Natural history and determinants of dysglycemia in Canadian children with parental obesity from ages 8-10 to 15-17 years: the QUALITY Cohort

***Short title*:** Natural history of dysglycemia in children

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ABSTRACT (248/250 words)

Background. In children, the mechanisms implicated in deterioration of glucose homeostasis vs. reversion to normal glucose tolerance (NGT) remain uncertain.

Objective. Describe the natural history of dysglycemia from childhood to late adolescence and to identify its early determinants.

Methods. We used baseline (8-10 yrs, n=630), 1st follow-up (10-12 yrs, n=564) and 2nd follow-up (15-17 yrs, n=377) data from the QUALITY cohort of White Canadian children with parental obesity. Children underwent a 2-h oral glucose tolerance test at each cycle with plasma glucose and insulin measured at 0/30/60/90/120 minutes. American Diabetes Association criteria defined dysglycemia (impaired fasting glucose, impaired glucose tolerance or type 2 diabetes). Longitudinal patterns of insulin sensitivity and beta-cell function were estimated using generalized additive mixed models. Model averaging identified biological, sociodemographic and lifestyle-related determinants of dysglycemia.

Results. Of the children NGT at baseline, 66 (21%) developed dysglycemia without reverting to NGT. Among children with dysglycemia at baseline, 24 (73%) reverted to NGT. In children with dysglycemia at 1st follow-up, 18 (53%) later reverted to NGT. Among biological, sociodemographic and lifestyle determinants at 8-10 yrs, only fasting and 2-h glucose were associated with developing dysglycemia (odds ratio [95% CI] per 1 mmol/L increase: 4.50 [1.06; 19.02] and 1.74 [1.11; 2.73], respectively). Beta-cell function decreased by 40% in children with overweight or obesity.

Conclusions. Up to 75% of children with dysglycemia reverted to NGT during puberty. Children with higher fasting and 2-h glucose were at higher risk for progression to dysglycemia, while no demographic/lifestyle determinants were identified.

Keywords (max. 5): insulin sensitivity, insulin secretion, children, lifestyle factors, type 2 diabetes.

Abbreviation list

DQI-I	diet quality index-international
GAMM	generalized additive mixed model
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
MVPA	moderate to vigorous physical activity
NGT	normal glucose tolerance
WHtR	waist-to-height ratio
zBMI	body mass index z-score
%BF	percentage of body fat

INTRODUCTION

The prevalence of pediatric type 2 diabetes increases by 4·3% every year in the USA[1]. Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is estimated to affect 18% of a nationally-representative sample of North American adolescents[2]. Most children with type 2 diabetes develop cardiovascular and microvascular complications in the years following diagnosis despite intensive medical therapy[3]. In addition, optimal control of pediatric type 2 diabetes is difficult to achieve, with 50% of youth failing to maintain adequate control on metformin monotherapy within four years of disease onset[4].

In adults, progression from IFG or IGT to overt type 2 diabetes is estimated to take eight to ten years[5]. The natural history of the development of type 2 diabetes in youth remains understudied. In weight management clinics in the United States, 23% of children with obesity and normal glucose tolerance (NGT) developed IGT[6] and 8-24% of children with IGT progressed to overt type 2 diabetes within two to three years[7,8]. However, these studies also observed that 46-65% reverted back to NGT over the same period[7,8]. An even higher rate of reversion to NGT (75% over four years) was documented in German children with obesity[9]. The mechanisms implicated in reversion to NGT versus further deterioration of glucose homeostasis remain uncertain. Dysglycemia will be used hereafter to refer to either IFG, IGT or type 2 diabetes.

Previous studies that documented variations in insulin sensitivity and beta-cell function to assess the physiological alterations preceding dysglycemia[6,7] were of short duration and failed to account for weight status and pubertal stage, despite their known association with transient

insulin resistance[10]. Determinants of dysglycemia in adolescents with overweight or obesity include higher 2-h post load glucose levels, higher BMI, higher leptin levels, lower c-peptide levels and Black ethnoracial status (vs. White)[6-9]. However, the longer-term impact of these determinants, beyond three years, is not known. Furthermore, none of these studies have examined lifestyle habits as potential modifiable risk factors, despite their demonstrated benefit in adults[11].

Our study aimed to: 1) document the natural history of dysglycemia from childhood to late adolescence based on glucose tolerance status and indices of insulin sensitivity, insulin secretion and beta-cell function among children and 2) identify biological, sociodemographic and lifestyle determinants in childhood of the development of dysglycemia in adolescence. Identifying modifiable determinants associated with the development of dysglycemia in children is critical to identify potential targets for effective prevention.

METHODS

The study used data from the Quebec Adipose and Lifestyle Investigation in Youth (QUALITY) Cohort, an ongoing longitudinal study of White Canadians recruited at age 8-10 years, with a parental history of obesity (based on parental BMI or waist circumference). Recruitment of families was done using school-based sampling through the distribution of information pamphlets in elementary schools in three major urban centers in the Province of Québec, Canada. The families who were interested to participate were asked to communicate with the study staff.

Children with type 1 or type 2 diabetes or taking medication interfering with glucose metabolism were ineligible. The complete methodology has been described elsewhere[12]

Research evaluations took place at the Centre Hospitalier Universitaire (CHU) Sainte-Justine Research Center or the Institut Universitaire de Cardiologie et de Pneumologie de Quebec (IUCPQ). A total of 630 children (8-10 years) were evaluated at baseline, 564 children (10-12 years) at first follow-up (retention: 90%) and 377 children (15-17 years) at second follow-up (retention: 60%). Written informed assent and consent were obtained from all children and their parents. The study was approved by the CHU Sainte-Justine and IUCPQ Ethic Boards.

Outcomes

At each evaluation cycle, children underwent a 2-h oral OGTT following a 12-h overnight fast. Blood samples were collected at 0, 30, 60, 90 and 120 min after ingesting 1.75g glucose/kg (max 75g). Plasma glucose concentrations were determined with the glucose oxidase method and insulin and C-peptide levels with radio-immunoassay on the Synchron LX20 machine (Beckman Coulter) and on the Architect C8200i machine (Abbott). As the primary outcome, we assessed participants' glucose tolerance status defined by the American Diabetes Association criteria: IFG if fasting glucose ≥ 5.6 but < 7 mmol/L; IGT if 2-h glucose ≥ 7.8 but <11·1 mmol/L and type 2 diabetes if fasting glucose ≥ 7 mmol/L or 2-h glucose ≥ 11.1 mmol/L[13]. Among children NGT at baseline, "deterioraters" were defined as children who developed dysglycemia without reverting to NGT during the follow-up of this study. We defined "reverters" as children who developed dysglycemia but reverted to NGT during follow-up; and as "maintainers" children who

maintained NGT across all evaluations. No children reported receiving hypoglycemic agents during the study.

As secondary outcomes, insulin sensitivity was estimated with the Matsuda Insulin Sensitivity Index (Matsuda-ISI, 10 000/√(fasting glucose (mg/dL) * fasting insulin (µU/mL) * mean OGTT glucose (mg/dL) * mean OGTT insulin (µU/mL))[14], which correlates well with clamp estimates of insulin sensitivity in children[15]. Insulin secretion was calculated as the ratio of the AUC of insulin (pmol/L) to the AUC of glucose (mmol/L) during the OGTT (first-phase: 0-30 minutes, second-phase: 0-120 minutes). First-phase insulin secretion is highly correlated with acute insulin response to glucose in children[16]. Beta-cell function was estimated using the oral disposition index (1/ fasting insulin (µU/mL) * (Δ insulin 0-30 minutes (µU/mL)/ Δ glucose 0-30 minutes (mg/dL))[17], which has good criterion validity compared with the clamp in children with overweight or obesity[17]. In sensitivity analyses, we analyzed the results using the oral disposition index based on C-peptide levels (ng/mL) instead of insulin levels[17].

Exposures

Pubertal stage was directly observed by trained nurses according to Tanner stages protocols[18,19]. Weight, height and waist circumference were measured using standardized protocols[12]. Age- and sex-specific BMI z-scores (zBMI) were computed[20]. Weight status was defined as: underweight (< -2 SD), normal weight (≥ -2 SD; < 1 SD), overweight (≥ 1 SD; < 2 SD) and obese (≥ 2 SD)[20]. The waist-to-height ratio (WHtR) was calculated by dividing waist circumference (cm) by height (cm). We measured percentage of body fat (%BF) by dual-energy x-ray absorptiometry

(DEXA, Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, Madison, USA).

Moderate to vigorous physical activity (MVPA) levels were measured with an accelerometer (Actigraph LS 7164, Actigraph LLC, Pensacola, USA) worn for seven days at each evaluation cycle. Details of data reduction procedures are available elsewhere[21]. Accelerometry data was considered as valid in children who worn the accelerometer at least 10 hours per day for 4 days. Sleep duration was estimated from the accelerometer diaries. Screen time was assessed by an interviewer-administered questionnaire on daily hours of television viewing and leisure computer or video game use. Cardiorespiratory fitness was estimated with peak oxygen consumption (VO_2 peak) during an adapted incremental exercise test on an electromagnetic bicycle. Average habitual consumption of sugar-sweetened beverages, fruits and vegetables and dietary fibers as a function of energy intake was assessed with three non-consecutive 24 hours dietary recalls. The Diet Quality Index-International (DQI-I) was calculated[22]. Biological parents' weight and height were measured and their BMIs computed. Parental questionnaires assessed highest educational attainment, household income, and history of type 2 diabetes.

Statistical analysis

We compared the baseline characteristics between "maintainers", "reverters", "deterioraters", and the children with IFG/IGT at study onset using ANOVA or Kruskal-Wallis (for non-normally distributed variables) and Chi-Square test for categorical variables. Contrasts between groups

were tested using Tukey post-hoc differences to manage potential type 1 error due to multiple comparisons.

To investigate the natural history of dysglycemia, we first described the variation of the four glucose homeostasis indices from 8-10 to 15-17 years in the "deterioraters", "reverters" and "maintainers" groups with diagrams in the children with glucose data at the three time points. We used fitted values from a linear model adjusting for age and sex. We also examined variations of adiposity (zBMI, WHtR and %BF) over time across groups with diagrams in girls and boys, separately.

Second, with the full cohort sample, we used generalized additive mixed models (GAMMs)[23] to estimate smooth patterns for the four glucose homeostasis indices stratified by baseline weight status and adjusted for sex, adiposity (zBMI), and pubertal stage as time-varying variables. The models for insulin secretion were additionaly adjusted for Matsuda-ISI. Because their distribution is skewed, the four indices were converted to sympercents[24]. Thus, the GAMMs' estimates represent the percentage changes from baseline. We used inverse probability censoring weighting at follow-ups to mitigate the impact of attrition[25]. In sensitivity analyses, we investigated longitudinal patterns of glucose homeostasis indices separately in girls and boys with scatterplots and smooth curves.

To identify the most important determinants in childhood associated with developing dysglycemia ("deterioraters") vs. remaining NGT across adolescence ("maintainers"), we

estimated odds ratios with model averaging based on the Akaike Information Criterion[26]. Baseline determinants included: age, sex, %BF, pubertal stage (pubertal vs prepubertal), fasting glucose, 2-h glucose, MVPA, screen time, sugar-sweetened beverage consumption, fiber intake, fruits and vegetables intake, DQI-I, sleep duration, cardiorespiratory fitness, parental highest educational attainment, maternal and paternal BMI and parental history of type 2 diabetes. Explanation on the model averaging method and justification for the selection of variables are provided in the Supplementary Material[27]. We estimated a second averaging model excluding determinants of dysglycemia that could be situated on the causal pathway (namely fasting glucose, 2-h glucose and %BF) between potentially modifiable determinants such as lifestyle habits and dysglycemia. Because of missing data at baseline, multiple imputation using an expectation-maximization with bootstrapping algorithm[28] was performed assuming a missing at random pattern.

A detailed description of the statistical analyses is in the Supplementary Material[27]. Level of significance was determined at 5% and hypothesis tests were two-sided. All data were analyzed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) with packages *mgcv*[29], *amelia*[30] and *MaMi*[31].

RESULTS

A total of 350 children had complete fasting and 2-h glucose data for the three evaluations, covering 7 years of follow-up. Characteristics of the "deterioraters", "reverters", "maintainers" and children with IFG/IGT at study onset are shown in Table 1. Children with IFG/IGT at

baseline were older and presented higher adiposity (zBMI, WHtR and %BF) than those who remained NGT. Among children NGT at baseline, the "deterioraters" presented higher baseline fasting and 2-h glucose levels compared to the "maintainers". In comparison to the full cohort sample (n=630), children with complete data at the three time points (n=350) presented a lower zBMI and a lower 2-h glucose on average at baseline than those excluded from the analyses (Supplementary Material Table S1).

Natural history of dysglycemia

Sample with complete glucose data at the three time points

Of the 317 children NGT at baseline (Figure 1, top panel), 233 remained NGT through late adolescence (in green) while 66 (21%) deteriorated to dysglycemia (in red). Fifty-three percent of the children with dysglycemia at 10-12 years reverted to NGT at 15-17 years (18 of 33, in blue). Seventy-three percent of children with dysglycemia at 8-10 years reverted to NGT across adolescence (24 of 33, Figure 1, bottom panel). Based on the single OGTT criterion, three children qualified as having diabetes, and one of these was confirmed as having type 2 diabetes and followed at the diabetes clinic of the CHU Sainte-Justine. Type 1 diabetes and maturity onset diabetes of the young (MODY) were ruled out for this participant with autoantibodies and genetic testing, and no data were available for the other two participants. The number of cases of IFG, IGT and presumed type 2 diabetes at each evaluation cycle appears in Supplementary Material, Table S2.

While insulin sensitivity decreased in all groups between 8-10 and 10-12 years, it continued to decrease in the "deteriorators", but improved in the "reverters" at 15-17 years (Figure 2). Similarly, beta-cell function decreased during puberty in all groups, but the steepest and most consistent decrease was noted among the "deteriorators". Patterns of variation in beta-cell function were similar when using the oral disposition index based on C-peptide levels instead of insulin levels.

When looking at adiposity variations in girls, slopes increased similarly across the three groups, with the "deterioraters" having systematically higher adiposity measures, followed by the "maintainers" and the "reverters" (Figure 3). In boys, the most notable feature was the increase in %BF and waist-to-height ratio in the "deterioraters", in contrast with "reverters" that eventually decrease their %BF.

Full cohort sample

Variations in the four indices of glucose homeostasis over time for the full cohort sample (n=630) are shown in Figure 4. Insulin sensitivity decreased from 8 to 14 years, and then increased by age 17 years. Beta-cell function in children with normal weight was stable, but in children with overweight or obesity, it deteriorated by 40% from age 8 to 17 years. Similar patterns were observed for first-phase and second-phase insulin secretion. Restricting this analysis to children who were NGT throughout the study did not change the results. Moreover, using the oral disposition index based on C-peptide instead of insulin to estimate beta-cell function led to a similar longitudinal pattern. The glucose homeostasis indices patterns by Tanner stage from

childhood to late adolescence did not differ between girls and boys (Supplementary Material Figure S1).

Determinants of dysglycemia

Among all biological, sociodemographic and lifestyle habits-based determinants investigated at 8-10 years, only fasting and 2-h glucose were identified as determinants of dysglycemia in adolescence (Table 2). Although glycemia at baseline was in the normal range, each additional 1 mmol/L of fasting glucose or 2-h glucose at 8-10 years of age was associated with an increased risk of dysglycemia during adolescence by 4.50 (95% CI: 1.06; 19.02) and 1.74 (95% CI: 1.11; 2.73) times respectively. After removing fasting and 2-h glucose from the model, no significant determinants of dysglycemia emerged. Similarly, when further removing %BF from the model averaging, no associations arose.

DISCUSSION

Although one in five children (21%) with NGT at baseline developed dysglycemia without reverting to NGT, among children with dysglycemia at 8-10 years of age, 73% reverted to NGT by the end of adolescence. In children with dysglycemia at 10-12 years of age, 53% reverted to NGT at 15-17 years. Similar incidence and rate of reversion to NGT were previously reported among adolescents with overweight or obesity followed over three to five years[7-9]. The similar incidence of dysglycemia in our study suggests that even young, normal weight children who have a parent with obesity are at risk of developing dysglycemia.

Insulin sensitivity decreases transiently during mid-puberty in healthy children[10]. We observed a transient 40% decline in insulin sensitivity between the ages of 8 and 14 years, independent of sex, pubertal status, and adiposity, after which insulin sensitivity increased. Cali *et al* observed a steady decreasing slope for age- and sex-adjusted insulin sensitivity over three years in children and adolescents living with obesity from various ethnic backgrounds[6]. The discrepancy is likely explained by differences in study population (Cali *et al* studied older children with obesity), the absence of adjustment for pubertal maturation and shorter duration of follow-up in the Cali *et al* study.

The beta-cell function in Cali *et al* was stable among children who remained NGT, and gradually decreased in those children who deteriorated to IGT[6]. In the present study, among children with complete glucose data at the 3 time points, beta-cell function slightly decreased between 10-12 and 15-17 years in the "reverters" and "maintainers", while it declined in a sustained fashion between 8-10 and 15-17 years of age in the "deterioraters". In contrast to Galderisi *et al*[7], the "reverters" did not improve their beta-cell function across adolescence. When we examined the full cohort (not restricting to those with complete glucose data at all 3 time points), we observed a persistent decrease in beta-cell function in the children with overweight or obesity from the ages of 8 to 17 years, even when restricting to those who remained NGT. The persistent decrease in beta-cell function is concerning for future incidence of youth-onset dysglycemia, given the high prevalence of children and adolescents with overweight or obesity in Canada[32] and worldwide. Alterations in beta-cell function, measured by clamp-derived disposition index, have been observed even in the NGT state among adolescents with overweight or obesity, and was

independently associated with a higher 2-h glucose two years later[33]. Deterioration in beta-cell function has been shown to predate type 2 diabetes development in adults[34].

In our study, fasting glucose levels were identified as the most important determinant of incident dysglycemia, followed by 2-h glucose levels, in children who were NGT at baseline. Data from the International Childhood Cardiovascular Cohort Consortium, including 6,738 participants from various cohorts, having been assessed in childhood (1970's-1990's) and again in adulthood (mean age of 40 years), observed that average childhood fasting glucose was predictive of adult-onset type 2 diabetes, and that the relationship existed even at normal glucose levels[35]. This relationship held true in normal weight children, suggesting that higher fasting glucose can also predict later type 2 diabetes risk among normal weight children. Hu *et al* also found that a higher average zBMI in childhood increased the risk of type 2 diabetes in adulthood[35]. In contrast, we did not observe an association between adiposity, measured by percentage of body fat (or zBMI, results not shown) at 8-10 years of age and risk of dysglycemia in adolescence among children who were NGT at baseline. Even when we excluded fasting and 2-h glucose from the averaging model, we did not detect any effect of baseline adiposity on dysglycemia development. In keeping with our findings, Giannini *et al* found that BMI was not associated with the risk of IFG two years later among adolescents with obesity but NGT[33]. Differences across studies may relate to different critical periods in the life cycle considered (childhood/adolescence versus adulthood) and differing populations under consideration (e.g., youth predisposed to or with overt obesity, versus general population). In addition, using adiposity at a single time point, instead of its average or its trajectory, could also explain lack of observed associations. Adiposity trajectories across childhood and adolescence could play a role.

Similarly, we did not observe associations between childhood lifestyle habits and dysglycemia in adolescence, despite the broad spectrum of lifestyle habits of our sample. It may be that early lifestyle habits influence insulin sensitivity and secretion, but that metabolic compensation mitigates any effect of adverse patterns on developing overt dysglycemia. While associations between specific lifestyle habits on insulin sensitivity and insulin secretion were observed by our group[21,36,37] and others[38,39], these did not translate into changes in glucose levels. Alternately, we considered the effect of lifestyle habits at a single point in development; it may be that *trajectories* in lifestyle habits across childhood and adolescence influence glucose levels, with the cumulative impact of poor lifestyle habits only manifesting as overt dysglycemia over several years. Finally, other factors, such as genetics, could influence dysglycemia more strongly than adiposity and lifestyle habits.

Strengths of our study include follow-up from prepuberty to postpuberty, and the use of repeated OGTT-derived indices that highlight natural variations in glucose metabolism in children. Trajectories in glucose homeostasis indices were computed using methods that allow for a flexible curve and estimate confidence bands that take into account intra-individual correlations overtime. We concurrently investigated many risk factors for type 2 diabetes in childhood using model averaging, notably lifestyle habits measured using state-of-the-art instruments. Unlike most studies investigating the natural history of pediatric type 2 diabetes[6-8], our sample did not originate from obesity or diabetes treatment programs, allowing us to describe the natural history without intervention effect. Nevertheless, we cannot exclude the possibility that some families sought behavioral counselling for their child.

A limitation of our study is that the characterization of glucose tolerance status relied on a single OGTT at each evaluation cycle. Given the limited repeatability of the OGTT[40], we cannot exclude measurement error in assessing glucose tolerance status. Nonetheless, fasting and 2-h glucose levels have excellent positive predictive value for diabetes in youth[41]. Although clamps are the gold standard when evaluating insulin sensitivity and secretion, those tests are invasive and therefore less practicable in large pediatric cohort studies. The OGTT offers an excellent validity/feasibility trade-off for the assessment of glucose homeostasis in such context. Moreover, antibody and genetic testing was not performed in children meeting the criteria for diabetes based on the single OGTT, thus we could not rule out other forms of diabetes in these children. Also, we defined the deteriorators as NGT children at baseline who developed dysglycemia without reverting during follow-up, but whether those children persisted with dysglycemia after the current study remains unknown. A longer follow-up is needed to determine whether these children continue to deteriorate or whether they revert to NGT later in adolescence and young adulthood. Another caveat is that genetic predisposition to deteriorating glycemic control was not examined in this study, although we assessed the contribution of parental history of type 2 diabetes. Furthermore, the sample size of the QUALITY cohort is limited. It is plausible that we were underpowered to detect associations with lifestyle habits given that only 66 "deteriorators" were observed. In addition, because our population was exclusively composed of White Canadian children, our conclusions may not be generalizable to other ethnoracial groups. The QUALITY cohort aimed to recruit children from Northern European ancestry because the cohort was designed in part to assess the genetic determinants of obesity and its cardiometabolic consequences, whereby including families from different racial backgrounds would have induced

genetic admixture. Moreover, there would likely have been insufficient power to study most associations of interest in the QUALITY cohort across several small different ethnoracial subgroups. Finally, while selection bias can be expected due to loss to follow-up, we used inverse probability of censoring weighting for the trajectories in glucose homeostasis indices to mitigate this bias.

In conclusion, we observed that 55-73% of children with IFG/IGT reverted to NGT from childhood to adolescence in White Canadian children. We also found that beta-cell function estimated by the OGTT appears to decline by 40% in children with overweight or obesity from 8-17 years of age, emphasizing the need for early interventions promoting healthy body weight in childhood. Moreover, while fasting and 2-h glucose in childhood were the most important determinants for distinguishing between “maintainers” and “deterioraters”, their levels fell within the normal clinical range. There is a critical need to comprehend the variations of glucose tolerance over a longer period, from early childhood to adulthood, and among at risk youth but also among those with normal weight. The contributions of trajectories in early lifestyle habits, as well as genetics and epigenetics, on the development of dysglycemia merit further study to better inform prevention.

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TABLES

TABLE 1. Distribution of biological, sociodemographic and lifestyle determinants at 8-10 years of age in children NGT at baseline according to glucose tolerance patterns overtime, and in children IFG/IGT at baseline

	Children NGT at baseline (n = 317)			Children with IFG/IGT at baseline (n = 33)
	Maintainers (n = 233)	Deterioraters (n = 66)	Reverters (n = 18)	
Age, median (IQR), years	9.4 (8.6 – 10.3)	9.5 (8.7 – 10.6)	9.7 (9.3 – 10.3)	10.2 (9.6 – 10.8)†
No. (%) female	118 (50.6)	25 (38.5)	7 (38.9)	11 (33.3)
No. (%) pubertal (Tanner stage ≥2)	51 (21.8)	13 (19.7)	5 (27.8)	11 (33.3)
BMI z-score, mean (SD)	0.7 (1.2)	1.1 (1.3)	1.0 (1.3)	1.4 (1.5)†
No. (%) overweight or obese	85 (36.5)	34 (51.5)	9 (50.0)	19 (57.6)
Body fat mass, median (IQR), % of total mass	22.5 (15.8 – 30.9)	25.4 (18.5 – 33.4)	25.7 (15.4 – 34.2)	30.1 (20.6 – 39.4)†
Waist-to-height ratio, median (IQR)	0.45 (0.43 – 0.49)	0.47 (0.43 – 0.52)	0.45 (0.42 – 0.53)	0.51 (0.45 – 0.55)†
Moderate and vigorous physical activity, median (IQR), min/day	50 (30 – 65)	55 (39 – 73)	40 (29 – 53)	41 (30 – 55)
Screen time, median (IQR), min/day	120 (72 – 188)	111 (69 – 191)	146 (85 – 263)	130 (90 – 313)
Sleep duration, median (IQR), hr/day	10.4 (10.1 – 10.9)	10.4 (10.0 – 10.8)	10.2 (9.8 – 10.5)	10.6 (10.2 – 10.9)
Cardiorespiratory fitness (VO_2 peak), median (IQR), ml/min/kg lean mass	57 (53 – 62)	59 (53 – 63)	55 (53 – 58)	59 (55 – 64)
Sugar-sweetened beverages, median (IQR), mL/1000 kcal/day	51 (0 – 116)	76 (12 – 141)	48 (22 – 70)	54 (0 – 137)
Fibers, median (IQR), g/1000 kcal/day	8.0 (6.8 – 9.6)	8.0 (6.6 – 9.2)	7.5 (6.5 – 9.6)	8.5 (6.6 – 9.8)
Fruits and vegetables, median (IQR), portions/1000 kcal/day	2.5 (2.0 – 3.3)	2.6 (1.8 – 3.3)	2.2 (1.7 – 3.1)	2.5 (1.8 – 3.2)
Diet Quality Index-International, median (IQR)	59 (54 – 64)	58 (53 – 63)	57 (51 – 61)	60 (57 – 64)

	Children NGT at baseline (n = 317)			Children with IFG/IGT at baseline (n = 33)
	Maintainers (n = 233)	**Deteriorators (n = 66)**	**Reverters (n = 18)**	
Fasting glucose, median (IQR), mmol/L	4.9 (4.7 – 5.1)	5.1 (4.8 – 5.2)[†]	5.1 (4.7 – 5.2)	5.2 (4.9 – 5.6)[†,‡,§]
2-h glucose, median (IQR), mmol/L	6.0 (5.5 – 6.5)	6.6 (5.9 – 7.0)[†]	6.1 (5.5 – 6.6)	8.1 (7.3 – 8.4)[†,‡,§]
Fasting insulin, median (IQR), pmol/L	24 (18 – 33)	25 (19 – 37)	31 (21 – 41)	38 (26 – 59)[†,‡]
2-h insulin, median (IQR), pmol/L	145 (93 – 220)	166 (118 – 235)	151 (106 – 186)	293 (178 – 585)[†,‡,§]
Fasting C-peptide, median (IQR), ng/mL	1.1 (0.9 – 1.5)	1.3 (1.0 – 1.7)	1.4 (1.1 – 1.6)	1.6 (1.2 – 2.1)[†]
2-h C-peptide, median (IQR), ng/mL	4.7 (3.6 – 6.4)	5.2 (4.3 – 7.4)	6.1 (4.2 – 7.0)	7.3 (5.8 – 13.1)[†,‡,§]
Matsuda-ISI, median (IQR)	10.8 (7.5 – 13.7)	9.4 (6.8 – 12.2)	8.3 (6.2 – 11.0)	5.4 (3.5 – 9.5)[†,‡]
Oral disposition index, median (IQR)	0.19 (0.14 – 0.26)	0.19 (0.13 – 0.23)	0.16 (0.13 – 0.19)	0.17 (0.12 – 0.22)
AUC insulin: AUC glucose first 30 minutes, median (IQR)	24.6 (16.4 – 37.0)	25.5 (17.1 – 38.4)	25.4 (16.7 – 34.6)	36.2 (19.9 – 56.5)
AUC insulin: AUC glucose over 120 minutes, median (IQR)	30.5 (21.3 – 42.8)	30.3 (23.0 – 40.0)	32.3 (27.8 – 41.5)	41.5 (28.2 – 65.9)[†,‡]
No. (%) with at least one parent with a university degree	133 (57.1)	33 (50.8)	8 (44.4)	19 (57.6)
Familial income, median (IQR), CAD[¶]	44.9 K (32.2 – 55.0)	45.0 K (29.1 – 55.0)	52.5 K (33.8 – 55.0)	40.2 K (32.5 – 49.2)
Mother's BMI, median (IQR), kg/m^2	28.1 (24.5 – 32.4)	29.6 (25.2 – 33.9)	26.5 (24.7 – 32.0)	29.3 (24.7 – 33.5)
Father's BMI, median (IQR), kg/m^2	29.9 (27.0 – 33.0)	30.8 (26.1 – 34.6)	30.7 (28.0 – 31.8)	30.3 (26.8 – 32.0)
No. (%) mother with type 2 diabetes	10 (4.5)	2 (3.1)	2 (12.5)	1 (3.0)
No. (%) father with type 2 diabetes	16 (10.8)	4 (10.3)	3 (21.4)	7 (26.9)

BMI: body mass index, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, NGT: normal glucose tolerance, VO_2 peak: peak oxygen consumption. Groups were compared using ANOVA for normally distributed variables, Kruskal-Wallis for variables that were not normally distributed. When p values < 0.05, contrast testing between groups was done using the Tukey post-hoc differences.

For categorical variables, Chi-square test were used (with Monte-Carlo simulations for variables with low cell numbers). The sample includes the children who have completed the 3 evaluation cycles (n=350).

[†]Significant group difference ($p < 0.05$) with the “Maintainers”.

[‡]Significant group difference ($p < 0.05$) with the “Deterioraters”.

[§]Significant group difference ($p < 0.05$) with the “Reverters”.

[¶]Divided by the number of persons living in the home.

TABLE 2. Associations between potential determinants at 8-10 years of age and risk of dysglycemia using model averaging (deterioraters [n = 66] compared to maintainers [n = 233])

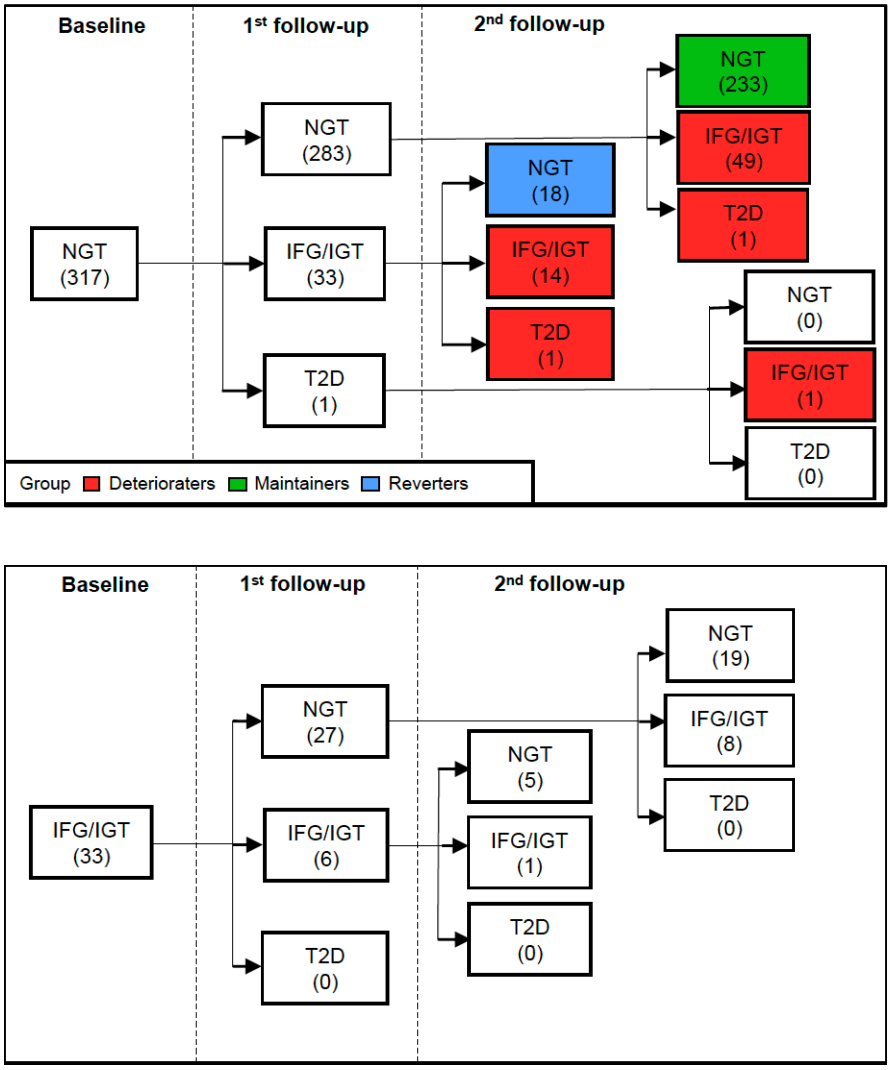
	Model averaging A[†] Odds ratio (95% CI)	**Model averaging B**[†] Odds ratio (95% CI)
Age, years	1.01 (0.90 ; 1.14)	1.05 (0.84 ; 1.31)
Girl vs. Boy	0.95 (0.68 ; 1.33)	0.79 (0.41 ; 1.49)
Body fat mass, % of total mass	1.002 (0.99 ; 1.02)	-
Puberty (Pubertal stage >2 vs 1)	0.97 (0.73 ; 1.30)	0.96 (0.66 ; 1.41)
Fasting glucose, for each increase in 1 mmol/L	**4.50 (1.06 ; 19.02)**	-
2-h glucose, for each increase in 1 mmol/L	**1.74 (1.11 ; 2.73)**	-
MVPA, 10 min/day	1.01 (0.95 ; 1.06)	1.01 (0.94 ; 1.09)
Screen time, hr/day	0.99 (0.93 ; 1.06)	0.99 (0.91 ; 1.07)
Sugar-sweetened beverages, 100 mL/1000 kcal/day	1.01 (0.89 ; 1.15)	1.02 (0.86 ; 1.21)
Diet Quality Index-International	0.99 (0.95 ; 1.03)	0.99 (0.96 ; 1.02)
Fruits and vegetables, servings/1000 kcal/day	0.98 (0.87 ; 1.11)	0.99 (0.88 ; 1.11)
Fibers, g/1000 kcal/day	0.99 (0.93 ; 1.06)	0.99 (0.94 ; 1.06)
At least one parent with a university degree	0.99 (0.82 ; 1.19)	0.95 (0.68 ; 1.32)
Mother's BMI, kg/m^2	1.01 (0.97 ; 1.04)	1.01 (0.97 ; 1.04)
Father's BMI, kg/m^2	1.001 (0.99 ; 1.02)	1.01 (0.98 ; 1.04)
Father or mother with T2D	0.97 (0.69 ; 1.37)	0.95 (0.60 ; 1.50)
Sleep duration, hr/day	1.02 (0.87 ; 1.20)	1.01 (0.88 ; 1.15)
Cardiorespiratory fitness (VO_2 peak), ml/min*kg lean mass	1.002 (0.98 ; 1.02)	1.001 (0.98 ; 1.02)

BMI: body mass index, MVPA: moderate to vigorous physical activity, VO_2 peak: peak oxygen consumption.

[†]Model A incorporates all the determinants analyzed simultaneously by model averaging. Model B includes the same risk factors minus body fat mass, fasting glucose and 2-h glucose

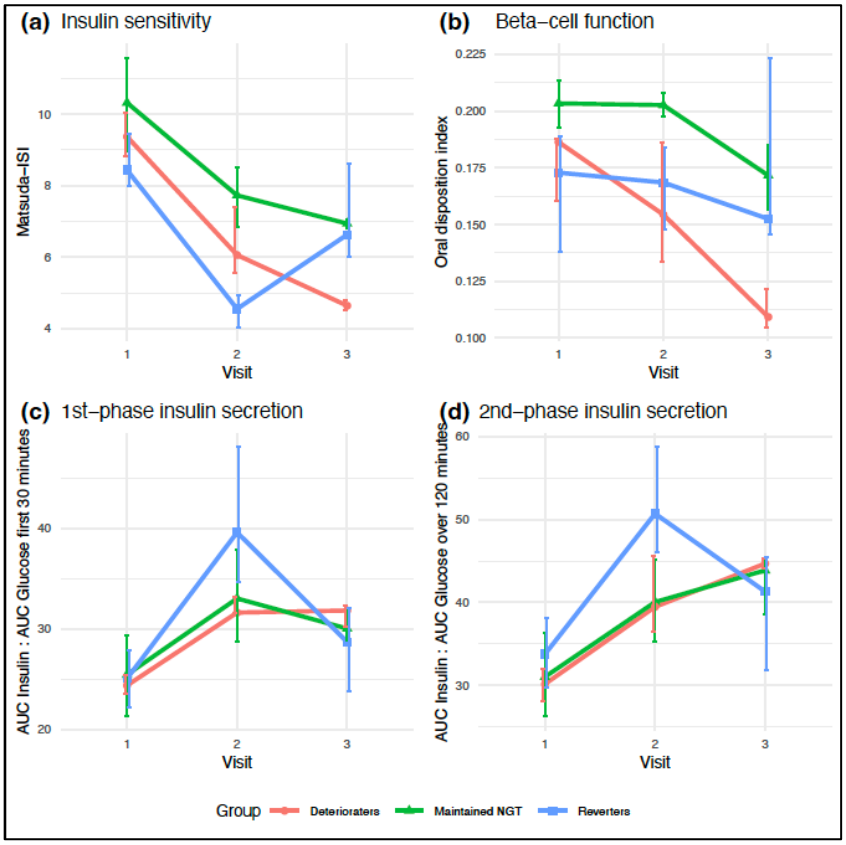
FIGURE LEGENDS

FIGURE 1. Tree diagrams of glucose tolerance status in children who were NGT at baseline (*top*) and IFG/IGT at baseline (*bottom*)



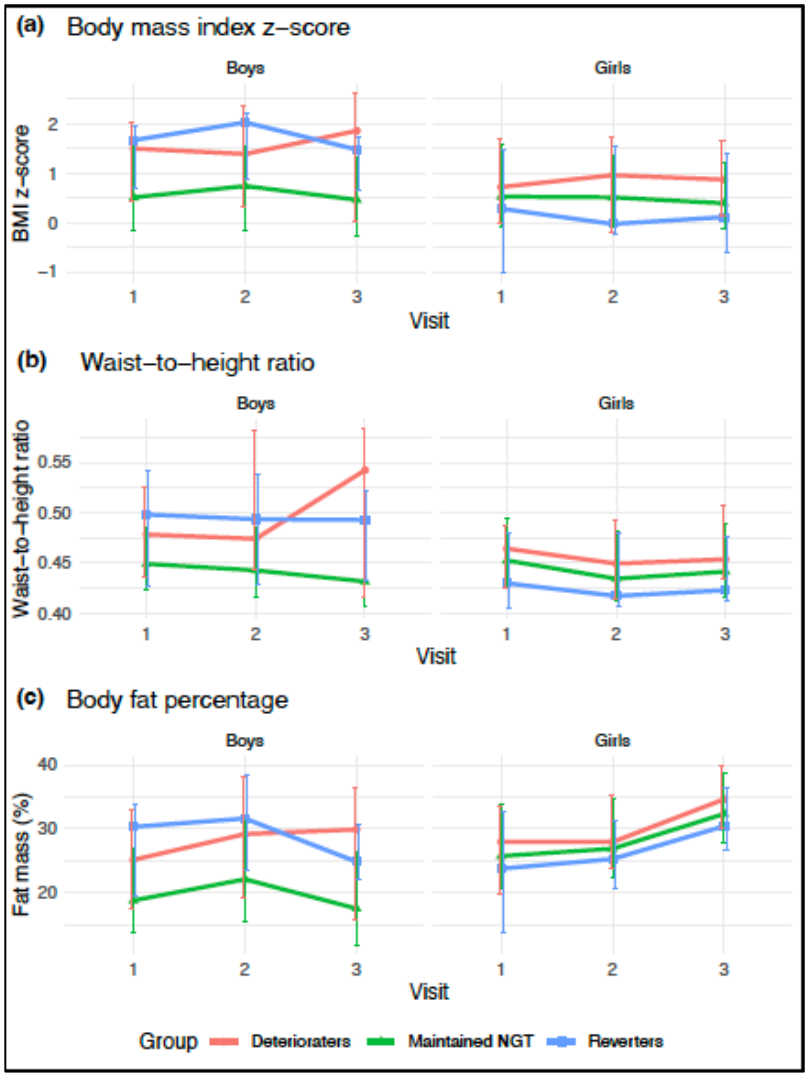
Legend: NGT: normal glucose tolerance, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, T2D: presumed type 2 diabetes. The tree diagrams of glucose tolerance status extend from childhood (8-10 yrs) to late adolescence (15-17 yrs). Only children with complete data (n=350) on fasting and 2-h glucose levels are retained for this figure.

FIGURE 2. Variation of insulin sensitivity, insulin secretion and beta-cell function in the "maintainers", "deteriorators" and "reverters"



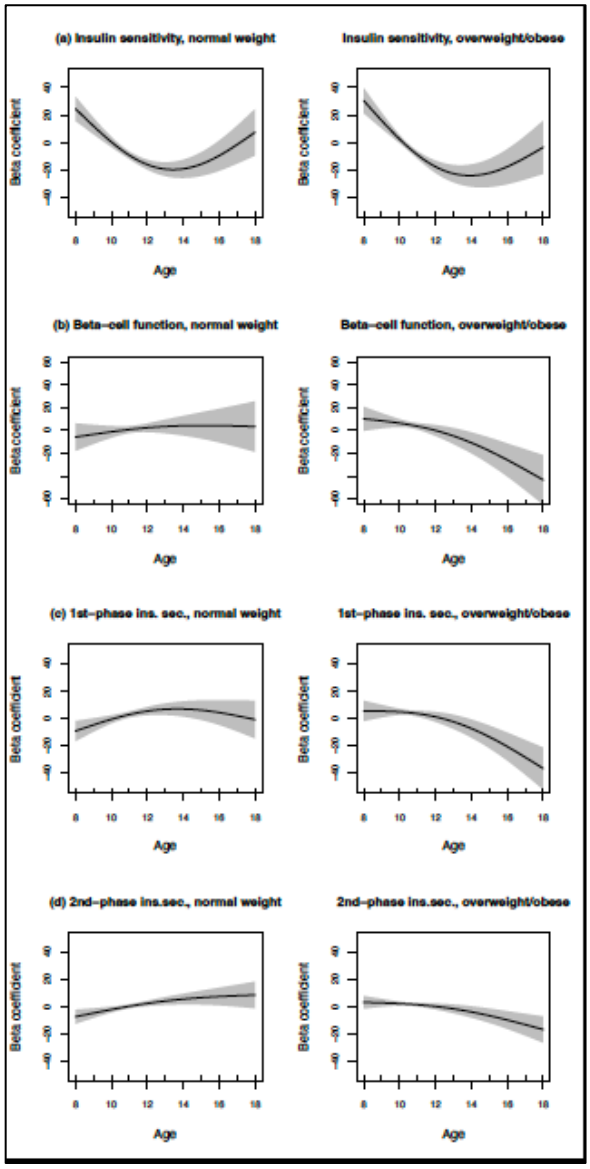
Legend: The line diagrams display variations in insulin sensitivity (a), beta-cell function (b), first-phase insulin secretion (c), and second-phase insulin secretion (d) from childhood (8-10 yrs) to late adolescence (15-17 yrs), adjusting for age and sex. Medians and interquartile ranges are obtained from the fitted values of a linear regression model. A total of 233 children were included in the "maintainers" group, 66 children in the "deteriorators" group, and 18 children in the "reverters" group.

FIGURE 3. Variation of adiposity in the "maintainers", "deteriorators" and "reverters", by sex



Legend: The line diagrams display variations in body mass index-score (a), waist-to-height ratio (b) and body fat percentage (c) from childhood (8-10 yrs) to late adolescence (15-17 yrs) using medians and interquartile ranges. A total of 118 girls and 115 boys were included in the "maintainers" group, 25 girls and 41 boys in the "deteriorators" group and 7 girls and 11 boys in the "reverters" group.

FIGURE 4. Variation of insulin sensitivity, insulin secretion and beta-cell function in normal weight children (*left*) and in children with overweight or obesity (*right*)



Legend: Each curve represents how insulin sensitivity (a), beta-cell function (b), first-phase insulin secretion (c), and second-phase insulin secretion (d) vary with age, in terms of % change from the mean, adjusted for sex, pubertal stage and adiposity (body mass index z-score), in the full cohort sample, by weight status. The grey area represents the 95% confidence intervals around the beta coefficient.