The effect of lifestyle interventions on excess ectopic fat deposition measured by non-invasive techniques in overweight and obese adults : a systematic review and meta-analysis

Title Page

THE EFFECT OF LIFESTYLE INTERVENTIONS ON EXCESS ECTOPIC FAT DEPOSITION MEASURED BY NON-INVASIVE TECHNIQUES IN OVERWEIGHT AND OBESE ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Ectopic fat accumulation plays an important role in the pathophysiology of insulin resistance. Therefore, reduction of ectopic fat is an important goal in people with overweight and obesity.

This systematic review and meta-analysis was conducted to summarize the current evidence for the use of non-invasive weight loss interventions (exercise or diet) on ectopic fat.

Methods: A systematic literature search was performed according to the PRISMA statement for reporting systematic reviews and meta-analyses. Clinical trials in PubMed, PEDro, and the Cochrane database were searched and scored.

Results: All 33 included studies described the effect of lifestyle interventions on ectopic fat storage in internal organs (liver, heart and pancreas) and intramyocellular lipids (IMCL), hereby including 1146, 157, 87 and 336 participants. Overall, a significant decrease of ectopic fat was found in internal organs and a trend towards decrease in IMCL. Meta-regression indicated a dose-response relationship between BMI reduction and decreased hepatic adiposity. Exercise decreased ectopic fat but the effect was greater when combined with diet.

Conclusion: Lifestyle interventions have a beneficial effect on ectopic fat accumulation in the internal organs of overweight and obese adults. The results on IMCL should be interpreted with care, keeping the 'athlete's paradox' in mind.

Introduction

In Europe, obesity has reached epidemic proportions and is considered a severe medical disorder due to its associated risk of cardiovascular diseases and premature death.[1, 2]

Guidelines for treatment of overweight and obesity outline the importance of the integration of an appropriate dietary regimen together with physical activity.[3] Weight loss interventions that succeed in decreasing body weight by 5 to 10%, can also have a significant effect on cardiovascular health.[4, 5] Nevertheless, it is recommended to 'look beyond weight loss' to evaluate the success of a weight loss program.[6-8] Despite the clear link between unhealthy Body Mass Index (BMI) and increased cardiovascular mortality[9], not every obese patient is characterized by cardiovascular risk factors.[10] BMI alone may not be suitable to predict health-oriented outcomes due to its inability to distinguish between metabolically healthy and unhealthy persons.[11, 10] Differences in regional fat distributions could possibly contribute to the heterogeneity in metabolic risk profiles across people with a comparable BMI.[12]

It is seen that subcutaneous adipose tissue (sometimes referred to as functional adipose tissue) has less harmful characteristics than internal or dysfunctional adipose tissue.[13] Ectopic fat deposition is defined as the excess of internal adipose tissue in locations not classically associated with adipose tissue storage.[14] This ectopic lipid overload in and around vital organs has destructive effects.[15, 16]

Recently, there is an increased focus on visceral adipose tissue (VAT). Visceral obesity is seen as a complex phenotype leading to ectopic fat accumulation and metabolic abnormalities.[17, 18, 13] A couple of mechanisms are involved in this process. Firstly, VAT seems to be hyperlipolytic and overexposes the liver (through the portal circulation) to nonesterified fatty acids. This results in an impairment in the liver metabolism and systemic hyperinsulinemia.[19, 20] Secondly, adipose tissue is a highly endocrine organ which contributes to the insulin resistant, proinflammatory, thrombotic and hypertensive state of visceral obesity.[21] Moreover, excess visceral adiposity may be a marker of dysfunctional subcutaneous adipose tissue. The possibility to store excess lipids in subcutaneous adipose tissue seems to have a protective role. When lipids can not be stored in the already saturated subcutaneous adipose tissue (due to its inability to expand or its dysfunctional state), lipids will be stored in VAT and other ectopic sites such as the liver, the heart or the skeletal muscles.[21] This kind of fat infiltration can be considered as an important manifestation of the metabolic syndrome.[22-26]

Little is known about the effect of conventional non-invasive weight loss programs on ectopic fat deposition. A previous meta-analysis showed that exercise even without an hypocaloric diet, has the potential to reduce VAT in overweight and obese adults.[27] However, little is known about the effect of lifestyle weight loss programs on ectopic fat deposition in internal organs and muscles. Therefore this meta-analysis systematically searched literature for lifestyle interventions (including at least diet, exercise or the combination of both) that describe the effect on adiposity of the liver, the skeletal muscles (Intra Myocellular Lipids - IMCL), the heart, the pancreas, the kidneys or blood vessels in overweight or obese adults.

Methods

This systematic review and meta-analysis was written following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[28]

Search strategies

A separate electronic search for each ectopic fat location, based on the PICO acronym, was conducted in PubMed, PEDro and the Cochrane database between January 2014 and July 2014 and updated in December 2014. Often, VAT is seen as the accumulation of all intrathoracic adipose tissue and intraabdominopelvic adipose tissue.[29] However, in numerous CT- studies the radiation dose is restricted by using single slice CT scans focusing primary on intra-abdominal fat. This implies that specific regions (e.g. fat around the heart, pancreas or kidneys) are not included. Since there is a substantial variation in the absolute amount of VAT depending on the location of the cross sectional slice taken[30-32], we wanted to be sure that all specific areas of ectopic fat deposition were searched. This was done by defining key words, depending on the specific region of ectopic fat. These keywords were combined and used in the PubMed database in the following combination: ("diabetes mellitus, type 2" OR "overweight" OR "insulin resistance" OR "metabolic Syndrome X") AND ("sports" OR "exercise therapy" OR "exercise" OR "lifestyle intervention" OR "anaerobic training" OR "diet" OR "aerobic training). Whenever possible, Medical Subject Headings (MeSH) were used. Limits were set on "clinical trials". This search strategy was adapted to the Cochrane and Pedro databases.

Study selection

The three databases were systematically searched for clinical trials using a priori defined inclusion and

exclusion criteria (table 2). To make sure that the majority of the participants in the different studies were clearly overweight, mean BMI at baseline had to be ≥ 26.5 kg/m^2. Since an intervention duration of at least four weeks was considered to be a critical time span to obtain results on insulin sensitivity[33] and beacuse insulin sensitivity correlates well with excessive adiposity[34, 20], only studies with a minimum duration of four weeks were eligible for inclusion. In order to obtain more homogeneous results, only studies using non-invasive imaging techniques for ectopic adiposity were included in this meta-analysis. Studies were included if valid and reliable imaging techniques were used, such as hydrogen based Magnetic Resonance Spectroscopy (H-MRs), Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT).[35-38] Despite the fact that ultrasound can be a useful screening tool, it was excluded as a measurement tool because of reported difficulties to quantify fat and its debatable sensitivity.[36] An exception was made for epicardial fat thickness measured by echocardiography because this measurement technique shows a high agreement with epicardial fat volume and has a good reproducibility.[39-41] This systematic review and meta-analysis focused on interventions based on healthy lifestyle (diet, exercise or a combination of both) and therefore overfeeding studies were excluded. For the present study, exercise was defined as any coordinated or supervised exercise program aiming to reduce weight or body fat. Physical activity intervention studies based on “advise only” were not included because literature showed an uncertain effect.[42]

Quality assessment

The Effective Public Health Practice Project (EPHPP) quality assessment tool was used by two independent investigators to assess the study quality.[43] This tool was chosen because it has an excellent inter-rater agreement of the final rate and can be used to score randomized clinical trials as well as cohort intervention trials, in which parameters before and after an intervention were described.[44, 45]
The decision was made not to exclude articles based on quality assessment or assuming skewness of results.

Manuscript screening and data-extraction

The achieved citations were screened by two independent investigators. Studies fulfilling the above mentioned criteria were included and reference lists were checked for relevant studies. Figure 1 presents the flow diagram of the systematic reviewing process. All data concerning the primary outcome parameters (changes in ectopic fat deposition) and related information necessary to pool study results were obtained. A standardized data-

extraction form was used to construct tables 3 to 6. Whenever methods or primary outcome data were not reported clearly, the corresponding author was contacted. If reported by the authors, significance (S) or non-significance (NS) was noted in table 3 to 6 and exact p-values were retrieved.

Statistical analysis

The extracted data was entered into the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, USA). Expecting an important degree of between studies heterogeneity (due to different measurement techniques, specific patient characteristics and differences in treatment interventions), a random-effects model was chosen to pool the individual study results and to examine the overall effect size of a lifestyle intervention on ectopic fat depots. Effect sizes (changes in ectopic adiposity) were calculated as standardized mean differences and expressed as Hedges' g to correct for overestimating the true effect in small studies. The 95% confidence intervals [95%CI] were calculated for the individual studies and the overall estimate. Raw data from the research of Shea et al.[46] were used to calculate the correlation coefficient between pre- and post-intervention values. In the case of heart adiposity, this correlation was set on 0.9 while for liver and muscular adiposity this correlation was set on 0.7.

The search strategy for excess liver fat deposition yielded 27 articles, allowing subgroup analysis and meta-regression to assess the possible confounding effects of covariates such as the change in BMI or insulin resistance, the study design or the intervention modality on the overall estimate.

The Cochran's Q statistic and its corresponding p-value were calculated for heterogeneity testing and the I^2 statistic was assessed to express the degree of heterogeneity across studies. Publication bias was assessed when 10 or more studies were available per anatomical site through visual analysis of the funnel plot and formal testing for funnel plot asymmetry ('trim and fill' and 'fail 'n safe' algorithms).

To facilitate the interpretation of the overall estimate of the liver studies for the clinician, its value was re-expressed to Intra Hepatic Lipids (IHL) referred to water in % (=unit as measured by the H-MRs technique). Baseline % IHL standard deviations of the intervention and control groups from the Hallsworth et al. study[47] were pooled and multiplied by the pooled standardized mean difference. Thus, the pooled effect was re-expressed in the original units of the H-MRs instrument with the goal to interpret clinical relevance and impact of the intervention more easily.[48] P-values less than 0.05 were considered significant.

Results

Study selection

The initial search in the three databases identified publications resulted in articles about the adiposity of the liver (399 articles), the heart (11 articles), the pancreas (48 articles), the kidneys (47 articles), the IMCL (266 articles) and perivascular fat (165 articles).

After removing duplicates and eliminating papers based on the eligibility criteria, 37 studies remained for further analysis. In these citations, the effect of an intervention on liver, heart, muscular or pancreatic fat was described. No studies were found in which the effect of an intervention on renal or perivascular fat was investigated. Four more citations were excluded as they reported on the same study population.[49-52]

For the qualitative and quantitative analysis, the results of 33 trials were examined. In 27 articles, the effect of a lifestyle intervention on hepatic fat was discussed.[47, 46, 50, 53-76] In the case of muscle[77, 61, 64, 66, 68, 70, 72, 76], heart[40, 46, 54, 74, 78-81] and pancreas[63] adiposity, the number of included papers was eight, eight and one respectively. There effects on multiple ectopic fat locations (e.g. the combination of heart and liver fat) were reported in 11 studies.

Methodological quality and study characteristics

The majority of the included studies (21 studies) were classified to have a strong design (randomized controlled trials or controlled trials – table 7). Nine articles were generally methodologically rated as “strong”, 16 articles were rated as “moderate” and eight articles were rated as “weak”. The most common shortcomings were inadequate or missing information addressing the eligible population group, blinding or controlling for confounders.

Adiposity of the liver, the heart, skeletal muscles or the pancreas was assessed including 1146, 157, 336 and 87 participants respectively in the intervention groups.

Applying the BMI-classification criteria [82], most studies assessed people with class 1 obesity (30.0≤BMI≤34.9).

Only in three trials [56, 59, 75] the effect of an intervention in people with class 3 obesity (BMI≥40) was investigated.

In 19 of the 33 included trials, the subjects didn’t suffer from overweight comorbidities (or possible prevalence percentage of the metabolic syndrome, (pre-)diabetes or an impaired liver function was not reported).

198

199 ***Intervention characteristics***

200 In the majority of the papers, the participants or the study groups received either an exercise intervention or a
201 hypocaloric diet. The combination of hypocaloric diet and exercise was only assessed in nine studies. .
202 Training volume could generally be interpreted as "moderate". The duration of physical activity was primarily
203 between 60 and 80 min/week with a moderate intensity of 50-80% VO_2peak.

204

205 ***Study outcomes: ectopic adiposity***

206 *Adiposity of the liver*

207 An overview of all 27 studies concerning hepatic adiposity is presented in table 3. The overall effect of a
208 lifestyle intervention on hepatic adiposity, expressed as Hedges' g, was -0.53 [95% CI: -0.65 to -0.40] ($p<0.001$).
209 (figure 2)
210 By re-expressing the observed overall effect size based on the population variability of the research of
211 Hallsworth et al.[47] , it could be concluded that an intervention with a duration of eight weeks had the ability
212 to decrease IHL with 5%. Heterogeneity analysis showed high heterogeneity (Cochran's Q= 160, df(Q) =41,
213 $p<0.001$; $I^2 = 74.4\%$). The 'fail'n safe' algorithm reported a low risk for publication bias because 2448 extra non-
214 significant studies would be needed to lower the p-value to the alpha level.
215 To evaluate a possible confounding effect of body weight reduction on the effect size, a meta-regression of the
216 individual studies effect sizes over BMI-change was conducted (figure 3). Analysing the studies with a
217 significant decrease in BMI or body weight, the corresponding change in hepatic adiposity expressed that the
218 decrease in hepatic adiposity was larger in studies with a greater decrease in BMI or body weight. The
219 regression coefficient was -0.11 [95% CI = -0.16 to -0.07] ($p<0.0001$).
220 Since insulin sensitivity was characterized to have a possible confounding effect on hepatic adiposity, a meta-
221 regression of the individual studies effect sizes over the change in insulin sensitivity was conducted. Through
222 meta-regression, no relation was found between the reduction in insulin resistance and decrease in hepatic
223 adiposity (regression coefficient = 0.0057 with $p = 0.97$).
224 Further subgroup analysis presented that the decrease in hepatic adiposity was higher in the uncontrolled
225 studies (Hedges' g = -0.55 [95% CI: -0.69 to -0.41], $p<0.001$) compared to the controlled studies (Hedges' g = -

0.45 [95% CI: -0.73 to -0.17], p=0.002).

Finally, a subgroup analysis was made based on the categorisation of the nature of the intervention (figure 4). Study groups were classified in “diet-only studies” (D), “exercise-only studies” (E) or the combination of “diet and exercise” (D+E). There was a high significant difference (p<0.001) in effect between the three intervention groups with the strongest effect in the diet-only groups (Hedges’ g = -0.77 [95% CI: -0.97 to -0.57], p<0.001) and the weakest effect in the exercise-only groups (Hedges’ g = -0.25 [95% CI: -0.49 to -0.01], p=0.004). Though, it should be emphasized that all intervention types showed a significant reduction on hepatic fat.

Adiposity of the heart

The majority of studies describing the effect of a lifestyle intervention on cardiac fat were uncontrolled trials (table 4). In seven studies, cardiac adiposity decreased after an intervention with an overall effect of -0.72 Hedges’ g [95%CI = -1.10 to -0.35] (p<0.001). Heterogeneity analysis showed a very high between studies heterogeneity (Cochran’s Q= 124.9, df(Q) =10, p<0.001; I^2 = 92%). Due to the anatomically differences between the fat around the heart (epicardial and pericardial fat) and intramyocardial fatty infiltration (cardiac lipid content measured by H-MRs), a subgroup analysis was made in which these results were split up. The overall effect of an intervention on cardiac lipid content was not significant (Hedges’g = -0.27 [95%CI = -0.97 to 0.38], p=0.391). The overall effect of an intervention on epicardial and pericardial fat was more pronounced with -1.26 Hedges’g [95%CI = -1.87 to -0.65] (p<0.001) and -0.565 Hedges’g [95%CI = -0.92 to -0.21] (p<0.001) resp.

Adiposity of the pancreas

Only one study described the effect of a lifestyle intervention (aerobic exercise) on adiposity in the pancreas (table 5). Although there was a trend towards a decrease in pancreatic fat in all intervention subgroups in this controlled study, the overall decrease was not significant (Hedges’ g = -0.55 [95% CI: -1.21 to 0.10], p=0.098).

Adiposity of skeletal muscle (Intramyocellular lipids)

Table 6 depicts the characteristics of the studies in which muscular adiposity is measured after a lifestyle intervention. In this meta-analysis, slow twitch oxidative (type I, M. Gastrocnemius) and fast twitch glycolytic (type II, M. Tibialis Anterior, M. Vastus Lateralis) muscle fibres have been analysed separately. Only two studies found significant changes in IMCL after an intervention[66, 76]. In the majority of the studies, a non-significant decrease was found. The overall effect of a lifestyle intervention on muscular adiposity in the M. Soleus

(predominantly type I fibres) was Hedges' g = -0.28 [95% CI: -0.46 to -0.10] (p =0.002) (Figure 5). The overall effect was lower in the fast twitch muscle fibres (M. Tibialis Anterior: Hedges' g = -0.19 [95% CI: -0.36 to -0.01] (p = 0.041) and M. Vastus Lateralis: Hedges' g = 0.13 [95% CI: -0.79 to 1.06] (p = 0.78)).
Heterogeneity analysis showed a low but non-significant between studies heterogeneity (Cochran's Q= 20.5, df(Q) =14, p = 0.116; I^2 = 31.6%).

Discussion

Diet and exercise are the cornerstones of a lifestyle treatment in people with overweight. By re-expressing the results, it can be concluded that interventions involving physical activity or hypocaloric diet could lead to a decrease in cardiac adiposity and a decrease in intra hepatic lipids of 5%.
It was remarkable that the effects of lifestyle intervention were less clear in research in which subjects were diagnosed with Non Alcoholic Fatty Liver Disease (NAFLD) or an impaired liver function.[47, 57, 67, 75, 76] Only in the study of Oza et al., the lifestyle modification program resulted in a significant decrease of IHL after 6 months.[67] This finding confirmed the hypothesis that subjects with a higher amount of hepatic fat have a lower chance of profiting from lifestyle interventions and intensified strategies or pharmacological approaches may be required.[52]
The high number of studies reporting on liver adiposity allowed for subgroup analysis and meta-regression. Since numerous trials described the existence of a J-shaped relationship between BMI and the risk on morbidity or mortality[9, 83], the influence of BMI reduction on hepatic fat was examined. Meta-regression result suggested a dose-response relationship between BMI reduction and decreased hepatic adiposity.
This confirms existing knowledge that a clinically important weight loss (5-10% of baseline weight) may proceed in an improvement of cardiovascular risk factors.[84, 4] However, it should be mentioned that in a few studies a reduction of IHL was obtained, without a decrease in BMI.[55, 69]
A subgroup analysis based on the type of intervention, concluded that all interventions significantly reduced liver adiposity but the effect size was larger in the diet-only studies. This could be explained by the fact that a hypocaloric diet remains the most important lifestyle factor for weight loss and amelioration of cardiovascular risk and thereby could mask additional effects of exercise therapy.[42, 8]
In the studies or subgroups in which participants were exposed to a "exercise only"- intervention with a moderate training intensity, the training volume almost never exceeded 180 min/week and could therefore be

insufficient to achieve a modest weight reduction.[85] In addition, results could be biased since adherence to exercise programs was only scarcely measured and physical activity levels of participants in the diet-only groups or control groups were rarely measured.

As expected, the effect size of the reduction of hepatic fat was higher in uncontrolled studies compared to the effect size in the controlled studies.[86]

In seven out of eight studies in which the effect of an intervention on heart adiposity was evaluated, a reduction of ectopic fat was found. Over the last decade, it was repeatedly confirmed that cardiac steatosis is a hallmark of obesity and diabetes mellitus type 2 (DMII).[87-89] A reduction of cardiac lipid content could be associated with an improvement of the left ventricular ejection fraction.[80] This could be explained by the fact that cardiac adiposity has a lipotoxic effect on heart (muscle) function.[90] In this analysis, the reduction in cardiac lipid content was not significant and thereby contradictory to the results concerning epicardial and pericardial fat. Since there was a very high heterogeneity between studies and cardiac lipid content was only evaluated in 25 patients, cautiousness is needed when drawing conclusions.

Only one intervention study was found in which pancreatic adiposity was measured.[63] In this study a training program of six months resulted in a non-significant reduction of pancreas fat. Clearly, more studies are necessary to look at the effect of lifestyle interventions on pancreatic adiposity.

The change in skeletal muscle adiposity after an intervention was twofold. In most studies, a trend towards decrease of IMCL was seen, but in some studies there was a trend towards increase. Keeping in mind “the athlete’s paradox”[91, 92], a possible explanation could be that IMCL accumulation is only related to insulin resistance when accompanied by a sedentary lifestyle because of low oxidative capacity.[93] The latter findings indicate that a correct interpretation of IMCL could only be made by evaluating the mitochondrial capacity or oxidative enzyme activity. In none of the included articles for this meta-analysis, an evaluation of oxidative capacity was done.

One of the strengths of this literature study is the extensive systematic review allowing for meta-analysis of the effects of lifestyle interventions on all well documented regions of ectopic fat deposition. Hence, this paper gives a comprehensive description on different anatomical sites of ectopic fat and provides information about the relationship between ectopic adiposity and BMI or insulin resistance. Moreover, the results of this meta-

analysis were made clinically interpretable by re-expressing Hedges' g as % IHL in the liver. Finally, the correlation coefficient between pre and post-values of fat in the liver and heart were real values based on the raw data given by the research team of Kritchevsky.[46]

Despite of all efforts, there are some limitations to this review and meta-analysis. In the quality assessment, the majority of included studies received only a moderate quality score. In most studies, adequate reporting of applied methodology was lacking. It was rarely mentioned which percentage of people eligible for inclusion effectively agreed to participate in the study. Only a few studies reported on a power measurement of the study sample. Blinding of the assessors was often described, however it mostly was not clear if study participants were aware of the research question There were only a few studies that objectively assessed patient adherence to the dietary or exercise program.

In some studies, results were not reported transparently. Repeatedly, outcomes were presented in figures without exact mean values, standard deviations or p-values and medians and interquartile ranges were used. Receiving additional information of the authors, suggested that this presentation of results sometimes masked the underlying skewness.

It should be noted that most patients regain body weight after an intervention.[94] Since in this meta-analysis the intervention period of the majority of the included studies was relative short (<1 year) and a motivational aspect was rarely reported, it was not possible to determine the long-term effect of an intervention. Only one of all included studies described a follow up period. This study indicated that the reduction in pericardial fat volume obtained by the hypocaloric diet remains stable after 14 months, despite a regain in body weight, visceral abdominal fat, and hepatic triglyceride content.[74]

It should be a challenge to design future intervention studies in a manner that a long-term improvement in lifestyle habits could be obtained and results of ectopic fat could be documented.

Given the observed high inter-study heterogeneity due to differences in population (age, gender, comorbidities, degree of overweight, ethnicity), nature and duration of the intervention (diet, exercise, combination of diet and exercise) and the assessment method of adiposity, conclusions should be drawn with care. More long-term follow-up studies research are needed to investigate the effect of lifestyle interventions on ectopic fat deposits (e.g. pancreatic, renal and perivascular tissues) . This is the only manner to get a more in-depth knowledge on the relation between body weight, body fat distribution and the reversibility of a

metabolic risk profile. Future studies should be designed carefully to avoid bias such as differences between intervention groups at baseline. Indeed, factors associated with body fat topography (e.g. age, sex, ethnicity, menopausal status, etc.) may confound the response to lifestyle modification programs.[95, 96]

Also, new studies in this field should plan and embed economic evaluations such as cost-effectiveness and cost-utility analyses. Such information may be important for a patient, a cost-payer or a societal perspective and may help policy makers in their decision making process.

Towards clinical practice, it is certain that a non-invasive intervention that aims to decrease body weight leads to a decrease in ectopic fat, particular in the liver and the heart. Since a significant decrease in body weight is most easily achieved by a diet intervention, caloric restriction is a good basis for obtaining a significant decrease in ectopic adiposity.[97, 85, 8] The effect of exercise training on ectopic fat seems to be rather small. However, clinicians should emphasize that effects of physical activity might be underestimated in most studies because of methodological shortcomings. Also, it must be recognized that numerous health benefits result from exercise programs (e.g. decrease in blood pressure, amelioration of the blood lipid profile and amelioration of insulin sensitivity).[8]

Since sedentarism is correlated with higher dietary intake and other health implications, physical activity can play a key role to achieve a healthier lifestyle.[98, 99] From a public health perspective it is important that overweight and obese people are getting aware of their unhealthy nutritional habits and physical sedentary behavior and to empower them to acquire a healthier lifestyle. For that purpose, it seems clear that physical activity is of uppermost importance.

Conclusion

This meta-analysis shows evidence to conclude that lifestyle interventions including hypocaloric diet, physical activity or a combined intervention have the potential to decrease ectopic adiposity in the liver and the heart in overweight and obese adults. While preliminary results of an intervention on pancreatic adiposity are promising, the results on IMCL after lifestyle interventions should be interpreted with care accounting for the athlete's paradox. A reduction of BMI seems to accompany the loss of ectopic adiposity; however it does not seem to be a prerequisite. Lifestyle interventions should be considered in treatment programs for obesity aiming further than weight loss because of their potential to reduce excess ectopic fat deposition, thereby

364 improving metabolic and cardiovascular risk factors.

365

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368

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