

The effect of diet or exercise on ectopic adiposity in children and adolescents with obesity: a systematic review and meta-analysis

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1 **The effect of diet or exercise on ectopic adiposity in children and adolescents with obesity: a**  
2 **systematic review and meta-analysis.**

3

4 **Introduction**

5 Overweight and obesity remain one of the most prevalent chronic health conditions in children and  
6 adolescents.<sup>1, 2</sup> The worldwide prevalence of overweight and obesity is increasing rapidly, with the  
7 fastest rise in low and middle-income countries.<sup>1</sup>

8 The increasing prevalence of childhood obesity is associated with the raise of metabolic and  
9 cardiovascular comorbidities including hypertension, dyslipidemia and type 2 diabetes mellitus.<sup>1, 3</sup>

10 Since disease progression into adulthood is plausible, this current situation constitutes a challenge  
11 for future demands on health services.<sup>3-7</sup>

12 However, children and adolescents with a “metabolically healthy obesity” (MHO) phenotype exist.

13 These individuals are currently not diagnosed with any common metabolic complication such as  
14 dyslipidemia, insulin resistance or arterial hypertension.<sup>8-10</sup> Comparable to adults, there are  
15 numerous reasons why some children and adolescents with obesity do not develop any metabolic  
16 complications.<sup>11</sup> One of the possible contributing factors is a difference in fat distribution. Individuals  
17 with MHO have a better ability to absorb free fatty acids in adipocytes and store less ectopic fat than  
18 individuals with unhealthy metabolic obesity.<sup>12</sup> Ectopic adiposity is defined as excess of fat in places  
19 not classically associated with adipose tissue storage and may contribute to inflammation and  
20 insulin resistance.<sup>13-16</sup> Furthermore, ectopic fat deposition is associated with an increased risk of  
21 cardiovascular disease and insulin resistance.<sup>17-19</sup>

22 Consequently, in addition to body weight and whole-body fat mass, a stronger focus on ectopic  
23 adiposity is necessary in the follow-up of children and adolescents with overweight or obesity. In  
24 adults, ectopic adiposity has been described in the abdomen, skeletal muscles, liver, heart and  
25 kidneys and such ectopic fat accumulation may lead to metabolic and cardiovascular diseases.<sup>20, 21</sup>

26 Fat deposits in the liver of children and adolescents can lead to paediatric Non-Alcoholic Fatty Liver  
27 Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)<sup>22-24</sup> Since a liver biopsy is still the gold  
28 standard for the diagnosis of NAFLD, the prevalence of NAFLD amongst children is relatively  
29 unknown due to its invasive character. Estimations, however, suggest that worldwide, 38% to 90% of  
30 all children with obesity develop NAFLD.<sup>22, 25-27</sup> Consequently, early diagnosis and treatment of  
31 paediatric NAFLD should be mandatory to prevent the development of NASH.<sup>23, 24</sup> It is equally  
32 important to obtain knowledge of the effect size of a liver steatosis treatment.

33 Diet or exercise have a significant effect on the decrease of ectopic adiposity in adults with  
34 overweight and obesity and simultaneously improve the cardio metabolic profile.<sup>28-30</sup> Although  
35 research in this area is still scarce concerning children or adolescents with overweight or obesity,  
36 previous investigation supports a decrease in visceral adiposity in children and adolescents.<sup>31</sup>  
37 Moreover, guidelines highlight the importance of weight loss and lifestyle modification in children  
38 and adolescents with overweight or NAFLD.<sup>32-35</sup>

39 The aim of this systematic review and meta-analysis is to summarize the evidence for the use of a  
40 non-invasive weight loss intervention (diet and/or exercise) in children and adolescents with  
41 overweight or obesity and its effect on ectopic adiposity located in and around skeletal muscles,  
42 liver, heart, pancreas and kidneys.

43

#### 44 **Methods**

45 This systematic review and meta-analysis is designed according to the PRISMA (Preferred Reporting  
46 Items for Systematic Reviews and Meta-analysis) statement.<sup>36</sup> The protocol of this review has been  
47 registered in PROSPERO under the number CRD42014015381.

#### 48 *Search Strategies*

49 The PubMed, PEDro and Cochrane databases were used to run an electronic search specified to each  
50 anatomical fat deposition area.

51 Key words were based on the PICO acronym and were combined with BOOLEAN operators “OR” and  
52 “AND”. The search strategy is shown in Table 1. When applicable, limits were set on “clinical trials”  
53 and “children”.

#### 54 *Study Selection and Quality Assessment*

55 The three databases were systematically searched using a priori defined in- and exclusion criteria. To  
56 obtain consistent results, only clinical trials in which the outcome measurement was ectopic fat were  
57 included. Studies in which echography evaluated hepatic adiposity were excluded because no  
58 quantifiable data were reported. Since histological abnormalities in liver biopsies are not always  
59 paired with elevated liver enzymes in children with NAFLD<sup>37,38</sup>, studies in which liver enzymes were  
60 used as an indication of liver adiposity were excluded. Papers describing children or adolescents  
61 (mean age < 19y) with obesity-related complications such as impaired glucose tolerance, NAFLD or  
62 impaired liver function were included. Overweight and obesity were identified in agreement with  
63 established international paediatric cut-off criteria and curves.<sup>39,40</sup> This meta-analysis focuses on  
64 lifestyle interventions aiming to reduce body weight including the achievement of a negative energy  
65 balance by implementing a hypocaloric diet, exercise, the combination of diet and exercise or healthy  
66 lifestyle advice. Studies or study arms in which medication or nutritional supplements were a part of  
67 the treatment, were excluded. The Cochrane risk of bias tool was used by two independent  
68 investigators to assess the study quality.<sup>41</sup>

#### 69 *Screening and Data Extraction*

70 Titles, abstracts and full-text articles were screened by two independent investigators. Studies  
71 fulfilling the criteria mentioned above were included. Figure 1 illustrates the flow diagram of the  
72 systematic reviewing process. A standardized data extraction form was used to compile Tables 2 and  
73 3. Whenever methods or data were not clearly reported, the corresponding authors were contacted.

#### 74 *Statistical Analysis*

75 The extracted data was entered into the CMA-2 software (Comprehensive Meta-Analysis 2nd

76 version, Biostat, Englewood, USA). A random-effects model was used to pool the individual study  
77 results and to examine the overall weighted effect size of a lifestyle intervention on ectopic adiposity.  
78 Effect sizes (changes in ectopic adiposity) were calculated as standardized mean differences. It is  
79 likely that the analysis, based on small study groups, results in an overestimation of the effect size.  
80 Therefore, a correction was made with a factor  $g$ , expressed as Hedges'  $g$ .<sup>42</sup> A negative or positive  
81 value for Hedges'  $g$  indicates a decrease or increase in ectopic adiposity, respectively. The value of  
82 the effect size is defined as 0.2=small, 0.5=moderate and 0.8=large.<sup>41</sup>  
83 The 95% confidence intervals [95%CI] were calculated for the individual studies and the overall  
84 weighted estimate. Using a correlation coefficient of 0.7 between pre- and post-intervention values  
85 and a random-effects model, a balanced and conservative approach is maintained which allows true  
86 variations in the effect size and heterogeneity across included studies.<sup>43</sup> The Cochran's Q statistic and  
87 its corresponding p-value were calculated for heterogeneity testing, and the  $I^2$  statistic was assessed  
88 to express the degree of heterogeneity across studies. To facilitate the clinician's interpretation of  
89 the overall effect of lifestyle intervention on hepatic adiposity, the value of Hedges'  $g$  was re-  
90 expressed to Intra Hepatic Lipids (IHL) and described as proton density fat fraction (%). Baseline %  
91 IHL standard deviations of the intervention and control groups from the Lee et al. study<sup>44</sup> were  
92 pooled and multiplied by the pooled standardized mean difference. Two additional subgroup  
93 analyses were performed based on commonly accepted confounding variables such as study design  
94 (Randomized controlled trials versus non-randomized controlled trials) and the ethnicity of subjects.  
95 Finally, an additional sensitivity analysis was done in which one study was excluded.  
96 P-values less than 0.05 were considered significant (2-tailed).

## 97 **Results**

### 98 *Study Selection*

99 The initial search resulted in 18 hits in the search strategy of muscular adiposity (Intra MyoCellular  
100 Lipids-IMCL) (search strategy a), 99 hits in the search strategy of hepatic adiposity (search strategy b)

101 and nine hits in the search strategy of pancreatic adiposity (search strategy c). The search strategy of  
102 ectopic adiposity of the heart and kidneys (search strategy d and e) yielded three hits each.

103 After removing duplicates and eliminating papers based on the eligibility criteria, 14 studies  
104 remained available for full-text analysis. Due to insufficient data reporting, one article was  
105 excluded.<sup>45</sup> After completion of the full-text screening, nine articles on the effect of lifestyle  
106 interventions on hepatic fat (320 patients) and three articles on IMCL (55 patients) remained for the  
107 meta-analysis. No articles were found on lifestyle interventions and the deposition of ectopic fat  
108 in/around the heart, kidneys or pancreas.

#### 109 *Risk of bias*

110 Four clinical trials and six randomized controlled clinical trials were included in this meta-analysis.  
111 The results of the risk of bias assessment are shown in Table 4. Since the aspect of blinding was often  
112 inadequately explained and the results were repeatedly not transparently presented, a risk of bias  
113 was plausible. Only two papers report the adherence to the exercise program or dietary regime.<sup>46,47</sup>

#### 114 *Population characteristics*

115 According to classification criteria of overweight and obesity in children and adolescents<sup>39,40</sup>, all  
116 articles addressed a lifestyle intervention in children or adolescents with obesity. Teenagers (Tanner  
117 stage between 4 and 5) without cardiometabolic comorbidities were examined in most studies. In  
118 three studies, (part of the) subjects were diagnosed with NAFLD or NASH.<sup>47-49</sup> Most studies described  
119 the exact number of ethnic groups to the total population.

#### 120 *Intervention Characteristics*

121 In the included studies, supervised physical activity or the advice to increase physical activity was a  
122 part of the lifestyle intervention. Study duration ranged between 3 and 12 months, and the weekly  
123 used exercise volume ranged between 90 and 180 minutes.

124 *Anthropometric Data*

125 A statistically significant reduction in BMI or BMI z-score was described in almost all studies. In only  
126 two studies conducted by Lee et al., the aerobic training<sup>44,50</sup> and a strength training<sup>44</sup> did not result  
127 in statistically significant BMI decreases. BMI changes were not reported in one study.<sup>51</sup> Changes in  
128 whole-body fat mass and fat-free mass were reported in the majority of studies. Only in one study,  
129 whole-body fat mass did not change.<sup>52</sup> These anthropometric parameters were not reported in three  
130 studies.<sup>46, 47, 51</sup>

131 *Adiposity of the liver*

132 Hepatic adiposity was evaluated in nine studies including 320 subjects (table 2). A forest plot of this  
133 analysis is shown in figure 2. A lifestyle intervention led to a decrease in hepatic adiposity (-0.54  
134 Hedges' g [95% CI: -0.69 to -0.38] with  $p < 0.0001$ ). By re-expressing the observed overall weighted  
135 effect size based on the population variability of Lee et al's research.<sup>44</sup>, it was confirmed that diet  
136 and/or exercise interventions resulted in an absolute IHL reduction of 2% in children and adolescents  
137 with obesity. No between-study heterogeneity was observed (Cochran's  $Q = 10.19$ ,  $df(Q) = 12$ ,  $p = 0.6$ ;  
138  $I^2 = 0\%$ ).

139 a) Subgroup analysis study design

140 A first subgroup analysis based on study design (non-randomized versus randomized clinical trials)  
141 showed a higher, non-significant overall weighted effect size ( $p = 0.71$ ) (-0.55 Hedges' g (CI) versus -  
142 0.48 Hedges' g)

143 b) Subgroup analysis modality of the intervention

144 In a second subgroup analysis, groups were compared by intervention modality. Exercise training  
145 seemed to lead to the greatest reductions in hepatic adiposity (-0.64 [95% CI: -1.00 to -0.27])  
146 compared to the combination of diet and exercise (-0.54 [95% CI: -0.74 to -0.34]) or diet-only (-0.47  
147 [95% CI: -1.00 to 0.05]). Though, the differences in effect size between groups were not significant

148 (p=0.86). There was no heterogeneity between the exercise-only studies or other study groups (with  
149 Cochran's Q = 1.79, df (Q) = 4, p=0.38; I<sup>2</sup> =5.48%) and heterogeneity in the studies applying diet and  
150 exercise was negligible (Cochran's Q = 4.23, df (Q) = 4, p=0.76; I<sup>2</sup> = 0%).  
151 Heterogeneity was moderate (albeit not statistically significant) in diet-only studies (Cochran's Q =  
152 3.65, df (Q) = 2, p=0.16; I<sup>2</sup> = 45.3%). Hasson et al's study<sup>51</sup> was the only study in which dietary advice  
153 was not described, changes in BMI or total whole-body fat mass were not reported and strength  
154 training was applied. Hereby it was uncertain that subjects obtained a negative energy balance.  
155 Moreover, since no decrease in hepatic adiposity was observed, it was considered to be an outlier. In  
156 a sensitivity analysis, Hasson et al. were therefore excluded. This analysis suggested that a  
157 hypocaloric diet has a greater effect on reducing hepatic adiposity (-0.76 [95% CI: -1.27 to -0.25])  
158 compared to exercise-only (-0.64 [95% CI: -1.01 to -0.27]) or to the combination of diet and exercise  
159 (-0.55 [95% CI: -0.81 to -0.30]). However, the differences between intervention groups were not  
160 statistically significant (p = 0.77) (Figure 3).

#### 161 *Intramyocellular lipids (IMCL)*

162 The effect of an intervention on IMCL was measured in three studies including 55 subjects (Table 3).  
163 The overall weighted mean effect size of diet or exercise on IMCL, expressed as Hedges' g was -0.03  
164 [95% CI: -0.52 to 0.47].  
165 Further analysis showed moderate, non significant heterogeneity across studies (Cochran's Q = 4.99,  
166 df(Q) = 3, p=0.17; I<sup>2</sup> = 39.9%).

167

#### 168 **Discussion**

169 Although the link between overweight or obesity and metabolic diseases in childhood obesity could  
170 be provoked by body fat distribution and ectopic adiposity<sup>15</sup>, research on ectopic adiposity patterns  
171 in children and adolescents is scarce.



172 This meta-analysis concerns only data of hepatic adiposity (nine studies, including 392 subjects) and  
173 intramyocellular lipids (three studies, including 76 subjects. The impact of lifestyle intervention on  
174 other anatomic sites of ectopic adiposity in children and adolescents with overweight or obesity  
175 remains to be studied.

176 Results of this meta-analysis demonstrate for the first time that a lifestyle intervention (diet and/or  
177 exercise) of at least 3 months may yield towards a 2% decrease in intra hepatic lipid content in  
178 children and adolescents with obesity. The effect of lifestyle interventions on changes in hepatic fat  
179 seems to be smaller compared to adults with overweight and obesity (5-10% IHL reduction).<sup>29</sup> The  
180 intra hepatic lipid content is expressed as proton density fat fraction (IHL = (lipid/ (lipid+water)\*100).  
181 Nevertheless, this is an absolute value of lipid quantification in the liver and an absolute 2% decrease  
182 has been observed. In reference to Lee et al's study<sup>44</sup> which was used for the re-expression of  
183 Hedges' g, baseline values range between 2.0±1.3% and 3.0±5.4%. Hereby, an absolute reduction by  
184 2% means a relative reduction of more than 50% of existing liver fat. Hepatic adiposity reduction  
185 involving lifestyle interventions may be as high as 77% in children and adolescents with obesity  
186 (Table 2).<sup>44</sup> Therefore, a lifestyle intervention does lead to substantial and clinically relevant  
187 reductions in IHL in children and adolescents with obesity.

195 Moreover, it is observed that baseline hepatic adiposity content is much lower in children and  
196 adolescents with obesity compared to adults with obesity. Furthermore, Lange et al.'s previous  
197 research confirms that the mean IHL of children with obesity is more than one order of magnitude  
198 smaller than the IHL content in adults with obesity (1.0±0.5% vs 17.0±8.7%).<sup>53</sup> This can clinically be  
199 explained by the fact that severe or fibrotic NASH need substantial time to develop. Therefore the  
200 prevalence is higher in adults with obesity than in children or adolescents with obesity.<sup>54</sup>

201 Since NAFLD can evolve towards NASH, it is important to observe the NAFLD progression during  
202 treatment of young patients by validated imaging techniques.<sup>23, 24</sup> In clinical settings, liver enzymes  
203 are used as a non-invasive screening tool for NAFLD in children.<sup>55</sup> Nevertheless, cohort studies in

204 children and adults show normal liver enzymes values in nearly 80% of patients with established fatty  
205 liver disease. Moreover, cut-off values in children and adolescents with NAFLD based on blood liver  
206 enzymes are discussable.<sup>24, 37, 38, 55-59</sup> Therefore, we preferred to analyze data based on direct  
207 measurements of hepatic adiposity. Studies in which liver enzymes were only used as markers of  
208 hepatic adiposity, were excluded. Despite the fact that ultrasound techniques have an important  
209 clinical value, it was not possible to use ultrasound results in this meta-analysis, because no  
210 quantifiable data were reported. Echography results are operator dependent and limit therefore  
211 sensitivity and specificity in mild NAFLD.<sup>60-63</sup> The most common technique to assess liver adiposity is  
212 Magnetic Resonance Spectroscopy (<sup>1</sup>H-MRS) which is considered to be a valid and accurate  
213 assessment method with good reproducibility. However, it is time-consuming and requires complex  
214 data analysis.<sup>64-67</sup> No clinical trials were found in which the effect of a conservative treatment (diet or  
215 exercise) on hepatic fat content was assessed by liver biopsy.

216 According to the different intervention stages described by Barlow et al., weight loss is a key factor in  
217 the treatment of pubertal children with obesity.<sup>68, 69</sup> Nevertheless, this meta-analysis shows that a  
218 BMI reduction does not relate to a decrease in hepatic adiposity. Shorter (up to 12 weeks) exercise-  
219 only studies did not result in significant BMI reductions while significant reductions of IHL were  
220 observed.<sup>44, 50, 70</sup> It can be explained by the fact that physical activity sensitizes muscles to insulin and  
221 modifies hepatic lipids.<sup>71-73</sup> Furthermore, it should be noted that a reduction in whole-body fat mass  
222 is achieved in these studies.

223 The variations in program duration, exercise modalities, exercise volume and degree of caloric intake  
224 made it difficult to conduct direct comparisons between studies and to identify the most effective  
225 intervention to reduce hepatic adiposity in children and adolescents with obesity. In order to  
226 overcome this limitation, a subgroup analysis was performed and outliers were detected. Since it was  
227 possible that no negative energy balance was obtained in Hasson et al.'s<sup>51</sup>, this research was  
228 considered to be an outlier. However, a sensitivity analysis without this study did not change our

229 results. Although there seems to be a difference in effect size between different study designs, this  
230 difference was not statistically significant.

231 The limited number of studies (with each small sample sizes) in the subgroup analyses evoked large  
232 confidence intervals partially explaining why the between-groups difference in effect size was not  
233 statistically significant.

234 It is remarkable that the exercise volume (90-180 minutes/week) applied in the exercise study groups  
235 did not often comply with the recommended guideline of one hour per day of exercise in children  
236 and adolescents with obesity.<sup>68, 74, 75</sup> It could be that a more rigorous exercise regimen would yield  
237 better results. It may be argued that the impact of lifestyle interventions on ectopic fat is  
238 underestimated in children and adolescents with obesity.

239 Although there were significant improvements in insulin resistance or sensitivity in all intervention  
240 groups, neither endurance nor resistance exercise training yielded significant changes in IMCL. This  
241 finding supports the results found by Larson-Meyer et al.<sup>76</sup>, who stated that IMCL content is  
242 metabolically inert and should not be considered as a determinant of insulin resistance in skeletal  
243 muscles. In this regard, it can be assumed that skeletal muscle oxidative capacity plays a role in the  
244 association between insulin resistance and excess IMCL in people with overweight or obesity.<sup>77, 78</sup>

245 In only three studies, (part of the) subjects were diagnosed with NAFLD or NASH.<sup>47-49</sup> Since NAFLD is  
246 defined as IHL content higher than 5.6% measured by <sup>1</sup>H-MRS<sup>79</sup>, only Lee et al.'s research addresses  
247 with children without liver disease.<sup>44, 50</sup>

248 One of the most challenging aspects for healthcare professionals in paediatric weight management  
249 programs is the difficulty in obtaining sustained long-term results. Rates of attrition are reported  
250 between 27% and 75%.<sup>80, 81</sup> Unfortunately, no long-term studies or studies with follow-up  
251 measurements were found.

252 One of the strengths of this study is the extensive systematic review of the literature providing a  
253 meta-analysis revealing the effects of lifestyle interventions on all well documented anatomic sites of  
254 ectopic adiposity in children and adolescents with obesity. In addition, the results of lifestyle  
255 interventions on hepatic adiposity were made clinically interpretable by re-expressing Hedges'g as  
256 absolute values of IHL. In general, clinical and statistical heterogeneity among the included studies  
257 was low.

258 There are, however, also some limitations to this study. The quality of this systematic review and  
259 meta-analysis is limited by the methodological quality of the included studies. In the majority of  
260 included studies, a risk of bias is plausible because due to inadequate reporting of applied  
261 methodology and patient adherence. In most studies, the prevalence of insulin resistance, type 2  
262 diabetes or liver diseases was not reported.

263 Finally, the included studies described rather small study populations.

264 To facilitate future systematic reviews and meta-analyses, researchers should be encouraged to  
265 report their methods and observed outcomes transparently (as well in changes as in means with  
266 standard deviations). Given the fact that long-term effectiveness of a lifestyle intervention is  
267 dependent on the sustainability of behaviour change, it is important that adherence to the  
268 prescribed intervention protocol is adequately assessed and reported. A comparison with habitual  
269 diet and exercise behaviour can result in a correct interpretation of the intervention effect.

270

## 271 **Conclusion**

272 This meta-analysis shows that diet and/or exercise is effective in reducing hepatic adiposity in  
273 children and adolescents with obesity, even without a BMI reduction. This reaffirms existing clinical  
274 guidelines in which complete lifestyle modification is promoted in the management of paediatric  
275 obesity. Although there were significant ameliorations in insulin sensitivity in all intervention groups,  
276 no significant changes in IMCL were found.

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