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ORIGINAL ARTICLE

Impaired fasting glucose and the metabolic profile in Danish children and adolescents with normal weight, overweight, or obesity

Julie T Kloppenborg[1,2] | Cilius E Fonvig[1,3,4] | Tenna R H Nielsen[1,3] | Pernille M Mollerup[1,3] | Christine Bøjsøe[1,3] | Oluf Pedersen[3,5] | Jesper Johannesen[2,5] | Torben Hansen[3,5] | Jens-Christian Holm[1,3,5]

[1]The Children's Obesity Clinic, Department of Pediatrics, Copenhagen University Hospital Holbæk, Holbæk, Denmark

[2]Department of Pediatrics, Copenhagen University Hospital Herlev, Herlev, Denmark

[3]Section of Metabolic Genetics, The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

[4]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[5]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence
Julie Tonsgaard Kloppenborg, PhD, Department of Pediatrics, The Children's Obesity Clinic, Copenhagen University Hospital Holbæk, Smedelundsgade 60, 4300 Holbæk, Denmark.
Email: jtkl@regionsjaelland.dk

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Objective: Whether the definitions of impaired fasting glucose (IFG) from the American Diabetes Association (ADA) and the World Health Organization (WHO) differentially impact estimates of the metabolic profile and IFG-related comorbidities in Danish children and adolescents is unknown.

Methods: Two thousand one hundred and fifty four (979 boys) children and adolescents with overweight or obesity (median age 12 years) and 1824 (728 boys) children with normal weight (median age 12 years) from The Danish Childhood Obesity Biobank were studied. Anthropometrics, blood pressure, puberty, and fasting concentrations of glucose, insulin, glycosylated hemoglobin (HbA1c), and lipids were measured.

Results: About 14.1% of participants with overweight or obesity exhibited IFG according to the ADA and 3.5% according to the WHO definition. Among individuals with normal weight, the corresponding prevalences were 4.3% and 0.3%. IFG was associated with a higher systolic blood pressure, higher concentrations of HbA1c, insulin, C-peptide ($P < .0001$) and triglycerides ($P = .03$), and lower HOMA2-IS and HOMA2-B ($P < .0001$) independent of sex, age, puberty, waist-to-height ratio, and degree of obesity. Furthermore, IFG was associated with a higher risk for hypertension (OR = 1.66 [95%CI: 1.21; 2.28], $P = .002$) and dyslipidemia (OR = 1.90 [95% CI: 1.38; 2.56], $P < .0001$) compared with the group without IFG independent of age, sex, and puberty.

Conclusions: The prevalence of IFG, when applying the ADA criterion compared with the WHO criterion, was 4 times higher in individuals with overweight and obesity and 14 times higher in individuals with normal weight in this study sample of children and adolescents. IFG was associated with a higher risk of hypertension and dyslipidemia compared with their normoglycemic peers regardless of the definition applied.

KEYWORDS

children, glucose metabolism, impaired fasting glucose, obesity

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; BP, blood pressure; CV, coefficients of variation; DBP, diastolic blood pressure; DL, detection limits; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SDS, standard deviation score; TCOCT, The Children's Obesity Clinic Treatment; TG, triglycerides; WC, waist circumference; WHO, World Health Organization; WHtR, waist-to-height ratio

1 | INTRODUCTION

The increasing prevalence of altered glucose metabolism in children and adolescents, and the development of type 2 diabetes at an earlier age, might be consequences of the childhood obesity pandemic.[1,2] In

Denmark, the prevalence of childhood obesity may seem abating in some age groups, but is still highly prevalent, with 10% to 12% of preschool children and 19% to 25% of adolescents suffering from overweight or obesity.[3,4] The prevalence of type 2 diabetes in children under the age of 16 years in Denmark has been stable during the past decade, with a low prevalence of 0.6 per 100 000,[5] whereas in the US, the prevalence reaches 12 per 100 000.[2] From the TODAY study, it is evident that diabetes-related comorbidities develop more aggressively in youths with type 2 diabetes than in youths with type 1 diabetes.[6] Additionally, the life expectancy is estimated to be reduced by 15 years in youths with type 2 diabetes.[7] Early identification and treatment of children with obesity with a concomitant high risk of developing impaired fasting glucose (IFG) is important to prevent the development of diabetes and diabetes-related comorbidities.

Prediabetes is defined by abnormal glycemic variables but with glucose concentrations below the diabetes threshold.[8] In observational studies in adults, prediabetes is associated with a higher risk of type 2 diabetes, cardiovascular disease, and cancer.[9,10] Comparable observations have been reported in children and adolescents with obesity.[11,12] However, the definition of prediabetes in children is adopted from the adult population, without taking the transient physiological insulin resistance during growth and puberty into consideration.[13]

Furthermore, the definitions of IFG by the American Diabetes Association (ADA) and the World Health Organization (WHO) are inconsistent, with different thresholds for IFG, and no consensus regarding the use of glycosylated hemoglobin (HbA1c) in the category of high diabetes risk in the pediatric population.[8,14] Due to these inconsistencies, varying prevalences of IFG in the pediatric population have been reported. A nationwide study in Germany, involving 32 907 children and adolescents with obesity, reported an IFG prevalence of 5.7% according to the ADA criteria and 1.1% according to the WHO criteria. The corresponding prevalences in Sweden were 17.1% and 3.9% (n = 2726), respectively.[15]

The aims of the present study are to describe the prevalence of prediabetes, defined by IFG according to the ADA and WHO criteria, in a population of Danish children and adolescents with normal weight, overweight, or obesity, to characterize their metabolic profile, and to investigate comorbidities related to IFG.

2 | METHODS

2.1 | Design and population

This cross-sectional study includes children and adolescents from The Danish Childhood Obesity Biobank. The Biobank comprises clinical data from children and adolescents with overweight or obesity who were enrolled in a multidisciplinary childhood obesity treatment program from February 2009 to February 2016 (The Children's Obesity Clinic Treatment (TCOCT) cohort), and a population-based cohort consisting of children and adolescents recruited from schools and high schools in 11 municipalities in Denmark from October 2010 to February 2015. The inclusion criteria for this study were a blood sample obtained after an overnight fast and anthropometrics performed at inclusion into the Biobank. The exclusion criteria for the present study were the diagnosis of diabetes or more than 60 days between treatment initiation and collection of the first blood sample (Figure 1).

2.2 | Anthropometrics and blood pressure

Anthropometrics were collected at baseline. Body weight was measured to the nearest 0.1 kg on a Tanita BC418 Scale (Tanita Corp., Tokyo, Japan) in the population-based cohort, and on a Tanita Digital Medical Scale, WB-110 MA (Tanita Corp.) in the TCOCT cohort. Height was measured by stadiometer to the nearest mm. The children wore light indoor clothes and no shoes during the measurements. Waist circumference (WC) was measured with a stretch-resistant tape at the umbilical level to the nearest 5 mm in an upright position after exhalation. Body mass index (BMI) standard deviation score (SDS) was used to evaluate the relative degree of obesity and was calculated using the LMS method[16] based on a Danish reference.[17]

Blood pressure (BP) was measured with an oscillometric devise (Omron 705IT, Omron Healthcare Co. Ltd., Kyoto, Japan) validated in children, using an appropriate cuff size as recommended by the manufacturer. Systolic and diastolic BP were measured 3 times on the right upper arm, in the supine position, after 5 minutes of rest. An average of the last 2 measurements was calculated and converted to a BP SDS-based on sex-, age-, and height-specific American references.[18]

2.3 | Pubertal developmental stage

Pubertal developmental stage was assessed on the basis of genital development in boys and breast development in girls according to the Tanner criteria.[19,20] In the TCOCT cohort, a trained pediatrician conducted a physical examination of the pubertal development stage. In the population-based cohort, the pubertal developmental stage was self-reported using a questionnaire with picture pattern recognition of the 5 different Tanner stages accompanied by written instructions. To be able to compare the pubertal development between the

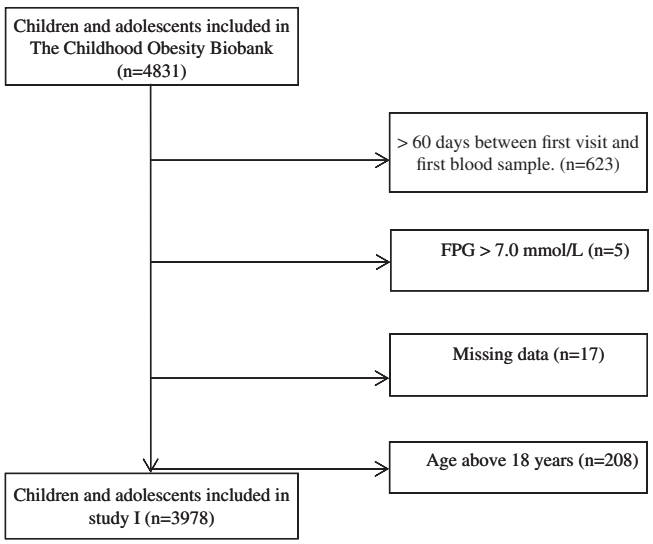

FIGURE 1 Flowchart of the exclusion of the participants from The Danish Childhood Obesity Biobank

2 cohorts, boys and girls were classified as prepubertal (Tanner 1) or pubertal (Tanner ≥2) in the present study.

2.4 | Blood samples

Blood samples were drawn between 7 and 9 AM from a peripheral venous catheter after an overnight fast. The blood samples included fasting plasma glucose (FPG), serum insulin, serum C-peptide, whole blood HbA1c, plasma total cholesterol, plasma triglycerides (TG), plasma high-density lipoprotein cholesterol (HDL-C), and plasma low-density lipoprotein cholesterol (LDL-C).

2.5 | Biochemical analyses

Concentrations of plasma glucose (intra- and inter-assay coefficients of variation (CV) for the concentration: 2.3% and detection limit (DL): 0.06 mmol/L) were determined on a Dimension Vista 1500 Analyzer (Siemens, Erlangen, Germany). Serum insulin (CV: 2.0%; DL: 1.4 pmol/L) and C-peptide (CV: 3.4%; DL: 0.003 nmol/L) concentrations were analyzed on a Cobas 6000 Analyzer (Roche Diagnostic, Mannheim, Germany). Whole blood HbA1c (CV: 1.9%; DL: 24.6 mmol/mol) was analyzed on a Tosoh High-performance Liquid Chromatography G8 Analyzer (Tosoh Corporation, Tokyo, Japan).

The samples for analysis of plasma glucose, serum insulin, and C-peptide were analyzed during the summer 2015 from the same batch number by biotechnicians who were blinded in this design. The samples were stored at −80°C before analysis in a period of 3 months to 6 years in the group of children from The Children's Obesity Clinic and in a period of 3 months to 2.5 years in the population-based cohort.

All participants were instructed not to eat or drink after midnight and until the blood sample was obtained at either the hospital or in a mobile laboratory at the schools.

After sampling, the blood samples were treated according to the regulations and analyzed at an ISO-15189 certified laboratory at the Department of Clinical Biochemistry, Copenhagen University Hospital Holbæk.

Concentrations of plasma total cholesterol (CV: 1%-2.6%; DL: 0.01 mmol/L), triglycerides (CV: 0.9%-2.4%; DL: 0.01 mmol/L), and HDL-C (CV: 0.8%-3.4%; DL: 0.08 mmol/L) were determined on a Cobas 6000 Analyzer (Roche Diagnostics, Mannheim, Germany) (n = 2002) or Dimension Vista 1500 Analyzer (Siemens Healthcare, Erlangen, Germany) (n = 2184) (total cholesterol [CV: 1.4%-2.8%; DL: 1.29 mmol/L], triglycerides [CV: 1%-2%; DL: 0.02 mmol/L], and HDL-C [CV: 2.7%-4.3%; DL: 0.05 mmol/L]). Corrections factors between the different assays were calculated and applied to the results of total cholesterol deducted by 0.26 mmol/L, HDL-C deducted by 0.06 mmol/L, and triglycerides multiplied by 1.17 and deducted with 0.16 mmol/L.[21] Afterwards LDL-C was calculated according to the Friedewald formula (LDL-C = total cholesterol−HDL-C−TG/5).[22]

2.6 | Definition of IFG

According to the criterion of ADA, IFG is defined by plasma glucose concentrations in the range of 5.6 to 6.9 mmol/L.[8] According to the criterion of WHO, IFG is defined by plasma glucose concentrations in the range of 6.1 to 6.9 mmol/L.[23]

2.7 | Definition of hypertension

Hypertension is defined as a systolic BP (SBP) and/or diastolic BP (DBP) ≥95th percentile for age, sex, and height as recommended by the American Academy of Pediatrics[18] and The European Society of Hypertension.[24]

2.8 | Definition of dyslipidemia

Dyslipidemia is, by the American Heart Association, defined as fasting lipid concentrations >95th percentile according to an American reference population corresponding to concentrations of total cholesterol >5.2 mmol/L (200 mg/dL), LDL-C > 3.4 mmol/L (130 mg/dL), HDL-C < 0.9 mmol/L (35 mg/dL), or triglycerides >1.7 mmol/L (150 mg/dL).

2.9 | Classification into groups

To investigate the prevalence of IFG among boys and girls with normal weight, overweight, or obesity, the participants were allocated into 3 groups according to their BMI SDS: (1) normal weight: <90th BMI percentile (corresponding to BMI SDS <1.28), (2) overweight: ≥90th and <99th BMI percentile (BMI SDS ≥1.28 and <2.33), and (3) obese: ≥99th BMI percentile (BMI SDS ≥2.33).[17]

To elucidate whether the definition of IFG by a low (ADA criteria) or high threshold (WHO criteria) impact the estimate of the metabolic profile differently, boys and girls were allocated into 3 new groups depending on their concentration of FPG: (1) non-IFG: FPG <5.6 mmol/L, (2) IFG_{LOW}: FPG ≥5.6 mmol/L <6.1 mmol/L, and (3) IFG_{HIGH}: FPG ≥6.1 mmol/L. When boys and girls exhibiting IFG, regardless of the definition applied, were pooled for comparison with non-IFG, the term $IFG_{LOW + HIGH}$ was used.

2.10 | Indices of insulin sensitivity and secretion

The updated computer model of Homeostasis Model Assessment (HOMA2) was downloaded from the internet (https://www.dtu.ox.ac.uk/homacalculator) and was used to calculate HOMA2-B, which is a surrogate measure of β-cell function from fasting plasma glucose and C-peptide, and HOMA2-IS, which is a proxy for insulin sensitivity based on FPG and serum insulin.[25] The computer model defined normal insulin sensitivity and normal β-cell function by 100%. HOMA2-IS values correlates well with the hyperinsulinemic-euglycemic clamp in adolescents and youths across the continuum of glucose tolerance including children with diabetes and obesity.[26]

2.11 | Data analysis

The software R version 3.2.2 was used for the statistical analyses.[27] The Kruskal-Wallis, Wilcoxon test or t test determined potential differences in the metabolic profile in boys and girls when allocated by either the degree of obesity or the concentration of fasting plasma glucose. The analyses were controlled for multiple testing by the Holm's method.

Comparisons of categorical variables including the pubertal developmental stages and sex were made by Chi-squared analyses. Multiple linear regression and general linear regression analyses, adjusted for age, sex, BMI SDS, waist-to-height ratio (WHtR) and puberty investigated possible associations between FPG, IFG, and the variables of the metabolic profile. The risk of developing dyslipidemia and hypertension in children and adolescents exhibiting IFG compared with children without IFG were investigated by logistic regression adjusted for age, sex, BMI SDS, WHtR, and puberty. *P*-values <.05 were considered statistically significant.

2.12 | Ethics and permissions

Informed written consent was obtained from participants older than 18 years or from parents of the participants who were younger than 18 years of age. All participants gave informed assent. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki 2013, approved by the Danish Data Protection Agency (REG-06-2014) and the Ethics Committee of Region Zealand, Denmark (SJ-104), and is registered at ClinicalTrials.gov (NCT00928473).

3 | RESULTS

In total, 3978 (1707 boys) children and adolescents were included in the study. The participants comprised of 1824 (728 boys) children and adolescents with normal weight, 689 (263 boys) with overweight, and 1465 (716 boys) with obesity. Ninety-two percent were of North-European white, 5.5% of Middle Eastern, 0.8% of Asian, 0.9% of African, 0.05% of Inuit, and 0.6% of Hispanic descent.

Boys and girls with obesity exhibited higher WHtR, FPG, insulin, C-peptide, total cholesterol, LDL-C, TG, DBP SDS, SBP SDS, HOMA2-B, and lower HOMA2-IS compared to the participants with normal weight or overweight ($P < .001$; Table 1).

3.1 | Prevalence of IFG according to ADA and WHO

The prevalences of IFG in children and adolescents with overweight or obesity were 14.1% and 3.1% according to the criterion of ADA and WHO, respectively.

The prevalences of IFG in children and adolescents with normal weight were 4.5% and 0.4% according to the definition of ADA and WHO, respectively (Table 2).

3.2 | Association with IFG and variables of the metabolic profile

The presence of IFG in children and adolescents was associated with a higher SBP SDS ($\beta = 0.32$, SE 0.05, $P < .0001$ [95%CI: 0.22; 0.42]), higher concentrations of HbA1c ($\beta = 1.21$, SE 0.18, $P < .0001$ [95% CI: 0.85; 1.57]), insulin ($\beta = 31.10$, SE 3.2, $P < .0001$ [95%CI: 24.84; 37.38]), C-peptide ($\beta = 0.16$, SE 0.01, $P < .0001$ [95%CI: 0.13; 0.19]), and triglycerides ($\beta = 0.06$, SE 0.03, $P = .03$ [95%CI: 0.007; 0.11]), and associated with lower levels of HOMA2-B ($\beta = -16.77$, SE 2.57, $P < .0001$ [95%CI: −21.81; −11.74]) and HOMA2-IS ($\beta = -18.21$, SE 2.95, $P < .0001$ [95%CI: −24.01; 12.43]) independent of age, sex, BMI SDS, WHtR, and puberty.

3.3 | Differences in the metabolic profile in the IFG_{LOW} vs IFG_{HIGH} groups

There were no differences in the concentrations of TG, HDL-C, LDL-C, total cholesterol, and HOMA2-IS, HOMA2-B, or DBP SDS in neither boys nor girls with IFG regardless of the criterion used. Children and adolescents with IFG_{HIGH} exhibited a higher concentration of fasting insulin compared with individuals with IFG_{LOW} (boys: $P = .0006$ [95%CI: 8.63; 3.34] and girls: $P = .01$ [95%CI: 4.81; 7.32]).

3.4 | Associations between FPG and obesity-related comorbidities

Investigation of the associations between the concentration of FPG and lipid fractions demonstrated associations between FPG and the concentration of TG ($\beta = 0.11$, SE 0.02, $P < .0001$ [95%CI: 0.06; 0.15], $r^2 = 0.20$), HDL-C ($\beta = -0.03$, SE 0.01, $P = .04$ [95%CI: −0.06; −0.002], $r^2 = 0.26$), SBP SDS ($\beta = 0.34$, SE 0.04, $P < .0001$ [95%CI: 0.26; 0.42], $r^2 = 0.53$), and DBP SDS ($\beta = 0.11$, SE 0.03, $P = .0003$, [95%CI: 0.05; 0.16], $r^2 = 0.26$) independent of age, sex, BMI SDS, WHtR, and puberty. No association between FPG and the concentration of total cholesterol or LDL were observed. The concentration of FPG was associated with BMI SDS ($\beta = 0.56$, SE 0.07, $P < .0001$ [95%CI: 0.43; 0.69], $r^2 = 0.06$) and WHtR ($\beta = 0.04$, SE 0.004, $P < .0001$ [95%CI 0.03; 0.04], $r^2 = 0.04$) independent of age, sex, and puberty.

3.5 | Hypertension

Boys and girls with $IFG_{LOW + HIGH}$ compared with boys and girls without IFG, had a higher risk of hypertension, with OR = 1.66 ([95%CI: 1.21; 2.28], $P = .002$) independent of age, sex, BMI SDS, WHtR, and puberty. Boys and girls with IFG_{LOW} exhibited a higher prevalence of hypertension compared to the non-IFG group (67% vs 42%, $P < .0001$). No differences in the prevalence of hypertension were observed in participants in the IFG_{HIGH} group compared to the IFG_{LOW} group (67% vs 57%, $P = .10$) or between the IFG_{HIGH} group compared to the non-IFG group (57% vs 42%, $P = .16$).

3.6 | Dyslipidemia

Dyslipidemia was more prevalent in participants with $IFG_{LOW + HIGH}$ compared to the individuals without IFG (OR = 1.90 [95%CI: 1.38; 2.56], $P < .0001$) independent of age, sex, and puberty. After adjusting for BMI SDS and WtHR, the association was non-significant. The prevalence of dyslipidemia was higher among boys and girls with IFG_{LOW} compared to the non-IFG group (25% vs 15%, $P = .0003$). No difference was observed between boys and girls with IFG_{HIGH} compared to the non-IFG group (22% vs 15%, $P = .25$). Furthermore, no difference in the prevalence of dyslipidemia was observed between boys and girls from the IFG_{LOW} compared with boys and girls from the IFG_{HIGH} group (25% vs 22%, $P = .64$).

TABLE 1 Characteristics of boys and girls with normal weight, overweight, and obesity

	Normal weight		Overweight		Obesity		*P*-value
BMI SDS	**<1.28**		**>1.28 < 2.33**		**>2.33**		
	Boys	Girls	Boys	Girls	Boys	Girls	
	728	1096	263	426	716	749	**<.001**
Age (y)	11.1 (9.0-13.8)	12.0 (9.6-14.6)	11.7 (10.1-13.6)	11.4 (9.3-13.7)	11.7 (9.62-13.6)	11.8 (9.13-14.4)	**<.001**
BMI SDS	0.05 (−0.50-0.58)	0.27 (−0.56-0.59)	1.84 (1.55-2.13)	1.89 (1.60-2.13)	3.2 (2.81-3.6)	2.88 (2.62-3.2)	**<.001**
Waist (cm)	63 (59-71)	64 (59-70)	77 (70-84)	78 (72-85)	93 (84-104)	93 (83-103)	**<.001**
Height for age *z*-score	0.65 (0.002-1.32)	0.59 (−0.05-1.21)	0.77 (0.13-1.47)	0.81 (0.20-1.39)	1.10 (0.39-1.7)	0.94 (0.30-1.6)	**<.001**
Glucose (mmol/L)	5.0 (4.8-5.3)	5.0 (4.7-5.2)	5.1 (4.9-5.3)	5.0 (4.8-5.3)	5.2 (4.9-5.4)	5.1 (4.8-5.4)	**<.001**
HbA1c (mmol/mol)*	34 (23-43)	33.7 (13-44)	33.92 (20-40)	34 (24-45)	34.21 (21-41)	34.18 (25-47)	**<.005**
Insulin (pmol/L)	51.2 (34.8-67.8)	62.2 (46.4-83.5)	69.4 (53.5-96.5)	85.4 (59.5-120.5)	105.4 (70.8-153.4)	122.8 (84.6-175.4)	**<.001**
C-peptide (nmol/L)	0.47 (0.38-0.60)	0.57 (0.44-0.71)	0.59 (0.48-0.76)	0.70 (0.54-0.89)	0.79 (0.60-1.0)	0.91 (0.69-1.2)	**<.001**
HOMA2-B (%)	89.8 (75.2-106.7)	106.9 (89.7-127.2)	106.7 (91.8-132.2)	127.0 (104.3-158.3)	141.1 (109.7-180.9)	159.9 (128-208.1)	**<.001**
HOMA2-IS (%)	104.2 (78.8-153.5)	86.3 (64.5-116.5)	76.7 (55.1-100.8)	62.9 (45.3-90.0)	50.7 (35.4-76.5)	44.30 (31.20-64.4)	**<.001**
Cholesterol (mmol/L)	3.7 (3.3-4.2)	3.9 (3.4-4.3)	3.9 (3.4-4.3)	3.9 (3.5-4.4)	3.94 (3.5-4.5)	3.94 (3.5-4.5)	**<.001**
LDL-C (mmol/L)	1.9 (1.6-2.3)	2.0 (1.7-2.4)	2.15 (1.8-2.6)	2.2 (1.8-2.6)	2.26 (1.9-2.7)	2.3 (1.88-2.8)	**<.001**
HDL-C (mmol/L)	1.5 (1.3-1.7)	1.5 (1.3-1.7)	1.3 (1.1-1.6)	1.3 (1.1-1.5)	1.14 (1.00-1.4)	1.14 (0.94-1.3)	**<.001**
Triglycerides (mmol/L)	0.5 (0.4-0.7)	0.6 (0.5-0.8)	2.2 (1.8-2.6)	0.8 (0.6-1.1)	0.89 (0.60-1.4)	1.01(0.77-1.5)	**<.001**
Systolic BP *z*-score	1.23 (0.33-2.37)	1.25 (0.44-2.02)	1.55 (0.65-2.66)	1.24 (0.43-2.12)	1.75 (0.81-2.9)	1.75 (0.79-2.7)	**<.001**
Diastolic BP *z*-score	0.09 (−0.28-0.49)	0.40 (0.02-0.84)	0.21 (−0.24-0.67)	0.5 (0.08-0.92)	0.54 (0.05-1.1)	0.78 (0.25-1.4)	**<.001**
Puberty: prepubertal/pubertal (%)*	30/70	30/70	34/66	27/73	50/50	34/66	**<.001**

Abbreviations: BMI SDS, body mass index standard deviation score; DBP SDS, diastolic blood pressure standard deviation score; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA2-B, β-cell function; HOMA2-IS, insulin sensitivity; LDL-C, low-density lipoprotein cholesterol; SBP SDS, systolic blood pressure standard deviation score; WC, waist circumference. Data are medians (interquartile range). Kruskal-Wallis test and Wilcoxon test investigated potential differences between the variables. *P*-value is the overall difference between the groups. **P*-value is based on Chi-squared test. Blood variables were obtained and analyzed after an overnight fast.

TABLE 2 Prevalence rates in boys and girls according to the American Diabetes Association (ADA) and the World Health Organization (WHO) criteria for impaired fasting glucose (IFG)

	IFG ADA	IFG WHO
Prevalence rate in total		
Normal weight	4.5	0.4
Overweight and obesity	14.3	3.1
P-value	*<0.0001*	*<0.0001*
Prevalence rates by sex		
Girls	8.5	1.5
Boys	11.2	2.2
P-value	***0.01***	*0.17*
Normal weight		
Girls	4.1	0.2
Boys	5.0	0.1
P-value	*0.41*	*0.58*
Overweight		
Girls	9.9	0.1
Boys	12.5	1.9
P-value	*0.32*	*0.86*
Obesity		
Girls	14.2	3.4
Boys	17.0	4.1
P-value	*0.22*	*0.67*

Prevalence rates of IFG are described in percentage. *P*-value based on Chi-squared test.

3.7 | Age and puberty

Age was not associated with the concentration of FPG in boys or girls (β = 0.16, SE 0.10, P = .13 [95%CI: −0.04; −0.35]) nor with IFG (β = 0.09, SE 0.14, P = .49 [95%CI: −0.18; 0.37]) when adjusting for BMI SDS, WHtR, and puberty. However, pubertal individuals had a higher risk of IFG compared with the prepubertal individuals (OR 1.89 [95%CI: 1.31; 2.74], P = .0007) regardless of age, sex, BMI SDS, and WHtR. Pubertal girls had a higher risk of exhibiting IFG (OR 2.53 [95%CI: 1.51; 4.30], P < .001) compared with prepubertal girls independent of age, BMI SDS and WHtR. The prevalence of IFG did not differ between prepubertal and pubertal boys (P = .35).

4 | DISCUSSION

IFG is prevalent in children and adolescents with overweight or obesity, regardless of whether the IFG criteria from ADA or WHO are applied. Furthermore, children and adolescents exhibiting IFG have a higher risk of obesity-related comorbidities, including hypertension and dyslipidemia.

The IFG prevalences observed in the present study are consistent with previous studies from USA and Europe.[15,28] In USA, a higher prevalence of IFG was observed in adolescents with obesity (17.8%) than in adolescents with overweight (5.4%) and normal weight (2.8%) (n = 915) according to the ADA criterion.[28] In 35 633 European children and adolescents with obesity, the prevalence of IFG were 5.7% in German children and 17.1% in Swedish children according to the ADA and 1.1% and 3.9% according to the WHO criterion.[15] Similar to this study, IFG in our study was associated with a higher degree of obesity. However, there was no association between the concentration of FPG or the prevalence of IFG and either sex or age. Nevertheless, pubertal development was associated with higher prevalence of IFG in boys and girls regardless of age and the degree of obesity, suggesting that the hormonal changes during puberty might influence the development of IFG more than age and sex. Several reports have observed that during puberty, adolescents develop a transient physiological insulin resistance independent of sex and the degree of obesity.[13,29] Moreover, obesity itself has been demonstrated to constitute an important predictor for insulin resistance.[30,31] Development of obesity and puberty may promote the appearance of overt type 2 diabetes in adolescents, as suggested in a retrospective study where 1838 young adults with normoglycemia, 90 with prediabetes, and 60 with type 2 diabetes were followed for 21 years and thus throughout childhood and adolescence into young adulthood. This study demonstrated that young adults who develop type 2 diabetes were predominantly obese, more insulin-resistant, and often burdened by dyslipidemia and hypertension already in adolescence.[32]

The existing ADA and WHO definitions of IFG are adopted from the adult population and are characterized by fixed cut-off levels of fasting plasma glucose regardless of sex, age, growth, and pubertal developmental stage. This implies potential weaknesses due to physiological and naturally occurring changes in the glucose metabolism during childhood growth and development. Different thresholds for the concentrations of fasting plasma glucose have already been suggested in different multinational cohorts of European children and adolescents, classified regarding the development of puberty according to age (7074 prepubertal boys and girls, aged 3-11 years[33] and 927 pubertal boys and girls, aged 13-17 years.[32–34] The reference populations are not fully representative of the pediatric population because children from 10.5 to 12.5 years, who are often in pubertal development,[13] were not represented in either of the cohorts.

Moreover, recent studies have observed that FPG concentrations in the high normal range is associated with deterioration of the glucose homeostasis and a higher prevalence of cardio-metabolic risk factors independently of obesity in children and adolescents.[35,36] O'Malley et al reported a reduction in insulin sensitivity and secretion when shifting from a low to a high concentration of FPG in the normal range (3.42-5.54 mmol/L) in 1020 normoglycemic children with obesity (mean age 12.9 years).[36] In addition, Di Bonito et al found that FPG concentrations in the range of 4.9-5.5 mmol/L were associated with a higher cardio-metabolic risk in 780 children and adolescents (aged 6-16 years) independently of the degree of obesity.[35] Furthermore, a longitudinal study of 700 children with type 2 diabetes, followed for an average of 3.9 years, observed a faster progression of type 2 diabetes, β-cell failure, and a more aggressive development of diabetes-related comorbidities in children compared with adults.[6,37]

We observed that children and adolescents exhibiting IFG were more deranged in their glucose metabolism, including higher concentrations of insulin, C-peptide, HbA1c, lower insulin sensitivity, and impaired β-cell function compared with the children and adolescents without IFG regardless of the definition applied (ADA or WHO). In

TABLE 3 The metabolic profile in boys and girls stratified by different concentrations of fasting plasma glucose (FPG)

	Non-IFG	Non-IFG	IFGLOW	IFGLOW	IFGHIGH	IFGHIGH	*P*-value
Concentration of FPG	**<5.6** mmol/L		**>5.6 < 6.1** mmol/L		**>6.1** mmol/L		
	Boys	Girls	Boys	Girls	Boys	Girls	
Number, boys/girls	1515	2078	154	157	38	36	**<.001**
Age (y)	11.3 (9.1-13.4)	11.7 (9.3-14.3)	13.1 (11.3-14.8)	12.4 (11.1-14.5)	12.6 (11.5-14.4)	11.6 (9.1-13.9)	**<.001**
BMI SDS	1.59 (0.13-2.99)	1.24 (0.01-2.56)	2.77 (−1.39-3.32)	2.33 (1.22-3.01)	2.96 (2.38-3.53)	2.61 (2.40-3.00)	**<.001**
WC (cm)	75 (63-145)	72 (63-85)	90 (74.5-100.00)	84 (72-98)	94 (86-107)	87 (78-96.5)	**<.001**
Height for age SDS	0.89 (0.15-1.53)	0.74 (0.10-1.37)	0.98 (0.08-1.53)	0.85 (0.27-1.50)	0.90 (0.24-1.34)	1.03 (0.33-1.66)	**.02**
Glucose (mmol/L)	5.0 (4.8-5.2)	5.0 (4.7-5.2)	5.7 (5.6-5.8)	5.7 (5.6-5.8)	6.2 (6.1-6.4)	6.3 (6.1-6.5)	**<.001**
HbA1c (mmol/mol)	34 (21-43)	34 (13-45)	35 (20-41)	35 (26-42)	36 (27-38)	37 (30-47)	**<.001**
Insulin (pmol/L)	64.95 (44.73-98.50)	74.88 (53.57-110.80)	113 (77.02-161.50)	122.8 (96.23-169.20)	133.8 (53.36-185.40))	124.5 (36.65-220.40)	**<.001**
C-peptide (pmol/L)	0.57 (0.44-0.76)	0.65 (0.50-0.86)	0.85 (0.65-1.11)	0.92 (0.77-1.18)	0.97 (0.67-1.29)	0.95 (0.73-1.46)	**<.001**
HOMA2-B (%)	106 (85.5-139.3)	123 (98.4-156.0)	118.1 (91.9-153.6)	125.9 (108.8-156.2)	112.9 (80.03-152.20)	115.2 (91.45-164.80)	**<.001**
HOMA2-IS (%)	82.60 (54.5-119.8)	72.20 (48.70-100.1)	46.30 (32.90-67.90)	43 (31.45-54.45)	38.7 (28.45-64.30)	41.7 (23.95-50.45)	**<.001**
SBP SDS	1.36 (0.50-2.55)	1.36 (0.48-2.19)	0.54 (0.13-1.00)	1.92 (1.08-2.68)	1.90 (1.07-2.98)	1.87 (0.88-2.53)	**<.001**
DBP SDS	0.23 (−1.59-0.74)	0.50 (0.07-1.02)	2.46 (1.52-3.41)	0.73 (0.34-1.10)	0.25 (−0.04-0.84)	0.95 (0.35-1.46)	**<.001**
Total cholesterol (mmol/L)	3.8 (3.4-4.3)	3.9 (3.5-4.4.)	3.9 (3.4-4.3)	3.9 (3.4-4.6)	3.8 (3.2-4.2)	3.84 (3.42-4.54)	.13
HDL-C (mmol/L)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.2 (1.0-1.4)	1.24 (1.04-1.44)	1.3 (1.0-1.3)	1.19 (1.02-1.34)	**<.001**
LDL-C (mmol/L)	2.2 (1.8-2.6)	2.2 (1.8-2.7)	2.3 (1.9-2.8)	2.3 (1.9-2.9)	2.20 (1.95-2.58)	2.4 (2.0-2.73)	.16
Triglycerides (mmol/L)	0.7 (0.5-0.9)	0.7 (0.5-1.0)	0.9 (0.5-1.4)	1.0 (0.7-1.48)	0.8 (0.5-1.1)	0.78 (0.66-1.16)	**<.001**
Prepubertal/pubertal (%)*	42/58	32/68	35/65	16/84	42/58	34/66	**.001**

Abbreviations: BMI SDS, body mass index standard deviation score; DBP SDS, diastolic blood pressure standard deviation score; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA2-B, β-cell function; HOMA2-IS, insulin sensitivity; LDL-C, low-density lipoprotein cholesterol; SBP SDS, systolic blood pressure standard deviation score; WC, waist circumference. Kruskal-Wallis and Wilcoxon tests investigated potential differences between the variables. *P*-value is the overall difference between the groups. **P*-value is based on Chi-squared test.

addition, we observed no difference in the prevalence of hypertension or dyslipidemia when the IFG_{HIGH} criteria were applied compared to the IFG_{LOW} criteria.

Children with obesity exhibited lower surrogate measures of insulin sensitivity and their proxy of β-cell function was higher compared with children with overweight or normal weight. The augmented β-cell function is plausibly a compensatory response to the lower insulin sensitivity to maintain normal glucose homeostasis.[38] Dysfunction of the β-cell, in the setting of low insulin sensitivity in adolescents with obesity, is the hallmark of type 2 diabetes development.[39] Studies of adolescents with obesity have shown that progression from impaired glucose tolerance to type 2 diabetes seems to be driven by impaired β-cell function, rather than a deteriorating insulin sensitivity.[39,40]

Even though studies have reported that the majority of children exhibiting impaired glucose tolerance may revert to normal glucose tolerance without intervention, the prevalence of children with prediabetes progressing to type 2 diabetes mandates concern as to whether or not we should treat children with IFG to prevent the development of type 2 diabetes.[41] In adolescents with obesity and impaired glucose tolerance, multidisciplinary family-based lifestyle intervention has demonstrated improved insulin sensitivity and resolution of prediabetes.[42,43] However, although these studies are randomized controlled trials, they are of small sizes consisting of only 23 and 75 participants, respectively. Pharmacological interventions have investigated the effect of metformin in children and adolescents with obesity and insulin resistance in short-term randomized clinical trials, demonstrating a reduction in BMI, fasting insulin, and plasma glucose.[44,45] Nonetheless, the study populations are of small sizes ($N < 100$) and short-term duration of 6 months.

Stronger evidence from pharmacological studies in larger sample sizes and of longer duration is needed to study the safety and efficacy in children with prediabetes. With the knowledge that the majority of children may revert to normal glucose tolerance during weight loss, the efficacy of multidisciplinary lifestyle intervention to prevent type 2 diabetes in children and adolescents still needs to be further elucidated[12] combined with investigation and validation of the cut-offs of IFG in the pediatric population.

Due to the higher risk of hypertension and dyslipidemia in children and adolescents who exhibit IFG, we recommend the criterion from ADA to be used as the screening threshold of IFG instead of the WHO criterion. Children with IFG at the lowest threshold of 5.6 mmol/L already exhibit a deranged metabolic profile and a higher risk of hypertension and dyslipidemia compared with children with normal glucose metabolism. The use of the lower threshold of IFG may lead to false positive results. However, identifying children at an early risk state will enable us to prevent the progressive loss of β-cell function leading to overt diabetes, and thereby reduce the increased morbidity and mortality resulting in a shortening of life expectancy in these patients.

Our study has limitations. According to guidelines from The European Society on Endocrinology and the Pediatric Endocrine Society, the recommended and best cost effectiveness screening strategy for dysglycemia is the 2-hour oral glucose tolerance test compared to the fasting plasma glucose and HbA1c.[46,47] However, several studies have demonstrated that the prevalence of IFG and IGT in the same pediatric population have little concordance and varies with ethnicity and degree of obesity.[48,49] In addition, evaluation of fasting and OGTT-derived surrogates for insulin sensitivity against the hyperinsulinemic-euglycemic clamp in 188 adolescents aged 10–20 years with obesity and normal or impaired glucose tolerance or diabetes have not offered additional advantage over the simpler fasting indices, which correlate strongly with clamp insulin sensitivity.[26] These results support the evidence for using fasting indices of impaired glucose metabolism in the present study. Nevertheless, there is no consensus regarding which of the prediabetes definitions will better predict long-term complications in the pediatric population, which accentuates the need for long-term studies and validation of the variables of the glucose metabolism in a representative pediatric cohort.

The self-reported assessments of pubertal staging might not be an exact measurement of pubertal developmental stage in the population-based cohort due to the potential over- and underestimation of the pubertal development. A physical examination would have been preferred. However, in a large number of participants, self-assessment has been suggested to be adequate for the simple distinction between prepuberty and puberty,[50] why the participants in the present study were stratified into whether they were prepubertal or pubertal and not by each of the Tanner stages.

Further, the concentrations of insulin and C-peptide were measured routinely in the in-house clinical laboratory why we did not use a mean of 3 samples, which is the gold standard due to the pulsatile insulin secretion.

In addition, we were unable to adjust for the natural day-to-day variation of FPG, since we only included 1 measurement of FPG. However, the large number of participants and the blood samples being collected at the same time every morning in the fasting condition would minimize the day-to-day variation. Furthermore, the biochemical analyses of the lipids changed during the study period; however, correction factors were calculated and validated by the Department of Biochemistry according to the regulations at an ISO 15189-certified laboratory, and applied when appropriate.[21]

The cross-sectional design also represents some limitations since this study design does not provide information regarding cause and effect. However, the aim of this study was to describe whether the use of the different cut-offs in a pediatric population was associated with a higher risk of comorbidities in this group of patients. Furthermore, the given time for the inclusion of the participants is not guaranteed to be representative for the population. Nevertheless, this present study includes a large number of children and adolescents with normal weight, overweight, and obesity that have been included into The Danish Childhood Obesity Biobank during a period of 5-7 years. Furthermore, the majority of the included children are from the same ethnic background, but from different areas in Denmark, which we believe makes the study population representative for the pediatric population in Denmark.

In conclusion, the present study demonstrated that the prevalence of IFG is 4 times higher in children and adolescents with overweight or obesity and 14 times higher in individuals with normal weight when applying the ADA criterion for IFG compared with

WHO criterion. Children exhibiting IFG are burdened by a deteriorated glucose metabolism and a higher prevalence of hypertension and dyslipidemia than their non-IFG peers regardless of the IFG definition used. Thus, the ADA criterion as the screening threshold for IFG is recommended in children and adolescents to detect IFG and prevent progression to diabetes and obesity-related comorbidities in children and adolescents until further investigation and validation of the cut-off levels of IFG have been described in the pediatric population.

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Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Julie T Kloppenborg http://orcid.org/0000-0002-9192-131X

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