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)

Running title: Nupponen et al.; Infancy-onset Intervention and Metabolic Syndrome

Mari Nupponen, BM; Katja Pahkala, PhD; Markus Juonala, MD, PhD; Costan G. Magnusson, PhD; Harri Niinikoski, MD, PhD; Tapani Rönnemaa, MD, PhD; Jorma S.A. Viikari, MD, PhD; Maiju Saarinen, MSSc; Hanna Lagström, PhD; Antti Jula, MD, PhD; Olli Simell, MD, PhD; Olli T. Raitakari, MD, PhD.

1Research Centre of Applied and Preventive Cardiovascular Medicine, Turku, Finland; 2Paavo Nurmi Centre, Sports & Exercise Medicine Unit, Dept of Health and Physical Activity, Turku, Finland; 3Dept of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland; 4Murdoch Children's Research Institute, Melbourne, Australia; 5Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia; 6Dept of Pediatrics and Adolescent Medicine; 7Clinical Physiology and Nuclear Medicine; University of Turku and Turku University Hospital, Turku, Finland; 8Turku Institute for Child and Youth Research, Turku, Finland; 9Institute for Health and Welfare, Turku, Finland

Address for Correspondence:
Mari Nupponen, BM
University of Turku
Research Centre of Applied and Preventive Cardiovascular Medicine
Kiinamyllynkatu 10
FI-20520 Turku, Finland
Tel: +358405788647
Fax: +35823337270
E-mail: mainnu@utu.fi

Journal Subject Codes: Atherosclerosis:[135] Risk factors, Etiology:[8] Epidemiology, Diabetes:[190] Type 2 diabetes
Abstract

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

**Methods and Results**—The STRIP study (Special Turku Coronary Risk Factor Intervention Project for Children) is a longitudinal, randomized atherosclerosis prevention trial, where 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, HDL-cholesterol) at the age of 15 (n=512), 16 (n=485), 17 (n=475), 18 (n=459), 19 (n=439) and 20 (n=407) years were included in the study. Modified International Diabetes Foundation criteria with 80th/20th percentile cut-off points for the components was primarily applied in statistical analyses, and the results were replicated using other pediatric MetS definitions. Between ages 15 and 20, the prevalence of Mets varied between 6.0-7.5% in participants in the intervention group and between 10-14% in the control group. The long-term relative risk (RR) of Mets was significantly lower in the intervention group (RR=0.59, 95%CI=0.40–0.88, p=0.009). Of the individual MetS components, the intervention decreased risk of high blood pressure in both sexes (RR=0.83, 95%CI=0.70–0.99) and high triglycerides in males (RR=0.71, 95%CI=0.52–0.98). A statistically non-significant reduction was seen in the risk of high waist circumference in the intervention individuals (RR=0.78, 95%CI=0.59–1.03).

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

**Clinical Trial Registration Information**—ClinicalTrials.gov. Identifier: NCT00223600.

**Key words:** atherosclerosis, diabetes mellitus, diet, metabolic syndrome, prevention, longitudinal study
Introduction

In adults, metabolic syndrome (MetS) predicts type 2 diabetes and cardiovascular diseases.\(^1,2\) MetS is also linked to cardiovascular and all-cause mortality\(^2,3\), even after adjustment for traditional cardiovascular risk factors\(^3\) or in the absence of baseline cardiovascular disease and diabetes.\(^2\) We have previously shown that adolescent MetS is associated with future risk of developing type 2 diabetes and subclinical atherosclerosis in adulthood\(^4\) and that resolving MetS can normalize the risks of these outcomes to levels seen in individuals who have never had MetS.\(^5\)

The Special Turku Coronary Risk Factor Intervention Project (STRIP) was launched to study the effect of dietary intervention initiated in infancy and maintained until age of 20 years on atherosclerosis risk factors.\(^6\) 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\(^7\), and led to lower LDL-cholesterol concentrations and blood pressure in the intervention group\(^8,9\), improved insulin sensitivity\(^10\), increased ideal cardiovascular health\(^11\), and enhanced endothelial function.\(^12\)

We have earlier reported preliminary data from the STRIP study that the intervention may reduce the clustering of overweight-related cardiometabolic risk factors between ages 5 to 15 years, i.e. suggesting a beneficial effect on the risk of MetS.\(^13\) In that analysis, however, we were unable to apply pediatric MetS definitions because of the lack of data on waist circumferences on some ages and the lack of data on serum glucose concentrations before age 15. 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 ages 15 to 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 intervention children also received counseling on e.g. 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 e.g. quality of cereals was given repeatedly during the study. Regarding 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 onwards 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 towards dietary changes (e.g. replacement of dairy fat blend spreads with vegetable oil based ones and low-fiber bread with whole-grain bread). The dietary recommendations were based on Nordic nutrition recommendations (30% of energy [E%] from fat, 10-15E% from protein and 50-60E% 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. A physically active lifestyle was encouraged but it was not a structured, continuous part of the intervention.

The control group was met biannually until the age of 7 years and annually thereafter until age 20. 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 one research center.

This study comprised participants who had all components of MetS measured within a study visit between 15 to 20 year 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 STRIP intervention group, 2 twins). The sex distribution was similar within the study groups (intervention group: 47% girls, control group: 49% girls at age 15, chi² p=0.57). Overweight (10.2% at age 15) and obese (2.7% at age 15) 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 the age of 15 years.

**Blood Pressure, Waist Circumference, Weight and Height**

Seated blood pressure was measured after an appropriate rest of at least 15 min twice from 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 with an electronic scale (S10, Soehnle, Murrhardt, Germany) to the nearest 0.1 kg.
and height to the nearest 0.1 cm using a Harpender stadiometer (Holtain, Crymych, UK). Body mass index (BMI) was calculated as weight (kg)/height(m)².

**Laboratory methods**

A venous blood sample was drawn in the morning after an overnight fast annually for the determination of triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and plasma glucose. The sample was allowed to clot at room temperature for 30–60 minutes and centrifuged at 3400×g for 12 minutes. Afterwards 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; inter-assay coefficient of variation 1.8%).¹⁰ Triglycerides were analyzed with the colorimetric glycerol-3-phosphate oxidase p-aminophenazone method (Merck, Darmstadt, Germany) with an automatic Olympus AU400 analyzer.⁸ Serum total cholesterol concentration was analyzed with a fully enzymatic cholesterol oxidase-p-aminophenazone method (CHOD-PAP; Merck).⁸ Serum HDL-C concentration was measured after precipitation of low-density lipoproteins (LDL) and very low-density lipoproteins with dextran sulfate

500 000.⁸,¹⁵ LDL cholesterol (LDL-C) was estimated using the Friedewald formula.¹⁶ 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 MetS¹⁷,¹⁸, we used various definitions used in previous reports.⁴ In total, five criteria to define MetS were applied. Cohort based percentiles and previously published normative values were used as cut-off 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 two of the following four 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 did a similar categorization using ≥85th percentiles (≤15th percentile for HDL-C) as cut-off points (mod_IDF85/15). Third, we used the modified National Cholesterol Education Program (mod_NCEP) definition with the same ≥80th percentile cut-off points as for the mod_IDF definition. For the mod_NCEP 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 cut-off points is provided in the online-only Data Supplement.

To complement the dichotomous definitions, a continuous metabolic syndrome 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

Due to the extensive duration of the study, some participants were lost to follow-up. We have previously shown that there is no association of BMI on the rate of discontinuation. We have also reported that loss to follow-up was not associated with saturated fat intake, weight, or TC concentration. In this analysis, 127 (24%) of the total of 534 participants were lost to follow-up between ages 15 and 20 years. The proportion of premature discontinuation was higher in the
intervention group than in the control group (29% vs. 19%; p=0.008, Cox regression model\textsuperscript{21}). 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 was there any STRIP study group-by-MetS component interactions (\textbf{eFigure 1}) indicating that the greater loss to follow-up in the intervention group was not modified by the MetS components.

\textbf{Statistical Analyses}

Descriptive data are presented as mean±SD or median (interquartile range [IQR]). Serum triglyceride and insulin values were log\textsubscript{e}-transformed for analyses. The association of STRIP study group with the risk of having MetS was studied with a modified Poisson regression model with generalized estimating equation estimation for repeated measures\textsuperscript{22,23} (risk ratios [RR] with 95\%CI were calculated for intervention vs. 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 analysis of variance (RM 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 sex and age were studied in all models initially (interaction terms included in separate analyses). Non-significant (p>0.05) interactions were excluded from the final models. In case of significant sex interaction, girls and boys were analyzed separately. Similarly, if significant study group-by-
age interaction was detected, the analysis was done separately for each age. For significant interactions, Bonferroni corrected CIs or t-tests were calculated. Interaction testing was done to avoid unnecessary splitting of the data which increases the risk of false non-significant findings. Differences in correlation coefficients between the individual components of MetS in the STRIP intervention and control groups, respectively, were tested using normal probability test for difference between Z-transformed correlation coefficients. For the analyses, a mean over all ages was calculated for the MetS components. Strengths of pair-wise correlations between the continuous MetS components in the intervention and control groups were compared to examine whether the study group was associated with the inter-correlations between the components. P-values ≤0.05 were considered statistically significant. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

**Results**

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

**Effect of Intervention on Metabolic Syndrome**

At ages 15 to 20 years, the prevalence of Mets varied between 6 to 7% in the intervention group and between 10 to 13% in the control group (Figure 1). 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, Figure 1; modified IDF with 80th/20th percentile cut-off points). 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, and at different ages. The difference between
intervention and control groups persisted when 85th/15th percentile cut-off points were used to define MetS (eFigure 2; study group-by-sex interaction: p=0.99, study group-by-age interaction: p=0.83). In addition, when the modified NCEP definition was applied, participants in the intervention group had 33% lower risk of MetS compared with the control participants (eFigure 3; study group-by-sex interaction: p=0.94, study group-by-age interaction: p=0.82). The result was also similar when the effect of height on blood pressure was standardized in the MetS definition (intervention vs. 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 cut-off points for the components of MetS (intervention vs. control: RR=0.69, 95%CI 0.46-0.98, p=0.039).

The intervention effect on MetS was further studied using 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 vs. control group p=0.041; intervention: mean±SD=-0.24±2.51, control: mean±SD=0.21±2.82).

**Effect of Intervention on Components of Metabolic Syndrome**

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 lower risk of high triglycerides (RR=0.71, 95%CI=0.54–0.94) while 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 age 18 (RR=0.60, 95%CI=0.38–0.96). The intervention participants had 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 while no association was found in girls. For other continuous components of MetS, there was no intervention effect.

**Effect of Intervention on Inter-correlations of the Components of Metabolic Syndrome**

Strengths of pair-wise correlations between continuous MetS components in intervention and control groups were compared to examine whether the intervention had an effect on the inter-correlations between the components. There was a tendency for stronger correlations between the components in the control participants than in their intervention peers for 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 have lower insulin levels compared with the control group indicating enhanced insulin sensitivity in the intervention participants.10 In this analysis, we therefore investigated whether the association of intervention with MetS persisted after inclusion of insulin to the analysis. When insulin was added to the model, the intervention effect on MetS (modified IDF with 80th/20th percentile cut-off points) was only slightly diluted (intervention vs. 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 ages 15 to 20 years. The intervention effect persisted when different MetS criteria were used. This study is the first longitudinal trial, started in infancy, which reports the effect of repeated dietary intervention on adolescent MetS. Thus, 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.

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.11 In line, prior analyses in childhood showed a lower clustering of cardiometabolic risk factors in the intervention group compared with control group from age 5 onwards to 15-year-old participants.13 We have also reported that the intervention effect on insulin sensitivity10 and LDL-cholesterol18 continues from childhood to early adulthood. Insulin sensitivity is known to be linked with MetS and to play a role in its pathogenesis.18,24 We also found a close association between insulin and MetS in this study. However, the beneficial intervention effect on MetS persisted when insulin was included in the analysis indicating that the effect on MetS was not entirely mediated by better insulin sensitivity among the intervention participants.

In theory, the beneficial intervention effect on MetS could be explained by shifts in the individual MetS components’ distributions and/or by changes in their inter-correlations between the intervention and control groups. We found evidence for the former mechanism. Although the intervention was only modestly associated with the components of MetS when continuous variables were used, we found significant differences when dichotomized components were
compared. When dichotomized as in the definition of MetS, we found that the intervention affected beneficially blood pressure, triglycerides in boys and, borderline significantly, waist circumference in both sexes. In our previous studies investigating the intervention effect on overweight-related cardiometabolic risk factor clustering\textsuperscript{11,13} similar phenomenon has been found: intervention effect on the components is less pronounced compared with the clustered outcome. As no other study similar to STRIP has been conducted, we cannot relate these findings to other cohorts. We additionally observed that the associations between the components of MetS seemed to be stronger in the control group than in the intervention group although statistical significance was not reached. Obviously, larger population studies are needed to specifically test the hypothesis that changes in diet would influence the physiologic links between metabolic risk variables. Taken together, we suggest that the small, favorable shifts in the individual components among the intervention group in combination with tendency to stronger associations between the components in the control group largely explain the observed result of strong protective intervention effect on MetS while weaker associations are found for the components.

In the mid-term analyses of the STRIP trial, we have previously found that the intervention is beneficially associated with blood pressure.\textsuperscript{9} Between ages 7 months and 15 years, the intervention children had on average 1 mmHg lower blood pressure compared with their control peers. In this study, the intervention reduced the risk of high blood pressure while no statistically significant association was detected when blood pressure was treated as a continuous variable. Reasons for the intervention effect may relate to tendency of a lower risk for high waist circumference in the intervention group and dietary factors e.g. quality of fat\textsuperscript{8,25,26}, fiber intake\textsuperscript{10,27} and vegetable/potassium intake\textsuperscript{9,28,29}, which are shown to associate with blood
pressure and are affected by the intervention. Additionally insulin sensitivity may play a role as better insulin sensitivity associates with lower blood pressure\(^{30}\), and the intervention adolescents have been shown to have lower insulin concentrations compared to the control peers.\(^{10}\) In addition, the present study further confirms that the intervention beneficially affects serum triglycerides in boys\(^{8}\), and that the intervention is associated with lower glucose levels in late adolescence.\(^{10}\) The intervention effect on triglycerides may be explained by higher fiber intake in the intervention group\(^{10}\), reflecting better quality of carbohydrates in the diet. The intervention was not associated with HDL-C as also reported in prior STRIP studies\(^{31}\); therefore the lack of intervention effect on HDL-C was anticipated. Although no statistically significant intervention effect on the prevalence of overweight has been found\(^{13}\), the trend towards 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 life-style factors during childhood are associated with a variety of cardiovascular health outcomes in adulthood including dyslipidemia, obesity, hypertension, MetS, type 2 diabetes and markers of subclinical atherosclerosis.\(^{32-36}\) Childhood diet and food patterns are one of the factors that have key role in the progression of cardiovascular diseases.\(^{37-39}\) In the Dietary Intervention Study for Children examining hypercholesterolemic children, benefits of a low-fat and high-fiber dietary intervention given in childhood on glycemic control were evident in adulthood.\(^{40}\) As 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 about 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 Caucasian, therefore the result may not be generalizable to other ethnicities. The insulin clamp technique was not performed in the participants, therefore 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 occurs. The most common reasons for discontinuing in the study were moving away from the community, recurrent infections or reluctance to blood sampling.6 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.6 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 indicates that the observed intervention effect on MetS was not biased by discontinuance of intervention participants with e.g. higher degree of obesity. Major strengths of the study are the long follow-up period beginning early in life and the large number of repeatedly studied participants, and the use of well-established methods. The intervention aspect of the study is unique as no other study similar to STRIP with life-long dietary intervention has been conducted.

In conclusion, the favorable effect of the STRIP intervention on MetS continues through adolescence into early adulthood. The results indicate that the prevalence of adolescent MetS can be reduced through dietary intervention. These data have important implications to the prevention of future type 2 diabetes and the promotion of cardiovascular health. As type 2
diabetes 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 reduction of 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.

**Funding Sources:** This study was supported by Academy of Finland [grant 206374, 251360]; Juho Vainio Foundation; Finnish Ministry of Education and Culture; Finnish Cultural Foundation; Finnish Cardiac Research Foundation; Sigrid Juselius Foundation; Yrjö Jahnsson Foundation; Special Governmental Grants for Health Sciences Research, Turku University Hospital, and Turku University Foundation. CGM is supported through a National Health and Medical Research Council Early Career Fellowship (APP1037559).

**Conflict of Interest Disclosures:** None.

**References:**


subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. *Circulation.* 2010;122:1604-1611.


Table 1. Characteristics of the study cohort and prevalence of the metabolic syndrome at ages 15 to 20 years.*

<table>
<thead>
<tr>
<th>Age</th>
<th>15</th>
<th>15</th>
<th>16</th>
<th>16</th>
<th>17</th>
<th>17</th>
<th>18</th>
<th>18</th>
<th>19</th>
<th>19</th>
<th>20</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
</tr>
<tr>
<td>Participants, No.</td>
<td>247</td>
<td>265</td>
<td>241</td>
<td>244</td>
<td>238</td>
<td>237</td>
<td>230</td>
<td>229</td>
<td>219</td>
<td>220</td>
<td>205</td>
<td>202</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>
<td>61±11</td>
<td>72±11</td>
<td>63±12</td>
<td>74±12</td>
<td>64±12</td>
<td>75±13</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>
<td>167±6</td>
<td>181±6</td>
<td>167±6</td>
<td>181±6</td>
<td>168±6</td>
<td>181±6</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>
<td>21.9±3.5</td>
<td>21.9±3.2</td>
<td>22.4±3.9</td>
<td>22.6±3.6</td>
<td>22.8±4.2</td>
<td>22.9±3.9</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>
<td>72.9±8.4</td>
<td>78.6±7.9</td>
<td>74.2±9.5</td>
<td>80.7±8.7</td>
<td>74.1±9.9</td>
<td>80.9±8.9</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>
<td>4.45±0.77</td>
<td>3.92±0.70</td>
<td>4.56±0.76</td>
<td>4.07±0.74</td>
<td>4.62±0.81</td>
<td>4.06±0.70</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>
<td>1.4±0.27</td>
<td>1.12±0.23</td>
<td>1.46±0.29</td>
<td>1.17±0.24</td>
<td>1.5±0.32</td>
<td>1.18±0.25</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>
<td>2.59±0.66</td>
<td>2.36±0.62</td>
<td>2.59±0.67</td>
<td>2.43±0.66</td>
<td>2.64±0.71</td>
<td>2.42±0.64</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>
<td>0.9±0.54</td>
<td>0.85±0.49</td>
<td>1.0±0.60</td>
<td>1.0±0.50</td>
<td>1.0±0.70</td>
<td>0.9±0.60</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>
<td>4.74±0.30</td>
<td>4.95±0.36</td>
<td>4.74±0.31</td>
<td>4.95±0.39</td>
<td>4.75±0.40</td>
<td>4.93±0.41</td>
</tr>
<tr>
<td>Systolic bp, mmHg</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>
<td>114.2±11.4</td>
<td>126.3±12.5</td>
<td>115.4±11.6</td>
<td>128.1±12.8</td>
<td>116.2±12.1</td>
<td>127.0±12.0</td>
</tr>
<tr>
<td>Diastolic bp, mmHg</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>
<td>61.8±6.5</td>
<td>63.1±7.6</td>
<td>65.1±7.1</td>
<td>66.0±8.0</td>
<td>66.2±7.6</td>
<td>65.8±8.3</td>
</tr>
<tr>
<td>Mod_IDF c</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Mod_NCEP</td>
<td>13</td>
<td>15</td>
<td>13</td>
<td>12</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; calculated as weight in kilograms divided by height in meters squared; HDL-C, high-density lipoprotein; bp, blood pressure; mod_IDF and mod_NCEP, modified IDF and NCEP criteria for MetS, respectively (80th/20th percentiles used as cut-off points).

SI conversion factors: To convert glucose to milligrams per decilitre, divide values by 0.0555; HDL-cholesterol to milligrams per decilitre, divide values by 0.0259; and triglycerides to milligrams per decilitre, divide values by 0.0113.

*Data are mean±SD or †median ±IQR or ‡%.
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# 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>High triglycerides# 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>

Abbreviations: HDL-C, high-density lipoprotein.

*Data are presented as risk ratios (95% confidence interval) using age and sex specific ≥80th (≤20th for HDL-C), ≥85th (≤15th for HDL-C) and ≥90th (≤10th for HDL-C) percentile cut-off points.

#Due to significant study group-by-sex interaction the girls and boys were analyzed separately. For other variables study group-by-sex interactions were non-significant.
Table 3. Association of the STRIP study intervention with the components of MetS*.

<table>
<thead>
<tr>
<th>Age</th>
<th>15</th>
<th>15</th>
<th>16</th>
<th>16</th>
<th>17</th>
<th>17</th>
<th>18</th>
<th>18</th>
<th>19</th>
<th>19</th>
<th>20</th>
<th>20</th>
<th>p for study group‡</th>
<th>p for age‡</th>
<th>p for sex‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRIP Study Group</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, No.</td>
<td>243</td>
<td>269</td>
<td>222</td>
<td>263</td>
<td>218</td>
<td>257</td>
<td>215</td>
<td>244</td>
<td>198</td>
<td>241</td>
<td>181</td>
<td>226</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist, cm</td>
<td>72.8±7.8</td>
<td>73.4±8.8</td>
<td>73.1±7.2</td>
<td>73.9±8.3</td>
<td>74.0±7.3</td>
<td>75.0±8.8</td>
<td>75.1±7.4</td>
<td>76.4±9.5</td>
<td>76.9±8.8</td>
<td>77.9±10.4</td>
<td>76.9±9.3</td>
<td>77.9±10.5</td>
<td>0.19 &lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.3±2.9</td>
<td>20.6±3.5</td>
<td>20.9±2.9</td>
<td>21.2±3.6</td>
<td>21.3±3.0</td>
<td>21.7±3.6</td>
<td>21.6±2.7</td>
<td>22.2±3.8</td>
<td>22.2±3.3</td>
<td>22.7±4.1</td>
<td>22.6±4.0</td>
<td>23.1±4.2</td>
<td>0.20 &lt; .001</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>1.15±0.23</td>
<td>1.14±0.24</td>
<td>1.15±0.26</td>
<td>1.14±0.26</td>
<td>1.21±0.29</td>
<td>1.18±0.26</td>
<td>1.26±0.30</td>
<td>1.26±0.28</td>
<td>1.34±0.30</td>
<td>1.30±0.31</td>
<td>1.35±0.34</td>
<td>1.33±0.32</td>
<td>0.17 &lt; .001</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Triglycerides†, mmol/l</td>
<td>0.75±0.49</td>
<td>0.75±0.39</td>
<td>0.85±0.49</td>
<td>0.85±0.39</td>
<td>0.95±0.59</td>
<td>0.85±0.49</td>
<td>0.90±0.64</td>
<td>0.90±0.54</td>
<td>1.10±0.60</td>
<td>0.95±0.60</td>
<td>1.10±0.70</td>
<td>1.00±0.70</td>
<td>0.19 &lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.90±0.36</td>
<td>4.93±0.35</td>
<td>4.98±0.35</td>
<td>4.94±0.35</td>
<td>4.88±0.41</td>
<td>4.92±0.33</td>
<td>4.88±0.32</td>
<td>4.88±0.37</td>
<td>4.82±0.37</td>
<td>4.87±0.37</td>
<td>4.83±0.43</td>
<td>4.85±0.40</td>
<td>0.16 &lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic bp, mmHg</td>
<td>117.3±12.3</td>
<td>118.6±12.7</td>
<td>116.0±11.7</td>
<td>116.6±13.0</td>
<td>118.5±12.7</td>
<td>118.9±13.5</td>
<td>120.7±12.6</td>
<td>119.8±14.0</td>
<td>122.1±12.5</td>
<td>121.5±14.7</td>
<td>121.1±11.8</td>
<td>121.9±14.8</td>
<td>0.47 &lt; .001</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Diastolic bp, mmHg</td>
<td>60.6±6.7</td>
<td>62.3±7.2</td>
<td>59.5±6.2</td>
<td>60.4±6.5</td>
<td>60.8±6.6</td>
<td>61.2±7.3</td>
<td>62.7±7.1</td>
<td>62.2±7.0</td>
<td>65.5±7.1</td>
<td>65.5±7.9</td>
<td>65.4±7.6</td>
<td>66.5±8.3</td>
<td>0.25 &lt; .001</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HDL-C, high-density lipoprotein; bp, blood pressure; Study groups I, intervention; C, control. SI conversion factors: To convert glucose to milligrams per deciliter, divide values by 0.0555; HDL-cholesterol to milligrams per deciliter, divide values by 0.0259; and triglycerides to milligrams per deciliter, divide values by 0.0113.

*Data are mean±SD or †median ±IQR. ‡P-values for main effects from model without interaction term. P-values from RM ANOVA.

DOI: 10.1161/CIRCULATIONAHA.114.010532
Table 4. Pearson correlation coefficients for the components of metabolic syndrome in the intervention (n=266) and control (n=301) participants.

<table>
<thead>
<tr>
<th></th>
<th>Waist, cm</th>
<th>Systolic bp, mmHg</th>
<th>Diastolic bp, mmHg</th>
<th>Triglycerides, mmol/l</th>
<th>HDL-C, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Systolic bp, mmHg</td>
<td>r=0.45</td>
<td>r=0.43</td>
<td>p=0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic bp, mmHg</td>
<td>r=0.11</td>
<td>r=0.18</td>
<td>r=0.55</td>
<td>r=0.54</td>
<td>p=0.40</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>r=0.23</td>
<td>r=0.22</td>
<td>r=0.019</td>
<td>r=0.12</td>
<td>r=0.015</td>
</tr>
<tr>
<td></td>
<td>p=0.90</td>
<td>p=0.11</td>
<td>p=0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>r=0.26</td>
<td>r=0.35</td>
<td>r=0.16</td>
<td>r=0.26</td>
<td>r=0.050</td>
</tr>
<tr>
<td></td>
<td>p=0.25</td>
<td>p=0.23</td>
<td>p=0.13</td>
<td></td>
<td>p=0.13</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>r=0.055</td>
<td>r=0.24</td>
<td>r=0.14</td>
<td>r=0.29</td>
<td>r=0.076</td>
</tr>
<tr>
<td></td>
<td>p=0.025</td>
<td>p=0.070</td>
<td>p=0.86</td>
<td></td>
<td>p=0.46</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein; bp, blood pressure; r, Pearson correlation coefficients. P-value is for difference in correlation coefficients between the study groups.
**Figure Legend:**

**Figure 1.** Prevalence (%) of metabolic syndrome according to the modified IDF criteria (80\textsuperscript{th}/20\textsuperscript{th} percentiles used as cut-off points) in the intervention (I) and control (C) groups between ages 15 and 20 years (RR=0.59, 95\%CI=0.40–0.88, p=0.009). RR=risk ratio for intervention vs. control group.
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)


Circulation. published online January 20, 2015;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2015/01/20/CIRCULATIONAHA.114.010532

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2015/01/20/CIRCULATIONAHA.114.010532.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

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.¹ Sex-specific high waist circumference was defined as >75th percentile at ages 15 to 20. Elevated blood pressure was defined according to age- and sex-specific cut-off points proposed by Kaelber and Pickett². The cut-off points correspond to the lower limit of height (5th percentile) in the prehypertensive blood pressure range (≥90th percentile) for a given age and sex in the NHBPEP tables.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 ≥1.47 mmol/l and low HDL-cholesterol <1.04 mmol/l.⁴ Metabolic syndrome was defined as having any three of the components at a non-normative level.

Supplemental References


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.
Figure 2.
Figure 3.