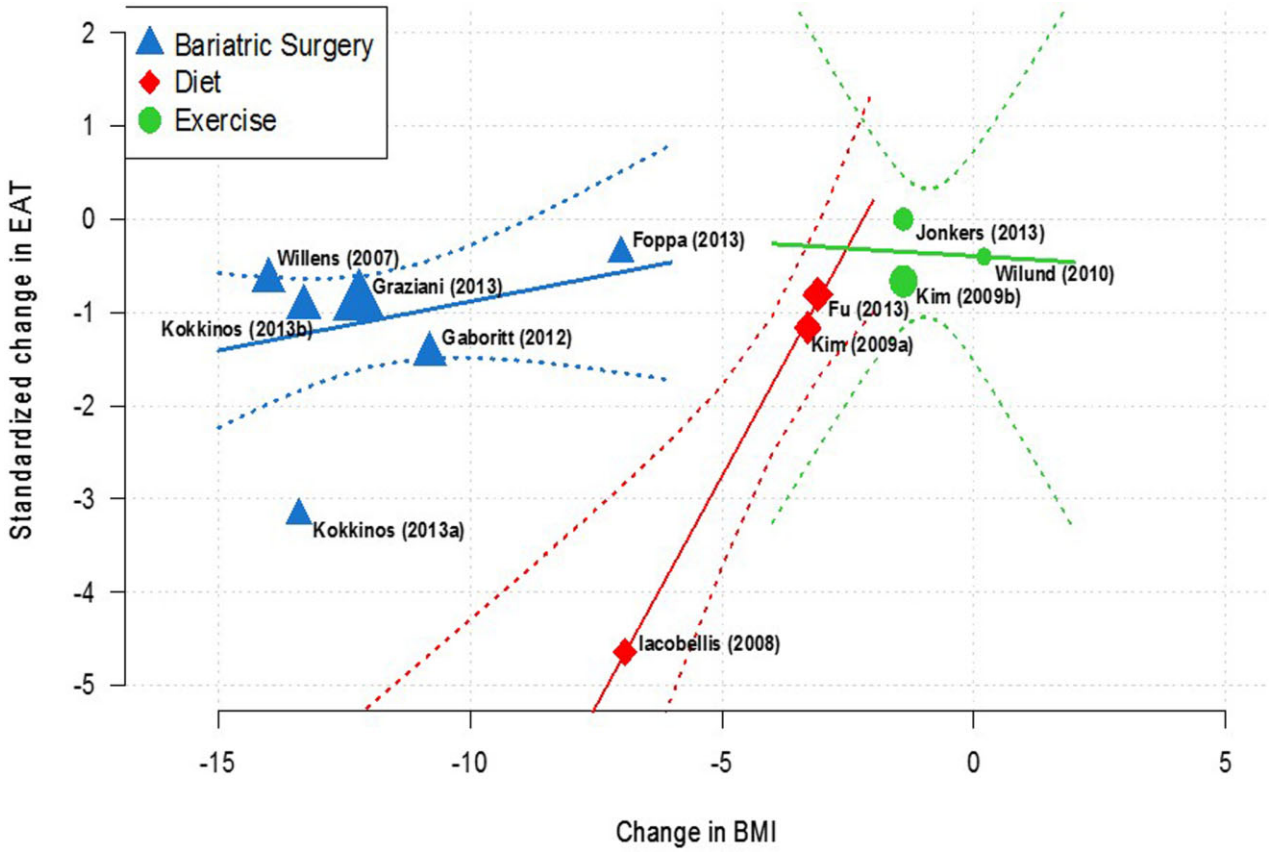

Figure 5 Regression analysis for each intervention type for the change in epicardial adipose tissue (EAT) and change in body mass index (BMI). The standard deviation is shown in the dotted lines around each relationship.

conclude: 'Unexpectedly, the percentage of E_{fat} [epicardial adipose tissue – EAT] loss was not correlated to the percentage of BMI or to subcutaneous fat loss, nor to the percentage of visceral fat loss' (23). Our data analysis confirms and extend that observation as it applies to the bariatric surgery procedure used by Gaborit *et al.* (23). Considering all studies of bariatric surgery, we found no convincing evidence of correlation between change in body weight and change in EAT. One potential explanation for this finding is that there is a limit on the possible amount of reduction in EAT. This concept is certainly consistent with the putative requirements for the physiologic functions of epicardial fat which we have previously outlined (1).

The large amount of weight loss observed in bariatric surgery would be anticipated to produce an improvement in insulin resistance and a resulting reduction in epicardial fat (31); yet this meta-analysis apparently conflicts with the assumptive relationship between weight loss from bariatric surgery with respect to insulin resistance and EAT. The relationship of generalized adiposity, increased EAT and insulin resistance is complex (32), and a simple relationship should not be expected. Second, the lipid composition of adipose tissue is also a determinant of the degree of insulin resistance (33). The bioactive lipids content in subcutaneous and epicardial fat tissues, which correlates with HOMA-IR (homeostasis model assessment-estimated insulin resistance) (33), may be different in the groups who changed their diet to lose weight or had different absorption after bariatric surgery. Another consideration, is the possibility that different genetic polymorphisms may influence the responses to changes in epicardial fat and insulin resistance in response to dietary-induced weight loss or bariatric surgery-induced weight loss (34).

Study limitations

The limitations of this meta-analysis mainly relate to the nature of the studies evaluated. The studies almost always consist of a small sample size. However, these kinds of studies in morbidly obese individuals or bariatric surgery enrol small numbers of individuals. Second, there are few studies in this field, and for most types of interventions there were only three studies. The small number of studies limits the possibility of conducting subgroup analysis. This issue is especially problematic when there is a marked discrepancy between the two studies, e.g. the largest reduction in EAT

occurred in a weight loss study (20). While some might argue that there is an insufficient sample size for a meta-analysis study, it is important to note that it has taken over 6 years to acquire the studies, and by their nature each study has a small sample size, so that it may take an unacceptably long time to acquire a large amount of additional data. Third, compilation of individual patient data across studies would have provided the opportunity for more robust meta-analyses. However, the resources, time and international cooperation required for meta-analysis of individual patient data make it less practical for most systematic reviews as in our case (35). Fourth, even the studies within the same type varied in their intervention protocols. Fifth, the largest study on change in EAT was an observational study over 4 years which cannot readily be compared to intervention studies. However, the exclusion of this study in meta-analysis did not influence the overall result. Lastly, the imaging techniques for assessment of EAT varied. The majority of the studies used echocardiography to measure EAT which permitted similar data examination. While computed tomography (CT) or magnetic resonance imaging (MRI) should provide a better assessment of the overall amount of EAT, CT or MRI measurements correlate well with the echo measurement (36). While CT provides high spatial resolution and true volume coverage of the heart, the lack of standard algorithms for data acquisition, interpretation and EAT quantification has led some investigators to recommend caution in application of CT or MRI technology to measure EAT (37). The caveats discussed above should be viewed within the context of the importance of reductions in EAT as recent data have shown that in swine fed with an atherogenic diet for 6 months, reduction in EAT mass by surgical resection decreased the progression of CAD (38).

Conclusions

This study synthesized the data on changes in EAT and demonstrates that EAT, a factor that is significantly associated with CAD, can be modified. In addition, it is likely that the type of intervention, in addition to the amount of weight loss achieved, is predictive of the amount of EAT reduction. While only a small number of studies each with a limited number of subjects were included in the meta-analysis, this represents the summary of more than 6 years of clinical research. There is a considerable need for additional research if the questions that have been discussed are to be fully addressed. With the caveat that there are no clinical trials on cardiovascular outcomes linked to changes in EAT, the analysis presented suggests further exploration of dietary-induced weight loss in obesity using EAT reduction as a target for cardiovascular prevention.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

SWR extracted the data and wrote the paper. HC analysed the data and contributed to writing the paper.

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