

PEDIATRIC HIGHLIGHT

Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada

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OBJECTIVES: To estimate the prevalence of insulin resistance syndrome (IRS) in a representative sample of youth. To test for the independent contribution of insulin resistance (IR) and adiposity to clustering of metabolic risk factors. To identify the underlying components of IRS. To examine the relationship between adiposity and fasting plasma levels of free fatty acids (FFA).

METHODS: In 1999, we conducted a school-based survey of a representative sample of youth aged 9, 13 and 16 y in Quebec, Canada. Age-specific questionnaire data, standardized clinical measurements and a fasting blood sample were available for 2244 subjects. Fasting insulin and HOMA were used as surrogate measures of IR.

RESULTS: In all age–sex groups, adiposity indices, blood pressure (BP), plasma glucose and triglycerides (TG) increased significantly with increasing insulin quartiles while HDL cholesterol (HDL-C) decreased. The overall prevalence of IRS defined as hyperinsulinaemia combined with two or more risk factors including overweight, high systolic BP, impaired fasting glucose, high TG and low HDL-C, was 11.5% (95% CI: 10.2–12.9). There were no significant differences in the prevalence of IRS across ages or between sexes. The independent contribution of adiposity to clustering of risk factors was stronger than that of fasting insulin (or HOMA-IR). Factor analysis revealed three factors (BMI/insulin/lipids, BMI/insulin/glucose and diastolic/systolic BP) consistent across ages suggesting that more than one pathophysiologic process underlies IRS. Although elevation of FFA might be in the causal pathway linking obesity to IR, we did not detect any consistent association between measures of fatness and fasting plasma FFA.

CONCLUSION: IRS is highly prevalent in youth, even among children as young as age 9 y. Factor analysis identifies three physiologic domains within IRS with a unifying role for markers of IR and adiposity.

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Introduction

Obesity is the most common nutritional disorder in North America.^{1–4} Insulin resistance (IR), at least in part, mediates the relation between obesity and an increased risk of cardiovascular diseases (CVD) and type II diabetes.⁵ Insulin resistance syndrome (IRS), also named the metabolic syndrome, is characterized by the clustering of hypertension, obesity, impaired glucose metabolism, abnormalities in fibrinolysis and coagulation, and dyslipidaemia. The distinctive dyslipidaemia associated with IRS includes elevated

plasma triglycerides (TG), low HDL cholesterol (HDL-C), and a preponderance of small dense LDL particles.⁶ IRS has been reported in both adults and children.^{7–12} Although IRS in paediatric populations may have a profound impact on the future burden of disease, there are no data on its prevalence in representative samples of North American or European youth. Thus, the primary objectives of this study were (i) to examine the association between IR, and adiposity, blood pressure (BP), plasma glucose and lipids, (ii) to assess the clustering of metabolic risk factors, and (iii) to estimate the prevalence of IRS in a representative sample of youth in the province of Quebec, Canada.

A critical issue to improved understanding of IRS is the extent to which the IR associated with obesity can explain variation in IRS metabolic components. Therefore, a secondary objective was to test for the independent contributions of

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IR and adiposity (i) to variation in each of BP, glucose and lipid levels, and (ii) to clustering of these risk factors. To further test if IR is the unifying abnormality underlying IRS, we performed factor analysis. Factor analysis is a multivariate correlation method used to reveal underlying structure among variables showing high degrees of intercorrelation, as in the case of risk variables comprising the IRS. Because an elevation in free fatty acids (FFA) might be in the causal pathway linking obesity to IR,¹³ we also examined the relationship between adiposity and fasting plasma levels of FFA.

Subjects and methods

Study population

The survey design and methods, which have been previously reported in detail,¹⁴ are summarized here. The Quebec Child and Adolescent Health and Social Survey used a stratified, cluster sampling design to draw three independent samples of Quebec youth aged 9, 13 and 16 y (one sample per age). The sampling frame represented 97% of all youth targeted. Data were collected in schools between January and May 1999. Response proportions were: (i) questionnaire and anthropometric measures: 83.4% (1267 of 1520 eligible children), 79.2% (1186/1498), and 77.6% (1160/1495) among 9-, 13- and 16-y-olds, respectively; (ii) blood sampling: 51.5% (783/1520), 54.6% (818/1498) and 58.5% (874/1495) among 9-, 13- and 16-y-olds, respectively. French Canadians comprised 79.6% of the sample. Of 2475 blood specimens available, seven were excluded because subjects reported they had diabetes (type unknown); a further 224 specimens were eliminated because (i) 107 parents refused consent for analyses other than glucose and lipids; and (ii) 117 samples were thawed upon arrival at the laboratory or were of insufficient amount. Age-specific comparisons of youth who provided blood samples ($n = 2244$) with those for whom samples were not available ($n = 1369$), revealed no differences in sex or weight category of youth, urban or rural residence, or parental income, education, history of CVD, diabetes, hyperlipidaemia and hypertension. The Ethics Review Board of Ste-Justine Hospital approved the study. Written informed assent and consent were obtained from the participants and their legal guardians.

BP and anthropometric measurements

Height, weight, and triceps and subscapular skinfold thickness were measured according to standardized protocols.¹⁴ Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Subscapular skinfold thickness was used as a marker of central adiposity. BP was measured on the right arm with the child in a sitting position and at rest for at least 5 min, using an oscillometric instrument (Dinamap XL, model CR9340, Critikon Co.). Three consecutive measures were obtained at 1-min intervals and the average of the last two were used in the analyses.

Biochemical analyses

Blood was obtained by venipuncture after an overnight fast in a 1 mg/ml EDTA collection tube. Samples were placed on ice, centrifuged on site, frozen on dry ice, and sent within 24 h to the laboratory where they were stored at -80°C . Plasma insulin was measured with the ultrasensitive kit, Access[®] immunoassay system (Beckman Coulter, Inc) which has no cross-reactivity with proinsulin or C-peptide. Plasma glucose and lipid concentrations were determined on a Synchron Cx[®]7 with Beckman Instruments reagents as previously described.¹⁴ Plasma FFA concentrations were quantified manually by an enzymatic colorimetric method (Wako chemicals). LDL cholesterol (LDL-C) concentrations were calculated according to the Friedewald equation.¹⁵ Homeostasis Model Assessment of IR (HOMA-IR) was calculated as: insulin (mU/l) \times glucose (mmol/l)/22.5.¹⁶

Definition of risk factors and IRS

Values of percentile cut points used to define risk factors were estimated from the study population. Cut points were age- and sex-specific (Table 1) and BP cut points were also height-specific. As recommended,¹⁷ children with BMI \geq 85th percentile were categorized as overweight. High TG, insulin and systolic BP were defined as values \geq 75th percentile, and low HDL-C was defined as values \leq 25th percentile. These thresholds are similar to those used in the Bogalusa Heart Study (BHS) and the Cardiovascular Risk in Young Finns Study (CRYFS).^{8,10} Impaired fasting glucose (IFG) was defined as values \geq 6.1 and $<$ 7.0 mmol/l.¹⁸ None had fasting plasma glucose \geq 7.0 mmol/l.

Although IRS is a well-recognized clinical entity,⁷ there is no internationally accepted definition of childhood IRS. For the purpose of our analyses, we used four related definitions. The first definition (IRS1) required the presence of any three or more of hyperinsulinaemia, overweight, high systolic BP, high TG, low HDL-C and IFG; the second definition (IRS2) required the presence of hyperinsulinaemia and at least two of the other five risk factors. For comparison purposes, we modified IRS1 and IRS2 definitions by using the Cole *et al*¹⁹ international cut points to define overweight and the National High Blood Pressure Education Program (NHBPEP) 90th percentile cut points to define high systolic BP.²⁰

Table 1 Cut points^a used to define risk factors by age and sex

Sex	Age (y)	BMI (kg/m ²)	Insulin (pmol/l)	Triglycerides (mmol/l)	HDL-C (mmol/l)
Boys	9	20.47	35.01	0.85	1.22
	13	23.95	60.04	1.05	1.11
	16	25.90	50.70	1.08	1.00
Girls	9	20.62	40.64	0.96	1.20
	13	23.90	69.92	1.07	1.13
	16	25.95	62.76	1.18	1.13

^aThese cut points correspond to the 85th percentile of the study population for BMI, the 75th percentile for insulin and TG, and the 25th percentile for HDL-C.

Statistical analyses

Means of adiposity indices, BP, glucose and lipid concentrations were compared across insulin quartiles using linear contrasts in one-way analysis of variance. We used Kendall's tau rank correlation to assess the extent to which increasing quartiles of insulin were associated with increasing numbers of risk factors per subject. A one-sided Cochran–Armitage test for trend was used to detect increasing prevalence of IRS across ages, and a χ^2 statistic was used to test for differences between sexes.

We used logistic regression to examine the independent contribution of IR and adiposity to clustering of risk factors (yes/no). Risk factors were considered clustered if subjects had at least three of high systolic BP, high TG, IFG and low HDL-C. Fasting insulin and HOMA-IR were each used in separate analyses as surrogate measure of IR. To assess for trends in clustering of risk factors across insulin or HOMA-IR quartiles, we modelled quartiles as a continuous variable. Z-scores for BMI and subscapular skinfold thickness were used as measures of adiposity in logistic regression analyses. Age- and sex-specific Z-scores were estimated from the study population distribution. We used standardized variables because all age and sex groups were analysed together in logistic regression.

Factor analysis was conducted using the FACTOR procedure in SAS. Principal component analysis was used to extract the initial components. Components were initially selected based on the commonly used criterion of the eigenvalue >1.0 ,^{8,21,22} but that criterion was relaxed to >0.95 ^{21,23} in one subgroup (13-y-olds) to determine if the allowance of a third component would result in a set of factors similar to those of the other subgroups. Once defined, the components were rotated using Varimax orthogonal rotation to facilitate their interpretation. After rotation the components are referred to as factors. Only variables with a factor loading >0.30 were used for interpretation.⁸ We used standardized variables because we conducted factor analysis in total sample (all age and sex groups pooled) as well as by age subgroups. Age- and sex-specific Z-scores for BMI, insulin, glucose, TG, HDL-C, and systolic and diastolic BP were estimated from the study population distribution.

We used Pearson's correlation coefficients adjusted for the variable length of fast (median, 13 h; range, 9–17 h) to examine the association between fasting plasma FFA concentrations and measures of adiposity.

TG, FFA, BMI, triceps and subscapular skinfold thickness values were \log_e -transformed for statistical analyses. To take the complex sampling design into account, sample weights and clustering effects were estimated and incorporated into all computations except those for Pearson's and Kendall's correlation coefficients, and factor analysis. Statistical analyses were performed with SAS statistical software (SAS Institute, Inc, Cary, NC, USA) and SUDAAN (Research Triangle Institute, Research Triangle Park, NC, USA).

Results

In all age and sex groups, the mean values of adiposity indices increased significantly across insulin quartiles (Table 2). Because BMI only indirectly assesses adiposity and because a central distribution of fat might have a more adverse influence than a peripheral distribution, we also examined the association between insulin quartiles and skinfold thickness after adjustment for BMI. Although imperfect, subscapular skinfold thickness is a marker of central adiposity and triceps skinfold thickness is a marker of peripheral adiposity.^{10,24} After adjustment for BMI, the association between subscapular skinfold thickness and insulin quartiles remained statistically significant in 9- and 13-y-old girls, and 16-y-old boys only. The association between triceps skinfold thickness and insulin quartiles remained significant in 16-y-old boys only.

Mean values of systolic BP, diastolic BP, plasma glucose and TG increased significantly across insulin quartiles in all age and sex groups, while HDL-C levels decreased, except in 16-y-old boys (Tables 3 and 4). No significant associations were observed between insulin quartiles and total cholesterol (TC) or LDL-C, with the exception that their concentrations increased with insulin quartiles in 16-y-old boys.

For each age, the distribution of the number of risk factors per subject differed across insulin quartiles (all $P < 0.001$) (Figure 1). Higher insulin quartiles were associated with a greater number of risk factors (Kendall's correlation coefficients (s.e.) = 0.29 (0.03), 0.38 (0.03), 0.25 (0.03), for 9-, 13- and 16-y-olds, respectively), indicating increased risk factor clustering with higher insulin concentrations. Among subjects in the fourth insulin quartile, 18.0, 17.5 and 24.9% of 9-, 13- and 16-y-olds, respectively, had at least three risk factors. Overall, the prevalence of IRS was 14.0% (95% CI: 12.5–15.5) according to the less stringent definition (IRS1) and 11.5% (95% CI: 10.2–12.9) according to the more stringent definition (IRS2). There were no significant differences in the prevalence of IRS across ages and between sexes (Table 5a). In an attempt to provide some, although imperfect, comparisons, we re-estimated the prevalence of IRS in our population by replacing the initial cut points used to define two of the IRS criteria, overweight and high systolic BP, by the international cut points recently published by Cole *et al*¹⁹ for overweight and by the NHBPEP 90th percentile cut points for systolic BP.²⁰ Prevalence of IRS computed according to the original or the modified definitions were similar (Table 5a and b). In all, 94.8% (95% CI: 91.3–96.9) of the subjects classified as having IRS according to the original IRS1 definition were also classified as having IRS according to the modified IRS1 definition; 96.4% (95% CI: 93.2–98.3) of the subjects classified as having IRS according to the original IRS2 definition were also classified as having IRS according to the modified IRS2 definition.

Since BMI and IR are correlated, in order to assess the independent contribution of IR, we examined the association between fasting plasma insulin and BP, glucose and

Table 2 Mean (s.e.) BMI and subscapular and triceps skinfold thickness across insulin quartiles by age and sex

Adiposity index	Sex	Age (y) (n)	Insulin quartile				P*	
			I	II	III	IV	Unadjusted	Adjusted
BMI [†] (kg/m ²)	Boys	9 (340)	15.77 (0.21)	16.58 (0.21)	17.23 (0.26)	19.66 (0.50)	<0.001	NA [‡]
		13 (370)	18.30 (0.23)	18.97 (0.22)	20.61 (0.35)	23.29 (0.54)	<0.001	NA
		16 (373)	21.60 (0.25)	21.18 (0.34)	21.92 (0.31)	25.16 (0.55)	<0.001	NA
	Girls	9 (367)	15.78 (0.21)	16.63 (0.28)	17.47 (0.32)	20.30 (0.50)	<0.001	NA
		13 (351)	18.58 (0.29)	20.35 (0.40)	20.12 (0.38)	23.58 (0.55)	<0.001	NA
		16 (435)	20.56 (0.25)	21.11 (0.30)	21.92 (0.34)	25.19 (0.50)	<0.001	NA
Subscapular skinfold [†] (mm)	Boys	9 (340)	5.80 (0.30)	6.78 (0.35)	8.21 (0.49)	12.31 (0.97)	<0.001	0.752
		13 (366)	7.37 (0.29)	8.18 (0.37)	10.60 (0.69)	15.54 (1.17)	<0.001	0.266
		16 (370)	9.34 (0.39)	9.57 (0.44)	10.91 (0.48)	16.68 (1.03)	<0.001	<0.001
	Girls	9 (365)	6.95 (0.40)	8.05 (0.48)	11.02 (0.83)	14.32 (0.78)	<0.001	0.005
		13 (347)	9.72 (0.41)	12.77 (0.63)	12.23 (0.71)	19.42 (1.18)	<0.001	0.007
		16 (427)	13.06 (0.49)	13.55 (0.47)	14.17 (0.60)	18.75 (0.84)	<0.001	0.361
Triceps skinfold [†] (mm)	Boys	9 (340)	10.14 (0.42)	11.70 (0.51)	13.65 (0.64)	17.24 (1.00)	<0.001	0.956
		13 (367)	11.15 (0.48)	12.20 (0.53)	13.94 (0.74)	18.61 (1.16)	<0.001	0.442
		16 (371)	9.60 (0.57)	9.92 (0.49)	11.80 (0.56)	17.95 (1.02)	<0.001	<0.001
	Girls	9 (365)	12.20 (0.44)	14.05 (0.51)	16.07 (0.68)	19.19 (0.78)	<0.001	0.318
		13 (348)	14.66 (0.51)	17.85 (0.70)	16.13 (0.72)	21.66 (0.84)	<0.001	0.715
		16 (428)	18.00 (0.51)	18.48 (0.58)	19.31 (0.62)	23.92 (0.80)	<0.001	0.176

*P-value for linear trend unadjusted and adjusted for log_e BMI. [†]Untransformed data are presented in the table; log_e-transformed values were used for formal statistical comparisons. [‡]Not applicable.

Table 3 Mean (s.e.) glucose and blood pressure (BP) across insulin quartiles by age and sex

Glucose and BP	Sex	Age (y) (n)	Insulin quartile				P*	
			I	II	III	IV	Unadjusted	Adjusted
Glucose (mmol/l)	Boys	9 (342)	4.99 (0.03)	5.14 (0.04)	5.23 (0.03)	5.31 (0.03)	<0.001	<0.001
		13 (370)	5.15 (0.04)	5.27 (0.04)	5.36 (0.03)	5.41 (0.04)	<0.001	<0.001
		16 (375)	5.17 (0.03)	5.25 (0.04)	5.36 (0.04)	5.46 (0.04)	<0.001	<0.001
	Girls	9 (369)	4.80 (0.04)	4.99 (0.03)	5.08 (0.04)	5.14 (0.04)	<0.001	<0.001
		13 (352)	5.05 (0.04)	5.09 (0.03)	5.27 (0.04)	5.30 (0.05)	<0.001	<0.001
		16 (436)	4.92 (0.04)	5.01 (0.04)	5.07 (0.03)	5.15 (0.04)	<0.001	<0.001
Systolic BP (mmHg)	Boys	9 (339)	101.8 (1.0)	101.9 (1.1)	102.7 (1.2)	106.0 (1.1)	0.005	0.473
		13 (366)	108.7 (1.0)	111.3 (1.2)	114.3 (1.3)	115.2 (1.4)	<0.001	0.410
		16 (375)	121.6 (1.3)	121.0 (1.5)	123.9 (1.4)	127.8 (1.5)	<0.001	0.111
	Girls	9 (364)	99.3 (1.1)	101.4 (0.9)	101.3 (1.0)	105.1 (1.0)	<0.001	0.141
		13 (351)	106.7 (1.0)	110.3 (1.1)	111.9 (1.3)	115.5 (1.3)	<0.001	0.011
		16 (435)	112.2 (1.0)	112.8 (1.0)	114.5 (1.0)	116.5 (1.2)	0.001	0.542
Diastolic BP (mmHg)	Boys	9 (339)	55.4 (0.7)	55.1 (0.7)	56.4 (0.7)	58.6 (0.6)	<0.001	0.006
		13 (366)	57.5 (0.6)	57.1 (0.6)	58.5 (0.8)	59.5 (0.8)	0.030	0.397
		16 (375)	59.0 (0.7)	60.4 (0.8)	61.0 (0.7)	63.3 (0.8)	<0.001	0.005
	Girls	9 (364)	54.9 (0.7)	57.1 (0.6)	55.7 (0.7)	57.8 (0.5)	0.003	0.306
		13 (351)	57.7 (0.8)	58.5 (0.7)	59.9 (0.9)	60.7 (0.7)	0.009	0.077
		16 (435)	60.9 (0.7)	61.2 (0.7)	61.8 (0.7)	62.8 (0.8)	0.046	0.145

*P-value for linear trend unadjusted and adjusted for log_e BMI.

lipids after adjustment for BMI. A strong positive association remained between insulin quartiles and glucose and TG levels (Tables 3 and 4). However, the positive association of

insulin quartiles with systolic or diastolic BP was no longer consistently statistically significant. Similarly, we could no longer consistently observe a significant negative association

Table 4 Mean (s.e.) lipid concentrations across insulin quartiles by age and sex

Lipids	Sex	Age (y) (n)	Insulin quartile				P*	
			I	II	III	IV	Unadjusted	Adjusted
TC (mmol/l)	Boys	9 (342)	3.98 (0.07)	4.04 (0.07)	4.10 (0.08)	4.10 (0.07)	0.231	0.855
		13 (370)	3.88 (0.07)	3.89 (0.06)	3.84 (0.07)	3.84 (0.08)	0.549	0.531
		16 (375)	3.51 (0.07)	3.65 (0.07)	3.56 (0.07)	4.00 (0.08)	<0.001	0.009
	Girls	9 (369)	4.13 (0.07)	4.23 (0.07)	4.29 (0.07)	4.22 (0.09)	0.549	0.927
		13 (352)	3.98 (0.08)	4.01 (0.07)	4.09 (0.08)	4.08 (0.09)	0.752	0.568
		16 (436)	4.02 (0.07)	4.13 (0.08)	4.13 (0.09)	4.26 (0.08)	0.084	0.247
LDL-C (mmol/l)	Boys	9 (342)	2.27 (0.06)	2.30 (0.06)	2.36 (0.06)	2.39 (0.06)	0.182	0.796
		13 (370)	2.23 (0.05)	2.22 (0.06)	2.16 (0.05)	2.17 (0.07)	0.364	0.388
		16 (375)	2.04 (0.06)	2.12 (0.06)	1.97 (0.06)	2.34 (0.06)	0.008	0.159
	Girls	9 (369)	2.41 (0.06)	2.49 (0.06)	2.52 (0.06)	2.49 (0.08)	0.420	0.796
		13 (352)	2.25 (0.06)	2.33 (0.06)	2.35 (0.08)	2.40 (0.07)	0.471	0.597
		16 (436)	2.29 (0.06)	2.31 (0.07)	2.35 (0.08)	2.52 (0.07)	0.033	0.207
HDL-C (mmol/l)	Boys	9 (342)	1.45 (0.03)	1.46 (0.03)	1.43 (0.03)	1.29 (0.02)	<0.001	0.011
		13 (370)	1.36 (0.02)	1.31 (0.02)	1.25 (0.02)	1.17 (0.02)	<0.001	0.006
		16 (375)	1.15 (0.02)	1.15 (0.02)	1.19 (0.03)	1.10 (0.02)	0.186	0.924
	Girls	9 (369)	1.42 (0.03)	1.37 (0.02)	1.38 (0.03)	1.27 (0.02)	<0.001	0.181
		13 (352)	1.39 (0.03)	1.28 (0.02)	1.28 (0.02)	1.22 (0.02)	<0.001	0.075
		16 (436)	1.35 (0.02)	1.37 (0.02)	1.35 (0.03)	1.25 (0.02)	0.004	0.180
TG [†] (mmol/l)	Boys	9 (342)	0.58 (0.03)	0.63 (0.03)	0.68 (0.03)	0.94 (0.05)	<0.001	<0.001
		13 (370)	0.65 (0.02)	0.79 (0.04)	0.95 (0.04)	1.09 (0.06)	<0.001	<0.001
		16 (375)	0.69 (0.03)	0.83 (0.04)	0.88 (0.03)	1.19 (0.08)	<0.001	<0.001
	Girls	9 (369)	0.66 (0.03)	0.80 (0.03)	0.85 (0.04)	1.03 (0.06)	<0.001	0.004
		13 (352)	0.76 (0.03)	0.87 (0.04)	0.99 (0.04)	1.01 (0.04)	<0.001	0.001
		16 (436)	0.85 (0.03)	0.98 (0.04)	0.95 (0.04)	1.07 (0.05)	0.002	0.059

*P-value for linear trend unadjusted and adjusted for log_e BMI. †Untransformed data are presented in the table; log_e-transformed values were used for formal statistical comparisons.

between insulin quartiles and HDL-C. The probability of having at least three of high systolic BP, IFG, high TG and low HDL-C (relative to less than three) increased across insulin quartiles and across Z-scores for BMI and triceps skinfold thickness (Table 6). However, after adjustment for BMI, insulin remained only weakly associated with clustering of risk factors. Conversely, after adjustment for insulin, BMI and triceps skinfold thickness were still strongly associated with clustering of risk factors. Similar results were obtained using HOMA-IR as surrogate measure of IR instead of fasting insulin (data not shown).

To assess for the presence of an underlying structure among metabolic variables, we conducted factor analysis. For each age as well as in the total sample, three factors emerged with eigenvalue >0.95 (Table 7). The lipid factor was characterized by positive correlations with BMI, insulin, and TG and negative correlation with HDL-C. This factor accounted for 22.6–27.1% of the total variance attributable to all variables we considered, by age. The BP factor was characterized by positive correlations with systolic and diastolic BP and accounted for 22.2–23.2% of the total variance, by age. The glucose factor was characterized by

positive correlations with BMI, insulin and glucose except in 13-y-olds, where BMI did not load on this factor. The glucose factor accounted for 17.9–23.4% of the total variance, by age. Using HOMA-IR instead of fasting insulin as proxy measure of IR in factor analysis gave similar results (data not shown).

Finally, we examined the relationship between adiposity and fasting plasma levels of FFA. We observed a weak but statistically significant positive association between BMI and fasting plasma FFA in 16-y-old boys ($r=0.15$, $P=0.003$). We did not detect any significant correlation in any of the other groups ($r=0.02$, 0.08 , 0.02 , 0.04 and -0.02 for 9-y-old boys and girls, 13-y-old boys and girls, and 16-y-old girls, respectively; all $P>0.05$). We obtained similar results for the association between skinfold thickness and FFA (data not shown).

Discussion

Our study is the first to document the extent of the metabolic consequences of the current paediatric obesity epidemic in a representative Canadian population. The BHS,

the Corpus Christi Child Heart Study, the CRYFS and the Belgian Luxembourg Child Study also reported clustering of CVD risk factors with increasing levels of adiposity as well as with increasing levels of fasting insulin in selected American and European populations.^{8–11} However, to our knowledge, prevalence of IRS was not estimated. Since IRS prevalence in

our survey was not different between sexes and across ages, our conservative estimate (IRS2) indicates that 10.2–12.9% of Quebec children and adolescents aged 9–16 y have IRS. The expected prevalence of IRS2 if the criteria used to define it had clustered by chance alone would be 5.6%. Whatever mechanisms are underlying clustering of these metabolic risk factors, our data corroborate other reports^{8–12} that they are operating at an early age.

Trends in childhood IRS should be monitored because of their public health and clinical importance. These trends are however, difficult to quantify or to compare internationally because there is no commonly accepted definition of paediatric IRS. The choice of appropriate thresholds to define CVD risk factors in youth has limitations specific to the paediatric population. BMI, BP and lipid levels change significantly with age and are influenced by sex and ethnicity. Moreover, it is difficult in a paediatric population to define cut points based on biological outcomes such as occurrence of CVD or type II diabetes because this would necessitate studies lasting decades. Although somewhat arbitrary, a statistical approach is usually taken in studies of children^{8,10,17,20} whereby cut points are defined relative to a selected percentile of a reference population based on age, sex and race-ethnicity. The consequence of this approach is that the absolute values of these thresholds differ in different populations, rendering comparisons between reports problematic. The thresholds we chose to define risk factors were similar to those used by the BHS and the CRYFS.^{8,10} Using alternative definitions for overweight and high systolic BP gave remarkably similar prevalence estimate of IRS. Our criteria to identify IRS were comparable to those recently suggested by the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults²⁵ with the exception that we added a measure of IR. Moreover, the difficulties

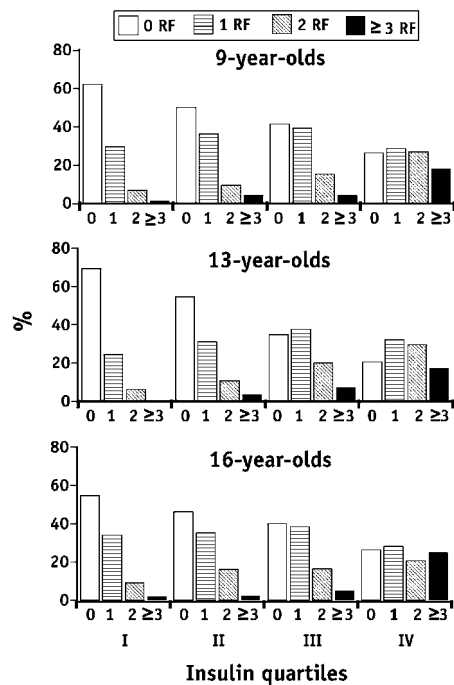


Figure 1 Distribution of the number of risks factors (RF) (overweight, high systolic BP, high TG, low HDL-C, impaired fasting glucose) per subject, by age, across insulin quartiles. For each age, the distribution of the number of risk factors per subject differed across insulin quartiles (all $P < 0.001$).

Table 5 Prevalence (%) (95% CI) of insulin resistance syndrome (IRS) by age and sex

A	IRS1 ^a		P [†]	IRS2 ^a		P [†]
	Boys	Girls		Boys	Girls	
Age (y)						
9	13.1 (9.4–16.8)	14.4 (10.6–18.1)	0.670	10.7 (7.3–14.2)	12.0 (8.5–15.5)	0.648
13	14.3 (10.5–18.1)	14.7 (11.0–18.4)	0.886	11.9 (8.4–15.4)	11.8 (8.4–15.2)	0.968
16	15.2 (11.4–18.9)	12.4 (9.3–15.6)	0.300	12.2 (8.8–15.5)	10.8 (7.8–13.8)	0.574
P (trend) [‡]	0.234	0.247		0.292	0.324	
B	IRS1-modified ^a		P [†]	IRS2-modified ^a		P [†]
	Boys	Girls		Boys	Girls	
Age (y)						
9	13.6 (9.8–17.4)	14.4 (10.6–18.1)	0.785	11.5 (8.0–15.0)	11.8 (8.3–15.2)	0.917
13	16.1 (12.1–20.1)	15.0 (11.3–18.8)	0.738	13.5 (9.8–17.2)	11.8 (8.4–15.1)	0.534
16	18.0 (14.0–22.0)	13.2 (10.0–16.5)	0.087	13.3 (9.8–16.8)	11.3 (8.2–14.3)	0.426
P (trend) [‡]	0.070	0.343		0.251	0.425	

^aIRS1: defined as three or more of hyperinsulinaemia, overweight, high systolic BP, impaired fasting glucose, high TG, low HDL-C. IRS2: hyperinsulinaemia and any two of the other risk factors. IRS1 and IRS2 modified definitions are similar to IRS1 and IRS2 except that cut points used to categorize subjects as overweight or as having high systolic BP were from Cole *et al*¹⁹ and NHBPEP,²⁰ respectively, instead of study population 85th and 75th percentiles, respectively (see Subjects and methods for more details). [†]P-value for comparisons between sexes. [‡]P-value for comparisons across ages.

Table 6 Odds ratios for clustering of risk factors according to fasting plasma insulin and measures of adiposity*

Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Insulin quartile [†]	2.4 (1.7–3.3)	1.4 (1.0–2.0) [‡]
Z-score for BMI [†]	2.8 (2.2–3.6)	2.4 (1.9–3.2) [§]
Z-score for subscapular skinfold thickness [†]	2.9 (2.2–3.8)	2.4 (1.8–3.2) [§]

*Odds ratio (OR) for clustering of risk factors per 1 unit increment in quartile of insulin (or Z-score of BMI or subscapular skinfold thickness); risk factor clustering defined as three or more of elevated systolic BP, impaired fasting glucose, high TG or low HDL-C. [†]Cut points that define quartiles, and Z-scores are age- and sex-specific. [‡]Adjusted for Z-score for BMI. [§]Adjusted for insulin quartile.

Table 7 Factor loadings^a of risk variables for IRS after varimax rotation by age and in total sample

Variable	Loading		
	Factor 1	Factor 2	Factor 3
9-y-olds (n = 700)			
Z-score for BMI	51	45	24
Z-score for insulin	75	37	9
Z-score for glucose	84	–13	–3
Z-score for TG	29	69	11
Z-score for HDL-C	8	–86	4
Z-score for systolic BP	10	–2	87
Z-score for diastolic BP	1	12	85
Variance explained (%)	23.4	22.6	22.2
Cumulative variance (%)	23.4	46.0	68.2
13-y-olds (n = 716)			
Z-score for BMI	64	30	23
Z-score for insulin	58	18	56
Z-score for glucose	–4	8	92
Z-score for TG	74	7	–3
Z-score for HDL-C	–77	12	4
Z-score for systolic BP	10	83	18
Z-score for diastolic BP	2	87	0
Variance explained (%)	27.1	22.8	17.9
Cumulative variance (%)	27.1	49.9	67.8
16-y-olds (n = 817)			
Z-score for BMI	64	21	31
Z-score for insulin	48	11	67
Z-score for glucose	–19	2	85
Z-score for TG	66	17	0
Z-score for HDL-C	–70	10	14
Z-score for systolic BP	18	86	6
Z-score for diastolic BP	0	89	5
Variance explained (%)	23.6	23.2	18.7
Cumulative variance (%)	23.6	46.8	65.5
Total sample (n = 2223)			
Z-score for BMI	60	25	33
Z-score for insulin	50	13	66
Z-score for glucose	–11	3	88
Z-score for TG	72	11	7
Z-score for HDL-C	–77	9	12
Z-score for systolic BP	10	86	10
Z-score for diastolic BP	4	87	3
Variance explained (%)	24.7	22.7	19.3
Cumulative variance (%)	24.7	47.4	66.7

^aFactor loadings represent the correlation between the individual variable and each factor; variables with a factor loading >0.30 are in bold.

encountered in defining IRS in youth should not detract from the clinical significance of having several metabolic risk factors clustered at the unfavourable extremity of the distribution since most of them exert their adverse consequences on a continuum rather than in a dichotomous manner.²⁶

BMI only indirectly assess adiposity and reflects total rather than regional fatness. We found that skinfold thickness gave little additional information above that provided by BMI on the association between IR and adiposity. The investigators of the CRYFS made similar observations.¹⁰ However, it was interesting to note that, in 16-y-old boys, both triceps and subscapular skinfold thickness, remained significantly associated with insulin levels after adjustment for BMI. The normal increase in BMI with growth and maturation reflects gains in fat-free mass more than fat mass. In 16-y-old boys, this phenomenon might be more important than in girls or younger boys, making skinfold thickness a valuable addition to the evaluation of fatness.

A critical question in the pathophysiology of IRS is whether the IR associated with obesity can account for all the metabolic abnormalities characteristic of IRS. Our data suggest that variation in fatness alone cannot explain all the variation in the metabolic components of IRS, and especially in glucose and TG concentrations. On the other hand, the independent contribution of adiposity to clustering of risk factors appears stronger than that of insulin (or HOMA-IR). It is possible that adiposity as proxied by BMI (or triceps skinfold thickness) is measured with greater precision than IR as estimated by fasting insulin levels (or HOMA-IR). Alternatively, mechanisms other than IR may link adiposity and the risk factors we examined. Batey *et al*⁹ also observed stronger correlations between BMI and systolic BP and HDL-C than between insulin and systolic BP and HDL-C. Srinivasan *et al*²⁷ showed that childhood BMI and insulin were significant predictors of adulthood clustering of risk factors with BMI being the strongest. Altogether these observations suggest that, although IRS is a clinically recognizable entity, there is more than one mechanism underlying its pathophysiology and that this heterogeneity can be detected early. This hypothesis is supported by factor analysis, which revealed three underlying factors that were consistent across ages. These factors explained 66–69% of the total variance and were interpreted as (1) BMI/insulin/lipids, (2) BMI/insulin/glucose and (3) diastolic/systolic BP. Two measured risk variables, BMI and insulin, were associated with more than one factor uncovering unifying commonalities between physiologic domains.

Previous factor analyses of IRS metabolic variables have found 2–4 factors underlying the overall correlation between risk variables.^{8,21–24,28} Most studies have been done in adults of diverse racial/ethnic groups.^{21–24} Only one study has been conducted in paediatric subjects. Chen *et al*,⁸ who applied factor analysis to the metabolic variables of IRS in the biracial population of children, adolescents and young

adults from the BHS, found two uncorrelated factors that were interpreted as ponderal index/insulin/glucose/lipids and insulin/BP. Differences in the race, sex and age composition of the study samples as well as variations in number of variables included and methods used for interpretation preclude formal comparisons between studies. However, it is worth noting that all studies have found more than one underlying factor, which does not support the unity hypothesis for IRS.

In spite of the growing evidence linking IR of obesity to FFA metabolism,^{5,13} we could not demonstrate any consistent relationship between fasting plasma FFA concentrations and BMI. The biological imprecision associated with a single measurement of FFA, the cross-sectional design of our study and the absence of other reports on the association between FFA and BMI in youth limit the interpretation of our results. However, among adults, both the Paris Prospective Study and the Quebec Cardiovascular Study^{29,30} failed to detect an association between fasting plasma FFA and BMI. These findings do not preclude an important role of elevated postprandial FFA levels and/or increased adipose tissue fatty acid flux to liver and muscle in IR; more likely, such elevations may only be poorly reflected in fasting plasma FFA concentrations.

In conclusion, IRS can be detected as young as age 9 y and its estimated prevalence in the paediatric population examined is as high as 11.5% (95% CI: 10.2–12.9). Although IRS is a clinically recognizable entity, our study and other reports suggest that there is more than one mechanism underlying its pathophysiology. However, increased adiposity is strongly associated with clustering of risk factors and concerted efforts by researchers, clinicians, public health and public policy experts are needed to prevent the adverse consequences of obesity on the health and well-being of future generations.

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