Universiteit Leiden
The Netherlands

Diagnosis and treatment of obese children with insulin resistance

Aa, M.P. van der

Citation
Aa, M. P. van der. (2016, December 13). *Diagnosis and treatment of obese children with insulin resistance*. Retrieved from https://hdl.handle.net/1887/44921

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/44921

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

Leiden University Repository

The handle http://hdl.handle.net/1887/44921 holds various files of this Leiden University dissertation

Author: Aa, Marloes van der
Title: Diagnosis and treatment of obese children with insulin resistance
Issue Date: 2016-12-13

Chapter 2

Population-based studies on the epidemiology of insulin resistance in children

Marloes P. van der Aa
Soulmaz Fazeli Farsani
Catherijne A.J. Knibbe
Anthonius de Boer
Marja M.J. van der Vorst

J Diabetes Res. 2015;2015:362375

Abstract

Background

In view of the alarming incidence of obesity in children, insight into the epidemiology of the pre-diabetic state insulin resistance (IR) seems important. Therefore, the aim of this systematic review was to give an overview of all population-based studies reporting on the prevalence and incidence rates of IR in childhood.

Methods

PubMed, Embase and Cochrane library were searched in order to find all available population-based studies describing the epidemiology of IR in pediatric populations. Prevalence rates together with methods and cut-off values used to determine IR were extracted and summarized with weight- and sex-specific prevalence rates of IR if available

Results

Eighteen population-based studies were identified, describing prevalence rates varying between 3.1 and 44 %, partly explained by different definitions for IR. Overweight and obese children had higher prevalence rates than normal weight children. In seven out of thirteen studies reporting sex-specific results, girls seemed to be more affected than boys.

Conclusion

Prevalence rates of IR reported in children vary widely which is partly due to the variety of definitions used. Overweight and obese children had higher prevalence and girls were more insulin resistant than boys. Consensus on the definition for IR in children is needed to allow for comparisons between different studies.

Introduction

Nowadays, the body mass index (BMI) is increasing in many populations and childhood obesity is an emerging problem [1-3]. In the United States the prevalence rates of obesity between 1971 and 1974 in 6-11 year old white/black children was 4%. Between 1999 and 2002, these prevalence rates increased to 13% and 20% in white and black children, respectively [4]. In 2012 the overall prevalence rate of obesity in 2-19 year old American children was 17.3% [1]. In developing countries, the prevalence rate of overweight and obesity in preschool children (<5 years old) in 2010 was estimated to be 6.1% and 11.7%, respectively [5]. Moreover, the prevalence of overweight in children <5 years of age raised in the African continent between 2000 and 2013 from 5.1 to 6.2% (+1.1%), while in the American Continents, the prevalence increased with 0.5% (6.9 to 7.4%). (http://apps.who.int/gho/data/view.main.NUTWHOOVERWEIGHTv?lang=en)

The rising prevalence of obesity will cause an increase in obesity related complications such as insulin resistance (IR), hypertension, dyslipidemia and type 2 diabetes mellitus (T2DM) [6, 7]. The energy excess in obesity may result in hyperplasia and hypertrophy of adipocytes, leading to oxidative stress. This oxidative stress of adipocytes induces a chronic low-level inflammation in adipose tissue and production of adipokines, free fatty acids and inflammatory mediators. This inflammation is related to peripheral IR, IR of hepatocytes and impaired insulin secretion by the pancreatic beta-cells. Finally, this process causes dysregulation of glucose homeostasis and development of T2DM [8]. Although obesity plays a key-role in the pathophysiology of IR, IR is an independent risk factor for cardiovascular and metabolic diseases [9-12]. Therefore, it is important to know the extent of IR in pediatric populations. Knowledge on the prevalence rates of IR and its clinical consequences during childhood will increase the awareness of physicians and other health care professionals. Despite the reported association between IR and increased cardiovascular risk in pediatric populations [13], there is no overview of data on the epidemiology of IR in this population. Many studies focus on the extent of IR in overweight and obese populations, but limited studies have a population based study design.

The aim of this study is to systematically review all available population-based studies on the epidemiology of IR in pediatric populations. We will describe the weight and sex specific prevalence and incidence rates of IR in the included studies, together with the study-specific definition used to define IR.

Methods

Systematic search and study selection

This review follows the guidelines of 'Meta-analysis of Observational Studies in Epidemiology (MOOSE) [14]. A systematic search was conducted in PubMed, Embase and the Cochrane library, using the search strategies as displayed in table 1. The search was performed in December 2014, and covered all publications in the time period between the inception of each database and the search date. All articles in English, French, German, Spanish and Dutch languages were included and their title and abstract were screened to find the relevant studies. All results were imported into a RefWorks file (www.refworks.com) and duplicate articles were removed. Subsequently, the title and abstract of all unique results were screened using the exclusion criteria. Articles were excluded if they were review articles, studied a population older than 19 years, or did not report prevalence and/or incidence rates of IR in the abstract. Furthermore, all conference abstracts without a full text publication were excluded. All available full text articles were retrieved and their design was scrutinized to select population-based studies. The reference lists of all included population-based studies were investigated to find relevant articles not included in the original search.

Data extraction and analysis

Data were extracted on the study design, sample size, calendar time of data collection, mean age of participants, ethnicity, criteria used to determine IR (method and cut-off value), prevalence and incidence rates of IR in the complete study population, and if available in subpopulations based on weight category (normal weight, overweight and obesity) and sex. Data were entered in an excel file. Pooling of data was not possible because of the large variability in study design, population and definitions used to determine IR. Data are presented in a descriptive manner.

Table 1. Search strategies

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.

Results

Systematic search and study selection

With the search strategy presented in Table 1, in PubMed, Embase and Cochrane 6,788 articles (with 4,596 unique studies) were retrieved. Screening of titles and abstracts led to the exclusion of 4,448 articles (figure 1). The full text of the 148 remaining articles was checked and 76 articles were excluded based on our exclusion criteria. Critical appraisal of the 72 remaining articles resulted in the final inclusion of 18 population-

based studies. All included studies reported prevalence rates of IR and none of them reported incidence rates. An overview of the included studies and extracted data is presented in supplemental table 1.

Study characteristics

The 18 included studies were performed in 13 countries. Except for the African continent, all continents are represented. The studies were performed between 1999 and 2011. Sample sizes varied from 80 to 3,373 children [15, 16]. Most studies recruited their study population at selected schools [15, 17-30]. The New Zealand study population were volunteer adolescents who were recruited by Pacific Island community workers, even though it was not reported where they recruited the participants [16].

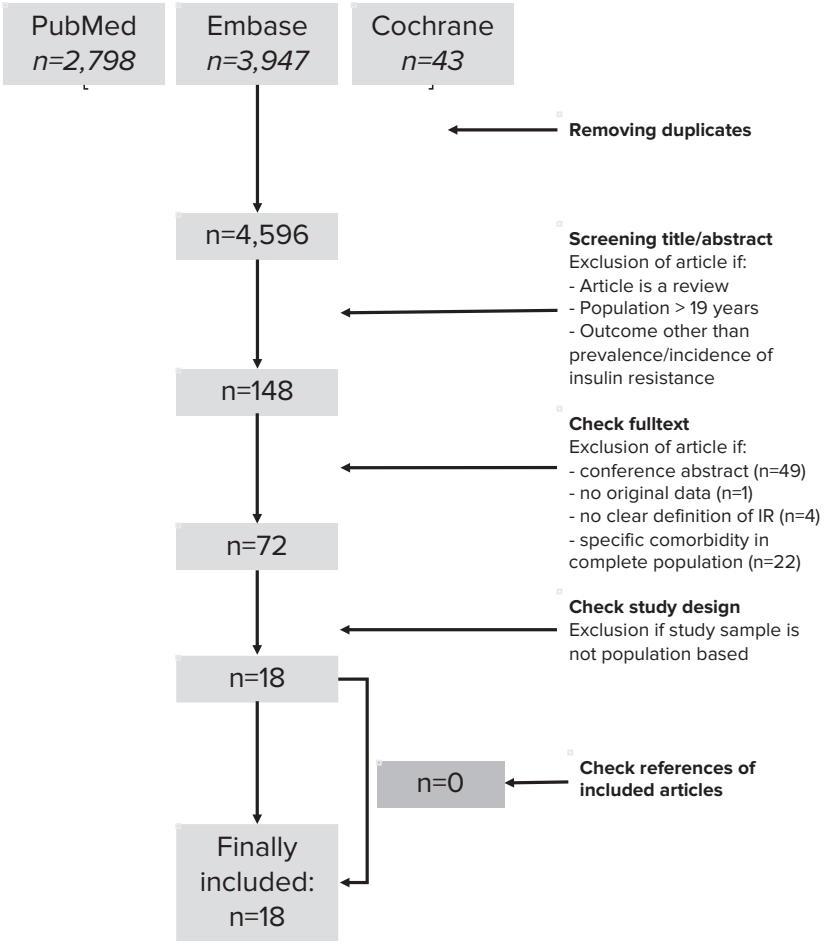

Figure 1. Flowchart of search and included studies

In the majority of the studies (n=14), the age of the study participants was above 10 years [16, 17, 19-24, 26-31]. Four studies included also children younger than 10 years, with ranges that varied between 6-19 years [15, 18, 25, 32]. Ethnicity was not reported in 50% of the studies. All study characteristics are presented in supplemental table 1.

Methods and cut-off values to define IR

In the studies, six different methods were used to determine IR (Table 2). These methods were Homeostasis Model Assessment Insulin Resistance (HOMA-IR), fasted plasma insulin (FPI), Quantitative Insulin sensitivity Check Index (QUICKI), fasted glucose/insulin ratio (FGIR), HOMA2 and the McAuley-index. All these indices are based on FPI; for HOMA-IR, QUICKI, FGIR and HOMA2 fasted plasma glucose (FPG) values are also needed (Table 2). The McAuley index is the only index for which fasted triglycerides are required besides FPG and FPI. None of the above-mentioned equations use anthropometric measurements or values derived from an oral glucose tolerance test. HOMA-IR, FPI and QUICKI were the most frequently used methods to determine IR (HOMA-IR: n=14 [15, 17-22, 24-28, 31, 32]; FPI: n=7 [16, 19, 21-23, 29, 30]; QUICKI n=2 [19, 26], Table 2).

The cut-off values used to define IR for HOMA-IR ranged from 2.1 to 5.56, while for FPI cut-off values varied between 9.85 and 23.7 µU/ml (corresponding with 68.4 and 164.8 pmol/l, respectively) (Table 2). The study of Budak et al. used a cut-off value different from the other studies, as their definition for IR was a HOMA-IR <3.16 which

Table 2. Methods used to calculate insulin resistance

Method	Parameters	Formula	Cut-off values (range)	Studies using the method
HOMA-IR	FPG, FPI	(FPG (mmol/l)*FPI(mU/l))/22.5	2.1 – 4.0	[15, 17-22, 24-28, 31, 32]
FPI	FPI	NA	9.85 – 23.7 µU/ml	[16, 19, 21-23, 29, 30]
QUICKI	FPG, FPI	1/[log (FPI (mU/l))+log (FPG (mg/dl))]	0.33 – 0.35	[19, 26]
FGIR	FPG, FPI	(FPG[mg/dL]/FPI [mU/L])	7	[26]
HOMA2	FPG, FPI	Computer model: HOMA2-calculator: http://www.dtu.ox.ac.uk/homa	2	[16]
McAuley-index	FPI, triglycerides	(2.63 − 0.28 ln[FPI] − 0.31 ln[fasting triglycerides])	6.3	[16]

FPG – Fasted Plasma Glucose; FPI – Fasted plasma insulin; FGIR – Fasted glucose insulin ratio; HOMA(-IR) – Homeostasis model assessment (for Insulin Resistance); QUICKI – Quantitative Insulin Sensitivity check Index)

was in contrast with other studies that defined IR as HOMA-IR greater than a specific value [20]. We did not succeed to contact Budak et al. to verify this cut-off value.

Age and sex specific cut-off values were reported in respectively one [29]. and three studies [22, 27, 29]. Girls had higher cut-off values for FPI and HOMA-IR compared with boys. For both sexes, adolescents aged 14-15 years had the highest cut-off values for FPI [29].

Prevalence of IR

The overall prevalence rates of IR in 17 out of 18 population based studies are presented in figure 2. The study of Ranjani et al. only reported sex specific prevalence rates [32]. The lowest prevalence rate of IR was reported from Greece with 3.1% in children aged 10-12 years (using the cut-off value of HOMA-IR > 3.16 for IR, figure 2) [26]. In the same study population, three other definitions of IR (HOMA-IR > 2.1, QUICKI < 0.35, and FGIR <7) were applied resulting in prevalence rates of 9.2, 12.8 and 17.4%, respectively.

The highest prevalence rate of IR was reported by Grant et al. for the 15-18 year old Pacific Island adolescents in New Zealand [16]. They reported a prevalence rate of 44% with IR defined as FPI > 12 µU/ml. This definition of IR has been used in another study by Bonneau et al. which resulted in a prevalence rate of 11.7% for the 12-18 year old Argentinian adolescents [19].

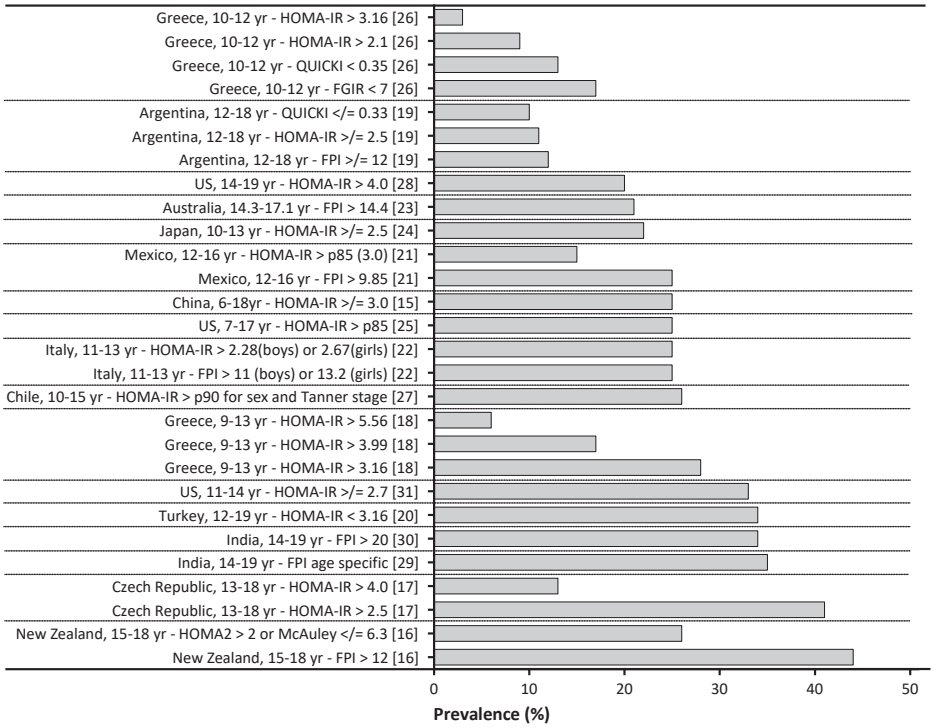

Figure 2. The overall prevalence rates (%) of IR in the included studies

Sex- and weight-specific prevalence of IR

Thirteen studies reported separate prevalence rates for boys and girls (figure 3a). In 7 out of 13 studies, IR was more prevalent in girls [16, 18, 20, 21, 23, 30, 32]. Three studies reported higher prevalence rates for boys [15, 17, 19]. In one study the prevalence rate of IR was similar for boys and girls [22]. In two studies it depended on the criteria used to determine IR whether boys or girls were having the highest prevalence rates [19, 26].

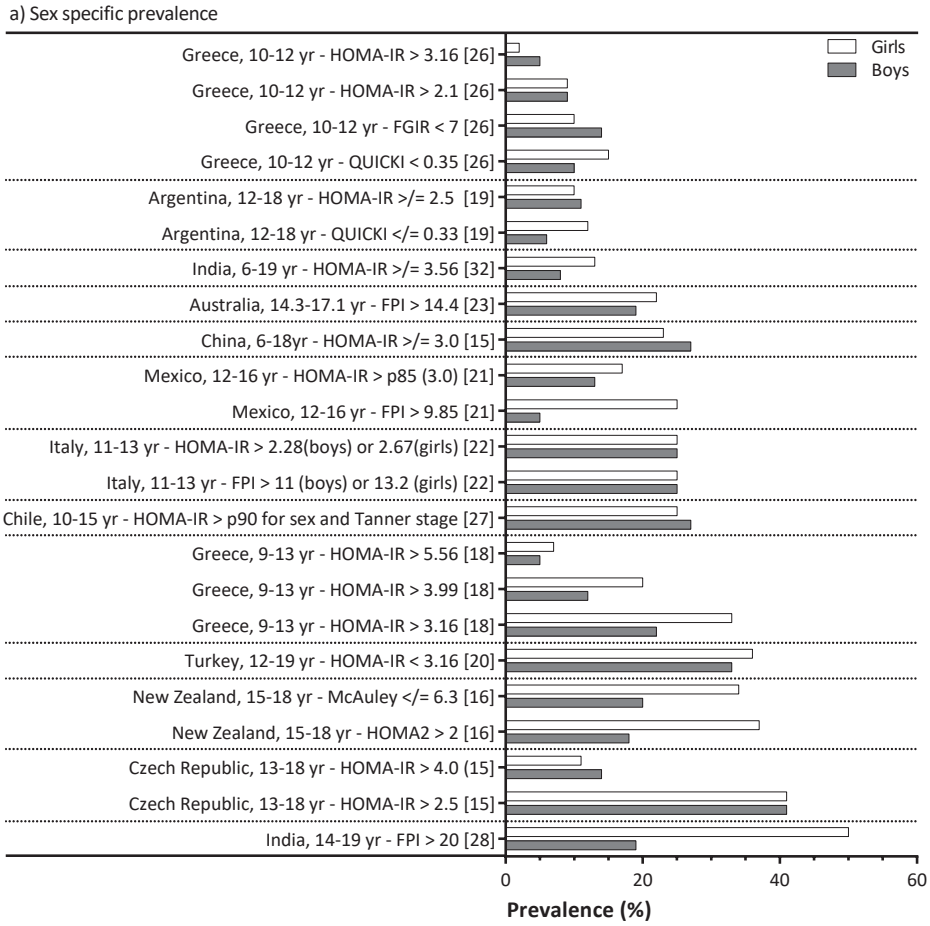

Figure 3b shows the influence of weight (normal, overweight and obesity) on the prevalence of IR. A major difference was observed between normal weight and obese populations. Normal weight populations had substantial lower prevalence rates of IR, irrespective of the used definition for IR. The maximum difference in weight specific prevalence rates of 61.3% was reported in Australian boys, with prevalence rates in normal weight and obese boys of 7.1% and 68.4%, respectively [23].

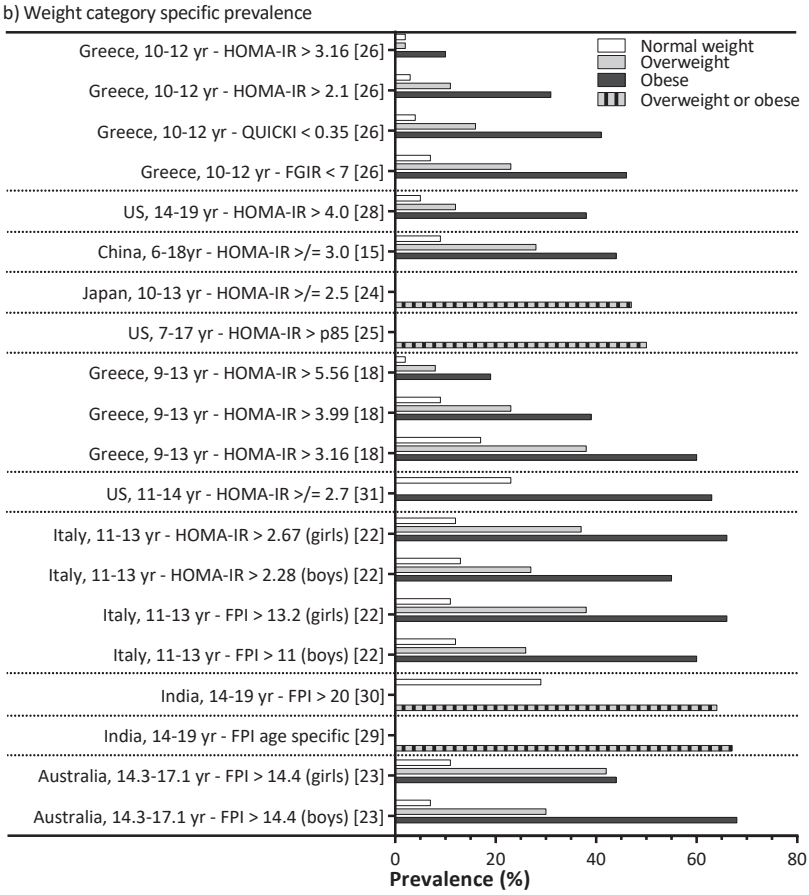

Figure 3. Prevalence of IR by sex (a) and weight category (b)

Discussion

To the best of our knowledge, this is the first systematic review summarizing all available population-based studies on the epidemiology of IR during childhood. While we could not find any population-based study reporting the incidence rate of IR in children, the reported prevalence rates varied between 3.1% in Greek children and 44% in Pacific Island teenagers living in New Zealand. There was not only variation in the prevalence rates of IR, but we also observed that these 18 included studies used 6 different methods combined with diverse cut-off values to determine IR. For instance, the FPI cut-off values varied between 9.85 and 23.7 μU/ml (corresponding with 68.4 and 164.8 pmol/l, respectively) [21, 29] and the HOMA-IR cut-off values ranged between 2.1

and 5.56 [18, 26]. The lack of a uniform definition and cut-off value to determine IR, impedes pooling of data and therefore reporting on overall prevalence rates.

Although substantial variation in the prevalence rates of IR could be partly explained by differences in the study population characteristics (e.g. age, weight, ethnicity, pubertal status, etc.), the use of different methods and cut-off values to determine IR may play an important role as well. As an example, in the study by Manios et al. in 481 Greek school children, different methods resulted in various prevalence rates (i.e. 3.1 versus 12.8 and 17.4 % for HOMA-IR, QUICKI and FGIR, respectively, Figure 2) [26]. Even if studies use the same method to measure IR, different cut-off values impede comparison between studies. Again, in the study by Manios et al., the use of different cut-off values for HOMA-IR method (> 3.16 and > 2.1) in the same study population resulted in prevalence rates of 3.1 and 9.2%, respectively [26]. A lower cut-off value results in a higher prevalence rate of IR and vice versa.

The highest reported prevalence rate for IR was 44% in Pacific Island teenagers (New Zealand) [16]. In that study IR was defined as FPI > 12 µU/ml, which is a relatively low cut-off value that might contribute to the high reported prevalence rate. In another study in Mexico, which used the lowest cut-off value for FPI (FPI > 9.85mU/l) a prevalence rate of 24.8% was reported [21]. When the same cut-off values would have been used in these two studies, the difference in prevalence rates would even have been larger. Even though the difference between these two populations cannot be quantified precisely, not only because of different cut off values, but also because others factors such as age, weight and pubertal stage were not taken into account, this analysis shows that prevalence rates of IR are variable in different populations, which was also observed in other studies.

Overweight or obesity is an important factor influencing the prevalence of IR. The effect of overweight or obesity on IR is clearly observed in all presented studies as prevalence rates in overweight or obese children and adolescents were reported to be higher than in normal weight children and adolescents (Figure 3b). Most studies (7 out 11 studies presenting weight specific prevalence rates) differentiated not only between normal weight and overweight/obesity, but stratified into normal weight, overweight and obese children and adolescents [15, 18, 22, 23, 26, 28, 31]. These studies show an increased prevalence in obese children compared to overweight children. In the study by Caserta et al., odds ratios for IR were calculated for obese and overweight boys and girls comparing to their normal weight peers. The odds ratios of 9.1 (95% confidence interval 4.0-20.4) and 13.2 (4.7-36.9) were reported for obese boys and girls and lower odds ratios of 2.4 (1.2-4.9) and 6.0 (3.1-11.9) were reported for overweight boys and girls, respectively [22]. These results show that with normal weight increasing to obesity the prevalence of IR is rising.

A higher prevalence rate of IR has been observed in girls compared with boys in 7 out of 13 studies reporting sex specific prevalence rates (Figure 3a) [16, 18, 20, 21, 23, 30, 32]. This is in line with the prevalence of T2DM, of which IR is a precursor, as population based studies on the prevalence of T2DM in children and adolescents also show higher prevalence rates in girls [33]. Hirschler et al. found no significant sex-related differences in IR. In their study, IR was associated with BMI and pubertal stage only, and not with gender. Their findings suggested that higher values in IR in girls compared to boys could be due to differences in pubertal development [34]. A study by Moran et al. measured IR using the euglycemic insulin clamp in children at all Tanner stages. At all Tanner stages, girls were more insulin resistant compared to boys. According to Moran et al, this difference in IR between boys and girls could partially be explained by higher levels of adipose tissue in girls compared to boys. However, in an obese subpopulation no difference in IR levels was observed between boys and girls [35]. It is known that pubertal development starts earlier in girls compared to boys (Tanner stage 2 at 11.4-11.9 years vs 11.9-12.3 years, respectively) [36]. Therefore, boys and girls between 10 and 14 years of age might be at another Tanner stage. Since IR is related to pubertal stage [34, 37], a comparison between pubertal girls and boys of same age might result in a higher prevalence rate for IR in girls, because of a higher Tanner stage. The best comparison between boys and girls in pubertal age, would be based on Tanner stages instead of age. Unfortunately, prevalence rates related to Tanner stages were not reported in any of the studies, so we were not able to check the effect of puberty on the prevalence of IR.

Our review has some limitations that should be addressed. At first, we could not compare results and pool the data of different studies, because of the heterogeneity in definition of IR in the presented studies. However, we were able to present an overview of the currently available population based studies, showing higher prevalence rates in girls compared to boys, and in overweight and obese children compared to normal weight children. Another limitation is that all included studies were conducted in recent years. All studies were published between 2004 and 2014 and the data were collected between 2000 and 2011. However, in eight of eighteen studies, the exact period of data collection was not mentioned [15-17, 20, 21, 29, 31, 32]. Therefore, we could not evaluate whether the prevalence of IR is rising along with the increasing prevalence of obesity and T2DM. Finally, as already discussed above, the influence of Tanner stage on prevalence of IR could not be studied because of a lack of data.

Conclusion

In conclusion, the overall prevalence rates of ir in population-based studies of children and adolescents ranged between 3.1 and 44%, which could be partly explained by the use of different methods and cut-off values to determine ir. The prevalence rate of ir was up to 68.4% in obese boys. Girls seemed to have higher prevalence rates of ir than boys, which may however be related to their earlier pubertal development. Consensus on the definition for ir in children is needed to allow for comparisons between different studies, and to assess the value of ir as a screening measure for children and adolescents with an increased risk of cardiometabolic diseases.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper

References

1. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. JAMA Pediatr. 2014 Jun;168(6):561-6.
2. WHO, "Childhood overweight and obesity" Available from: http://www.who.int/dietphysicalactivity/childhood/en/.
3. NOO Data Fact Sheet Child Weight, 2012 Available from: http://www.noo.org.uk/uploads/doc/vid_16006_ChildWeightFactsheet-July2012.pdf.
4. Lakshman R, Elks CE, Ong KK. Childhood obesity. Circulation. 2012 Oct 2;126(14):1770-9.
5. de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010 Nov;92(5):1257-64.
6. Cruz ML, Shaibi GQ, Weigensberg MJ, Spruijt-Metz D, Ball GD, Goran MI. Pediatric obesity and insulin resistance: chronic disease risk and implications for treatment and prevention beyond body weight modification. Annu Rev Nutr. 2005;25:435-68.
7. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004 Jun 3;350(23):2362-74.
8. Ode KL, Frohnert BI, Nathan BM. Identification and treatment of metabolic complications in pediatric obesity. Rev Endocr Metab Disord. 2009 Sep;10(3):167-88.
9. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA. 2005 Jul 20;294(3):334-41.
10. Saely CH, Aczel S, Marte T, Langer P, Hoefle G, Drexel H. The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. J Clin Endocrinol Metab. 2005 Oct;90(10):5698-703.
11. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenez X, Hernandez G, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med. 2004 May 4;140(9):700-8.
12. Bacha F, Saad R, Gungor N, Arslanian SA. Are obesity-related metabolic risk factors modulated by the degree of insulin resistance in adolescents? Diabetes Care. 2006 Jul;29(7):1599-604.
13. Bocca G, Ongering EC, Stolk RP, Sauer PJ. Insulin resistance and cardiovascular risk factors in 3- to 5-year-old overweight or obese children. Horm Res Paediatr. 2013;80(3):201-6.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.
15. Wang Q, Yin J, Xu L, Cheng H, Zhao X, Xiang H, et al. Prevalence of metabolic syndrome in a cohort of Chinese schoolchildren: comparison of two definitions and assessment of adipokines as components by factor analysis. BMC Public Health. 2013 Mar 21;13:249,2458-13-249.
16. Grant AM, Taungapeau FK, McAuley KA, Taylor RW, Williams SM, Waldron MA, et al. Body mass index status is effective in identifying metabolic syndrome components and insulin resistance in Pacific Island teenagers living in New Zealand. Metabolism. 2008 Apr;57(4):511-6.
17. Aldhoon-Hainerova I, Zamrazilova H, Dusatkova L, Sedlackova B, Hlavaty P, Hill M, et al. Glucose homeostasis and insulin resistance: prevalence, gender differences and predictors in adolescents. Diabetol Metab Syndr. 2014 Sep 16;6(1):100,5996-6-100. eCollection 2014.

18. Androutsos O., Moschonis G., Mavrogianni C., Roma-Giannikou E., Chrousos G.P., Kanaka-Gantenbein C., et al. Identification of lifestyle patterns, including sleep deprivation, associated with insulin resistance in children: The healthy growth study. Eur J Clin Nutr. 2014;68(3):344-9.
19. Bonneau G, Pedrozo W, Castillo Rascon M, Albrekt A. Prevalence of insulin resistance in adolescents in the city of Posadas. Recommended diagnostic criteria. Rev Argent Endocrinol Metab. 2011;48:78-86.
20. Budak N, Ozturk A, Mazicioglu M, Yazici C, Bayram F, Kurtoglu S. Decreased high-density lipoprotein cholesterol and insulin resistance were the most common criteria in 12- to 19-year-old adolescents. Eur J Nutr. 2010 Jun;49(4):219-25.
21. Cardoso-Saldana GC, Yamamoto-Kimura L, Medina-Urrutia A, Posadas-Sanchez R, Caracas-Portilla NA, Posadas-Romero C. Obesity or overweight and metabolic syndrome in Mexico City teenagers. Arch Cardiol Mex. 2010 Jan-Mar;80(1):12-8.
22. Caserta CA, Pendino GM, Alicante S, Amante A, Amato F, Fiorillo M, et al. Body mass index, cardiovascular risk factors, and carotid intima-media thickness in a pediatric population in southern Italy. J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):216-20.
23. Denney-Wilson E, Cowell CT, Okely AD, Hardy LL, Aitken R, Dobbins T. Associations between insulin and glucose concentrations and anthropometric measures of fat mass in Australian adolescents. BMC Pediatr. 2010 Aug 11;10:58,2431-10-58.
24. Fujii C, Sakakibara H. Association between insulin resistance, cardiovascular risk factors and overweight in Japanese schoolchildren. Obes Res Clin Pract. 2012 Jan-Mar;6(1):e1-e90.
25. Hughes P, Murdock DK, Olson K, Juza R, Jenkins K, Wegner A, et al. School children have leading risk factors for cardiovascular disease and diabetes: the Wausau SCHOOL project. WMJ. 2006 Jul;105(5):32-9.
26. Manios Y, Moschonis G, Kourlaba G, Bouloubasi Z, Grammatikaki E, Spyridaki A, et al. Prevalence and independent predictors of insulin resistance in children from Crete, Greece: the Children Study. Diabet Med. 2008 Jan;25(1):65-72.
27. Mardones F, Arnaiz P, Barja S, Giadach C, Villarroel L, Dominguez A, et al. Nutritional status, metabolic syndrome and insulin resistance in children from Santiago (Chile). Nutr Hosp. 2013 Nov 1;28(6):1999-2005.
28. Turchiano M, Sweat V, Fierman A, Convit A. Obesity, metabolic syndrome, and insulin resistance in urban high school students of minority race/ethnicity. Arch Pediatr Adolesc Med. 2012 Nov;166(11):1030-6.
29. Vikram NK, Misra A, Pandey RM, Luthra K, Bhatt SP. Distribution and cutoff points of fasting insulin in Asian Indian adolescents and their association with metabolic syndrome. J Assoc Physicians India. 2008 Dec;56:949-54.
30. Vikram NK, Misra A, Pandey RM, Luthra K, Wasir JS, Dhingra V. Heterogeneous phenotypes of insulin resistance and its implications for defining metabolic syndrome in Asian Indian adolescents. Atherosclerosis. 2006 May;186(1):193-9.
31. Bindler RC, Daratha KB. Relationship of weight status and cardiometabolic outcomes for adolescents in the TEAMS study. Biol Res Nurs. 2012 Jan;14(1):65-70.
32. Ranjani H, Sonya J, Anjana R, Mohan V. Prevalence of glucose intolerance among children and adolescents in urban South India (ORANGE-2). Diabetes technology & therapeutics. 2013 2013 Jan;15(1):13.

33. Fazeli Farsani S, van der Aa MP, van der Vorst MM, Knibbe CA, de Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. Diabetologia. 2013 Jul;56(7):1471-88.
34. Hirschler V, Maccallini G, Karam C, Gonzalez C, Aranda C. Are girls more insulin-resistant than boys? Clin Biochem. 2009 Jul;42(10-11):1051-6.
35. Moran A, Jacobs DR,Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes. 1999 Oct;48(10):2039-44.
36. Blondell RD, Foster MB, Dave KC. Disorders of puberty. Am Fam Physician. 1999 Jul;60(1):209,18, 223-4.
37. d'Annunzio G, Vanelli M, Pistorio A, Minuto N, Bergamino L, Lafusco D, et al. Insulin resistance and secretion indexes in healthy Italian children and adolescents: a multicentre study. Acta Biomed. 2009 Apr;80(1):21-8.

SUPPLEMENTARY MATERIAL TO CHAPTER 2

Supplemental table 1. Overview of the included studies and extracted data

Nr	Country, calender time	Methods	Sample representative for / ethnicity	Sample size	Participation degree	Age	Measurements to determine IR	Criteria IR	Prevalence IR (%)					
									Overall	Normal weight	Over-weight	Obese	Boys	Girls
ASIA														
1	China, NR	Cross-sectional population based survey	Chinese children living in Beijing / Chinese	3373	NR	6-18	Fasted blood sample (FPG and FPI)	HOMA-IR ≥ 3,0	25*	8.9*	28.1*	43.8*	26.9*	23.0*
2	India, NR	Randomly selected sample of population based study (Epidemiological Study of Adolescents and Young adults (ESAY))	Adolescents (14-19 yr) in New Delhi region. / Asian Indian	948	NR	14-19	Fasted blood sample (FPI)	14-15 yr: ♂FPI > 128.5 pmol/l, ♀ >164.8 pmol/l; 16-17yr: ♂FPI > 126.1 pmol/l, ♀ >152.6 pmol/l; 18-19 yr: ♂FPI > 121.2 pmol/l, ♀ >162.4 pmol/l	35.4		67.3			
3	India, NR	Door-to-door demographic survey of representive wards of Chennai city.	Children and adolescents in urban South-India / Asian Indian	1519	74%	6-19	Fasted blood sample (FPG and FPI)	HOMA-IR ≥ 3.56					7.8	12.5
4	India, 2000-2003	Randomly selected sample of population based study (ESAY)	Adolescents (14-19 yr) in New Delhi region / Asian Indian	793	NR	14-19	Fasted blood sample (FPI)	FPI> 20 µU/ml	34.2*	29	63.9		18.9*	49.7*
5	Japan, 2009	Cross-sectional study of standard health examination with additional blood sampling in schoolchildren in 5th and 8th grade	Children and adolescents (10-13 yr) in region of Nagano Prefecture / Japanese	310	99,0%	10-13	Fasted blood sample (FPG and FPI)	HOMA-IR ≥ 2.5	21.6		46.8			
AUSTRALIA														
6	Australia, 2004	Cross-sectional population survey of Grade 10 students in NSW School Physical Activity and Nutrition Survey 2004 (SPANS 2004)	Grade 10 students in Sydney metropolitan area (population 4.2 million) / NR	495	NR	14.3-17.1	Fasted blood sample (FPI)	FPI > 100pmol/l	20.6*	♂ 7.1 ♀ 10.9	♂ 29.5 ♀ 41.9	♂ 68.4 ♀ 44.4	19.3	22.4
7	New Zealand, NR	Observational study of pacific island teenagers living in New Zealand, recruited by PI community workers	PI teenagers living in the community in Dunedin, New Zealand / Pacific Island [a]	80	83.0%	15-18	Fasted blood sample (FPG, FPI and fasted triglycerides)	FPI > 12 µIU/ml HOMA2 > 2 or McAuley index ≤ 6.3	44 26.9				17.5 20.0	36.8 34.2

Supplemental table 1. Overview of the included studies and extracted data (continued)

Nr	Country, calender time	Methods	Sample representative for / ethnicity	Sample size	Participation degree	Age	Measurements to determine IR	Criteria IR	Prevalence IR (%)					
									Overall	Normal weight	Over-weight	Obese	Boys	Girls
CARIBBEAN AND CENTRAL AMERICA														
8	Mexico, NR	Cross-sectional survey in subjects randomly selected from public schools in Mexico-City	Adolescents 12-16 yr in Mexico-City / NR	1850	40.1%	12-16	Fasted blood sample (FPG and FPI)	FPI > 9.85 µIU/ml (p75)	24.8*				4.9*	24.7*
								HOMA-IR > p85 (~3.0)	15.3 *				12.7*	17.2*
EUROPE														
9	Czech Republic, NR	Cross-sectional study of a general population cohort	Czech adolescents 13.0-17.9 yr /NR	1518	NR	13.0-17.9	Fasted blood sample (FPG and FPI)	HOMA-IR > 2.5	40.7 *				40.9	40.5
								HOMA-IR > 4.0	13.2 *				14.3	10.8
10	Greece, 2007	Large scale, cross-sectional epidemiological study	Greek schoolchildren 9-13yr / NR	2026	64.1%	9-13	Fasted blood sample (FPG and FPI)	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
11	Greece, 2005-2006	Observational population based study on school children in Crete	Adolescents 10-12yr on Crete / NR	248	NR	10-12	Fasted blood sample (FPG and FPI)	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
12	Italy, 2007-2008	Cross-sectional study of children randomly selected from schools	Adolescents 11-13yr in Southern Italy / NR	575	68.2%	11-13	Fasted blood sample (FPG and FPI)	FPI > p75 (♂ 11.0 pmol/l; ♀ 13.2 mol/l) [b]	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) [b]	25.0 *	♂ 13.1 ♀ 11.8	♂ 26.7 ♀ 37.1	♂ 54.7 ♀ 65.5	25.0*	25.1*
13	Turkey, NR	Cross-sectional survey in randomly selected school children, schools stratified for geographical location and socioeconomic levels.	Turkish adolescents 12-19yr living in region of Kayseri / NR	790	97.3%	12-19	Fasted blood sample (FPG and FPI)	HOMA-IR <3.16 [c]	34.7				33.0	36.1

Supplemental table 1. Overview of the included studies and extracted data (continued)

Nr	Country, calender time	Methods	Sample representative for / ethnicity	Sample size	Participation degree	Age	Measurements to determine IR	Criteria IR	Prevalence IR (%)					
									Overall	Normal weight	Over-weight	Obese	Boys	Girls
NORTH-AMERICA														
14	U.S., 2008-2011	Cross-sectional convenience sample of school-based medical screening	Children attending public high school in New York / Hispanic, African-American, other	1185	63%	14-19	Fasted blood sample (FPG and FPI)	HOMA-IR > 4	19.5	4.5	12.4	37.8		
15	U.S., NR	Observational cross-sectional study in middle-school students (TEAMS project)	Adolescents 11-14 yr in inland Pacific Northwest of US / NR [d]	151	NR	11-14	Fasted blood sample (FPG and FPI)	HOMA-IR ≥ 2.7	33.5 *	22.7	62.5			
16	U.S., 2002-2003	Cross-sectional observational study among schoolchildren of schools in Wausau school district	Children and adolescents in urban region of Wausau, U.S. / 13% minority students	535	NR	7-17	Fasted blood sample (FPG and FPI)	HOMA-IR > p85 of normal weight children (BMI <p85) [e]	~25 [e]		50			
SOUTH-AMERICA														
17	Argentina, 2005	Descriptive study of high-school students in the city of Posadas (total amount of adolescents 12-18yr: 35,000)	Adolescents in urban region of Posadas, Argentina / NR	420	60%	12-18	Fasted blood sample (FPG and FPI)	FPI ≥ 12 mU/l	11.7					
								HOMA-IR ≥ 2.5	10.5				10.6	10.4
								QUICKI ≤ 0.33	9.8				6.3	11.9
18	Chile, 2009-2011	Cross-sectional study of children in public schools in Puente Alto County	Chilean children / Chilean	3325	59.2%	10-15	Fasted blood sample (FPG and FPI)	HOMA-IR > p90 for sex and Tanner stage (♂ Tanner I and II: 3.2; Tanner III and IV: 4.2; ♀ Tanner I and II 4.1, Tanner III and IV: 5.0)	25.9				26.9	24.8

Abbreviations: 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

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. [a] 40% of sample is overweight, 36% is obese; [b] Cut-off point for FPI and HOMA-IR based on p75 of this population; [c] Cut-off point <3.16, while all other studies that use HOMA-IR define IR as HOMA-IR > (...); [d] > 27% of participants BMI > p95; [e] Specific cut-off value for IR not mentioned in the article. Specific prevalence also not mentioned.

REFERENCES SUPPLEMENTARY MATERIAL CHAPTER 2

1. Wang Q, Yin J, Xu L, et al. Prevalence of metabolic syndrome in a cohort of Chinese schoolchildren: comparison of two definitions and assessment of adipokines as components by factor analysis. BMC Public Health 2013; 13:249.
2. Vikram NK, Misra A, Pandey RM, Luthra K, Bhatt SP. Distribution and cutoff points of fasting insulin in Asian Indian adolescents and their association with metabolic syndrome. J Assoc Physicians India 2008; 56: 949-54.
3. Ranjani H, Sonya J, Anjana R, Mohan V. Prevalence of glucose intolerance among children and adolescents in urban south india (ORANGE-2). Diabetes technology & therapeutics. 2013;15(1):13
4. Vikram NK, Misra A, Pandey RM, Luthra K, Wasir JS, Dhingra V. Heterogeneous phenotypes of insulin resistance and its implications for defining metabolic syndrome in Asian Indian adolescents. Atherosclerosis 2006; 186: 193-99.
5. Fujii C, Sakakibara H. Association between insulin resistance, cardiovascular risk factors and overweight in Japanese schoolchildren. Obes Res Clin Pract 2012; 6: e1-e8.
6. Denney-Wilson E, Cowell CT, Okely AD, Hardy LL, Aitken R, Dobbins T. Associations between insulin and glucose concentrations and anthropometric measures of fat mass in Australian adolescents. BMC Pediatr 2010; 10: 58.
7. Grant AM, Taungapeau FK, McAuley KA, et al. Body mass index status is effective in identifying metabolic syndrome components and insulin resistance in Pacific Island teenagers living in New Zealand. Metabolism 2008; 57: 511-16.
8. Cardoso-Saldana GC, Yamamoto-Kimura L, Medina-Urrutia A, Posadas-Sanchez R, Caracas-Portilla NA, Posadas-Romero C. [Obesity or overweight and metabolic syndrome in Mexico City teenagers.]. Arch Cardiol Mex 2010; 80: 12-18.
9. Aldhoon-Hainerova I, Zamrazilova H, Dusatkova L, et al. Glucose homeostasis and insulin resistance: Prevalence, gender differences and predictors in adolescents. Diabetol Metab Syndr. 2014;6(1):100-5996-6-100.
10. Androutsos O., Moschonis G., Mavrogianni C., et al. Identification of lifestyle patterns, including sleep deprivation, associated with insulin resistance in children: The healthy growth study. Eur J Clin Nutr. 2014;68(3):344-349
11. Manios Y, Moschonis G, Kourlaba G, et al. Prevalence and independent predictors of insulin resistance in children from Crete, Greece: the Children Study. Diabet Med 2008; 25: 65-72.
12. Caserta CA, Pendino GM, Alicante S, et al. Body mass index, cardiovascular risk factors, and carotid intima-media thickness in a pediatric population in southern Italy. J Pediatr Gastroenterol Nutr 2010; 51: 216-20.
13. Budak N, Ozturk A, Mazicioglu M, Yazici C, Bayram F, Kurtoglu S. Decreased high-density lipoprotein cholesterol and insulin resistance were the most common criteria in 12- to 19-year-old adolescents. Eur J Nutr 2010; 49: 219-25.
14. Turchiano M, Sweat V, Fierman A, Convit A. Obesity, metabolic syndrome, and insulin resistance in urban high school students of minority race/ethnicity. Arch Pediatr Adolesc Med 2012; 166: 1030-36.
15. Bindler RC, Daratha KB. Relationship of Weight Status and Cardiometabolic Outcomes for Adolescents in the TEAMS Study. Biol Res Nurs 2012; 14: 65-70.
16. Hughes P, Murdock DK, Olson K, et al. School children have leading risk factors for cardiovascular disease and diabetes: the Wausau SCHOOL project. WMJ 2006; 105: 32-39.

17. Bonneau GA, Pedrozo WR, Castillo Rascon MS, Albrekt AL. Prevalence of insulin resistance in adolescents in the city of Posadas. Recommended diagnostic criteria. Rev Argent Endocrinol Metab 2011; 48: 78-86.
18. Mardones F, Arnaiz P, Barja S, et al. Nutritional status, metabolic syndrome and insulin resistance in children from santiago (chile). Nutr Hosp. 2013;28(6):1999-2005.