


# Paediatric Obesity Evaluation for Metabolic Susceptibility (POEMS)

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## ABSTRACT

**Introduction** Our aim was to determine whether there are risk factors which increase the risk of developing dysglycemia in a child who has increased body mass index (BMI) (overweight/obese).

**Research design and methods** This was a retrospective cohort study of 715 children who had increased BMI (overweight/obese). They presented to tertiary care at KK Women's and Children's Hospital, Singapore, for metabolic risk assessment. Subjects who had more than one oral glucose tolerance test were included in order to track and analyze risk factors associated with worsening glycemic status from a previously normal glucose tolerance, impaired fasting glucose, or impaired glucose tolerance (IGT) state. Demographic characteristics, birth history, family history of metabolic syndrome, metabolic comorbidities, and interventions received were recorded. Statistical analysis was performed to determine odds ratio (OR) of worsening glycemic status progression in association with an analyzed variable, adjusted for intervention received.

**Results** Risk factors of developing dysglycemia can be present right from birth, as participants who were born preterm had increased odds of IGT (OR: 3.49 (1.10 to 11.03)), and a greater proportion of large-for-gestational-age (LGA)/small-for-gestational-age (SGA) babies had dysglycemia (SGA-IGT: 8.8%, SGA-diabetes mellitus (DM): 5.9%, LGA-IGT: 10.6%, LGA-DM: 11.8%) even at baseline. Being born preterm (OR: 3.49 (1.10 to 11.03)), with comorbidities of hypertension (OR: 1.61 (1.01 to 2.57)), hyperlipidemia (OR: 1.80 (1.19 to 2.72)), and fatty liver disease (OR: 2.08 (1.39 to 3.13)), was significantly associated with an increased OR of developing IGT. Risk factors for developing a worsening glycemic status, either to IGT or DM, included age >10 years (OR 4.94 (1.21 to 20.25)), BMI rise (OR 1.71 (1.17 to 2.49)), BMI increase >1.08 kg/m<sup>2</sup> (OR 1.71 (1.16 to 2.51)), comorbidities of hyperlipidemia (OR 1.67 (1.12 to 2.50)), and fatty liver disease (OR 2.11 (1.43 to 3.12)).

**Conclusions** A child who has increased BMI (overweight/obese) and possesses risk factors for worsening glycemic status, if intervened with routine lifestyle modification advice, may still have increased risk of developing dysglycemia and type 2 DM. Therefore, understanding their risk profile provides opportunities to have a tiered and individualized approach.

## INTRODUCTION

The rising trend of childhood obesity is concerning. Global age-standardized

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidence of childhood obesity is increasing globally, along with an earlier onset of metabolic complications in children.

### WHAT THIS STUDY ADDS

⇒ This study aims to delineate risk factors of developing dysglycemia and type 2 diabetes mellitus in children who have increased body mass index (overweight/obese).

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In identifying pertinent risk factors of developing worsening glycemic status in a child who has increased body mass index (overweight/obese), therapeutic options can be customized to each pediatric patient who presents with increased body mass index. This allows for personalized care, with greater allocation of resources and efforts to those who are 'high risk'. Future research efforts can examine the impact of a tiered management algorithm on metabolic outcomes with applications in precision medicine as well.

prevalence of obesity has increased from 0.7% (0.4%–1.2%) in 1975 to 5%–6% (4.8%–6.5%) for girls in 2016, and from 0.9% (0.5%–1.3%) in 1975 to 7.8% (6.7%–9.1%) for boys in 2016.<sup>1</sup> The rising trends in children's and adolescents' body mass indices (BMIs) have plateaued in many high-income countries at high levels, and have accelerated in several parts of Asia.<sup>1</sup> Childhood obesity sets the stage for being overweight and obese as an adult,<sup>2</sup> along with its increased metabolic risks such as type 2 diabetes mellitus (T2DM) and ischemic heart disease.<sup>3</sup> As the age of onset of obesity occurs earlier in childhood, metabolic diseases such as T2DM and associated long-term complications will also manifest early in the pediatric age group. This not only leads to the increased prevalence of type 2 diabetes, but also the intermediate condition of prediabetes in adolescents and youths. Even before transitioning to adulthood, children with metabolic syndrome (MetS) and T2DM



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already show a rapid accumulation of diabetic complications.<sup>4</sup> This poses an increased healthcare burden not only in the present, but for future generations, due to epigenetic changes and fetal programming.<sup>5</sup>

As we manage this global pandemic of non-communicable disease, it is no longer appropriate to have a 'one-size-fits-all' approach for obesity. An obese state should be considered as an evolving spectrum, and interventions should be targeted in a 'tiered' approach in order to allocate resources effectively. There is suggestion of a transitional state between obesity and developing metabolic complications,<sup>6</sup> termed 'metabolically healthy obesity' (MHO) and 'metabolically unhealthy obesity' (MUO). While the definition of being 'metabolically healthy' is an amorphous one in pediatrics, most define MetS as having three or more of the following: increased waist circumference, hypertension, dyslipidemia, hypertriglyceridemia, and dysglycemia.<sup>7-10</sup> Closer attention and more intensive therapy would be required for those on the threshold between MHO and MUO.

Even though there is no direct evidence that early diagnosis of pre-diabetes improves long-term outcomes of diabetes in children and adolescents, there is indirect evidence that identifying pre-diabetes in youth may be valuable.<sup>11</sup> Studies indicate that lifestyle modifications can prevent or delay the onset of T2DM. Hence, targeted screening of adolescents with risk factors for diabetes is recommended. The Paediatric Endocrine Society, Endocrine Society, European Society of Endocrinology, and the American Diabetes Association endorse screening for pre-diabetes/T2DM in high-risk youth.<sup>12-14</sup> High risk is defined as (1) age  $\geq 10$  years or pubertal (if this occurs before age 10 years), and meeting the following weight criteria: BMI  $\geq 85$ th percentile for age and sex on the standard Centers for Disease Control and Prevention growth charts, weight for height  $>85$ th percentile, or weight  $>120\%$  of ideal (50th percentile) for height; and (2) the presence of at least two of the following risk factors: family history of T2DM in a first-degree or second-degree relative; minority race/ethnicity (Native American, African American, Hispanic, Asian American, Pacific Islander); conditions or signs associated with insulin resistance (acanthosis nigricans, polycystic ovarian syndrome (PCOS), hypertension, dyslipidemia, small for gestational age); and maternal diabetes or gestational diabetes during the child's gestation. There is no consensus recommendation for screening South-East Asian children and adolescents, although the same risk factors may hold true but their risk of MetS occurs at a lower BMI. Therefore, in this retrospective study, we evaluated a referred cohort of children and adolescents who were assessed to have obesity/overweight for pre-diabetes and factors associated with dysglycemia progression.

We focused on identifying a group of individuals with increased BMI (overweight/obese) who are at increased risk of developing dysglycemia or pre-diabetes, a marker of insulin resistance, impaired insulin secretion and increased hepatic gluconeogenesis. Developing

dysglycemia may herald the onset of T2DM subsequently if left unchecked without interventions, either non-pharmacologically with lifestyle measures, or pharmacologically with metformin and other newer agents such as glucagon-like peptide 1 agonists. Therefore, it is essential to identify this at-risk group as a primary preventive measure, as children who develop T2DM have poor treatment outcomes with more rapid manifestation of diabetic complications.<sup>15</sup> We aim to identify possible contributory risk factors affecting the progression of glycemic status.

## RESEARCH DESIGN AND METHODS

This was a retrospective cohort study conducted in KK Women's and Children's Hospital, Singapore.

### Study population

Our cohort included participants (below 18 years old) who were referred from primary care clinics in the community to general pediatric, weight management, and endocrine clinics for further assessment. Our main intention was to determine risk factors of developing dysglycemia or a worsening glycemic status from a previously normal glucose tolerance (NGT), impaired fasting glucose (IFG), or impaired glucose tolerance (IGT) state. From this cohort of children who were assessed to have increased BMI in the overweight or obese range (defined as BMI 85th–<95th centile for age and  $\geq 95$ th centile, respectively<sup>16,17</sup>), those who had two or more oral glucose tolerance tests (OGTTs) done in our center over a period of 10 years from 2008 to 2018 were identified and included in the selection criteria.

### Baseline assessment

Baseline data included demographics, birth weight and family history of MetS. Participants' anthropometric measurements (height, weight, BMI) and the presence of comorbid complications including hypertension, hyperlipidemia, fatty liver disease, PCOS, and obstructive sleep apnea were also recorded. Based on the initial OGTT results, they were classified at baseline into NGT, IFG, IGT, and DM. All participants were recommended lifestyle modification measures with diet and exercise. If pharmacological intervention was administered, such as the use of metformin and lipid-lowering agents, these were also recorded. As this was a retrospective study, there was incomplete information regarding certain demographic data, including anthropometric measurements, gestational age, and birth weight. These were indicated as missing data.

### Progression and outcomes

At the time point of each subsequent OGTT, repeat anthropometric measures (height, weight, BMI) were recorded. A participant then either maintained the same OGTT and glycemic status classification, or changed according to one of the following permutations based on first and last visits to the hospital: NGT-IFG, NGT-IGT, NGT-DM, IFG-IGT, IFG-DM, IGT-IFG, and IGT-DM.

### Statistical analyses

Primary outcome was change in glycemic status between the participant's first and last visits with categories as NGT-IFG, NGT-IGT, NGT-DM, IFG-IGT, IFG-DM, IGT-IFG, and IGT-DM. Outcome was treated as categorical variable. All demographic, anthropometric and clinical characteristics were summarized based on the participant's baseline glycemic status. Continuous and categorical variables were summarized as frequency (percentages) and mean (SD). Difference between categories of baseline glycemic status was tested using  $\chi^2$  and analysis of variance test for categorical and continuous data, respectively. Univariate and multivariable generalized estimating equations (GEEs) for repeated measure multinomial data were fit to find associated risk factors for change in glycemic status from baseline. Quantitative association from GEE was expressed as OR with 95% CI. Backward variable selection method was used to finalize multivariable model. Categories of primary outcomes were later combined based on worsening change from baseline. A separate univariate and multivariable GEE for binary data with repeated measure was also fit to find associated risk factors for worsening status change compared with no change in status. Statistical significance was set at  $p$  value of  $<0.05$  and all tests were two tailed. Data analysis was performed using SAS V.9.4 software (SAS Institute).

## RESULTS

### Baseline characteristics

A total of 715 participants met inclusion criteria for analysis. **Table 1** presents their baseline characteristics. The mean age of our study population was 12.3 (9.4–15.2) years old, with 440 boys (61.5%). A total of 55% of them were Chinese, and 45% of them were non-Chinese (Malay/Indian/Others). Baseline OGTT was normal in 458 (64.0%), IGT in 214 (29.9%), IFG in 3 (0.4%) and DM in 40 (5.6%) of them. The mean time interval between OGTTs was 2.2 years apart. Due to the extremely small number of participants with IFG at baseline, this category was excluded in subsequent analysis, and participants starting with NGT and IGT status were analyzed. The mean BMI ( $\text{kg}/\text{m}^2$ ) was comparable among the three categories at baseline (normal: 31.1 (25.1–37.1), IGT: 31.0 (24.0–38.0), DM: 31.6 (27.3–36.0)).

A greater proportion of participants with baseline IGT and DM were found to be born premature (8.1% and 8.6%, respectively) and small/large (SGA/LGA) for gestational age (SGA-IGT: 8.8%, SGA-DM: 5.9%, LGA-IGT: 10.6%, LGA-DM: 11.8%) as compared with their normal OGTT counterparts (preterm 4%, SGA 4.4%, LGA 4.9%).

Family history of hyperlipidemia was more prevalent among those with IGT (37.4%) and DM (35.0%) at baseline, in comparison with those with normal OGTT (29.3%). This was also true of those with family history of DM (normal OGTT 43.2%, IGT 46.7%, DM 75.0%). Prevalence of comorbid conditions such as hypertension,

hyperlipidemia, fatty liver disease and PCOS was also progressively higher in participants with baseline IGT and DM as compared with those with normal OGTT at baseline.

### Factors associated with worsening glycemic status

**Table 2** shows the number of occurrences in glycemic status change throughout the follow-up time period (NGT-NGT: 617, NGT-IGT: 124, IFG-IGT: 2, IGT-DM: 23, NGT-DM: 15). The median time interval between glycemic status change was 2.01 years for NGT-IGT, 1.86 years for IGT-DM, and 3.61 years for NGT-DM. **Table 3** presents the factors associated with worsening glycemic status, substratified into the individual status change, with those progressing to IGT (NGT-IGT) and to DM (IGT-DM, NGT-DM).

The odds of a girl who has increased BMI (overweight/obese) progressing to DM status were 2.17 (1.11–4.23) compared with male participants. Children who were born premature were shown to develop IGT with odds 3.14 (1.15–8.58) times of others who were born term. Those with a family history of hyperlipidemia showed greater odds of developing dysglycemia from a previously normal OGTT status (OR IGT: 1.51 (1.00 to 2.28), OR DM: 2.57 (1.32 to 4.99)), and increased odds of progressing to DM if there was a family history of DM (OR DM: 2.80 (1.40 to 5.61)). The odds of developing IGT from a previously normal OGTT in girls who had PCOS were more than two times (OR NGT-IGT: 2.17 (1.02 to 4.64)) of those who did not have PCOS. Girls with PCOS, when compared with those without, also had three times the odds of progressing to DM (OR DM: 3.07 (1.08 to 8.76)). After adjustment for treatment received (lifestyle and dietary modifications alone, or combined with pharmacological agents such as metformin, insulin, lipid-lowering agents), being preterm at birth (OR: 3.49 (1.10 to 11.03)), with comorbidities of hypertension (OR: 1.61 (1.01 to 2.57)), hyperlipidemia (OR: 1.80 (1.19 to 2.72)), and fatty liver disease (OR: 2.08 (1.39 to 3.13)) continued to be associated with increased odds of developing IGT.

Further analysis involved grouping the different dysglycemic progressions (NGT-IGT, NGT-DM, IGT-DM) together as a worsening glycemic status (**Table 4**). Girls were again found to have a higher OR of progressing on to have worsening glycemic status (OR: 1.38 (0.95 to 2.00)), but not statistically significant. Birth history wise, being born premature (OR: 2.66 (1.01 to 7.05)) greatly increased these odds. Family history of MetS, particularly that of hyperlipidemia and DM, increased the OR of worsening glycemic status as well (OR 1.72 (1.18 to 2.51) and OR 1.65 (1.15 to 2.38), respectively). A rise in BMI (OR: 1.06 (1.01 to 1.11)), particularly at an upper threshold of more than  $1.08 \text{ kg}/\text{m}^2$ , was found to significantly increase the odds as well (OR 1.68 (1.17 to 2.42)). The presence of hypertension (OR: 1.93 (1.27 to 2.93)), hyperlipidemia (OR: 2.08 (1.43 to 3.03)), fatty liver disease (OR: 2.20 (1.52 to 3.18)) and PCOS (OR: 2.38 (1.20 to 4.69)) was

**Table 1** Baseline characteristics of study population

Characteristics	Baseline oral glucose tolerance test status					P value
	Normal n=458	IFG n=3	IGT n=214	DM n=40	Total n=715	
Age (years)						<0.001
Mean (SD)	11.9 (2.96)	15.3 (3.21)	12.9 (2.60)	13.7 (2.21)	12.3 (2.88)	
Gender, n (%)						0.096
Male	294 (64.2)	1 (33.3)	126 (58.9)	19 (47.5)	440 (61.5)	
Female	164 (35.8)	2 (66.7)	88 (41.1)	21 (52.5)	275 (38.5)	
BMI (kg/m <sup>2</sup> )						0.791
n	392	3	188	34	617	
Mean (SD)	31.1 (6.00)	34.4 (2.65)	31.0 (7.03)	31.6 (4.35)	31.2 (6.24)	
Gestational age, n (%)						<0.001
n	370	3	172	35	580	
Term	355 (95.7)	1 (33.3)	158 (91.9)	32 (91.4)	546 (94.1)	
Preterm	15 (4.0)	2 (66.7)	14 (8.1)	3 (8.6)	34 (5.9)	
Birth weight, n (%)						0.053
n	366	3	170	34	573	
AGA	332 (90.7)	3 (100)	137 (80.6)	28 (82.4)	500 (87.3)	
SGA	16 (4.4)	0	15 (8.8)	2 (5.9)	33 (5.8)	
LGA	18 (4.9)	0	18 (10.6)	4 (11.8)	40 (7.0)	
Race, n (%)						0.502
n	458	3	214	40	715	
Chinese	236 (51.5)	1 (33.3)	130 (60.7)	26 (65.0)	393 (55.0)	
Malay	144 (31.4)	1 (33.3)	53 (24.8)	8 (20.0)	206 (28.8)	
Indian	66 (14.4)	1 (33.3)	27 (12.6)	5 (12.5)	99 (13.8)	
Other	12 (2.6)	0	4 (1.9)	1 (2.5)	17 (2.4)	
Family history, n (%)						
n	458	3	214	40	715	
Hyperlipidemia	134 (29.3)	1 (33.3)	80 (37.4)	14 (35.0)	229 (32.0)	0.311
DM	198 (43.2)	3 (100)	100 (46.7)	30 (75.0)	331 (46.3)	<0.001
Hypertension	14 (3.1)	0	8 (3.7)	1 (2.5)	23 (3.2)	0.019
Obesity	24 (5.2)	0	9 (4.2)	0	33 (4.6)	0.416
Comorbidity, n (%)						
n	458	3	214	40	715	
Hypertension	66 (14.4)	1 (33.3)	52 (24.3)	11 (27.5)	130 (18.2)	0.006
Hyperlipidemia	121 (26.4)	1 (33.3)	77 (36.0)	17 (42.5)	216 (30.2)	0.025
Fatty liver	151 (33.0)	1 (33.3)	91 (42.5)	22 (55.0)	265 (37.1)	0.009
PCOS	25 (5.5)	0	27 (12.6)	8 (20.0)	60 (8.4)	<0.001
OSA	206 (45.0)	3 (100)	66 (30.8)	14 (35.0)	289 (40.4)	<0.001
Presence of 2 comorbidities	98 (21.4)	1 (33.3)	53 (24.8)	7 (17.5)	159 (22.2)	0.635
Presence of 3 comorbidities	44 (9.6)	1 (33.3)	26 (12.1)	8 (20.0)	79 (11.0)	0.111
Presence of 4 comorbidities	13 (2.8)	0	8 (3.7)	3 (7.5)	24 (3.4)	0.441
Presence of 5 comorbidities	1 (0.2)	0	1 (0.5)	1 (2.5)	3 (0.4)	0.203
Treatment received, n (%)						
Lifestyle advice	458 (100)	3 (100)	214 (100)	40 (100)	715 (100)	
Metformin	39 (8.5)	1 (33.3)	41 (19.2)	26 (65.0)	107 (15.0)	<0.001

Continued

**Table 1** Continued

Characteristics	Baseline oral glucose tolerance test status					P value
	Normal n=458	IFG n=3	IGT n=214	DM n=40	Total n=715	
Insulin	3 (0.7)	0	2 (0.9)	5 (12.5)	10 (1.4)	<0.001
Lipid-lowering drugs	423 (92.4)	3 (100)	189 (88.3)	33 (82.5)	648 (90.6)	0.095

P values for categorical and continuous variables are calculated based on  $\chi^2$  and ANOVA test, respectively. AGA, appropriate for gestational age; ANOVA, analysis of variance; BMI, body mass index; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LGA, large for gestational age; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; SGA, small for gestational age.

also associated with increased odds. After adjustment for treatment received (lifestyle and dietary modifications alone, or combined with pharmacological agents such as metformin, insulin, lipid-lowering agents), age >10 years (OR 4.94 (1.21 to 20.25)), BMI rise (OR 1.71 (1.17 to 2.49)), BMI increase >1.08 kg/m<sup>2</sup> (OR 1.71 (1.16 to 2.51)), comorbidities of hyperlipidemia (OR 1.67 (1.12 to 2.50)) and fatty liver disease (OR 2.11 (1.43 to 3.12)) continued to be significantly associated with higher odds of worsening glycaemic status.

We sought to understand if the propensity for developing worsening glycaemic status increased if the participant had a greater number of metabolic risk factors. There were five metabolic comorbidities of interest in our study including hypertension, hyperlipidemia, fatty liver disease, PCOS, and obstructive sleep apnea. The presence of three comorbidities increased the OR to 2.32 (1.45 to 3.73), having four comorbidities almost doubled it (OR: 1.88 (1.02 to 3.48)), and having all five conditions more than tripled the odds of those who had at least three of them (OR: 7.70 (1.90 to 31.16)). After adjustment for treatment received, presence of three comorbidities continued to be associated with an increased OR

of developing worsening glycaemic status (OR: 2.07 (1.18 to 3.64)).

### DISCUSSION

Obesity associated with pre-diabetes in children and adolescents has become a more frequent challenge facing patients, families and care providers alike. As we learn more about the natural history of pre-diabetes and T2DM, investigators have found distinct differences between these conditions in youth and adults, making extrapolation of adult practice problematic. Moreover, there is a lack of evidence-based management and treatment guidelines for pre-diabetes in children and adolescents. Although current approaches may differ, best clinical practice indicates that providers should screen at-risk patients for pre-diabetes. This should be followed by intervention with intensive lifestyle modification through improved nutrition and exercise. In some cases, pharmacological intervention may also be warranted, but always in the context of lifestyle and behavioral changes.

Our retrospective study of Paediatric Obesity Evaluation for Metabolic Susceptibility in a referred population of children and adolescents who had increased BMI (overweight/obese) in a multi-ethnic Asian population is the first of its kind in South-East Asia. It examines the risk factors which lead to evolution of dysglycaemia on a background of obesity alluding to the pathophysiology of lipotoxicity as a key primer to glucotoxicity. The root of this complex metabolic disease starts in the pre-conception phase with maternal health, continuing through conception, and into early childhood. The first 1000 days of a child's life is key to lifelong health and well-being as it is a period of rapid growth and neurodevelopment. As the body is sensitive to inappropriate nutrition, there is epigenetic programming of obesity, metabolic risk factors, and non-communicable diseases such as insulin resistance and T2DM.<sup>18 19</sup> Results from our analysis demonstrate that risk factors of developing dysglycaemia can be present even from birth, as participants who were born preterm had increased odds of IGT, and a greater proportion of LGA/SGA babies having dysglycaemia even at baseline as compared with appropriate-for-gestational-age babies. This reflects the impact of Barker's hypothesis, where the

**Table 2** Number of occurrences in glycaemic status change over follow-up time period

Glycaemic status change		Number of occurrences	Time interval between glycaemic status change (years)
			Median (IQR)
Normal	NGT-NGT	617	–
Impaired glucose tolerance (IGT)	NGT-IGT	124	2.01 (1.21–3.22)
	IFG-IGT	2	–
Diabetes mellitus (DM)	IGT-DM	23	1.86 (1.01–3.66)
	NGT-DM	15	3.61 (2.46–4.84)

IQR, inter-quartile range = 25th–75th percentile.  
DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

**Table 3** Univariate logistic regression analysis examining factors associated with glycemic status change in comparison with participants who maintained a normal oral glucose tolerance test (OGTT) result

Factor	OGTT status change to	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Age	IGT	1.04 (0.98 to 1.11)	0.218	1.02 (0.96 to 1.09)	0.509
	DM	1.07 (0.94 to 1.21)	0.289	0.96 (0.83 to 1.11)	0.611
Female gender	IGT	1.19 (0.79 to 1.80)	0.403	1.26 (0.83 to 1.92)	0.278
	DM	2.17 (1.11 to 4.23)	<b>0.023</b>	2.13 (0.94 to 4.78)	0.068
Preterm	IGT	3.14 (1.15 to 8.58)	<b>0.026</b>	3.49 (1.10 to 11.03)	<b>0.033</b>
	DM	1.20 (0.15 to 9.93)	0.863	1.16 (0.07 to 19.34)	0.916
SGA/LGA	IGT	1.60 (0.84 to 3.05)	0.151	1.53 (0.92 to 2.87)	0.182
	DM	0.60 (0.14 to 2.68)	0.508	0.20 (0.05 to 0.92)	0.390
Family history of hyperlipidemia	IGT	1.51 (1.00 to 2.28)	<b>0.047</b>	1.28 (0.84 to 1.97)	0.255
	DM	2.57 (1.32 to 4.99)	<b>0.005</b>	1.60 (0.73 to 3.51)	0.245
Family history of DM	IGT	1.41 (0.95 to 2.09)	0.087	1.13 (0.74 to 1.71)	0.568
	DM	2.80 (1.40 to 5.61)	<b>0.003</b>	1.12 (0.45 to 2.81)	0.804
Family history of obesity	IGT	1.25 (0.82 to 1.90)	0.300	1.18 (0.77 to 1.80)	0.455
	DM	1.31 (0.65 to 2.64)	0.444	1.24 (0.58 to 2.65)	0.576
Family history of hypertension	IGT	1.24 (0.83 to 1.86)	0.300	1.06 (0.70 to 1.60)	0.801
	DM	1.90 (0.98 to 3.68)	0.059	1.36 (0.60 to 3.10)	0.468
BMI rise	IGT	1.06 (1.01 to 1.11)	<b>0.021</b>	1.02 (0.99 to 1.05)	0.323
	DM	1.07 (1.01 to 1.13)	<b>0.030</b>	0.98 (0.93 to 1.03)	0.354
Hypertension	IGT	1.94 (1.25 to 3.03)	<b>0.003</b>	1.61 (1.01 to 2.57)	<b>0.045</b>
	DM	1.89 (0.88 to 4.06)	0.103	1.10 (0.36 to 3.41)	0.868
Hyperlipidemia	IGT	2.10 (1.41 to 3.13)	<b>0.001</b>	1.80 (1.19 to 2.72)	<b>0.005</b>
	DM	2.04 (1.04 to 4.01)	<b>0.040</b>	1.20 (0.49 to 2.91)	0.693
Fatty liver disease	IGT	2.12 (1.45 to 3.23)	<b>0.001</b>	2.08 (1.39 to 3.13)	<b>&lt;0.001</b>
	DM	2.30 (1.17 to 4.50)	<b>0.015</b>	2.17 (0.97 to 4.84)	0.060
PCOS	IGT	2.17 (1.02 to 4.64)	<b>0.045</b>	1.72 (0.74 to 4.03)	0.211
	DM	3.07 (1.08 to 8.76)	<b>0.036</b>	0.99 (0.26 to 3.76)	0.996
OSA	IGT	0.88 (0.60 to 1.31)	0.529	0.85 (0.57 to 1.26)	0.426
	DM	0.68 (0.34 to 1.33)	0.254	0.65 (0.29 to 1.45)	0.293

OGTT status change to IGT and DM indicates NGT-IGT and NGT-DM/IGT-DM, respectively.

Bolded values are the statistically significant p-values ( $p < 0.05$ ).

\*OR was adjusted for treatment received, including lifestyle, metformin, insulin, and lipid-lowering agents.

BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucose tolerance; LGA, large for gestational age; NGT, normal glucose tolerance; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; SGA, small for gestational age.

quality of a baby's in-utero environment is directly proportional to his or her subsequent metabolic health. Furthermore, genetic predisposition to developing obesity and MetS could be inherent non-modifiable risk factors, and family history of unhealthy nutritional habits may accelerate this process, predisposing the child to a 'metabolic milieu' with a predetermined ability, or lack thereof, to cope with increased calories and body mass.<sup>20 21</sup>

As children become older than 10 years old, the odds of developing worsening glycemic status increased by almost fivefold. This is most likely related to the onset and peak of puberty. The pathophysiology is explained by increased insulin resistance during this transitional

phase of a child's life.<sup>22</sup> Even in children without obesity or diabetes, euglycemic clamp studies have demonstrated that insulin sensitivity is reduced by approximately 30%–36% during Tanner stages 2–4 (mid-puberty) in comparison with pre-pubertal or Tanner 5 individuals.<sup>23</sup> This is most likely related to increased mean growth hormone levels.<sup>24</sup> This aligns with a Cochrane review by Mead *et al* that behavior, lifestyle, and dietary changes are less effective for children aged 10 years and above, in comparison with their younger counterparts.<sup>25</sup>

The presence of certain comorbid conditions also predisposes a child to developing dysglycemia. In females, PCOS is a particularly significant risk factor.

**Table 4** Univariate and multivariable analyses examining factors associated with the composite outcome of worsening glycemic status\* in comparison with participants who maintained a normal oral glucose tolerance test result

Factor	Unadjusted OR (95% CI)	P value	Adjusted OR† (95% CI)	P value
Age	1.05 (0.99 to 1.11)	0.138	1.01 (0.95 to 1.07)	0.749
Female	1.38 (0.95 to 2.00)	0.095	1.39 (0.93 to 2.07)	0.107
LGA/SGA	1.34 (0.71 to 2.54)	0.364	1.09 (0.56 to 2.11)	0.798
Preterm	2.66 (1.01 to 7.05)	<b>0.048</b>	2.80 (0.81 to 9.65)	0.102
Age >10 years	6.44 (1.52 to 27.36)	<b>0.012</b>	4.94 (1.21 to 20.25)	<b>0.027</b>
Family history of hyperlipidemia	1.72 (1.18 to 2.51)	<b>0.005</b>	1.32 (0.88 to 1.98)	0.174
Family history of DM	1.65 (1.15 to 2.38)	<b>0.007</b>	1.12 (0.75 to 1.68)	0.571
Family history of obesity	1.26 (0.85 to 1.87)	0.241	1.18 (0.79 to 1.77)	0.418
Family history of hypertension	1.37 (0.94 to 1.99)	0.097	1.09 (0.73 to 1.63)	0.676
BMI rise	1.06 (1.01 to 1.11)	<b>0.012</b>	1.71 (1.17 to 2.49)	<b>&lt;0.001</b>
BMI increase >1.08 kg/m <sup>2</sup>	1.68 (1.17 to 2.42)	<b>0.005</b>	1.71 (1.16 to 2.51)	<b>&lt;0.001</b>
Hypertension	1.93 (1.27 to 2.93)	<b>0.002</b>	1.51 (0.94 to 2.41)	0.09
Hyperlipidemia	2.08 (1.43 to 3.03)	<b>&lt;0.001</b>	1.67 (1.12 to 2.50)	<b>0.012</b>
Fatty liver disease	2.20 (1.52 to 3.18)	<b>&lt;0.001</b>	2.11 (1.43 to 3.12)	<b>&lt;0.001</b>
PCOS	2.38 (1.20 to 4.69)	<b>0.013</b>	1.49 (0.63 to 3.54)	0.365
OSA	0.83 (0.58 to 1.19)	0.311	0.82 (0.56 to 1.20)	0.301
Presence of 2 comorbidities‡	1.30 (0.85 to 2.00)	0.227	1.24 (0.79 to 1.95)	0.351
Presence of 3 comorbidities‡	2.32 (1.45 to 3.73)	<b>0.001</b>	2.07 (1.18 to 3.64)	<b>0.012</b>
Presence of 4 comorbidities‡	1.88 (1.02 to 3.48)	<b>0.044</b>	1.84 (0.95 to 3.57)	0.07
Presence of 5 comorbidities‡	7.70 (1.90 to 31.16)	<b>0.004</b>	0.49 (0.02 to 11.34)	0.659

Bolded values are the statistically significant p-values (p < 0.05).

\*Worsening glycemic status: NGT-IGT, NGT-DM, IGT-DM.

†OR was adjusted for treatment received, including lifestyle, metformin, insulin, and lipid-lowering agents.

‡Comorbidities included any of the following: hypertension, hyperlipidemia, fatty liver disease, PCOS, and OSA.

BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucose tolerance; LGA, large for gestational age; NGT, normal glucose tolerance; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; SGA, small for gestational age.

The prevalence of PCOS was progressively higher in participants with baseline IGT and DM in comparison with those with normal OGTT at baseline. Even in lean individuals with PCOS, there was an inherent 27% reduction in insulin sensitivity detected via euglycemic-hyperinsulinemic clamp studies.<sup>26</sup> An inverse relationship exists between sex hormone-binding globulin (SHBG) levels and risk of T2DM,<sup>27</sup> and PCOS is inherently associated with lower SHBG levels.<sup>28 29</sup> There is an additive effect from increased adiposity and body mass, exacerbating hyperinsulinemia and ultimately glucose intolerance. Similar results were demonstrated in adult women, with the risk of developing T2DM tripling in women with PCOS compared with unaffected women.<sup>30</sup> The degree of hyperandrogenism correlates significantly with insulin resistance. Females with higher free androgen indices have a higher risk of developing T2DM.<sup>27</sup> In our study, even though PCOS was shown to be associated with an increased OR of developing worsening glycemic status initially, this was no longer statistically significant after adjusting for treatment received.

The occurrence of fatty liver disease, hyperlipidemia, and hypertension signifies ‘metabolic health

decompensation’ in an individual, indicating that the body is under excessive caloric, glycemic, and adipotoxic stress as BMI increases. Our analysis revealed that having hyperlipidemia and fatty liver disease significantly increased the odds of worsening glycemic status. There was a dose-dependent relationship as well, with the presence of three or more risk factors shown to cumulatively amplify these odds. This corresponds to the concept of visceral fat, especially that of hepatic and pancreatic steatosis. The rise of alanine transferase and triglycerides heralds dysglycemia and the onset of type 2 diabetes,<sup>31</sup> with hepatic insulin sensitivity decreasing as hepatic fat content increases,<sup>32</sup> and vice versa.<sup>33</sup> The pancreatic  $\beta$ -cell is also a victim of this process, with chronic exposure to triglycerides and fatty acids impairing their insulin secretory functions,<sup>34</sup> with further fat-mediated metabolic insults.<sup>35</sup> This forms the basis of the twin-cycle hypothesis,<sup>36</sup> with long-term caloric excess initiating self-reinforcing accumulation of liver fat, increasing hepatic output of very low-density lipoprotein-triglycerides. This leads to ectopic visceral and pancreatic fat accumulation, gradually impairing  $\beta$ -cell function culminating in dysglycemia and T2DM. Importantly, each individual has his/

her own susceptibility to these deleterious effects,<sup>37</sup> and an increase in BMI manifests this vulnerability. Our study showed that a BMI increase of more than 1.08 kg/m<sup>2</sup> is a clinically appreciable threshold associated with higher OR of worsening glycemc status.

The main strengths of our study would be our large sample size, with 715 participants meeting criteria for inclusion in the analysis. Each participant had two or more OGTTs performed, and this enabled longitudinal follow-up on glycemc status. However, there are also several limitations. It involved a select population of referred children and adolescents who had increased BMI (overweight/obese) for assessment of dysglycemc and associated metabolic risks. As a retrospective study, there were missing data with regard to study population demographics and anthropometric measures. These children were managed in general pediatric, weight management, and paediatric endocrinology clinics. As such, there was heterogeneity in their management. Not all of them underwent a full metabolic evaluation with assessment for fatty liver disease, hypertension, and hyperlipidemia. Not all girls were assessed for PCOS, and pubertal staging was not clearly recorded in many participants, leading to the use of age as a crude proxy in this study. In addition, those who were diagnosed with dysglycemc/T2DM without undergoing an OGTT were missed. Some may have been diagnosed with a raised fasting plasma glucose and/or subsequent blood glucose monitoring demonstrating hyperglycemc. There were also participants who defaulted follow-up and therefore missed out on being assessed for worsening dysglycemc. Their compliance to the treatment regimen they were initiated on, whether non-pharmacological or pharmacological, was also not determined, but this is reflective of actual clinical practice, where therapeutic adherence may not be present in everyone. We also had very small numbers with baseline IFG (n=3), so this group was excluded from our subsequent data analysis.

In conclusion, with routine lifestyle and dietary interventions, a child who has increased BMI (overweight/obese) and possesses risk factors for worsening glycemc status would still be in grave danger of developing dysglycemc and T2DM. It is important to be aware of and understand that each individual who has obesity/overweight is unique, with nuances setting their risk profile apart from the next patient. This allows for triaging and prioritization of resources and efforts, with closer follow-up, more aggressive emphasis on weight loss, earlier use of pharmacological agents, and employing advanced therapeutics potentially averting the sure road to dysglycemc and diabetes. Furthermore, the findings from our study should allow us to communicate patients' risks effectively, hopefully imparting insight and empowering them to change for the better as well. This also provides a direction to formulate guidelines and policies for the systematic assessment of metabolic diseases and its complications in at-risk children and adolescents, hopefully reducing the burden of

the obesity epidemic by enforcing early assessment and intervention.

**Contributors** DC and RFV were involved in the conception and design of the study. DC, CC, and CL reviewed and collected data for all the eligible participants. RS cleaned and analyzed the data. DC, RS and RFV collectively interpreted the analyzed data and findings. DC, RS, CC, and CL drafted the manuscript, which was reviewed and revised by RFV. DC is responsible for the overall content as the guarantor.

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**Data availability statement** All data relevant to the study are included in the article.

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