Metabolic Syndrome From Adolescence to Early Adulthood

Effect of Infancy-Onset Dietary Counseling of Low Saturated Fat: The Special Turku Coronary Risk Factor Intervention Project (STRIP)

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Background—Adolescent metabolic syndrome (MetS) predicts type 2 diabetes mellitus and subclinical atherosclerosis in adulthood. Our aim was to establish the relationship between an infancy-onset dietary intervention and risk of having MetS between 15 and 20 years of age.

Methods and Results—The Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study is a longitudinal, randomized atherosclerosis prevention trial in which repeated dietary counseling aiming at reducing intake of saturated fat took place from infancy to early adulthood. Participants who had complete data on the MetS components (waist circumference, blood pressure, triglycerides, glucose, high-density lipoprotein cholesterol) at 15 (n=512), 16 (n=485), 17 (n=475), 18 (n=459), 19 (n=439), and 20 (n=407) years of age were included in the study. Modified International Diabetes Foundation criteria with 80th/20th percentile cutoff points for the components were primarily applied in statistical analyses, and the results were replicated with the use of other pediatric MetS definitions. Between the ages of 15 and 20 years, the prevalence of MetS varied between 6.0% and 7.5% in participants in the intervention and control groups and between 14% and 14% in the control group. The long-term relative risk of MetS was significantly lower in the intervention group (relative risk, 0.59; 95% confidence interval, 0.40–0.88; P=0.009). Of the individual MetS components, the intervention decreased risk of high blood pressure in both sexes (relative risk, 0.83; 95% confidence interval, 0.70–0.99) and high triglycerides in male subjects (relative risk, 0.71; 95% confidence interval, 0.52–0.98). A statistically nonsignificant reduction was seen in the risk of high waist circumference in the intervention individuals (relative risk, 0.78; 95% confidence interval, 0.59–1.03).

Conclusion—Repeated infancy-onset dietary intervention is effective in the prevention of MetS in adolescence.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00223600.

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Key Words: atherosclerosis ▪ diabetes mellitus ▪ diet ▪ longitudinal studies ▪ metabolic syndrome X ▪ prevention and control

In adults, metabolic syndrome (MetS) predicts type 2 diabetes mellitus and cardiovascular diseases.1,2 MetS is also linked to cardiovascular and all-cause mortality,2,3 even after adjustment for traditional cardiovascular risk factors1 or in the absence of baseline cardiovascular disease and diabetes mellitus.2 We have previously shown that adolescent MetS is associated with future risk of developing type 2 diabetes mellitus and subclinical atherosclerosis in adulthood4 and that resolving MetS can normalize the risks of these outcomes to levels seen in individuals who have never had MetS.5

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The Special Turku Coronary Risk Factor Intervention Project (STRIP) was launched to study the effect of dietary intervention initiated in infancy and maintained until the age
of 20 years on atherosclerosis risk factors. The intervention aimed to guide the study participants toward a diet beneficial for cardiovascular health. The personalized dietary counseling was safe for the children’s growth and development and led to lower low-density lipoprotein cholesterol concentrations and blood pressure in the intervention group, improved insulin sensitivity, increased ideal cardiovascular health, and enhanced endothelial function.

We have previously reported preliminary data from the STRIP study that the intervention may reduce the clustering of overweight-related cardiometabolic risk factors between the ages of 5 to 15 years, suggesting a beneficial effect on the risk of MetS. In that analysis, however, we were unable to apply pediatric MetS definitions because of the lack of data on waist circumferences for some ages and the lack of data on serum glucose concentrations before the age of 15 years. Therefore, to extend these preliminary findings to the rest of the trial duration, we have now tested the hypothesis that the infant-onset intervention reduces the risk of pediatric MetS between the ages of 15 and 20 years.

Methods

Study Design and Participants

The STRIP study, a prospective, randomized, controlled trial to prevent atherosclerosis beginning in infancy, recruited families with 5-month-old infants at well-baby clinics in Turku, Finland, between February 1990 and June 1992. At the age of 6 months, 1062 infants (56.5% of the eligible age cohort) were randomly allocated to an intervention (n=540) or a control (n=522) group.

The intervention group received individualized dietary counseling at least biannually until the age of 20 years. The main target of the counseling was to replace saturated fat with unsaturated fat in the child’s diet (reduction in total fat intake was not targeted). The children in the intervention group also received counseling on, for example, how to reduce salt intake and to favor whole-grain products, fruit, and vegetables. Use of whole-grain products was encouraged to increase fiber intake and to introduce better-quality carbohydrates to the diet. Counseling on fiber and, for example, quality of cereals was given repeatedly during the study. In terms of protein, specific counseling related to plant- or animal-based sources was not given. The counseling was given to the parents until the child was 7 years old, and from then onward, gradually more information was given directly to the child. A fixed diet was never ordered; the counseling was individualized, and the child’s recent food record was used as a basis of suggestions for dietary changes (eg, replacement of dairy fat–blend spreads with vegetable oil–based spreads and low-fiber bread with whole-grain bread). The dietary recommendations were based on Nordic nutrition recommendations (30% of energy from fat, 10%–15% of energy from protein, and 50%–60% of energy from carbohydrates). Because of the lack of ready-made counseling material, most of the material used was developed in the STRIP trial. The primary prevention of smoking was introduced at the age of 8 years. Physically active lifestyle was encouraged, but it was not a structured, continuous part of the intervention.

The control group was seen biannually until the age of 7 years and annually thereafter until 20 years of age. Similar measurements were performed for both study groups, and they met the same study personnel. Children in the control group received only the basic health education given at Finnish well-baby clinics and school health care. Topics related to the intervention were not discussed. All STRIP study visits were completed in 1 research center.

This study comprised participants who had all components of MetS measured within a study visit between 15 to 20 years of age, but a complete sequence of visits was not required. Still, 82% of the participants had data from at least 5 of the 6 measurements. A total of 534 participants were included (260 [49%] female; 254 [48%] in the STRIP intervention group; 2 twins). The sex distribution was similar within the study groups (at 15 years of age: intervention group, 47% girls; control group, 49% girls; P=0.57, χ2). Overweight (10.2% at 15 years of age) and obese (2.7% at 15 years of age) participants were included in the study sample.

The Joint Commission on Ethics of the Turku University and the Turku University Central Hospital approved the study. Written informed consent was received from the parents in the beginning of the trial and from the children at 15 years of age.

Blood Pressure, Waist Circumference, Weight, and Height

Seated blood pressure was measured after an appropriate rest of at least 15 minutes twice on the right arm with an oscillometric device (Criticon Dinamap Compact T). The mean of the 2 measurements was used. Waist circumference was measured midway between the iliac crest and the lowest rib at the midaxillary line with a flexible measuring tape to the nearest 0.5 cm. Weight was measured to the nearest 0.1 kg with an electronic scale (S10, Soehnle, Murrhardt, Germany) and height to the nearest 0.1 cm with a Harpenden stadiometer (Holtain, Crymych, UK). Body mass index was calculated as weight in kilograms divided by height in meters squared.

Laboratory Methods

A venous blood sample was drawn in the morning after an overnight fast annually for the determination of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and plasma glucose. The sample was allowed to clot at room temperature for 30 to 60 minutes and centrifuged at 3400 g for 12 minutes. Afterward, the serum was separated and stored at −25°C. The samples used for plasma glucose concentration analyses were centrifuged immediately. Plasma glucose was analyzed by a hexokinase method (Glucose Olympus System Reagent, Olympus, Ireland; interassay coefficient of variation, 1.8%). Triglycerides were analyzed with the colorimetric glycerol-3-phosphate oxidase p-aminophenazone method (Merck, Darmstadt, Germany) with an automatic Olympus AU400 analyzer. Serum total cholesterol concentration was analyzed with a fully enzymatic cholesterol oxidase-p-aminophenazone method (Merck). Serum HDL-C concentration was measured after precipitation of low-density lipoprotein and very-low-density lipoproteins with dextran sulfate 500 000. Low-density lipoprotein cholesterol was estimated from the Friedewald formula. None of the adolescents had triglycerides ≥4.52 mmol/L (>400 mg/dL).

Definition of MetS

Characteristics included in the definition of MetS were waist circumference, blood pressure, triglycerides, glucose, and HDL-C. Because there is no single or universally accepted definition of adolescent MetS, we used various definitions used in previous reports. In total, 5 criteria to define MetS were applied. Cohort-based percentiles and previously published normative values were used as cutoff points to define the individual MetS components.

First, according to the modified International Diabetes Federation (IDF) definition (mod_IDF80/20), a participant was categorized as having MetS if he/she had elevated waist circumference (≥80th percentile, age and sex specific) plus any 2 of the following 4 components: systolic or diastolic blood pressure ≥80th percentile, triglycerides ≥80th percentile, glucose ≥80th percentile, or HDL-C ≤20th percentile (all age and sex specific). Second, we performed a similar categorization using ≥85th percentiles (≤15th percentile for HDL-C) as cutoff points (mod_IDF85/15). Third, we used the modified National Cholesterol Education Program definition with the same ≥80th percentile cutoff points as for the mod_IDF definition. For the modified National Cholesterol Education Program definition, a participant was categorized as having MetS if he/she had any 3 of the 5 components. Fourth, in the definition of mod_IDF80/20, we standardized blood pressure for height in addition to age and sex.
Expanded methodology for the fifth definition using normative cutoff points is provided in the online-only Data Supplement.

To complement the dichotomous definitions, a continuous MetS risk score was calculated. For the continuous score, the components were first standardized (z-scored) for age and sex (HDL-C was multiplied by $-1$) and then summed by age to form a continuous score. As a representation of blood pressure, mean of the systolic and diastolic blood pressure values was used.

**Loss to Follow-Up**

As a result of the extensive duration of the study, some participants were lost to follow-up. We have previously shown that there is no association of body mass index with the rate of discontinuation. We have also reported that loss to follow-up was not associated with saturated fat intake, weight, or total cholesterol concentration. In this analysis, 127 of the total 534 participants (24%) were lost to follow-up between 15 and 20 years of age. The proportion of premature discontinuation was higher in the intervention group than in the control group (29% versus 19%; $P=0.008$, Cox regression model). However, none of the components of MetS was associated with loss to follow-up (waist circumference, $P=0.69$; glucose, $P=0.52$; HDL-C, $P=0.82$; triglycerides, $P=0.58$; and systolic blood pressure, $P=0.86$), nor were there any STRIP study group–by–MetS component interactions (Figure I in the online-only Data Supplement), indicating that the greater loss to follow-up in the intervention group was not modified by the MetS components.

**Statistical Analyses**

Descriptive data are presented as mean±SD or median (interquartile range). Serum triglyceride and insulin values were log$_{10}$-transformed for analyses. The association of STRIP study group with the risk of having MetS was studied by use of a modified Poisson regression model with generalized estimating equation estimation for repeated measures (risk ratios [RRs] with 95% confidence intervals [CIs] were calculated for intervention versus control group). The main effect of STRIP study group on prevalence of MetS was also assessed with a model containing insulin (potential mediator). An identical analysis was used to study the intervention effect on dichotomous components of MetS. Repeated-measures ANOVA with random subject effect was used to study the association of STRIP study group with the continuous components of MetS. All models included sex and age as covariates, and study subject was used as the random effect. Similar analysis was used to study the association of STRIP study group with the continuous MetS risk score. Participants with missing visits in the sequence were included in the analyses (intention-to-treat analysis). The interactions of STRIP study group with the continuous MetS score was calculated. For the continuous score, the components of MetS was studied, the intervention participants had a borderline significantly lower risk of high waist circumference (RR, 0.78; 95% CI, 0.59–1.03; Figure III in the online-only Data Supplement). The result was also similar when the effect of height on blood pressure was standardized in the MetS definition (intervention versus control: RR, 0.60; 95% CI, 0.40–0.91; $P=0.015$). In line with previous definitions, the intervention effect was sustained when normative values were used as cutoff points for the components of MetS (intervention versus control: RR, 0.69; 95% CI, 0.46–0.98; $P=0.039$).

The intervention effect on MetS was further studied by use of a continuous MetS score. In line with the results on dichotomous MetS, the STRIP study intervention was favorably associated with the continuous MetS score (intervention versus control group, $P=0.041$; intervention mean±SD, −0.24±2.5; control mean±SD, 0.21±2.82).

**Effect of Intervention on the Components of MetS**

When the effect of study group on dichotomous MetS components was studied, the intervention participants had lower risk of high blood pressure (Table 2). There was a significant study group–by–sex interaction in triglycerides ($P=0.006$): The intervention boys had a lower risk of high triglycerides (RR, 0.71; 95% CI, 0.54–0.94), whereas no association was found in girls. A study group–by–age interaction on glucose indicated that the effect of intervention was different by age ($P=0.016$). In pairwise comparisons, the risk for high glucose was lower in intervention participants at 18 years of age (RR, 0.60; 95% CI, 0.38–0.96). The intervention participants had a borderline significantly lower risk of having high waist circumference (RR, 0.78; 95% CI, 0.59–1.03; $P=0.09$).

When the effect of intervention on continuous components of MetS was analyzed, there was a significant study group–by–sex interaction with triglycerides (Table 3). This indicated that the effect of intervention was different between sexes; intervention was associated with lower triglycerides in boys, whereas no association was found in girls. For other continuous components of MetS, there was no intervention effect.

**Results**

Key cohort characteristics in participants 15 to 20 years of age are shown in Table 1. The prevalence of MetS differed according to definition, ranging from 7% to 11% for the modified criteria and from 10% to 15% for the modified NCEP criteria.

**Effect of Intervention on MetS**

At 15 to 20 years of age, the prevalence of MetS varied between 6% and 7% in the intervention group and between 10% and 13% in the control group (Figure). Participants in the intervention group had 41% lower risk of MetS compared with the control participants (RR, 0.59; 95% CI, 0.40–0.88; mod_IDF80/20; Figure). There was no study group–by–sex (P=0.80) or study group–by–age (P=0.95) interactions, indicating that the intervention effect was similar among girls and boys at different ages. The difference between the intervention and control groups persisted when mod_IDF85/15 was used to define MetS (study group–by–sex interaction, P=0.99; study group–by–age interaction, P=0.83; Figure II in the online-only Data Supplement). In addition, when the modified NCEP definition was applied, participants in the intervention group had a 33% lower risk of MetS compared with the control participants (study group–by–sex interaction, P=0.94; study group–by–age interaction, P=0.82; Figure III in the online-only Data Supplement).
Effect of Intervention on Intercorrelations of the Components of MetS

Strengths of pair-wise correlations between continuous MetS components in the intervention and control groups were compared to examine whether the intervention had an effect on the intercorrelations between the components. There was a tendency for stronger correlations between the components in the control participants than in their intervention peers for the majority of the analyses, although statistical significance was not reached except for correlations between waist circumference and glucose (Table 4). Overall, correlations between the components were relatively weak.

Role of Insulin

We have previously reported that those in the intervention group had lower insulin levels compared with the control group, indicating enhanced insulin sensitivity in the intervention participants. In this analysis, we therefore investigated whether the association of intervention with MetS persisted after the inclusion of insulin in the analysis. When insulin was added to the model, the intervention effect on MetS (mod_IDF80/20) was only slightly diluted (intervention versus control group: RR, 0.62; 95% CI, 0.43–0.91; P=0.02). In the analysis, insulin also had a strong association with MetS (P<0.0001).

Discussion

We have demonstrated that the intervention given in the STRIP study substantially (by 41%) decreased the risk of MetS among healthy participants between 15 and 20 years of age. The intervention effect persisted when different MetS criteria were used. This study is the first longitudinal trial, started in infancy, to report the effect of repeated dietary intervention on adolescent MetS. Thus,

Table 1. Characteristics of the Study Cohort and Prevalence of MetS in Participants at 15 to 20 Years of Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>247</td>
<td>265</td>
<td>241</td>
<td>244</td>
<td>238</td>
<td>237</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57±9</td>
<td>62±12</td>
<td>59±10</td>
<td>66±11</td>
<td>60±10</td>
<td>70±12</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166±6</td>
<td>174±8</td>
<td>167±6</td>
<td>178±7</td>
<td>167±6</td>
<td>180±7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.6±3.1</td>
<td>20.4±3.4</td>
<td>21.3±3.3</td>
<td>20.9±3.3</td>
<td>21.6±3.4</td>
<td>21.5±3.4</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>71.2±7.4</td>
<td>75.0±8.8</td>
<td>71.7±7.6</td>
<td>75.3±7.7</td>
<td>72.0±7.6</td>
<td>77.1±7.9</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.15±0.74</td>
<td>3.76±0.71</td>
<td>4.20±0.76</td>
<td>3.79±0.68</td>
<td>4.35±0.76</td>
<td>3.81±0.66</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.22±0.22</td>
<td>1.08±0.22</td>
<td>1.24±0.27</td>
<td>1.048±0.22</td>
<td>1.33±0.27</td>
<td>1.06±0.21</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.52±0.63</td>
<td>2.27±0.63</td>
<td>2.54±0.64</td>
<td>2.30±0.60</td>
<td>2.56±0.63</td>
<td>2.31±0.59</td>
</tr>
<tr>
<td>Triglycerides,† mmol/L</td>
<td>0.75±0.49</td>
<td>0.75±0.49</td>
<td>0.85±0.39</td>
<td>0.85±0.49</td>
<td>0.85±0.49</td>
<td>0.85±0.39</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>4.82±0.31</td>
<td>5.01±0.36</td>
<td>4.87±0.34</td>
<td>5.05±0.34</td>
<td>4.81±0.34</td>
<td>5.00±0.36</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114.2±11.2</td>
<td>121.5±12.7</td>
<td>111.4±10.4</td>
<td>121.1±12.4</td>
<td>113.1±10.6</td>
<td>124.3±13.1</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>61.1±6.6</td>
<td>61.9±7.4</td>
<td>59.6±6.3</td>
<td>60.4±6.5</td>
<td>60.4±6.6</td>
<td>61.6±7.3</td>
</tr>
<tr>
<td>Mod_IDF, %</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Mod_NCEP, %</td>
<td>13</td>
<td>15</td>
<td>13</td>
<td>15</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

To convert glucose to milligrams per deciliter, divide values by 0.0555; to convert HDL-C to milligrams per deciliter, divide values by 0.0259; and to convert triglycerides to milligrams per deciliter, divide values by 0.0113. BMI indicates body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; Mod_IDF, modified International Diabetes Federation criteria for metabolic syndrome (80th/20th percentiles used as cutoff points); and Mod_NCEP, modified National Cholesterol Education Program criteria for metabolic syndrome (80th/20th percentiles used as cutoff points).

*Data are mean±SD or †median±IQR.

Figure. Prevalence (%) of metabolic syndrome (MetS) according to the modified International Diabetes Federation criteria (80th/20th percentiles used as cutoff points) in the intervention and control groups between 15 and 20 years of age (risk ratio for intervention vs control group, 0.59; 95% confidence interval, 0.40–0.88; P=0.009).
dietary intervention begun early in life may protect against the development of risk profiles that have been shown to predict future cardiovascular disease and type 2 diabetes mellitus.

Recently, we showed that the STRIP intervention had a beneficial effect on ideal cardiovascular health, a cluster of health behaviors and factors described by the American Heart Association. In agreement with this, prior analyses in childhood showed a lower clustering of cardiometabolic risk factors in the intervention group compared with the control group in 5- to 15-year-old participants. We have also reported that the intervention effect on insulin sensitivity and low-density lipoprotein cholesterol continues from childhood to early adulthood. Insulin sensitivity is known to be linked to MetS and to play a role in its pathogenesis. Therefore, the lack of intervention effect on HDL-C may relate to the tendency for a lower risk for high waist circumference,8 as also reported in prior STRIP studies. We suggest that the small, favorable shifts in the individual components among the intervention group, combined with a tendency for stronger associations between the components in the control group, largely explain the observed result of a strong protective intervention effect on MetS and weaker associations for the components.

In the midterm analyses of the STRIP trial, we have previously found that the intervention is beneficially associated with blood pressure. Between the ages of 7 months and 15 years, the intervention children had on average 1-mm Hg-lower blood pressure compared with their control peers. In this study, the intervention reduced the risk of high blood pressure, whereas no statistically significant association was detected when blood pressure was treated as a continuous variable. Reasons for the intervention effect may relate to the tendency for a lower risk for high waist circumference in the intervention group and dietary factors, for example, quality of fat, fiber intake, and vegetable/potassium intake, which are shown to be associated with blood pressure and are affected by the intervention. Additionally, insulin sensitivity may play a role because better insulin sensitivity is associated with lower blood pressure, and the intervention adolescents have been shown to have lower insulin concentrations compared with their control peers. The present study further confirms that the intervention beneficially affects serum triglycerides in boys8 and that the intervention is associated with lower glucose levels in late adolescence. The intervention effect on triglycerides may be explained by higher fiber intake in the intervention group, reflecting better-quality carbohydrates in the diet. The intervention was not associated with HDL-C, as also reported in prior STRIP studies; therefore, the lack of intervention effect on HDL-C.

Table 2. Influence of the Intervention on the Components of MetS*

<table>
<thead>
<tr>
<th>Component</th>
<th>≥80th RR (95% CI)</th>
<th>≥85th RR (95% CI)</th>
<th>≥90th RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High waist</td>
<td>0.78 (0.59–1.03)</td>
<td>0.77 (0.55–1.06)</td>
<td>0.69 (0.46–1.05)</td>
</tr>
<tr>
<td>High glucose</td>
<td>0.86 (0.71–1.05)</td>
<td>0.81 (0.65–1.02)</td>
<td>0.78 (0.59–1.05)</td>
</tr>
<tr>
<td>High triglycerides†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>1.25 (0.95–1.65)</td>
<td>1.25 (0.91–1.71)</td>
<td>1.44 (0.97–2.15)</td>
</tr>
<tr>
<td>Boys</td>
<td>0.71 (0.54–0.94)</td>
<td>0.62 (0.44–0.86)</td>
<td>0.67 (0.44–1.00)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>0.83 (0.70–0.99)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.79 (0.61–1.02)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>0.96 (0.75–1.23)</td>
<td>0.95 (0.71–1.27)</td>
<td>0.80 (0.55–1.16)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; and RR, risk ratio.

*Data are presented as RRs (95% CI) using age- and sex-specific ≥80th (≤20th for HDL-C), ≥85th (≤15th for HDL-C), and ≥90th (≤10th for HDL-C) percentile cutoff points.
†As a result of a significant study group–by–sex interaction, girls and boys were analyzed separately. For other variables, study group–by–sex interactions were nonsignificant.
was anticipated. Although no statistically significant intervention effect on the prevalence of overweight has been found, the trend toward lower risk of high waist circumference observed here may in part underlie the observed lower prevalence of MetS in the intervention group.

Early life exposures are shown to have marked effects on future health. Several studies have demonstrated that environmental and lifestyle factors during childhood are associated with a variety of cardiovascular health outcomes in adulthood, including dyslipidemia, obesity, hypertension, MetS, type 2 diabetes mellitus, and markers of subclinical atherosclerosis. Childhood diet and food patterns are factors that have a key role in the progression of cardiovascular diseases. In the Dietary Intervention Study for Children examining hypercholesterolemic children, the benefits of a low-fat, high-fiber dietary intervention given to childhood on glycemic control were evident in adulthood. Because atherosclerotic cardiovascular diseases are rooted in childhood, their prevention should also start at an early age, preferably before the risk factors have been developed (primordial prevention).

A potential limitation of the STRIP trial is the possible selection bias in the initial recruitment of the participants; families that took part in the trial might have been more interested in health issues. In addition, even though the control group did not receive any dietary counseling, the control children are probably more aware of their health-related factors than typical Finnish children. Such potential biases may have diluted the intervention effects. The children in the STRIP study are all white.

<table>
<thead>
<tr>
<th>Table 3. Association of the STRIP Study Intervention With the Components of MetS*</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>Participants, n</td>
</tr>
<tr>
<td>Waist, cm</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
</tr>
<tr>
<td>Triglycerides,†‡ mmol/L</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
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<tr>
<td>Diastolic BP, mmHg</td>
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</table>

To convert glucose to milligrams per deciliter, divide values by 0.0555; to convert HDL-C to milligrams per deciliter, divide values by 0.0259; and to convert triglycerides to milligrams per deciliter, divide values by 0.0113. BMI indicates body mass index; BP, blood pressure; C, control group; HDL-C, high-density lipoprotein cholesterol; I, intervention group; MetS, metabolic syndrome; and STRIP, Special Turku Coronary Risk Factor Intervention Project.

*Data are mean±SD or median±IQR.
†‡As a result of a significant study group–by–sex interaction, girls and boys were analyzed separately. For other variables, study group–by–sex interactions were nonsignificant.
§P values for the main effects from the model without an interaction term. P values from repeated-measures ANOVA.

Table 4. Pearson Correlation Coefficients (r) for the Components of MetS in the Intervention (n=266) and Control (n=301) Participants*
result may not be generalizable to other ethnicities. The insulin clamp technique was not performed in the participants, so we cannot rule out the possibility of including insulin-resistant participants in the study sample. During an extensive 20 years of follow-up, it is inevitable that loss to follow-up occurred. The most common reasons for discontinuing in the study were moving away from the community, recurrent infections, or reluctance to have blood sampled. We have previously reported that no systematic differences in key study variables such as total cholesterol levels or weight have been found in those continuing in the study and those lost to follow-up. In this analysis, we examined whether waist circumference or other components of MetS influenced loss to follow-up between the intervention and control groups and found no modifying effect. This finding indicates that the observed intervention effect on MetS was not biased by discontinuance of intervention participants with, for example, a higher degree of obesity. Major strengths of the study are the long follow-up period beginning early in life, the large number of repeatedly studied participants, and the use of well-established methods. The intervention aspect of the study is unique in that no other study similar to STRIP with lifelong dietary intervention has been conducted.

Conclusions

The favorable effect of the STRIP intervention on MetS continues through adolescence and into early adulthood. The results indicate that the prevalence of adolescent MetS can be reduced through dietary intervention. These data have important implications for the prevention of future type 2 diabetes mellitus and the promotion of cardiovascular health. Because type 2 diabetes mellitus is beginning to emerge already in childhood, lifestyle choices supporting metabolic health early in life are of great importance. Despite the firm evidence from observational studies that elevated cardiometabolic risk status begins in childhood, no long-term intervention trials exist that would have specifically tested the hypothesis that a reduction in risk factor exposure in childhood decreases the risk of cardiometabolic outcomes in adulthood. Future follow-ups in the STRIP participants will show whether the intervention effect persists into later adulthood and is reflected in cardiometabolic morbidity.

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Disclosures

None.

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Metabolic syndrome is a cluster of cardiometabolic risk factors, typically comprising waist circumference, blood pressure, serum glucose, triglyceride, and high-density lipoprotein cholesterol concentrations. To date, there is no uniform definition for pediatric metabolic syndrome. In adults, metabolic syndrome predicts type 2 diabetes mellitus and cardiovascular diseases, and it is linked to cardiovascular and all-cause mortality. Having metabolic syndrome in adolescence is associated with future risk of type 2 diabetes mellitus and subclinical atherosclerosis. Importantly, resolving metabolic syndrome by adulthood can normalize these risks. This study is the first longitudinal trial to report the effect of repeated, infancy-onset dietary intervention on adolescent metabolic syndrome. In the randomized Special Turku Coronary Risk Factor Intervention Project (STRIP), individualized dietary counseling was given to introduce a heart-healthy diet to the intervention children and subsequently to reduce their risk of atherosclerosis. The main target of the counseling, maintained until participants were 20 years of age, was to replace dietary saturated fat with unsaturated fat. The counseling has led to lower low-density lipoprotein cholesterol concentrations and blood pressure, improved insulin sensitivity, and increased ideal cardiovascular health in the intervention group. This study shows that the intervention given in STRIP decreased substantially, by 41%, the risk of metabolic syndrome in healthy adolescents studied repeatedly between 15 and 20 years of age. The intervention effect was similar regardless of the metabolic syndrome criteria used. An important message to clinicians is that dietary counseling in childhood and adolescence may protect against the development of risk profiles that predict future cardiovascular disease and type 2 diabetes mellitus.
Metabolic Syndrome From Adolescence to Early Adulthood: Effect of Infancy-Onset Dietary Counseling of Low Saturated Fat: The Special Turku Coronary Risk Factor Intervention Project (STRIP)

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Supplemental Methods

The fifth definition for MetS using normative cut-off points for the components was created to complement the use of cohort based cut-off points. For high waist circumference we used data from the NHANES III, where anthropometrics are reported from 1988-1994, prior to the current obesity pandemic. Sex-specific high waist circumference was defined as >75\textsuperscript{th} percentile at ages 15 to 20. Elevated blood pressure was defined according to age- and sex-specific cut-off points proposed by Kaelber and Pickett\textsuperscript{2}. The cut-off points correspond to the lower limit of height (5\textsuperscript{th} percentile) in the prehypertensive blood pressure range (\geq 90\textsuperscript{th} percentile) for a given age and sex in the NHBPEP tables.\textsuperscript{3} High fasting glucose was defined as a concentration >5.6 mmol/l. High triglyceride and low HDL-cholesterol concentration was described using the NCEP criteria: high triglycerides \geq 1.47 mmol/l and low HDL-cholesterol <1.04 mmol/l.\textsuperscript{4} Metabolic syndrome was defined as having any three of the components at a non-normative level.

Supplemental References


\textsuperscript{2}Kaelber DC, Pickett F. Simple table to identify children and adolescents needing further evaluation of blood pressure. Pediatrics 2009;123:e972-e974.


Supplemental Figures and Figure Legends

**Figure legends:**

eFigure 1. Loss to follow-up rates in groups of high or low values of MetS components within STRIP study groups. MetS components were dichotomized using median as a cut-off point. Black solid line: intervention, above median; black dotted line: intervention, below median; grey solid line: control, above median; grey dotted line: control, below median. P-values are from Cox regression models.

eFigure 2. Prevalence (%) of metabolic syndrome according to the modified IDF criteria (85th/15th percentiles used as cut-off points) in the intervention (I) and control (C) groups between ages 15 and 20 years (RR=0.57, 95 % CI=0.37–0.87, p=0.010). RR=risk ratio for intervention vs. control group.

eFigure 3. Prevalence (%) of metabolic syndrome according to the modified NCEP criteria (80th/20th percentiles used as cut-off points) in the intervention (I) and control (C) groups between ages 15 and 20 years (RR=0.67, 95 % CI=0.49–0.91, p=0.011). RR=risk ratio for intervention vs. control group.
Figure 1.
eFigure 2.
Figure 3.