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ORIGINAL ARTICLE

Association of BMI and fasting insulin with cardiovascular disease risk factors in seven-year-old Icelandic children

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Abstract

Objective. To look at overweight and common cardiovascular disease (CVD) risk factors, and associations with body mass index (BMI) and fasting insulin in seven-year-old schoolchildren in Reykjavik, Iceland. *Study design.* Cross-sectional study of seven-year-old schoolchildren. *Setting.* Six elementary schools in Reykjavik. *Subjects.* All children attending second grade in these six schools were invited to participate. *Main outcome measures.* Overweight, fasting serum insulin, CVD risk factors. *Results.* Some 14% of the participating children were classified as overweight. Overweight children had higher fasting insulin, higher fasting glucose, and higher systolic and diastolic blood pressure. Furthermore, they had significantly lower total cholesterol (TC), lower high-density lipoprotein (HDL), and lower low-density lipoprotein (LDL) but a similar TC/LDL ratio to normal-weight children. The factors that were strongly associated with BMI were serum fasting insulin, systolic blood pressure (SBP), HDL and fasting glucose, while the sum of four skinfolds, triglycerides, glucose, and LDL were highly associated with fasting insulin. *Conclusion.* Overweight children are likelier to have unfavourable levels of common CVD risk factors included in metabolic syndrome, but surprisingly had lower LDL and TC. Skinfold thickness, higher triglyceride and glucose levels, and being female were associated with increased serum insulin.

Key Words: *Blood pressure, children, cholesterol, family practice, insulin, overweight*

In the last two decades the prevalence of overweight among children has increased substantially in Europe [1,2] and the estimated burden of paediatric obesity is still expected to rise [3]. The World Health Organization views childhood overweight and obesity as important risk factors for serious chronic diseases, including type 2 diabetes and CVD in adulthood [4] and the importance of early intervention is becoming clearer [5].

Several studies have demonstrated that overweight and obesity in children are associated with adverse metabolic effects [6], higher risk of hypertension, and high resting heart rate [7]. Atherosclerotic lesions in children have been shown to correlate significantly with elevations of CVD risk factors such as low-density lipoprotein (LDL), triglyceride (TG), blood pressure (BP), and body mass index (BMI)

The prevalence of obesity and cardiovascular risk factors among children and adolescents is increasing.

- There are important differences in cardiovascular risk factors between overweight and normal-weight children, observed at the age of seven.
- Overweight children are likelier to have unfavourable levels of common CVD risk factors included in the metabolic syndrome.
- Intervention underlining the importance of positive lifestyle in early childhood is needed to prevent the increasing prevalence of obesity.

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during childhood. Furthermore, these lesions have been shown to rise exponentially with an increasing number of risk factors [8,9].

Studies in both adults and children have shown a link between insulin resistance and bodyweight, dyslipidemia, and increased blood pressure [10,11]. It has been suggested that insulin resistance, rather than obesity itself, is the key contributor to important CVD risk factors such as dyslipidemia and hypertension in obese children [12]. In recent years intervention studies using a variety of methods to modify children's lifestyle are showing promising results by improving the metabolic profile of children [13]. However, further knowledge is needed to improve our understanding of the association between insulin and various CVD risk factors in pre-pubertal children.

The objectives of this study were to assess the current prevalence of overweight among seven-year-old children in Iceland and to investigate the association of overweight and insulin and other risk factors for CVD.

Material and methods

Study population

This cross-sectional study obtained data on various cardiovascular risk factors from seven-year-old Icelandic schoolchildren. From a pool of all elementary schools in the city of Reykjavik that had more than 30 students in second grade, a total of six elementary schools were randomly selected and invited to participate. Of the total 326 children invited, 267 (82.2%) gave informed consent and underwent some or all of the measurements.

All measurements were conducted between September 2006 and December 2006. The study was approved by the National Bioethics Committee as well as the Icelandic Data Protection Commission (Study number: VSN b2006050002/03).

Anthropometric measurements

Height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured using standard procedures, and BMI was calculated (kg/m^2). The criteria for overweight and obesity were based on age- and sex-specific BMI reference cut-off points proposed by Cole et al. [14]. This definition categorizes overweight and obesity among seven-year-old boys as BMI over 17.92 and 20.63, respectively. Similarly, the cut-off points for overweight and obese girls at this age are 17.75 and 20.53, respectively. Blood pressure was measured on the left arm of seated participants and the average of three measurements was used for analysis. Subcutaneous skinfold measurements were taken three times at four sites: biceps, triceps, subscapular and suprailiac positions, using a Harpenden skinfold calliper. The mean value was used for analysis.

Blood samples

Fasting blood samples were obtained using standard procedures after overnight fasting. Due to lower participation in this part of the study and a few unsuccessful attempts at collecting blood specimens, a total of 164 usable blood samples were collected (62% of total participants).

Statistics

Descriptive results were expressed as mean and standard deviation, with a 95% confidence interval (95% CI). An independent t-test was used to assess differences between means. Simple linear regression and multiple linear regression were used to investigate the association between both primary dependent variables (BMI and fasting insulin) and common cardiovascular risk factors. Various models using Akaike Information Criterion (AIC) selection criteria were developed and the most parsimonious models used to estimate the strength of the association between independent variables and the two outcomes. The statistical software R version 2.6.2 was used for analysis throughout the study.

Results

Differences between girls and boys

Baseline characteristics of the study populations are given in Table I. The 267 children included in this study were on average 7.3 (SD 0.3) years old, with mean BMI of 16.2 (SD 1.9). Boys were slightly taller and heavier than girls but these differences in height and weight did not yield significant differences in BMI. However, the girls in the study had on average thicker skinfolds (mean difference = 4.7 mm). The average BP of the sample was 94/56 mm/Hg with no significant difference between the sexes. The only significant differences in blood measures between sexes were fasting serum insulin and triglyceride levels, boys having lower levels in both cases.

Differences between overweight and normal-weight children

Approximately 14% of children were either overweight or obese according to cut-off points [14]. Overweight and normal-weight children are contrasted in Table II. Overweight children had significantly lower TC, lower LDL, and lower HDL

Table I. Descriptive statistics of the study population.

	All		Girls		Boys			
	Sample size	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p	95% CI
Age (years)	267	7.3 (0.3)	148	7.3 (0.3)	119	7.2 (0.3)	0.3	−0.01, 0.14
Height (cm)	267	127 (5.2)	148	126.4 (5.6)	119	127.8 (4.7)	0.04	0.12, 2.63
Weight (kg)	267	26.3 (4.4)	148	25.9 (4.5)	119	26.8 (4.2)	0.1	−0.14, 1.96
BMI (kg/m^2)	267	16.2 (1.9)	148	16.1 (1.9)	119	16.3 (1.9)	0.32	−0.22, 0.70
Sum of four skinfolds (mm)	223	27.0 (10.5)	125	28.7 (11)	98	24.7 (9.4)	0.005	1.23, 6.72
Total cholesterol (mmol/L)	164	4.4 (0.7)	88	4.4 (0.6)	76	4.3 (0.7)	0.16	−0.06, 0.34
HDL cholesterol (mmol/L)	164	1.55 (0.3)	88	1.5 (0.3)	76	1.6 (0.3)	0.25	−0.04, 0.14
LDL cholesterol (mmol/L)	164	2.5 (0.6)	88	2.6 (0.5)	76	2.5 (0.6)	0.09	−0.02, 0.32
Triglycerides (mmol/L)	164	0.64 (0.22)	88	0.7 (0.2)	76	0.6 (0.2)	0.003	0.03, 0.17
Fasting glucose (mmol/L)	152	4.6 (0.3)	84	4.6 (0.3)	68	4.7 (0.3)	0.35	−0.05, 0.15
HbA1C (%)	164	5.42 (0.26)	88	5.4 (0.4)	76	5.4 (0.3)	0.86	−0.12, 0.10
S. insulin (mU/L)	164	3.89 (2.05)	88	4.25 (2.11)	76	3.44 (1.91)	0.12	0.19, 1.44
SBP (mmHg)	220	94 (6)	125	94 (7)	97	95 (6)	0.29	−0.8, 2.6
DBP (mmHg)	220	56 (5)	125	55 (5)	97	57 (4)	0.04	0.1, 2.6

Notes: P-values and 95% confidence intervals are shown for the mean difference between boys and girls calculated with an unpaired t-test. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1C: haemoglobin A1C; SBP: systolic blood pressure; DBP: diastolic blood pressure.

cholesterol. These overweight children also had higher fasting glucose and higher insulin levels. Finally, overweight children had significantly higher SBP and higher DBP compared with normal-weight children.

BMI and important cardiovascular risk factors

Table III shows estimated associations between BMI and important independent variables in this study population. Results from simple linear regression are contrasted with the coefficients from the most parsimonious multiple linear regression model, which allows for evaluation of possible confounding by a third variable. Thus elevated levels of insulin, higher fasting glucose, higher SBP, and lower HDL are independently associated with higher BMI value in this study population.

Differences between subjects with high and low fasting insulin

Results from both simple linear regression and multiple linear regression models assessing the relationship between serum insulin and independent variables are given in Table IV. When combined, these variables accounted for approximately 44% of the variability in fasting insulin levels. Children with more subcutaneous fat had higher concentration of serum insulin in their blood. Similarly, having higher

Table II. Comparison of various cardiovascular risk factors between normal-weight and overweight children.

	Normal weight		Overweight			
	Sample size	Mean (SD)	Sample size	Mean (SD)	p	95% CI
BMI	230	15.6 (1.2)	37	19.6 (1.6)	<0.001	3.4, 4.5
Total cholesterol (mmol/L)	142	4.4 (0.7)	22	4 (0.5)	0.004	0.14, 0.72
HDL cholesterol (mmol/L)	142	1.6 (0.3)	22	1.4 (0.3)	0.005	0.05, 0.32
LDL cholesterol (mmol/L)	142	2.6 (0.6)	22	2.3 (0.4)	0.046	0.00, 0.51
Triglycerides (mmol/L)	142	0.6 (0.2)	22	0.7 (0.3)	0.393	−0.15, 0.06
Fasting glucose (mmol/L)	132	4.6 (0.3)	20	4.8 (0.3)	0.007	0.06, 0.35
S. insulin (mU/L)	142	3.9 (2.4)	22	6 (3.8)	<0.001	0.91, 3.34
SBP (mmHg)	190	93.7 (6.5)	30	96.8 (5.1)	0.018	0.68, 5.59
DBP (mmHg)	190	55.6 (4.8)	30	57.5 (4.1)	0.034	1.03, 5.23

Notes: P-values and 95% confidence intervals are shown for the mean difference between normal weight and overweight children calculated with an independent t-test. 95% confidence interval shows the estimated interval where population average may lie. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1C: haemoglobin A1C; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table III. Comparison of estimated coefficients that associate BMI from simple linear regression and multiple linear regression best model.

	Simple linear regression			R-squared = 0.26 Multiple linear regression*		
	Beta	p	95% CI	Beta	p	95% CI
S. insulin (mU/L)	0.36	<0.001	0.22, 0.50	0.23	0.004	0.07, 0.40
SBP (mmHg)	0.08	0.001	0.04, 0.11	0.08	0.001	0.03, 0.13
HDL cholesterol (mmol/L)	−1.92	<0.001	−2.92, −0.93	−1.29	0.01	−2.30, −0.29
Fasting glucose (mmol/L)	1.42	0.005	0.43, 2.40	1.24	0.049	0.10, 2.28

Notes: Beta of 1.42 for fasting glucose means that increasing fasting glucose by one unit (for example from 4.5 mmol/L to 5.5 mmol/L) will on average increase BMI by 1.42 kg/m^2. The same applies for other coefficients. *Best and most parsimonious model was selected using AIC (Akaike information criterion) selection criteria. S. insulin: serum insulin; SBP: systolic blood pressure; HDL: high-density lipoprotein.

serum triglyceride concentration or higher fasting blood glucose was associated with a higher insulin level. However, lower LDL level was associated with higher insulin concentration in this study sample.

Discussion

This study showed that seven-year-old children in Iceland defined as overweight have higher fasting insulin and higher fasting glucose compared with normal-weight children. In addition, BMI was associated with a majority of other CVD risk factors that together comprise metabolic syndrome [15]. Surprisingly, overweight children had lower LDL and TC compared with normal-weight children and girls had higher levels of fasting serum insulin concentration in blood compared with their male counterparts.

Overweight and insulin

Previously, body fatness and fasting insulin were shown to be positively associated in nine- and 15-year-old Icelandic children [16]. This study showed that seven-year-old children who were overweight had both higher fasting insulin and higher fasting glucose compared with normal-weight children, possibly implying insulin resistance in these children. Insulin resistance has been defined as a state in which a given amount of insulin yields a subnormal biological response from fat, muscle, and liver cells [17]. Consequently the body needs to produce more insulin to manage proper blood glucose balance. When the pancreas fails to keep up with the body's need for insulin we see excess glucose in the blood. As higher fasting glucose levels, even within the normoglycaemic range, are an independent risk factor for type 2 diabetes among young men [18] it is likely that these children who are currently overweight at the age of seven will remain at higher risk of developing type 2 diabetes and atherosclerosis in the future.

In our study, being female is associated with higher insulin levels (see Table IV). It has been shown that at birth girls have higher insulin concentrations than boys [19] and girls in the United Kingdom at the age of five are more likely to be insulin resistant than boys of the same age [20]. However, a study from the United States, which tracked children aged 11 to 19, recently reported on

Table IV. Comparison of estimated coefficients that associate serum insulin from simple linear regression and multiple linear regression best model.

	Simple linear regression			R-squared = 0.44 Multiple linear regression*		
	Beta	p	95% CI	Beta	p	95% CI
Sum of 4 SKF (mm)	0.09	<0.001	0.06, 0.12	0.05	0.001	0.02, 0.08
Triglycerides (mmol/L)	3.26	<0.001	1.92, 2.71	2.29	<0.001	1.13, 3.45
LDL (mmol/L)	−0.63	0.032	−1.21, −0.05	−0.71	0.003	−1.17, −0.25
Glucose (mmol/L)	2.58	<0.001	1.61, 3.54	2.81	<0.001	1.88, 3.73
Sex (0=girl, 1=boy)	−0.82	0.012	−1.45, −0.18	−0.62	0.02	−1.17, −0.08

Notes: Beta of 3.26 for triglycerides means that increasing triglycerides by one unit (for example from 0.5 mmol/L to 1.5 mmol/L) will on average increase serum insulin by 3.26 mU/L in univariate analysis. The same applies to other coefficients. *Best and most parsimonious model was selected using AIC (Akaike information criterion) selection criteria. S. insulin: serum insulin; LDL: low-density lipoprotein; SKF: skinfolds.

how sex-specific risk of insulin resistance changes over time [21]. Our results are in line with the results from the United Kingdom suggesting that before puberty sets in girls have higher fasting insulin levels after controlling for fat mass [20]. Dyslipidemia in those with insulin resistance is often characterized by elevated blood TG concentrations and low HDL [22]. Our study showed that triglyceride level is associated with fasting insulin but HDL is not. Even though LDL has not been shown to be associated with insulin resistance [23] it was somewhat surprising to observe a negative association between LDL and fasting insulin in this study sample. We do not propose a biological explanation for this finding, but rather suggest it simply may have occurred due to chance.

Impaired insulin sensitivity has been shown to be a risk factor for atherosclerosis in adults [24], independent of obesity [11]. In obese children and non-diabetic normotensive offspring of type 2 diabetic patients insulin resistance is an independent risk factor for increased carotid artery intima-media thickness (IMT) [25,26]. Girls in our study sample had significantly higher fasting insulin compared with boys. They also had thicker skinfolds, suggesting more subcutaneous fat mass, but when we compared BMI between sexes we found no difference. A hypothetical explanation for this similarity in BMI is that the boys may have had relatively more muscle mass than fat mass, which could further explain the difference in fasting insulin levels since fat mass is thought to be positively associated with fasting insulin concentration in children [16].

Overweight, cholesterol, and metabolic syndrome

In contrast to many other studies [9] the TC, and LDL and HDL levels of participants in our study were all statistically lower in overweight children compared with normal-weight children. However, after controlling for SBP, serum insulin, and fasting glucose, only lower levels of HDL are associated with higher BMI, and the TC/LDL ratio is not significantly different in normal-weight children compared with overweight children.

It has been reported that obese children have a higher risk of developing metabolic syndrome [27]. Our study showed that BMI in seven-year-old children was highly associated with all of the CVD risk factors, which together produce metabolic syndrome. Because obese adults who were obese as children have an especially high risk of developing metabolic syndrome [28] early intervention is of great importance. Furthermore, prevalence of elevated blood pressure has been shown to increase with overweight and obesity in schoolchildren [29]. These findings are in line with our results.

Since atherosclerosis begins in early childhood, and obese children have increased carotid IMT [30] and higher risk of metabolic syndrome [27], the fact that higher BMI during childhood is associated with increased risk of coronary heart disease in adulthood should be of no surprise [31]. As carotid IMT can decrease significantly with weight loss [6,32] it is of utmost importance for early diagnosis and intervention in order to dampen the overweight and obesity epidemic in children worldwide [1].

Despite the fact that knowledge of those who did not participate is important [33], we think that the strength of this study was that all the children were of the same age at study entry, and with a high participation rate it should represent the population at this age in Reykjavik. The cross-sectional design is a limitation, making it difficult to determine causality.

We conclude that overweight among young children is associated with many CVD risk factors, which emphasizes the importance of positive lifestyle habits in early childhood. Intervention is needed to prevent increasing prevalence of serious chronic diseases that result from overweight and obesity. Among seven-year-old children serum fasting insulin is associated with BMI and is a possible marker of high-risk individuals for future development of CVD.

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