Diagnosis and treatment of obese children with insulin resistance

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Chapter 3

Definition of Insulin Resistance affects prevalence rate in pediatric patients; A systematic review and call for consensus

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Accepted for publication in JPEM

Abstract

Background

As a result of the rising prevalence of childhood obesity, there is an increasing interest in the type 2 diabetes mellitus precursor insulin resistance (IR). The aim of this study is to review definitions (methods and cut-off values) to define IR in children and to apply these definitions to a previously described obese pediatric population.

Methods

A systematic literature review on prevalence and/or incidence rates in children was performed. The extracted definitions were applied to an obese pediatric population.

Results

In the 103 identified articles, 146 IR definitions were reported based on 14 different methods. Fasted definitions were used 137 times, whereas oral/intravenous glucose tolerance test derived methods were used 9 times. The homeostasis model for the assessment of insulin resistance (HOMA-IR) and fasted plasma insulin (FPI) were the most frequently used fasted methods (83 and 37 times, respectively). A wide range in cut-off values to define IR was observed, resulting in prevalence rates in the pre-defined obese pediatric population between 5.5% (FPI > 30 mU/l) and 72.3% (Insulin Sensitivity $Index_{Matsuda} \leq 7.2$).

Conclusions

To compare IR incidence and prevalence rates in pediatric populations, a uniform definition of IR should be defined.

Introduction

As the prevalence of childhood obesity and consequently type 2 diabetes mellitus (T2DM) is rising [1-3], there is an increasing interest in Insulin Resistance (IR) as a well-known precursor and risk factor for T2DM [4-7]. The recognition of IR in (obese) children and adolescents at risk for T2DM is important in order to implement preventive measures for T2DM, since T2DM causes major health care costs and burden for the patient [8-11]. Early prevention by recognising IR is therefore important.

The gold standard to determine IR is the euglycemic-hyperinsulinemic clamp study [12,13]. The euglycemic-hyperinsulinemic clamp study measures the glucose uptake, while the subject receives exogenous insulin, resulting in a hyperinsulinemic state. Subjects who are sensitive for insulin will require higher amount of glucose infusion than subjects who are less sensitive for insulin (insulin resistant) to remain euglycemic. This technique requires infusion of both insulin and glucose, and frequent blood sampling to control the hyperinsulinemic and euglycemic state, which is a large burden for the patients. Moreover, expertise in managing the glucose and insulin infusions is essential in order to guarantee patients safety and reliable test results. Because of this invasive and time consuming character, the euglycemic-hyperinsulinemic clamp study is not standard of care in pediatric patients [13].

As alternatives, many less invasive methods have been developed to establish IR in daily clinical practice [14-17]. These methods vary in terms of parameters that are needed to calculate IR and in invasiveness. Some methods are based on measurements in fasted blood samples, whereas others require measurements derived from an oral glucose tolerance test (OGTT), which is used in daily practice or a (frequently sampled) intravenous glucose tolerance test ((FS)IVGTT), which is not suitable for daily practice. Most frequently used methods based on fasted blood samples are the homeostasis model for the assessment of insulin resistance (HOMA-IR), the quantitative insulin-sensitivity check index (QUICKI) and the fasted glucose/insulin ratio (FGIR). The use of fasted plasma insulin as measure for IR has been described frequently as well [18]. Most often used methods based on OGTT or (FS)IVGTT are the Insulin sensitivity indexes of Cederholm, Belfiore or Stumvoll (based on OGTT) or the Minimal model analysis of frequently sampled intravenous glucose tolerance test [13,19].

However, there seems no consensus yet on which method and cut-off value is the preferable one [12,18,20]. Therefore, all methods are being used concurrently, which impedes comparison of incidence and prevalence rates of IR between populations and countries and to study these rates over time. Therefore, the aim of this study is to review the different methods and definitions of IR as used to estimate prevalence rates of IR in pediatric populations. First, we present an overview of the definitions and cut-off values used to determine IR in publications describing the prevalence of IR in

children and adolescents. Secondly, to illustrate the impact of the definition on the prevalence of IR, we calculated the prevalence of IR using the different definitions in a previously described population of obese children and adolescents from a pediatric obesity outpatient clinic [21].

Methods

Systematic review of definitions of IR

A systematic review of available literature in The Cochrane library, PubMed and Embase was performed in December 2014. The search strategy is displayed in Appendix 1. After importing the results into Refworks (www.refworks.com) and removing duplicates, abstracts were screened for title and abstract. The exclusion criteria were: language (other than English, French, German, Spanish or Dutch); review articles; study population > 19 years of age; and the lack of reporting on the prevalence of IR in the aim or results part of the abstract. Publications were checked for full text availability. Conference abstracts without a full text publication were excluded, as well as articles not clearly describing a definition for IR. From the articles that fulfilled the criteria, methods defining IR (including mathematical formula), parameters used in the method and the used cut-off values were extracted.

Application of reported definitions to a previously described population of obese children

The definitions reported in the above-described publications were applied to a previously reported population of 311 obese children and adolescents from a pediatric obesity outpatient clinic [21]. As part of standard of care, all these children underwent an OGTT. Data were collected retrospectively. Collected data were anthropometric measurements, fasted plasma glucose (FPG), fasted plasma insulin (FPI) and 2-hour plasma glucose measured during an OGTT. A detailed description of the data collection is provided in a previously published study [21]. The characteristics of the population of obese children are displayed in table 1.

If the same cut-off values were reported in different studies as less or greater than (< or >) and less or greater than or equal to (≤ or ≥), we only calculated the prevalence of IR with the definition using less or greater than (< or >).

Table 1. Characteristics of the population of obese children visiting a pediatric obesity outpatient clinic between January 2006 and December 2009 (n=311) [21]

	Mean	Range
Age	10.83 (3.20)	2.4 – 17.7
Male (%)	50.5	-
Height, cm	149.4 (18.5)	90.5 – 185.8
Weight, kg	66.7 (25.9)	20.7 – 153.9
BMI, kg/m^2	28.71 (5.23)	20.24 – 47.83
BMI-SDS	2.93 (.49)	2.31 – 5.52
FPG, mmol/l	5.0 (0.5)	3.4 – 8.6
FPI, µU/l	12.7 (10.0)	2 – 61
2hr-PG, mmol/l	6.4 (1.5)	3.3 – 20.3
T2DM, n (%)	5 (1.6)	-

Abbreviations: BMI – Body mass index; BMI-SDS – Body mass index standard deviation score

Data analysis

IBM-SPSS version 21.0 was used to calculate IR according to the different definitions, and to calculate the percentage of the population being insulin resistant according to the different definitions.

Results

Searching the three databases yielded 4.596 unique results. Screening of title and abstract led to exclusion of 4430 articles. Of the remaining 166 articles, 103 articles could be included for data extraction (figure 1). Study characteristics of all included studies are summarized in Supplementary Table 1.

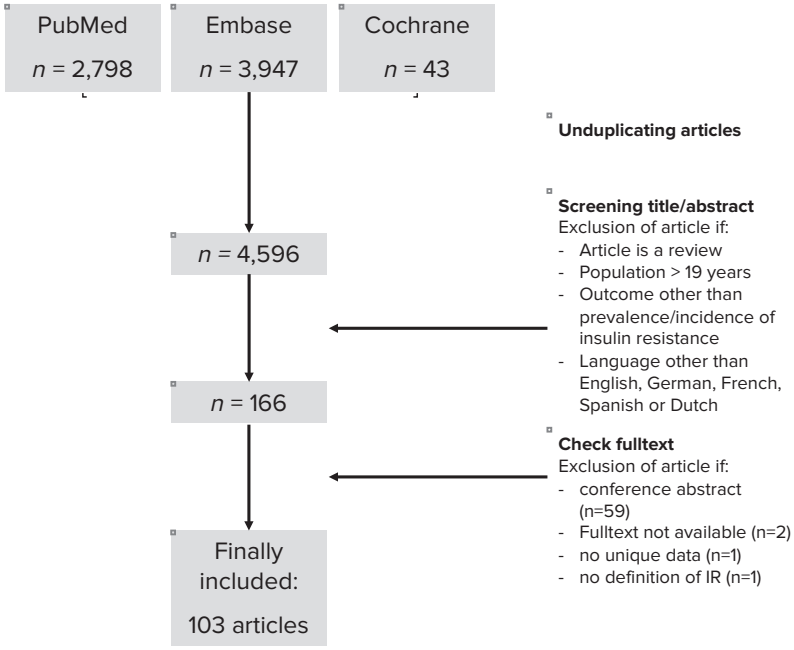

Figure 1. Flowchart of literature search

Methods to determine IR

Table 2 gives an overview of the reported methods to determine IR extracted from the 103 articles. These articles were reporting on 146 definitions. Fasted definitions were used 137 times, whereas OGTT/IVGTT derived methods were used 9 times.

Overall we identified 14 methods to determine IR. Seven (50%) methods are based on parameters derived exclusively from fasted blood samples, the other seven use parameters of fasted blood samples combined with parameters obtained from an OGTT or IVGTT. Out of the fasted methods, HOMA-IR and FPI were the most frequently used methods to determine IR: these were reported 83 and 37 times, respectively. The other five fasted methods were each used one to nine times, and the seven OGTT/IVGTT based methods were used one or two times.

FPI was used as parameter in 11 out of 14 methods. In two methods, the insulin concentration derived from the OGTT was used; one definition defined IR based on the insulin value after 120 minutes and the other method used the maximum concentration during the OGTT. The only method not using insulin was the definition based on C-peptide (Table 2).

Table 2. Overview of reported methods and range of used cut-off values to determine IR in children.

Method	Parameters	Formula	Range of used cut-off values	Number of studies using method*
Based on fasted samples				
HOMA-IR	FPG, FPI	(FPG (mmol/l)*FPI(mU/l))/22.5	> 1.14 – 5.56	83
FPI	FPI	NA	7.34 – 30 mU/l	37
QUICKI	FPG, FPI	1/[log (FPI (mU/ml))+log (FPG (mg/dl))]	0.300 – 0.360	9
FGIR	FPG, FPI	(FPG[mg/dL]/FPI [mIU/L])	< 6 - 7	4
HOMA2	FPG, FPI	Computer model: HOMA2-calculator: http://www.dtu.ox.ac.uk/homa	> 1.53 - 2	2
McAuley-index	FPI, triglycerides	(2.63 − 0.28 ln[FPI] − 0.31 ln[fasted triglycerides])	≤ 6.3	1
C-peptide	C-peptide	NA	≥4.4 ng/ml	1
Based OGTT/IVGTT derived samples				
Insulin during OGTT	Insulin at 120’	NA	>45-75 mU/l	2
OGIS	Glucose at 0’, 90’ and 120’. Insulin at 0’ and 90’	Webcalculator: http://webmet.pd.cnr.it/ogis/ogis.php	<400 -436	2
Maximum insulin during OGTT	Insulin max	NA	>150 mU/l	1
$ISI_{Matsuda}$	FPG, FPI, Glucose and insulin during OGTT at 30’, 60’, 90’ and 120’	10.000/ √((FPG (mg/dl) × FPI (µU/ml) × (Mean OGTT Glucose (mg/dl) × Mean OGTT Insulin (mU/l))	≤ 7.2	1
Si(IVGTT)	Glucose and insulin during IVGTT at -5’, -1’, 2’, 4’, 8’, 10’, 19’, 22’, 30’, 40’, 50’, 60’, 70’, 90’, 180’ and 240’.	Computerized model, using the program MINMOD.[19]	$4.5x10^4$ µU/ml/min	1
$IRI_{Belfiore}$	Glucose and insulin during OGTT at 0’, 60’ and 120’.	2/[[1/(GLYp x INSp)]+1]	> 1.27	1
Σ insulin during OGTT	Insulin during OGTT at 0’, 30’, 60’, 90’ and 120’	$Insulin_0$ + $insulin_{30}$ + $insulin_{60}$ + $insulin_{90}$ + $insulin_{120}$	> 300 µU/ml	1

* Some studies used more than one definition.

Abbreviations: *FGIR – Fasted glucose to insulin ratio; FPG – fasted plasma glucose; FPI – Fasted plasma insulin; HOMA(-IR) – Homeostasis Model Assessment (for Insulin Resistance); IRI – insulin resistance index; ISI – Insulin sensitivity index; NA – not applicable; OGIS – oral glucose insulin sensitivity; OGTT – oral glucose tolerance test; Si(IVGTT) – insulin sensitivity from intravenous glucose tolerance test; QUICKI – quantitative insulin-sensitivity check index.*

Cut off values

Table 2 provides for each of the methods to determine IR, the range in reported cut-off values. For the fasted methods, typically wide ranges in cut-off values were observed: for the commonly used method HOMA-IR, cut-off values ranged from 1.14 to 5.56. The same was observed for FPI with cut-off values ranging from 7.34 to 30 mU/l. In the less frequently used OGTT derived methods, a wide range in cut-off values was reported as well: for insulin at 120 minutes during the OGTT this range varied between 45-75 mU/l (Table 2).

In addition, some studies used separate cut-off values for boys and girls, for example for HOMA-IR 2.28 and 2.67, respectively, and for prepubertal and pubertal children, for example QUICKI <0.33 for prepubertal and <0.36 for pubertal children.

Application of definitions for IR to a population of obese children and adolescents

Figure 2 shows the results of the application of the different definitions to the available clinical data of a population of 311 obese children and adolescents from our pediatric obesity outpatient clinic [21].

All fasted methods except C-peptide could be applied as well as prevalence rates based on different cut-off values per pubertal stage. For the OGTT/IVGTT based methods, results of Si(IVGTT)and $IRI_{Belfiore}$ could not be presented from the available data.

Comparing the prevalence rates of definitions based on fasted blood samples only, the lowest prevalence was 5.5% (FPI > 30 mU/l) and the highest prevalence was 64.0% (FPI > 7.34 mU/l). For the definitions based on OGTT/IVGTT derived values, the lowest prevalence was 18.8%, based on oral glucose insulin sensitivity (OGIS) < 400, and the highest prevalence was 72.3% ($ISI_{Matsuda} \leq 7.2$).

For the HOMA-IR and the QUICKI, the range in prevalence due to the variation in cut-off values was 10.0-62.0% and 10.9-65% respectively. For FPI this range was even wider: 5.5-64.0%. For the OGTT derived definition based on insulin at 120' the prevalence rates were 34.5-63.2%.

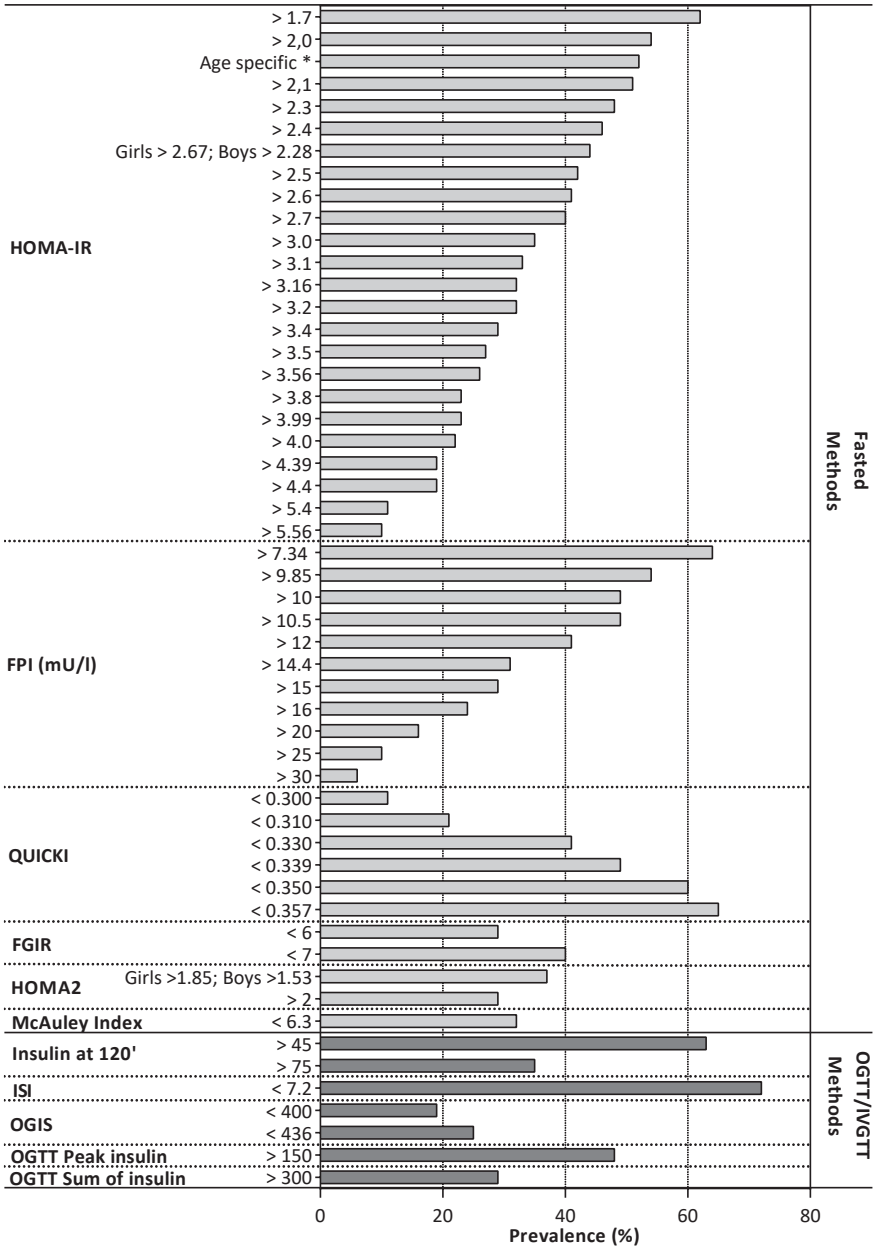

Figure 2. Prevalence of IR in a pediatric population visiting an obesity outpatient clinic (n=311) using different methods and cut-off values of IR.

Abbreviations: *FGIR – Fasted glucose to insulin ratio; FPI – Fasted plasma insulin; HOMA(-IR) – Homeostasis Model Assessment (for Insulin Resistance); ISI – Insulin sensitivity index; OGIS – oral glucose insulin sensitivity; OGTT – oral glucose tolerance test; QUICKI – quantitative insulin-sensitivity check index.*

** Age-specific cut-off values for HOMA-IR: 2-5 yr > 1.14; 5.1-10 yr > 1.67 ; 10.1-15 yr > 2.53; 15.1-19yr > 2.52*

Discussion

The current review of the pediatric literature shows that many different methods and cut-off values are used to determine IR in children and adolescents. The impact of these different definitions on prevalence rates is demonstrated by applying the various definitions to a given dataset of obese children and adolescents, which resulted in a wide range of prevalence rates (i.e. 5.5 – 72.3%). This finding emphasizes the need for a standard definition to be able to compare incidence and prevalence rates of IR between populations and countries and particularly to study these rates over time.

The gold standard test for IR is the euglycemic-hyperinsulinemic clamp. However, this test is not useful for screening purposes in clinical practice because of the expertise needed to perform the test on one hand, and the invasive and time-consuming character of the test, resulting in high burden for the patient on the other hand. As a result, the euglycemic-hyperinsulinemic clamp is only used in experimental settings. Due to the invasive character of the gold standard test for IR, many surrogate methods have been developed. Different studies have been performed to determine the correlations of the methods with the euglycemic-hyperinsulinemic clamp. However, most of these studies were performed in adults, and few of them in pediatric populations. In pediatric populations, the methods based on fasted blood samples, i.e. HOMA-IR, QUICKI and FGIR, have moderate to strong correlations with IR assessed with the euglycemic-hyperinsulinemic clamp, respectively 0.51-0.81, 0.43-0.91 and 0.25-0.92 [6,12,13,22-24]. For the OGTT derived methods, the $ISI_{Matsuda}$ index has a moderate to good correlation as well (0.74-0.78). No data are available for the correlation between the euglycemic-hyperinsulinenic clamp and the $IRI_{Belfiore}$ index in pediatric populations [13]. Since all indices have moderate to good correlations, this criterion does not distinguish in which method would be the best to use.

The optimal test to define IR in children and adolescents should be in our opinion minimally invasive and pose a minimal burden to the child, in order to be widely applicable in the growing population of obese children and adolescents. Therefore, methods based on fasted blood samples have an advantage over methods using blood samples obtained during an OGTT or IVGTT. Although an OGTT or IVGTT is less invasive than the euglycemic-hyperinsulinemic clamp, repetitive vena punctures or a venous cannula over 120 minutes are necessary for collecting blood samples, while fasted methods only require one vena puncture to collect the blood sample.

Another criterion for the preferred method is the reproducibility. The test has to be reliable in repeated measurements, as it will be used for the follow up of children with IR. As described previously, many studies in pediatric populations focus on the correlation of surrogate methods with a gold standard test, unfortunately they do not describe the reproducibility. The available data for reproducibility for the methods to

determine IR are from adult studies. Henriquez et al studied in 78 adults without T2DM the reproducibility of HOMA-IR, QUICKI and FPI. Fasted blood samples were taken twice from each participant within 30 minutes on the same day. This resulted in a coefficient of variation (CV) for HOMA-IR of 11.8% (7.8-11.9), for QUICKI 1.8% (1.1 – 2.9) and for FPI 13.4% (8.8 – 21.9) [25]. The low CV reported for the QUICKI was however debated by Antuna et al. because this measure is composed of log transformed values of FPG and FPI [26]. When the CV of log transformed HOMA-IR values are compared to the CV of the QUICKI, similar, low CV's were found for both measures. Since all of these formulas are based on the same measurements of glucose and insulin, the CV is not discriminating between HOMA-IR and QUICKI either.

Finally, the method should preferably be easy to use in daily clinical practice. HOMA-IR is easier to calculate than QUICKI, because the QUICKI uses log-transformed glucose and insulin values (Table 2), even though in this era of apps this may be debated. While there seems not much difference between the HOMA-IR and the QUICKI, we propose to use the HOMA-IR because its ease of use and because our study shows that HOMA-IR is already the most frequently used method to determine IR in pediatric study populations

In addition to the different methods described, we observed a wide range in cut-off values within the different methods. This wide range of cut-off values leads to a large variation in the prevalence of IR even when one method (e.g. HOMA-IR) is used (Figure 2). The definition of a cut-off value for IR with clinical relevance to identify children and adolescents at risk for T2DM, will help the clinician to select the patients who require lifestyle intervention to prevent or delay the onset of T2DM.

In this study, more than 25 cut-off values for HOMA-IR have been described, and still it is not clear which cut-off value is the best to define IR. To date, studies are available on the use of HOMA-IR as screening measure to identify children and adolescents with impaired glucose tolerance and T2DM during an OGTT. To identify T2DM in a population of obese children and adolescents, Shah et al. reported a HOMA-IR value of 7.9 as the best critical value with a sensitivity of 62% and specificity of 70%. Unfortunately, they did not report on the best value to identify impaired glucose tolerance in their study population [27]. The study of Brar et al, who studied the optimal threshold for impaired glucose tolerance or T2DM, identified a cut-off value of 3.4 in a population of obese pediatric patients [28]. This cut-off value resulted in a sensitivity of 72.2% (46.4-89.3) and a specificity of 60.7% (50.8-69.9%) for impaired glucose tolerance or T2DM during an OGTT. Other cut-off values studied were 2.7, 3.1 and 4.0, resulting in lower sensitivity and specificity [28]. In a study from our own group in overweight and obese children screening with FPG and HOMA-IR of 3.4 identified all cases of T2DM and up to 64% of cases of impaired glucose tolerance [21]. The use of HOMA-IR with cut-off value of 3.4 resulted in sensitivity of 70% and specificity 72.6%, with a positive predic-

tive value of 21.4% and a negative predictive value of 95.7%. However, to properly define the cut off value for the HOMA-IR and use it as a screening measure in obese children to predict impaired glucose tolerance and T2DM in the future, longitudinal epidemiological studies of a cohort of obese children and adolescents should be performed, with regular checks of their insulin sensitivity state and glucose metabolism including an eventual diagnosis of T2DM. Future studies should also focus on the need for age, sex and pubertal stage specific cut-off values, since studies providing data on HOMA-IR in large study populations, found differences in IR values for different age, sex and Tanner stages [29, 30]. In our opinion, until further evidence becomes available, the lowest reported HOMA-IR value from the above reported studies (i.e. 3.4) improving detection of T2DM in obese children and adolescents could be used as additional screening measure. This screening should be used in addition to the ADA recommended three-yearly screening with FPG [31].

To our best knowledge, our report is the first to show the large variety in prevalence rates of IR in a given obese pediatric population caused by the heterogeneity of the different definitions. A strength of our study is the availability of data from a previously described population of 311 obese children and adolescents, who underwent an OGTT for clinical reasons. We were able to calculate all fasted methods except C-peptide. As C-peptide has been described to be a measure of insulin secretion and is produced in equal amounts along with insulin, it is possible to use it as a measure for endogenous insulin production. Especially in patients using exogenous insulin, C-peptide was reported useful to establish endogenous insulin production [32]. In order to define IR in a non-diabetic population, we think that C-peptide does not have any advantage over insulin. Moreover, from the OGTT/IVGTT based methods, we were not able to calculate Si(IVGTT) and $IRI_{Belfiore}$. Finally, a comparison with the gold standard method was not possible, as we do not use the euglycemic-hyperinsulinemic clamp test as part of standard of care in our clinic.

Conclusion

In conclusion, we reported in this study all published methods and cut off values used to define IR in pediatric populations. When these definitions were applied to a known population of 311 obese children and adolescents, a large variety of prevalence rates of IR was found. As a result, we conclude that a uniform definition for IR is needed to allow comparison between studies and populations and to be able to follow trends in incidence and prevalence rates over time. Longitudinal, epidemiological studies are necessary to investigate which level of IR is clinically relevant, and will help the

clinician to select the patients who require lifestyle intervention to prevent or delay the development of T2DM.

Conflicts of interest

None of the authors reports a conflict of interest regarding publication of this paper.

Acknowledgement

M.A. performed the literature review and data analysis and wrote a first version of the manuscript. All authors discussed study design, data and interpreted the results. C.K., A.B. and M.V. reviewed and edited the manuscript. All authors take full responsibility for the contents of the manuscript, M.V. is the guarantor of this work.

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SUPPLEMENTARY MATERIAL TO CHAPTER 3

Appendix 1. Search strategies of literature search

Database	Search strategy
Pubmed	(("Insulin Resistance"[Mesh] OR insulin resistan*[tiab] OR insulin sensitivity[tiab] OR (resistan*[tiab] AND insulin*[tiab]) OR metabolic syndr*[tiab]) AND ("Prevalence"[Mesh] OR prevalence*[tiab] OR "Incidence"[Mesh] OR incidence*[tiab]) AND ("Child"[Mesh:noexp] OR "Adolescent"[Mesh] OR "Puberty"[Mesh:noexp] OR "Minors"[Mesh] OR Pediatrics[MeSH:noexp] OR child[tiab] OR children[tiab] OR child care[tiab] OR childhood[tiab] OR child*[tiab] OR childc*[tiab] or childr*[tiab] OR childh*[tiab] OR adoles*[tiab] OR boy[tiab] OR boys[tiab] OR boyhood[tiab] OR girl[tiab] OR girls[tiab] OR girlhood[tiab] OR junior*[tiab] OR juvenile*[tiab] OR kid[tiab] OR kids[tiab] OR minors*[tiab] OR paediatr*[tiab] OR pediatr*[tiab] OR prepubert*[tiab] OR pre-pubert*[tiab] OR prepubesc*[tiab] OR pubert*[tiab] OR pubesc*[tiab] OR school age*[tiab] OR schoolchild*[tiab] OR teen[tiab] OR teens[tiab] OR teenage*[tiab] OR youngster*[tiab] OR youth[tiab] OR youths* OR Primary school*[tiab] OR Secondary school*[tiab] OR Elementary school*[tiab] OR High school*[tiab] OR Highschool*[tiab])
Embase	(prevalence/ or incidence/ or (prevalence* or incidence*).ti,ab.) AND (insulin resistance/ or insulin sensitivity/ or metabolic syndrome X/ or (resistan* and insulin*).ti,ab. or insulin sensitivity.ti,ab. or metabolic syndr*.ti,ab.) AND (child/ or boy/ or girl/ or hospitalized child/ or school child/ or exp adolescent/ or adolescence/ or puberty/ or pediatrics/ or (child or children or child care or childhood or child* or childc* or childr* or childh* or adoles* or boy or boys or boyhood or girl or girls or girlhood or junior* or juvenile* or kid or kids or minors* or paediatr* or pediatr* or prepubert* or pre-pubert* or prepubesc* or pubert* or pubesc* or school age* or schoolchild* or teen or teens or teenage* or youngster* or youth).ti,ab. or youths*.ti,ab. or Primary school*.ti,ab. or Secondary school*.ti,ab. or Elementary school*.ti,ab. or High school*.ti,ab. or Highschool*.ti,ab.)
Cochrane	((prevalence* or incidence*) and ((resistan* and insulin*) or insulin sensitivity or metabolic syndr*) and (child or children or child care or childhood or child* or childc* or childr* or childh* or adoles* or boy or boys or boyhood or girl or girls or girlhood or junior* or juvenile* or kid or kids or minors* or paediatr* or pediatr* or prepubert* or pre-pubert* or prepubesc* or pubert* or pubesc* or school age* or schoolchild* or teen or teens or teenage* or youngster* or youth or youths* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*)).ti,ab.

Supplementary table 1. Study characteristics of all included studies

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
AFRICA															
1	Egypt, 2015	Cross-sectional study in overweight and obese children referred from a Pediatric Endocrinology to a Pediatric Hepatology unit	76	2008-2009	2-15	Overweight and obese	NR	HOMA-IR ≥ 3.5	34.2						
								QUICKI < 0,33	43.4						
2	Egypt, 2011	Observational study of patients referred because of hepatomegaly or elevated ALT	33	NR	2-13	Overweight and obese	NR	HOMA-IR ≥ 3.5	48.5						
ASIA															
3	China, 2013	Cross-sectional population based survey	3373	NR	6-18	All	Chinese	HOMA-IR ≥ 3,0	25*	8.9*	28.1*	43.8*	26.9*	23.0*	
4	China, 2013	Cross-sectional study of high risk participants of a population based study and of a group of schoolchildren	3203	April - October 2004	6-18	All	Chinese	HOMA-IR > 1.7		33.6	68.9	80.1			
								HOMA-IR > 2.3		17.9	47.7	63.2			
								HOMA-IR > 2.6		12.9	38.5	55.4			
								HOMA-IR > 3.0		8.9	28.6	44.3			
								HOMA-IR > 3.2		7.1	24.5	40.5			
5	China, 2010	Cross-sectional case-control study of patients with PCOS	128	2004-2009	19.0	All	Asian	HOMA-IR > p95							PCOS: 46.9, control 17.5
								FPI > p95							PCOS: 29.7 control 7.5

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
6	India, 2013	Door-to-door demographic survey of representive wards of Chennai city.	1519		6-19	All	Indian	HOMA-IR ≥ 3.56					7.8	12.5	
7	India, 2013	Cross-sectional analysis of school going adolescents in a South-Indian population	120	NR	11-18	All	NR	HOMA-IR > 3.16		0	26	64			
8	India, 2011	Cross-sectional, case-control study	94	2006-2007	6-11	All	Bengali	FPI > 15 µIU/ml	40.4	18	61				
								HOMA-IR > 2.5	41.5	18	63				
9	India, 2010	Case series of patients with PCOS	49	2006-2008	12-19	All	NR	Glucose/insulin ratio < 7.0	69.4						
10	India, 2008	Cross-sectional population based study	948	NR	14-19	All	NR	FPI > 128.5 pmol/l (14-15yr); >126.1 pmol/l (16-17yr); >162.4 pmol/l (18-19yr)	35.4	29.3	67.3				14-15 yr: 32.6; 16-17 yr: 39.1; 18-19 yr: 32.7
11	India, 2006	Randomly selected sample of population based study	793	2000-2003	14-19	All	NR	FPI> 20 µU/l		29	63.9				
12	Iran, 2010	Retrospective study	110	2006-2008	4-18	Obese	NR	HOMA-IR > 4.0	28.2*				36.7	26.1	<10 yr: 23.8, > 10 yr 31.8
13	Iran, 2009	Cross-sectional study among survivors of childhood ALL	55	2003-2007	6-19	All	NR	FPI > 24 mU/l]	16						
14	Israel, 2005	Retrospective review of medical records	256	1997-2003	Mean: 13	Overweight obese	Jewish, Arabs	HOMA-IR >2	81.2				39.2	60.8	Tanner stage I: 63.2; II-III: 82.1; IV-V: 88.7
								QUICKI <0.339	77.7						
15	Japan, 2012	Cross-sectional study in schoolchildren	310	2009	10-13	All	Japanese	HOMA-IR ≥ 2.5	21.6		46.8				

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
16	Korea 2009	Review of medical records of children with NAFLD	80	1995-2008	12.0 (2.8)	Overweight and obese	NR	HOMA-IR > 2.0	96						
17	Kuwait, 2014	Baseline analysis of data from an intervention study	80		10-14	Obese	Kuwaiti	HOMA-IR > 3.16	67.5						
18	Lebanon, 2010	Cross-sectional survey in subjects selected from private and public schools, exclusion of children with chronic illness, antihypertensive, antihyperglycemic or lipid metabolism drugs.	140	2007-2008	~10	All	NR	FPI ≥ 15 mIU/l		28.6	56.0	67.8			
								HOMA-IR > 3.16		25.0	56.0	70.1			
19	Middle East, 2010	Cross-sectional study in children with impaired glucose tolerance	31	NR	13.2 (3.5)	Overweight, obese	Iranian	HOMA-IR > 3.0	19.4 *						
20	Thailand, 2011	Cross-sectional study in obese children of a nutrition clinic	89	2007	4-18	Obese	Thai	HOMA-IR > 3.16				58.4			
								FPI > 25 µIU/ml				27.3			
21	Thailand, 2010	Retrospective review of medical records of children surviving ALL	131	1997-2004	Apr-20	All	NR	FPI ≥ 20 µU/ml WBISI < 5 Insulinogenic index	30.5						
22	Thailand, 2009	Cross-sectional substudy of a longitudinal cohort study among HIV-infected children	54	NR	9.8 (2.5)	"Small and thin", (weight-for age Z score -1.91 (1.03))	NR	HOMA-IR ≥ 3.16	6.5						<10yr: 3.7; >10yr: 10.5
								c-peptide ≥ 4.40 ng/ml	0						<10yr: 0; >10yr: 0

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
								FPI ≥ 25.0 µU/ml	2.0						<10yr: 0; >10yr: 4.5
AUSTRALIA															
23	Australia, 2010	Cross-sectional study of Grade 10 students	495	2004	14.3-17.1	All	NR	FPI > 100pmol/l	20.6*	♂ 7.1 ♀ 10.9	♂ 29.5 ♀ 41.9	♂ 68.4 ♀ 44.4	19.3	22.4	
24	Australia, 2006	Cross-sectional, baseline analysis of randomized controlled trial	99	NR	6-9	Overweight obese	NR	FPI > 51 pmol/l	74						
								FPI ♀ > 35 pmol/l (~5 mU/l), ♂ > 40.6 pmol/l (~6 mU/l)	85						
25	New Zealand, 2008	Observational study of pacific island teenagers living in New Zealand	80	NR	15-18	All	NR	FPI > 12 µIU/ml	44						
								HOMA2 > 2 or	26.9				17.5	36.8	
								McAuley index ≤ 6.3					20.0	34.2	
CARIBBEAN AND CENTRAL AMERICA															
26	Costa Rica, 2009	Cross-sectional survey among overweight and obese schoolchildren	214	NR	8-10	Overweight and obese	NR	HOMA-IR ≥ 2.4	55.1				50.0	60.6	
								FPI >10.5 µU/l	59.8				51.8	68.3	
27	Costa Rica, 2008	Observational study of prepubertal overweight or obese children	214	NR	8-10	Overweight and obese	Tri-ethnic heritage (Spanish, indige-nous, Africans)	FPI > 20 mIU/l	20.6		2.8	17.8			
								HOMA-IR > 5.4	10.7		1.9	8.8			

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
								QUICKI < 0.300	11.7		1.9	9.8			
								FGIR < 7	46.7		10.8	35.9			
28	Cuba, 2010	Cross-sectional observational study in first degree family of T1DM patients	193	NR	2-19	All	146 white	HOMA-IR >1.14 (2-5yr); > 1.67 (5.1-10yr); >2.53 (10.1-15yr); >2.52 (15.1-19yr)	24.9						
29	Mexico, 2013	Cross-sectional study in children recruited from primary schools	174	NR	6-13	Normal weight and obese	NR	HOMA-IR ≥ 2.4	32.75	16.85		49.41			
30	Mexico, 2012	Cross-sectional analysis of baseline data from children participating in Health Workers Cohort Study	916	NR	7-18	All	NR	HOMA-IR ≥ 3.5	20.3				17.1	23.4	
31	Mexico, 2010	Cross-sectional survey in subjects randomly selected from public schools	1850	NR	12-16	All	NR	FPI > p75 (~9.85 µIU/ml)	24.8 *				4.9*	24.7*	
								HOMA-IR > p85 (~3.0)	15.3 *				12.7*	17.2*	
32	Mexico, 2010	Cross-sectional observational study among obese schoolchildren	466	NR	11-13	Obese	NR	FPI≥ 15 µU/ml	56				45	71	
								HOMA-IR ≥ 3.4 (=p90)	51				43	63	
33	Mexico, 2007	Comparative, observational study in obese and non-obese subjects	240	NR	10-19	All	NR	FPI > 16 µU/ml	27.1*	4		50			

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
34	Mexico, 2006	Cross-sectional observational study among randomly selected schoolchildren	317	NR	10-14	All	NR	FPI> 16 µU/l	15.1						Family history T2DM: positive 72.9; negative 27.1
EUROPE															
35	Austria, 2007	Case control study of NAFLD patients with age and sex matched controls	40	NR	5-18	Obese	NR	HOMA-IR > 3.2 or OGIS < 436 ml/min/m^2	72*						With NAFLD: 81%; Without NAFLD: 63%
36	Czech Republic, 2014	Cross-sectional study of a general population cohort	1518	NR	13.0-17.9	All	NR	HOMA-IR > 2.5	40.7 *				40.9	40.5	
								HOMA-IR > 4.0	13.2 *				14.3	10.8	
37	Czech Republic, 2013	Cross-sectional study in obese children referred to a obesitology department by their pediatrician	274	NR	9-17	Obese	NR	HOMA-IR > 3.16	53						With metabolic syndrome: 70%, without metabolic syndrome: 43%
								QUICKI <0.357	86						
38	Finland, 2009	Cross-sectional study among survivors of childhood brain tumors	52	NR	14.2 (3.8-28.7)	All	NR	FPI > 20 mU/l	4						No cranial irradiation: 3%; Cranial irradiation: 5%
39	France, 2009	Retrospective study of medical records of children visiting an obesity clinic	244	2003-2006	0-18	Obese	NR	HOMA-IR>75th percentile	61.4				75.7	53.1	
40	France, 2009	Observational study in children visiting an obesity clinic	50	NR	6-16	Overweight and obese	NR	HOMA-IR >75th percentile	68						

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
41	Germany, 2011	Retrospective chart review of children visiting an obesity clinic	1053	2001-2008	1-17	Overweight, obese, extremely obese	German, Turkish, other	Elevated HOMA-IR according to Allard et al. [43]	40.3						
42	Germany, 2005	Cross-sectional observational study in children with normal glucose tolerance	90	NR	3-16	Obese	NR	HOMA-IR ≥ 2.0, ISI Matsuda < 7.2	68						
43	Greece, 2008	Observational population based study on school children in Crete	522	2005-2006	10-12	All	NR	HOMA-IR >2.1	9.2	2.9	10.5	31.0	9.20	9.17	
								HOMA-IR > 3.16	3.1	1.9	1.8	10.3	4.60	1.83	
								QUICKI < 0.35	12.8	3.9	16.2	41.4	10.34	14.68	
								FGIR < 7	17.4	6.8	22.8	45.9	13.79	20.18	
44	Greece, 2014	Large scale, cross-sectional epidemiological study	2026	2007	9-13	All	NR	HOMA-IR > 3.16	28.4	16.7	38.0	59.6	22.4	33.2	
								HOMA-IR > 3.99	16.6	8.5	22.8	39.1	12.2	20.0	
								HOMA-IR > 5.56	6.0	2.4	8.0	19.1	4.5	7.4	
45	Greece, 2007	Observational study among young ALL survivors	80	NR	5.2-24.1	All	NR	FPI > 28.7 µU/ml	8						
46	Hungary, 2009	Cross-sectional study of children visiting an obesity clinic	113	NR	13.1 (2.4)	Obese	Caucasian European	FPI > 25 mU/l	73						
								HOMA-IR > 4.0	84.1						
								Insulin at 120' > 45 mU/l	89.3						

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
47	Hungary, 2008	Cross-sectional observational study of children visiting an obesity clinic	250	NR	13.0 (6.9)	Obese	Caucasian European	FPI > 25 mU/l	70.0						
								HOMA-IR > 4.0	77.6						
								Insulin at 120' > 45 mU/l	88.0						
48	Hungary, 2008	Baseline analysis of data from an intervention study	114	NR	5-17	Overweight and obese	NR	HOMA-IR > 4.4	32.5 *						
								OGIS < 400	37.7 *						
49	Italy, 2010	Cross-sectional study of children randomly selected from schools	575	2007-2008	11-13	All	NR	FPI > p75 (♂ 11.0 pmol/l; ♀ 13.2 mol/l)	25.2 *	♂ 12.4 ♀ 11.2	♂ 25.6 ♀ 38.2	♂ 60.4 ♀ 65.5	25.3*	25.1*	
								HOMA-IR > p75 (♂ 2.28, ♀ 2.67)	25.0 *	♂ 13.1 ♀ 11.8	♂ 26.7 ♀ 37.1	♂ 54.7 ♀ 65.5	25.0*	25.1*	
50	Italy, 2008	Cross-sectional, case-control study	191 cases, 76 controls	2003-2006	Cases: 11.15 (3.4) Control: 10.69 (3.3)	Overweight and obese	Caucasian	HOMA-IR >2.5 (prepubertal), > 4 (pubertal)	42.7*	3.2	33.3	43.6			Severe obese: 63.5 %
51	Italy, 2006	Cross-sectional, case-control, observational study	100 cases, 50 controls	NR	3-16	Normal and obese	NR	HOMA-IR >2.5 prepubertal, >4 pubertal	28*						Normal weight: children 3.0; adolescents 0; Obese: children 40.8; adolescents 41.2
52	Italy, 2001	Observational study in children with IUGR	49	NR	9.1 (3.3)	All	NR	Glucose/insulin ratio < 6	22			42.9*			

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
53	Nether-lands, 2013	Baseline analysis of data from an intervention study			3-5	Overweight and obese		HOMA2 > 1,53 (boys) or > 1.85 (girls)	7.7		4.0	10.0			
54	Nether-lands, 2011	Analysis of a paediatric obese cohort	1007	2004-2009	3-18	Overweight and obese	Dutch, Turkish, Moroccan, other	HOMA-IR ≥ 3.5	54.1						Prepubertal 34.6; pubertal 69.7
															Dutch 56.6; Turkish 59.7; Moroccan: 45.2
55	Nether-lands, 2009	Cross-sectional study of cohort of patients referred for obesity	528	2004-2007	3-16	Overweight and obese	Dutch, Turkish, Moroccan, Surinamese, other	HOMA-IR ≥ 3.5	47.7						< 10 yr 21.8, > 10 yr 60.1
56	Nether-lands 2009	Cross-sectional study of cohort of patients referred for obesity	516	2004-2008	3-18	Overweight and obese	Dutch, Turkish, Moroccan, other	HOMA-IR ≥ 3.5	48.8						Prepubertal 26.1; pubertal 62.3
															Turkish 54.9, Moroccan 37.4, Dutch: 46.8, other: 49.4
57	Neth-erlands 2008	Observational pilot study	155	2005-2007	2-18	Obese	Caucasian, others	HOMA-IR >3.1	60						
58	Poland, 2010	Evaluation of children born SGA	91	NR	4.78-9.75	All	NR	HOMA-IR > 4.0	0.0						
								$IRI_{Belfiore}$>1.27	14.3						

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
59	Portugal, 2010	Cross-sectional study in a population based sample of obese children	82	NR	7-9	Overweight and obese	NR	FPI ≥ 15 µU/ml	7.3						
								HOMA-IR ...	8.5						
60	Slovakia, 2010	Cross-sectional study of children visiting an obesity clinic	98	NR	5.2-16	Obese	NR	HOMA-IR > 3.16							<10 yr 4.8; >10yr 37.7
61	Spain, 2011	Retrospective review of obese children	100	2008	6-14	Overweight and obese	Caucasian, hispanic	FPI > 2SD	32						
								HOMA-IR >2SD	29						
								Insulin in OGTT >150 µU/ml	31						
								Insulin in OGTT >75 µU/ml at 120'	45						
								QUICKI < 2SD	93						
62	Spain, 2007	Observational study	97	NR	6-14	Obese	NR	HOMA-IR ≥ 3.8	45.4						
63	Spain, 2005	Cross-sectional observational study in children born SGA	46	NR	6-9	Normal	NR	Insulin > 10 IU/ml	11						
64	Spain, 2003	Cross-sectional study	95	NR	4-16	Obese	Spanish-Caucasian, Hispanic, Gypsie	HOMA-IR >4		4.1		35.8			
65	Turkey, 2014	Cross-sectional study of cohort of patients referred for obesity	451	2008-2012	8-18	Obese	NR	HOMA-IR > 3.16	54.8 *						NAFLD: 72%; without NAFLD: 39%

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
66	Turkey, 2011	Cross-sectional study in children with chronic kidney disease	66	2007	5-21	Normal weight	Turkish	HOMA-IR >p95	15.6 *						Predialysis: 7/20 (35 %); Dialysis: 3/46 (6.5%)
67	Turkey, 2010	Cross-sectional survey in randomly selected school children	790	NR	12-19	All	NR	HOMA-IR <3.16	34.7				33.0	36.1	
68	Turkey 2008	Retrospective, cross-sectional study of children visiting an obesity out-patient clinic	112	2002-2004	2-18	Obese	NR	FPI ≥15 mU/l (TS I), ≥30 mU/l (TS II-IV), ≥20 mU/l (TS V)	20.5						
								Peak insulin during OGTT ≥ 150 mIU/	34.8						
69	Turkey, 2008	Observational, cross-sectional, case-control study of children referred for obesity	169	2003-2005	Mean: ~10	Normal and obese	Turkish	HOMA-IR > 2.5	39.6	10.3		59.4*			
70	Turkey, 2007	Cross-sectional observational study	148	NR	8-18	Obese	NR	Σ insulin during OGTT > 300 µU/ml	37.1						
71	Turkey, 2007	Cross-sectional cohort study	196	2000-2005	7-18	Obese	Turkish	HOMA-IR >3.16	43						Prepubertal 34; pubertal 45
72	Turkey, 2006	Observational, cohort study	169	NR	7-18	Obese	Turkish	HOMA-IR > 3.16	40.2						Prepubertal 20; pubertal 43.7
								FPI > 15 mIU/l (prepubertal), > 30 mIU/l (TS II-IV)	29.5						Prepubertal 29; pubertal 56.5
73	Turkey, 2006	Multicenter cross-sectional, observational study	105	NR	10-18	All	NR	HOMA-IR > 2.5	63.8						

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
								FPI > 20 µU/ml	57.1						
74	UK, 2005	Cross-sectional observational study of clinical sample	103	1999-2002	2-18	Obese	White, black, South Asian, mixed	FPI ≥15 mU/l (TS I), ≥30 mU/l (TS II-IV), ≥20 mU/l (TS V)	40				36	42	
NORTH-AMERICA															
75	Canada, 2010	Cross-sectional analysis of children with fatty liver detected with ultrasound	38	2005-2006	5.5-19.9	All	Caucasian, Hispanic, Asian, other	HOMA-IR > 3.0	66						
								QUICKI < 0.31	50						
76	Canada, 2008	Follow-up study of cohort of children born from women with GDM	68	NR	7-11	All	Caucasian	HOMA-IR >2.5	15	4	38	45			
77	USA, 2013	Cross-sectional data analysis of a sample of participants of the NHANES study	766	2003-2008	12-19	All	White, black, MA, other race	HOMA-IR > 4.39	17.6						
78	USA, 2012	Cross-sectional convenience sample of school-based medical screening	1185	2008-2011	14-19	All	Hispanic, African-American, other	HOMA-IR > 4	19.5	4.5	12.4	37.8			
79	USA, 2012	Observational cross-sectional study in middle-school students	151	NR	11-14	All	NR	HOMA-IR ≥ 2.7	33.8 *	22.7		62.5			
80	USA, 2011	Cross-sectional analysis of fasting laboratory data of HIV-infected patients	402	2007-2009	7-16	All	NR	HOMA-IR >2.5 prepubertal, >4 pubertal	15.2						Prepubertal: 12.5%, pubertal 15.9%
81	USA, 2011	Population based sample (NHANES)	1571	1999-2002	12-18	All	White, black, MA, other race	HOMA-IR > 4.39	11.8						Black: 16.8, MA 16.9, white 9.3

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
82	USA, 2011	Cross-sectional data analysis of a sample of participants of a community based lifestyle program	105	2007	9-13	Overweight and obese	AA	HOMA-IR > 2.5	38.1*						
83	USA, 2007	Cross-sectional observational study in children with chronic kidney disease	43	NR	6-21	Normal and overweight	White, AA	FPI > p95	33						
								HOMA-IR > 4.39	16						
84	USA, 2007	Cross-sectional study	86	2001-2003	8-20	Obese	Caucasian, African, Hispanic, Asian	Si(IVGTT) < $4.5x10^4$ µU/ml/min	70.9						
85	USA, 2006	Cross-sectional observational study among schoolchildren	716	2002-2003	7-17	All	13% minority students	HOMA-IR > p85	~25		50				
86	USA, 2006	Population based study	1802	1999-2002	12-19	All	NHW, black, MA	HOMA-IR > 4.39				52.1			
87	USA, 2006	Observational cross-sectional study among schoolchildren	247	NR	7-17	All	89% Caucasian	QUICKI < p15 (~0.33 prepubertal, ~0.36 postpubertal)			2^{nd} grade: 47 11^{th} grade: 51				Prepubertal 24.5; postpubertal 26.2
88	USA, 2006	Observational study among schoolchildren	1740	2003	13.6 (0.6)	All	Hispanic, AA, Caucasian, Native American, other.	FPI ≥ 30 µU/ml	36.2	16.0	36.2	72.3			Hispanic 44.3; AA 29.3; Caucasian 20.5; Native American 36.4

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
89	USA, 2004	Cross-sectional observational study in children previously identified at risk for T2DM.	139	NR	10-12	All	MA	FPI > 15 µU/ml	59.7						
SOUTH-AMERICA															
90	Argentina, 2013	Cross-sectional, descriptional study.	75	2011-2012	2-14	Overweight and obese	NR	FPI > 15 µIU/ml	60				64	57.9	
								HOMA-IR > 3	66.6						
91	Argentina, 2011	Descriptive study of high-school students	420	2005	12-18	All	NR	Insulin ≥ 12 mU/l	11.7						
								HOMA-IR ≥ 2.5	10.5				10.6	10.4	
								QUICKI ≤ 0.33	9.8				6.3	11.9	
92	Bolivia, 2008	Cross-sectional observational study of patients with obesity	61	2006-2007	5-18	Obese	Bolivian	HOMA-IR >3.5	39.4				50	29	
93	Brazil, 2014	Cross-sectional study in adolescents visiting an obesity outpatient clinic	79	2011-2012	10-18	Obese	NR	HOMA-IR > 3.16	29.1				43.5	56.5	
94	Brazil, 2011	Cross-sectional descriptive study in vertically HIV-infected children	119	2007	6-19	All	NR	HOMA-IR ≥ 2.5	16.7						
95	Brazil, 2009	Cross-sectional, population based epidemiological study	109	NR	7-11	All	NR	HOMA-IR > p90	10*	0	0	20.0			
								FPI ≥ 20 µU/ml	11*	0	0	21.8			
96	Brazil, 2009	Transversal observational study of students with central obesity	175	2005-2006	11-18	Overweight and obese	71.4% nonwhite	HOMA-IR ≥ 3.16	22.9						
97	Brazil, 2008	Two stage cross-sectional observational study among schoolchildren with obesity, low birth-weight, positive FH on CVD	205	NR	6-10	All	NR	HOMA-IR > 3.1	8.6*	0.9	6.8	10.3			

Supplementary table 1. Study characteristics of all included studies (continued)

Nr.	Country, year of publication	Methods	Sample size	Calender time	Age range	Weight category	Ethnicity	Criteria IR	Prevalence IR (%)						
									Overall	Normal weight	Over-weight	Obese	Boys	Girls	Other subpopulations
98	Brazil, 2005	Cross-sectional analysis of adolescents with family history of T2DM	99	NR	10-19	All	Brazilian	HOMA-IR > 2.5	22.2	10.9	23	43.5			
99	Brazil/Italy 2008	Cross-sectional study among obese adolescents	509	NR	15-19	Obese	Brazilian, Italian	FPI ≥ 20 µIU/ml	0.2*						
								HOMA-IR >3.16	30.5*						
100	Chile, 2014	Retrospective cohort study of children from public schools linking present data to perinatal records	3290		10-15	All	Chilean	HOMA-IR > p90 for sex and TS (♂ TS I-II: 3.2; TS III-IV: 4.2; ♀ TS I-II 4.1, TS III-IV: 5.0)	25.5				26.4	25.2	
101	Chile, 2013	Cross-sectional study of children in public schools in Puente Alto County	3325	2009-2011	10-15	All	Chilean	HOMA-IR > p90 for sex and TS (♂ TS I-II: 3.2; TS III-IV: 4.2; ♀ TS I-II 4.1, TS III-IV: 5.0)	25.9				26.9	24.8	
102	Chile, 2010	Cross-sectional analysis from a cohort study, childen with negative family history of T1DM, astma and no steroid use.	324	2006	~4.0	All	Chilean	HOMA-IR ≥ 3.2	1.54 *				1.1	2.1	
103	Chile, 2003	Cross-sectional study in children from an obesity clinic	88	NR	12 (2.4)	All	NR	HOMA-IR >3.8				79			

Abrreviations: FPG: fasted plasma glucose; FPI: fasted plasma insulin; HOMA-IR: Homeostasis Model assessment Insulin resistance; MA: Mexican-American; NR: not reported; QUICKI: quantitative insulin sensitivity check index; TS: Tanner Stage

Calculations: HOMA-IR = FPG (mmol/l)*FPI (mU/l) / 22,5 or FPG (mg/dl)*FPI (mU/l) / 405; HOMA2: calculated with HOMA2calculator http://www.dtu.ox.ac.uk/homacalculator/index.php; McAuley index= 2.63 -0.28 ln[fasting insulin] -0.31 ln[fasting triglycerides]; QUICKI= 1/ [(log (FPI (mU/l))+ log (FPG (mg/dl))]

Notes: * Calculated by the authors; † extracted from graph

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