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Developing a risk assessment tool for identifying individuals at high risk for developing insulin resistance in European adolescents: the HELENA-IR score

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Abstract

Objectives: To develop and validate an easy-to-use screening tool for identifying adolescents at high-risk for insulin resistance (IR).

Methods: A total of 1,053 adolescents (554 females), aged 12.5 to 17.5 years with complete data on glucose and insulin levels were included. Body mass index (BMI), fat mass index (FMI) and the homeostasis model assessment for insulin resistance (HOMA-IR) were calculated. VO_2max was predicted using 20 m multi-stage fitness test. The population was randomly separated into two cohorts for the development (n=702) and validation (n=351) of the index, respectively. Factors associated with high HOMA-IR were identified by Spearman correlation in the development cohort; multiple logistic regression was performed for all identified independent factors to develop a score index. Finally, receiver operating characteristic (ROC) analysis was performed in the validation cohort and was used to define the cut-off values that could identify adolescents above the 75th and the 95th percentile for HOMA-IR.

Results: BMI and VO_2max significantly identified high HOMA-IR in males; and FMI, TV watching and VO_2max in females. The HELENA-IR index scores range from 0 to 29 for males and 0 to 43 for females. The Area Under the Curve, sensitivity and specificity for identifying males above the 75th and 95th of HOMA-IR percentiles were 0.635 (95%CI:

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0.542–0.725), 0.513 and 0.735, and 0.714 (95%CI: 0.499–0.728), 0.625 and 0.905, respectively. For females, the corresponding values were 0.632 (95%CI: 0.538–0.725), 0.568 and 0.652, and 0.708 (95%CI: 0.559–0.725), 0.667 and 0.617, respectively. Simple algorithms were created using the index cut-off scores.

Conclusions: Paediatricians or physical education teachers can use easy-to-obtain and non-invasive measures to apply the HELENA-IR score and identify adolescents at high risk for IR, who should be referred for further tests.

Keywords: adolescents; body fatness; insulin resistance; screening tool; type 2 diabetes; VO_2max.

Introduction

According to the International Diabetes Federation, 537 million adults globally are living with type 2 diabetes (T2D); this number is expected to reach 643 million by 2030 and 784 million by 2045 [1]. In the last few decades, T2D cases have been increasing also in children and adolescents but reliable data are scarce [2, 3], and mostly coming from North America and China [4–8].

The importance of early identification of T2D has been well documented [9, 10]. A diagnosis comes after assessing fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, or glycated haemoglobin [11]. Children and adolescents that have overweight plus one or more additional risk factors (e.g. maternal history of diabetes, or gestational diabetes during the child's gestation, signs of insulin resistance) should be screened for prediabetes or T2D [10]. However, some T2D cases in these age groups remain undiagnosed or untreated, and knowledge on the extent of this issue is limited. In Europe, several studies have evaluated the incidence and prevalence of diagnosed T2D in children and adolescents but have not assessed the level of undiagnosed T2D cases [12–14]. Demmer et al. [15] tried to address this lack of data in the United States and found that T2D accounted for half of adolescent diabetes, and 1/3 of such cases were undiagnosed. The reasons for this could be multifold. Parents of children with overweight and obesity tend to underestimate the weight of their children [16], which could mean that children at high risk for T2D are not properly screened for prediabetes or T2D. Thus, comprehensive, coordinated and innovative strategies for the investigation and prevention of youth-onset IR or T2D are urgently needed; however the cost and practical arrangements (i.e. children would have to miss school) needed to perform the screening itself may be an inhibitory factor. This highlights the need for a low-cost method that healthcare professionals could easily apply to identify the children in need of more elaborate screening.

Insulin resistance (IR) is a major component of metabolic syndrome, which in turn is a precursor of T2D, and it has been associated with cardiovascular disease and metabolic disorders, such as hypertension, dyslipidaemia, hepatic steatosis and endothelial dysfunction [17–20]. Several modifiable and non-modifiable risk factors such as genetics, age, obesity (especially central obesity), diet and physical activity (PA) have been associated with IR [21–26]. There is a growing number of screening tools assessing glycaemic risk status (using IR as the dependent factor) by simple measures such as age, history of disease, sex, ethnicity, body mass index (BMI), medication, etc. [27–30]. However, they have not been developed for use on teen populations, and most of them incorporate (history of) measurements of blood glucose, which is difficult in young populations.

The aim of the current study is to develop and validate a single risk assessment tool (HELENA-IR score) for the identification of adolescents with IR via easy-to-obtain demographic, anthropometric, dietary and lifestyle parameters, based on a large European cross-sectional study.

Materials and methods

Study protocol and recruitment

The Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS) was carried out between 2006 and 2007 in 10 European cities: Athens (Greece), Dortmund (Germany), Ghent (Belgium), Heraklion (Greece), Lille (France), Pécs (Hungary), Rome (Italy), Stockholm (Sweden), Vienna (Austria) and Zaragoza (Spain). A total of 3,528 adolescents aged 12.5–17.5 years were recruited at school-setting and met the general HELENA-CSS inclusion criteria: not participating simultaneously in another clinical trial; be free of any acute infection lasting less than 1 week before the inclusion; and having valid information for age, sex and BMI. One-third of the adolescents were randomly invited to have a blood sampling for additional analysis. More details are presented elsewhere [31, 32]. Thus, in the current study, 1,053 adolescents (554 females) with complete data on glucose and insulin levels were included.

The HELENA study adhered to the Declaration of Helsinki and the conventions of the Council of Europe on human rights and biomedicine. All participating countries obtained ethical clearance from the relevant Ethical Committees and local authorities. Participants and their parents or guardians provided signed informed consent prior to their enrolment in the study [33].

Data collection

Physical examination: Trained researchers performed the anthropometric measurements using standard protocols [34]. Body weight

was measured to the nearest 0.1 kg using an electronic scale (Type SECA 861). Height was measured to the nearest 0.1 cm with a telescopic height-measuring instrument (Type SECA 225). Both measurements were performed in underwear and barefoot. The BMI was calculated as body weight (kg) divided by the height squared (m^2). Age- and sex-standardized BMI cut-off points according to the International Obesity Task Force (IOTF) were used to define healthy weight, overweight and obesity [35, 36]. Waist circumference was measured in triplicate at the midpoint between the lowest rib and the iliac crest (measuring tape SECA 200) and was used as a proxy for central body fat. Bioelectrical impedance analysis was conducted using BIA 101 AKERN SRL, using standard protocols; body fat mass is calculated in kg, and fat-free mass is calculated by subtracting fat mass from total body mass in kg. Fat mass index (FMI) is calculated by dividing body fat mass in (kg) by height squared (m^2). Pubertal stage was recorded by a researcher of the same sex as the child, after brief observation, according to Tanner and Whitehouse [37]. The FMI reference curves for children developed by Gätjens and colleagues [38] were additionally used to evaluate levels of body fatness.

Physical activity: Physical activity was measured via a modified version of the long International Physical Activity Questionnaire (the IPAQ-A) [39]. Time spent on moderate-to vigorous PA (MVPA, in mins/day) was calculated by summing the time spent in moderate (3–6 metabolic equivalents) and vigorous activities (>6 metabolic equivalents).

Sedentary behaviours: A self-reported sedentary behaviours questionnaire (designed ad hoc) was administered during the school hours [39]. Adolescents reported the daily minutes spent on the following sedentary items: TV viewing, playing with computer games and console games, using the internet for reasons other than study, separately on weekdays and weekends. Participants were divided into three groups based on their TV watching time, as follows: <1, 1–2 and ≥2 h/day [16]; the two latter groups were merged as their results did not differ. Moreover, the total self-reported sedentary time was calculated by summing the time spent on TV viewing, playing with computer and console games and using the internet. Sleeping hours were from total self-reported sleeping hours during weekdays and weekends.

Physical fitness: Adolescents participated in a 20 m shuttle-run fitness test, according to HELENA study protocols [40]. The VO_2 maximal oxygen uptake (VO_2max, in mL/kg/min) was predicted from age and maximal speed of the shuttle-run fitness test [41]. We used international normative cut-off values [42, 43] to identify adolescents with physical fitness at low, medium and healthy zones.

Dietary intake: A computer-assisted self-administrated 24-hr dietary recall tool (HELENA-DIAT) was used for dietary assessment in the HELENA CSS [32]. The adolescents completed the HELENA-DIAT on 2 non-consecutive days in a period of 2 weeks. Usual intakes were estimated by statistical modelling technique assuming two non-consecutive 24-h recalls.

Blood indices: Finally, fasting serum concentrations of glucose (G_F) and insulin (I_F) were measured after an overnight fast. The HOMA-IR was calculated as I_F (μlU/mL) × G_F (mmol/L)/22.5 (to convert I_F values in μlU/mL to pmol/L multiplying factor was 6.945) [44]. A detailed description of the blood analysis has been reported elsewhere [45].

Statistical analysis

Categorical variables are presented with absolute and relative frequencies (%). Continuous variables are presented with mean and standard deviation (SD) when they were normally distributed and with median and interquartile range when they were not. Normality was evaluated using histograms and Kolmogorov–Smirnov test. Associations between categorical variables were tested by using the Chi-Square test. The associations between the continuous and binary variables (i.e., sex) were evaluated through Student's t-test or Mann–Whitney when the data were normally or skewed distributed, respectively. Associations between HOMA-IR and continuous variables were evaluated with Spearman's rho correlation coefficient.

The total sample (n=1,053) was randomly separated to an index development sub-sample (n=702) and an index validation sub-sample (n=351).

For the development of the risk assessment indices, logistic regression was performed, with the dependent variable being the HOMA-IR binary indicator of being above or below 2.43 IU/mL (i.e., third tertile of HOMA-IR values in this population). The exclusion criteria of candidate variables were set at $p>0.10$ considering the total population. To assign scores to the corresponding risk factors, the adjusted β-coefficients were divided by the lower coefficient and then rounded to the nearest integer values. In this manner, the indices scores begin with one point. The minus sign indicates that increasing the variable value decreases the chance of developing insulin resistance. To choose the cut-offs based on the combination of best sensitivity (Se) and specificity (Sp) of the score, Receiver Operating Characteristic (ROC) curves were performed; the closest top left method in the ROC curve is used to calculate the thresholds for assigning scores in continuous variables such as the hours of TV watching, BMI, VO_2max and FMI.

Following the assignment of sub-scores to patients, the total score was derived from their sum. Two-thirds of the total data, or 702 children, were used to run the logistic regression model. The remaining sample of 351 adolescent participants was used to validate the scoring model. ROC analysis was performed to the validation sub-sample and the Area Under the Curve (AUC) was identified for adolescents having HOMA values above the 75th and 95th percentile. The points with the best combination of Se and Sp (as determined previously) were used as the cut-off values to guide the development of the algorithm. We used R 4.0.4 (2021-02-15) [46] to conduct all statistical analyses.

Results

The descriptive characteristics of the study population are presented in Table 1. The study sample included 1,053 adolescents (52.6% females). The mean age, BMI and waist circumference of the sample used for this study had no significant differences from those of the overall HELENA sample. There were no differences observed between the Index Development and the Index Validation sub-samples (results not shown).

Table 2 presents the correlation coefficients of HOMA-IR with different anthropometric, dietary, physical activity, physical fitness and sedentary parameters by sex. After the stepwise procedure, several body fatness indicators and VO_2max were retained for both males and females, and additionally TV watching for girls. These

Table 1: Descriptive characteristics of the sample.

	Total (n=1,053) Mean (SD)	Males (n=499) Mean (SD)	Females (n=554) Mean (SD)	p-Value
Age, years	14.7 (1.20)	14.8 (1.23)	14.7 (1.18)	0.718
Weight, kg	58.6 (12.5)	61.6 (13.9)	55.7 (10.1)	<0.001
Height, cm	165.5 (9.39)	169.7 (9.88)	161.7 (7.07)	<0.001
BMI, kg/m^2	21.3 (3.59)	21.4 (3.84)	21.3 (3.34)	0.647
BMI z-score	0.48 (1.10)	0.59 (1.15)	0.37 (1.05)	0.002
Waist circumference, cm	72.4 (8.64)	74.5 (9.06)	70.5 (7.80)	<0.001
Waist/height ratio	0.44 (0.05)	0.44 (0.05)	0.44 (0.05)	0.836
Hip circumference, cm	91.6 (8.71)	90.4 (9.03)	92.7 (8.29)	<0.001
Waist/hip ratio	0.79 (0.06)	0.82 (0.05)	0.76 (0.06)	<0.001
Total fat mass, kg	14.4 (8.38)	13.5 (10.1)	15.1 (6.50)	<0.001
Body fat, %	23.5 (9.44)	20.3 (11.0)	26.2 (6.86)	<0.001
FMI, kg/m^2	4.51 (2.63)	3.51 (2.39)	5.42 (2.50)	<0.001
Fat free mass, kg	44.2 (8.16)	48.6 (8.95)	40.7 (5.23)	<0.001
FFMI, kg/m^2	16.8 (1.8)	17.8 (1.83)	15.8 (1.12)	<0.001
Total energy intake, kcal/day	2,269.0 (1,016.5)	2,642.0 (1,131.0)	1941.1 (768.0)	<0.001
Total fat intake, g/day	90.5 (38.7)	103.6 (42.7)	79.0 (30.5)	<0.001
Carbonated soft drinks, mL/day	308.7 (303.3)	386.9 (350.0)	236.5 (231.0)	<0.001
MVPA, min/day	59.4 (24.4)	69.4 (25.2)	51.2 (20.4)	<0.001
Time spent inactive, min/day	541.6 (85.8)	534.7 (93.2)	547.3 (78.8)	0.172
TV watching, min/day	115.9 (67.4)	119.0 (67.3)	113.0 (67.4)	0.100
Sleeping time, hrs/day	8.11 (1.19)	8.21 (1.22)	8.01 (1.15)	0.007
VO_2max, mL/kg/min	42.5 (10.9)	50.5 (8.99)	34.8 (5.85)	<0.001
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
HOMA-IR	1.95 (1.38–2.72)	1.87 (1.33–2.68)	2.04 (1.39–2.76)	0.073

BMI, body mass index; FFMI, fat free mass index; FMI, fat mass index; HOMA-IR, homeostasis model assessment for insulin resistance; MVPA, moderate to vigorous physical activity.

Table 2: Spearman correlations between HOMA and various anthropometric, dietary, physical activity, physical fitness and sedentary parameters, by sex.

	Males		Females	
	Spearman rho	p-Value	Spearman rho	p-Value
Age, years	−0.064	0.157	−0.140	0.001
Weight, kg	0.281	<0.001	0.203	<0.001
Height, cm	0.023	0.610	0.019	0.651
BMI, kg/m2	0.340	<0.001	0.207	<0.001
BMI z-score	0.325	<0.001	0.199	<0.001
Waist circumference, cm	0.293	<0.001	0.246	<0.001
Waist/height ratio	0.291	<0.001	0.229	<0.001
Hip circumference, cm	0.292	<0.001	0.128	0.003
Waist/hip ratio	0.100	0.027	0.185	<0.001
Total fat mass, kg	0.358	<0.001	0.239	<0.001
Body fat (%)	0.325	<0.001	0.210	<0.001
FMI, kg/m^2	0.311	<0.001	0.222	<0.001
Fat free mass, kg	0.023	0.628	0.096	0.024
FFMI, kg/m^2	0.314	<0.001	0.133	0.002
Total energy intake, kcal/day	−0.050	0.375	−0.049	0.357
Total fat intake, g/day	−0.038	0.503	−0.026	0.626
Carbonated soft drinks, mL/day	−0.092	0.101	−0.044	0.406
MVPA, min/day	−0.023	0.689	−0.098	0.054
Time spent inactive, min/day	−0.103	0.067	0.053	0.299
TV watching, min/day	0.092	0.055	0.108	0.012

Table 2: (continued)

	Males		Females	
	Spearman rho	**p-Value**	**Spearman rho**	**p-Value**
Sleeping time, hrs/day	0.025	0.582	0.036	0.400
VO_2max, mL/kg/min	−0.264	<0.001	−0.279	<0.001

BMI, body mass index; FFMI, fat free mass index; FMI, fat mass index; HOMA-IR, homeostasis model assessment for insulin resistance; MVPA, moderate to vigorous physical activity.

Table 3: Logistic regression results and derived scores by sex, using data from the index development sub-sample (n=702). For the age- and sex-standardised cut-offs used, please see Tables S1 and S2.

Predictor	Cut-offs	β± SE	p-Value	Allocated scores	Score range
Males					**0–29**
BMI, kg/m^2	Healthy weight	Reference		0	
	Overweight[a]	1.016	0.008	12	
	Obesity[a]	1.609	0.007	19	
VO_2max	Medium and healthy fitness	Reference		0	
	Low fitness[b]	0.834	0.048	10	
Females					**0–43**
FMI, kg/m^2	Healthy and overfat	Reference		0	
	Obesity[c]	1.547	0.001	18	
VO_2max	Medium and healthy fitness	Reference		0	
	Low fitness[d]	1.320	<0.001	15	
Tv viewing	<1 h/day	Reference		0	
	1 h/day	0.876	0.014	10	

BMI, body mass index; FMI, fat mass index; [a]Age- and sex-standardized BMI cut-offs (from [36], see S1); [b]Age- and sex-standardized fitness cut-offs (from [42, 43], see S1); [c]Age- and sex-standardized FMI cut-offs (from [38], see S2); [d]Age- and sex-standardized fitness cut-offs (from [42, 43], see S2).

parameters were used to run the logistic regressions; since the different body fatness indicators were interrelated, the ones performing better in the model were retained and the final models are presented in Table 3. Table S1 provides the sex- and age-standardized cut-offs for body mass index (from [36]) and VO_2max (from [42, 43]) used for the calculation of the HELENA-IR risk score in males. Table S2 provides the sex- and age-standardized cut-offs for FMI (from [38]) and VO_2max (from [42, 43]) used for the calculation of the HELENA-IR risk score in females.

For males, the ROC analysis in the validation cohort indicated an AUC 0.635 (95%CI: 0.542–0.728) and an AUC 0.714 (95%CI: 0.499–0.728) for identifying adolescents with HOMA-IR values above the 75th and the 95th percentile, respectively (Figure 1, Table 4). For females, the ROC analysis in the validation cohort indicated an AUC 0.632 (95%CI: 0.538–0.725) and an AUC 0.708 (95%CI: 0.559–0.725) for identifying adolescents with HOMA-IR values above the 75th and the 95th percentile, respectively (Figure 2, Table 4).

Table 4 displays the ROC characteristics of the HELENA-IR score in the validation cohort. The index cut-off scores for identifying male and female adolescents above the 75th percentile for HOMA-IR were 5 out of 29 points, and 16.5 out of 43 points, respectively. Similarly, the index cut-off scores for identifying male and female adolescents above the 95th percentile for HOMA-IR were 15.5 out of 29 points, and 21.5 out of 43 points, respectively (Table 4). Figures 3 and 4 present the algorithms for identifying male and female adolescents, respectively, above the 75th percentile and the 95th percentile of HOMA-IR.

Discussion

The increase in the prevalence of T2D and its acknowledged impact on public health highlights the need for more appropriate strategies and diagnostic tools for its prevention and early treatment. Since this metabolic abnormality may be provoked by the interaction of various risk

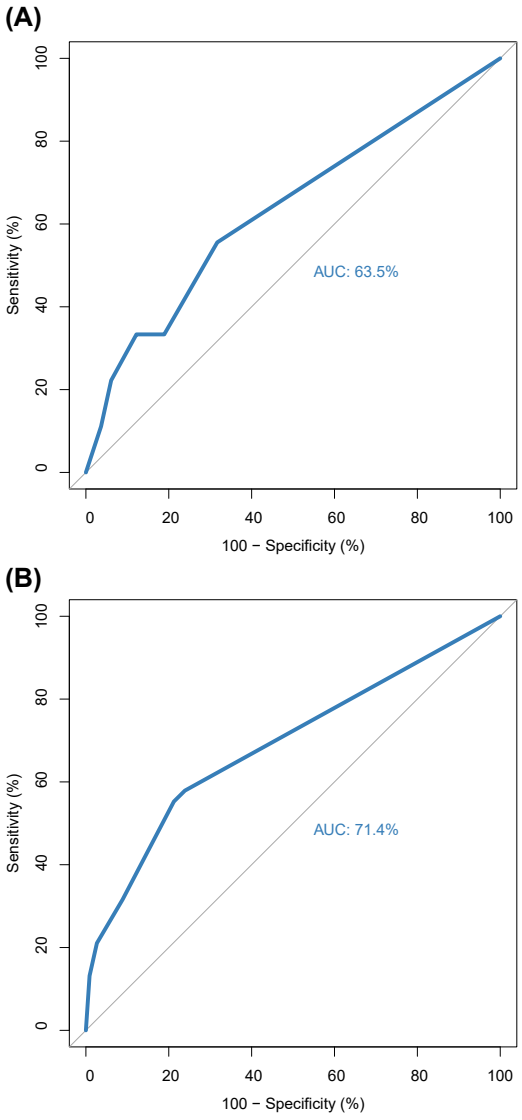

Figure 1: ROC curves for identifying males above the (A) 75th percentile and (B) 95th percentile of HOMA-IR.

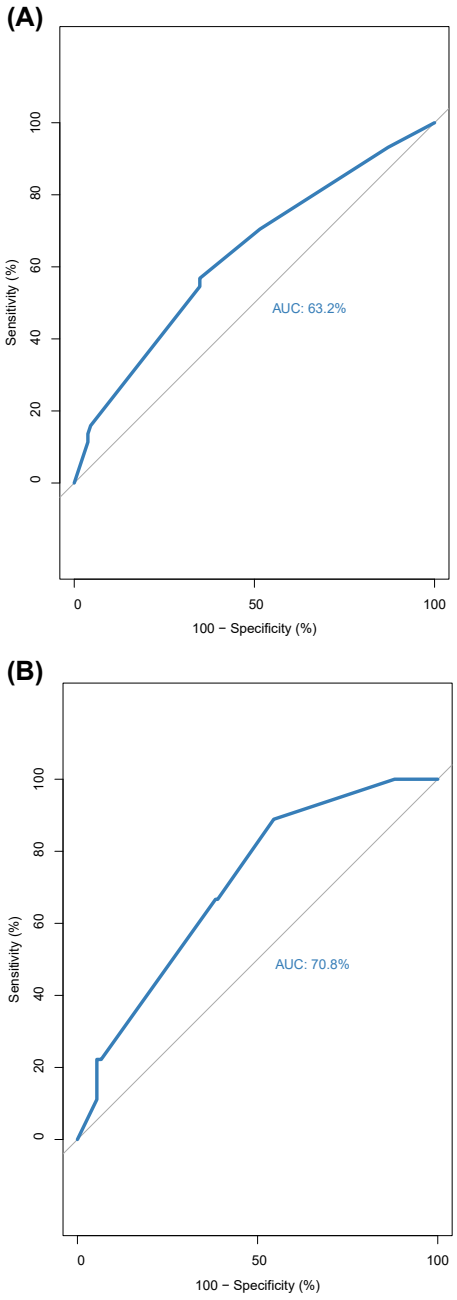

Figure 2: ROC curves for identifying females above the (A) 75th percentile and (B) 95th percentile of HOMA-IR.

factors relevant to family history, anthropometric indices and lifestyle parameters, such as dietary behaviours and physical fitness, their assessment is necessary to design effective prevention strategies. Therefore, the development

Table 4: ROC characteristics of HELENA-IR score in the validation cohort.

	Score	AUC	95%CI	Se	Sp
Males					
Cut off score for identifying individuals above 75th percentile of HOMA-IR	5	0.635	0.542–0.728	51.282	73.504
Cut off score for identifying individuals above 95th percentile of HOMA-IR	15.5	0.714	0.499–0.728	62.500	90.541
Females					
Cut off score for identifying individuals above 75th percentile of HOMA-IR	16.5	0.632	0.538–0.725	56.820	65.15
Cut off score for identifying individuals above 95th percentile of HOMA-IR	21.5	0.708	0.559–0.725	66.670	61.68

AUC, area under the curve; HOMA-IR, homeostasis model assessment for insulin resistance; Se, sensitivity; Sp, specificity.

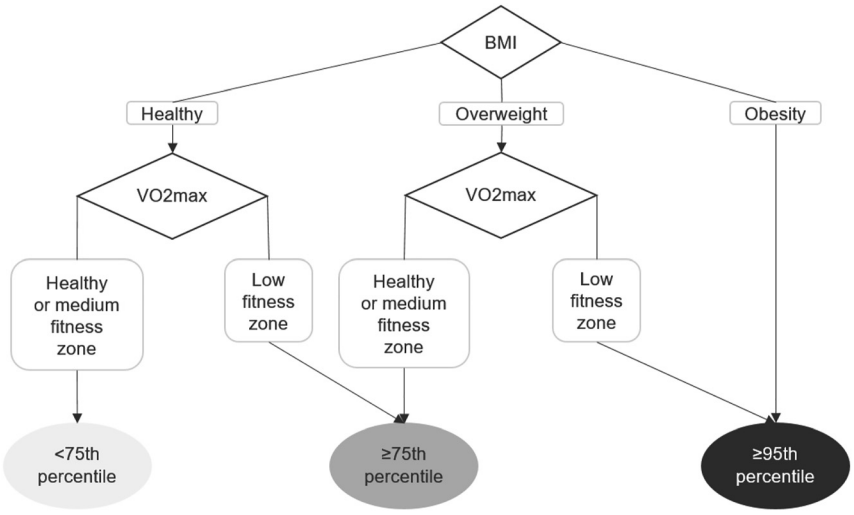

Figure 3: Algorithm for identifying male adolescents above the 75th percentile and the 95th percentile of HOMA-IR. See S1 for the age-standardised cut-offs for BMI and VO_2max.

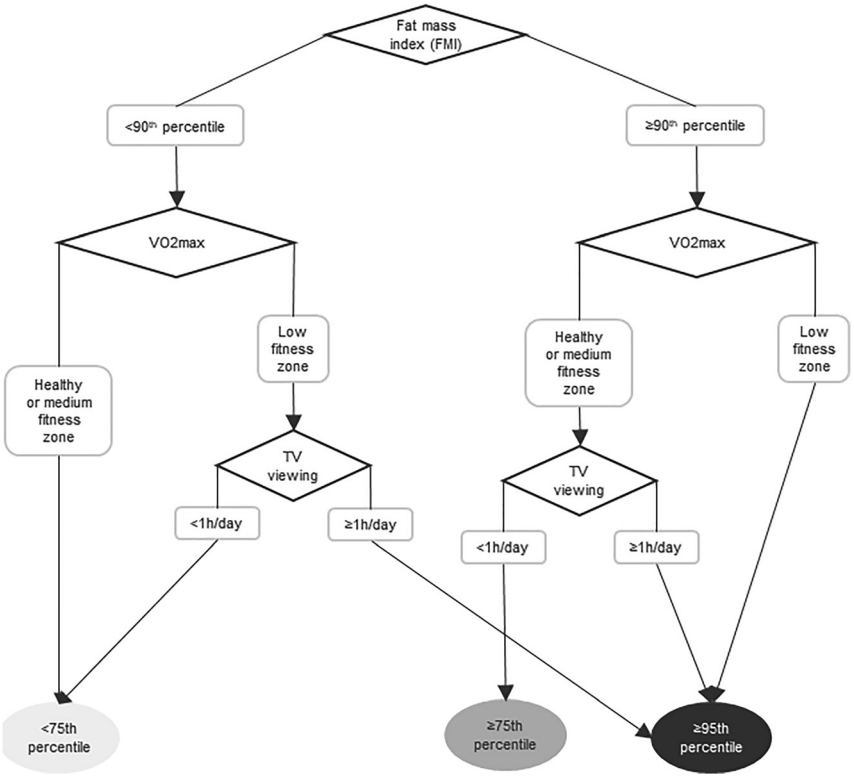

Figure 4: Algorithm for identifying female adolescents above the (A) 75th percentile and (B) 95th percentile of HOMA-IR. See S2 for the age-standardised cut-offs for % of body fat or FMI and VO_2max.

and implementation of screening tools evaluating holistically various health-related variables can be of a great importance to easily identify people at risk, to be then referred for further evaluation at primary healthcare settings. The priority of the current study was to develop a risk assessment index for the identification of IR among undiagnosed adolescents.

The American Diabetes Association recommends that asymptomatic children and adolescents should be screened for T2D if they are aged ≥10 years, have a BMI ≥85th percentile and have at least one additional risk factors following the assessment of either fasting plasma glucose, plasma glucose during oral glucose tolerance test or glycated haemoglobin [11]. Similar screening protocols are available from WHO and other countries [47, 48]. However, these methods require specialized tests and are invasive and costly.

The early identification and management of IR may significantly decrease the risk for developing T2D and cardiovascular disease [18, 49, 50] and could further

contribute to the decrease of their economic and public health burden [51]. Several reliable and valid non-invasive tools have been developed for the identification of adults at increased risk for T2D, like the FINDRISC [30, 52–57], the Leicester Risk Assessment Score [58], the CANRISK [30] or the AUSDRISK [29]. However, all these tools are more appropriate for use in adults; for example, the lack of a history of measurements for blood indices or the lack of awareness of an unfavourable glycaemic profile make them unsuitable for the screening of prediabetes and T2D in children and adolescents.

In the current study, we developed a risk assessment index, the HELENA-IR risk score, that can identify adolescents with high HOMA-IR values; it is calculated from 2 to 3 components, none of which requires biochemical tests or other invasive procedures. This makes this index very easy-to-apply and applicable for a wide range of adolescent populations regardless of their access to specialized medical equipment or healthcare services. The index consists of some simple anthropometric measurements that could be performed by the school health services or a paediatrician, and the estimation of VO_2max that schools could easily incorporate as part of the physical fitness assessment of the children. Simple algorithms were created for the easy identification of adolescents above the 75th or 95th percentile for HOMA-IR (see Figures 3 and 4). Tables S3 and S4 provide an overview of the steps someone should follow in order to be able to use the tool for males and females, respectively. One potential limitation of the study is that the cohorts recruited from each country are not representative of the general population but are all coming from urban settings. However, the fact that the current index has been developed upon and validated against a population sample from nine countries across Europe makes the index easily applicable in other Caucasian adolescent populations. Further studies could be designed to validate the findings in adolescent populations living in other settings. In addition, as the AUC achieved in all analyses was below 0.8, further verification of the score is needed by other studies in other adolescent population samples.

Conclusions

The HELENA-IR score is the first predictive tool for IR, consisting of the major risk factors that were found to be associated with IR in European adolescents. Receiving HELENA-IR scores that indicate high risk warrants the prescription of blood exams. It may be used to identify cases of undiagnosed IR, thus providing an easy-to-apply, valid, non-invasive and low-cost index for identifying European adolescents at high risk for developing T2D. Since no biochemical parameters are needed for its estimation, it is easier to be applied in children and adolescents. By using it and identifying children at high risk for IR, lifestyle modifications may be prompted and clinical manifestations of T2D prevented, thus reducing, in the long run, the burden of T2D on national health systems.

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