Poor In Utero Growth, and Reduced β-Cell Compensation and High Fasting Glucose From Childhood, Are Harbingers of Glucose Intolerance in Young Indians

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OBJECTIVE

India is a double world capital of early-life undernutrition and type 2 diabetes. We aimed to characterize life course growth and metabolic trajectories in those developing glucose intolerance as young adults in the Pune Maternal Nutrition Study (PMNS).

RESEARCH DESIGN AND METHODS

PMNS is a community-based intergenerational birth cohort established in 1993, with serial information on parents and children through pregnancy, childhood, and adolescence. We compared normal glucose-tolerant and glucose-intolerant participants for serial growth, estimates of insulin sensitivity and secretion (HOMA and dynamic indices), and β-cell compensation accounting for prevailing insulin sensitivity.

RESULTS

At 18 years (*N* = 619), 37% of men and 20% of women were glucose intolerant (prediabetes *n* = 184; diabetes *n* = 1) despite 48% being underweight (BMI <18.5 kg/m^2). Glucose-intolerant participants had higher fasting glucose from childhood. Mothers of glucose-intolerant participants had higher glycemia in pregnancy. Glucose-intolerant participants were shorter at birth. Insulin sensitivity dec-reased with age in all participants, and those with glucose intolerance had consistently lower compensatory insulin secretion from childhood. Participants in the highest quintile of fasting glucose at 6 and 12 years had 2.5- and 4.0-fold higher risks, respectively, of 18-year glucose intolerance; this finding was replicated in two other cohorts.

CONCLUSIONS

Inadequate compensatory insulin secretory response to decreasing insulin sensitivity in early life is the major pathophysiology underlying glucose intolerance in thin rural Indians. Smaller birth size, maternal pregnancy hyperglycemia, and higher glycemia from childhood herald future glucose intolerance, mandating a strategy for diabetes prevention from early life, preferably intergenerationally.

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India is experiencing a rapidly escalating epidemic of type 2 diabetes (1) and simultaneously has the world's highest burden of low birth weight and undernutrition in children <5 years (2). Current thinking about the etiology of type 2 diabetes is mostly based on studies in adults and ascribes type 2 diabetes to overnutrition and sedentariness in genetically susceptible individuals. Against this background, the high prevalence of diabetes in Indians, at a younger age and lower BMI than Europeans, appears paradoxical (3). Recent reports suggest high rates of prediabetes in Indian adolescents and young adults (2) and faster conversion from prediabetes to diabetes (4,5). The greatest rise in prevalence in the last 25 years has occurred in the most deprived Indian states, and in some places, there has been a reversal of the socioeconomic trend from a previous excess prevalence among the most affluent (6). Taken together, these findings raise the possibility that historical deprivation and undernutrition are contributory factors to diabetes in a rapidly transitioning society like India.

There is growing acceptance of a life course model (Developmental Origins of Health and Disease [DOHaD]) for the evolution of type 2 diabetes. Adverse environmental exposures in early life, classically reflected in low birth weight, are associated with an increased risk of adult type 2 diabetes (7,8). The thrifty phenotype hypothesis proposes that intrauterine undernutrition disrupts the structure and function of key organs, which manifests as an increased risk of diabetes through both diminished insulin secretion and sensitivity (9). While there is considerable information on newborn size and childhood growth as predictors of later type 2 diabetes risk (10,11), there is little data on childhood measures of glucose, insulin secretion, and sensitivity as predictors. It is therefore unknown at what age metabolic susceptibility to future diabetes becomes evident or whether impaired insulin sensitivity or secretion is the primary defect. Consequently, diabetes prevention trials still mainly target middle-aged individuals who already have obesity and advanced metabolic abnormalities (12).

In the Pune Maternal Nutrition Study (PMNS), we had a unique opportunity to construct the first life course trajectory of glucose-insulin indices and growth in rural Indian young adults, along with data on parental size and glucose intolerance.

RESEARCH DESIGN AND METHODS

Overview of the PMNS Cohort

PMNS (Fig. 1 and Supplementary Fig. 1) was established in 1993 in six villages near Pune, India, to prospectively study associations of maternal nutritional status with fetal growth and later diabetes risk in the offspring (13). Married nonpregnant women (F0 generation; n = 2,466) were followed up, and those who became pregnant (n = 797) were recruited to the study if a singleton pregnancy of <21 weeks' gestation was confirmed by ultrasound. Most delivered at home, and only 4.2% required Caesarean section; 3 women had diabetes in pregnancy (World Health Organization [WHO] 1985 criteria).

Measurements of Babies and Children (F1 generation)

Detailed anthropometry was carried out using standardized methods at birth and every 6 months postnatally (14). Glucose and insulin concentrations, body composition, and socioeconomic status (SES) were measured at ages 6, 12, and 18 years at the Diabetes Unit. All families were visited by field staff a week before the study to explain the procedures and to stress that they should eat normally and perform usual daily activities. Participants arrived at the Diabetes Unit the evening before the investigations, had a standard dinner, and fasted overnight. In the morning, a single fasting blood sample was collected. At age 6 years, an oral glucose tolerance test (OGTT) (1.75 g/kg anhydrous glucose) was performed. At 12 years, only a fasting sample was collected. At 18 years, an OGTT (75 g anhydrous glucose) was repeated. Glucose was measured by the glucose oxidase/peroxidase method, and specific insulin by ELISA (coefficients of variation for glucose and insulin were <4% and <8%, respectively, at all time points). Insulin assays were calibrated against the same WHO standard (WHO first international reference preparation [66/304]) and are therefore directly comparable (Supplementary Table 3). Insulin sensitivity (HOMA-S) and β-cell function (HOMA-β) were calculated using data from the fasting samples in iHOMA2 program (15). We calculated the Matsuda index for insulin sensitivity (16,17) and the insulinogenic index (ln [insulin(30-min/fasting)/glucose(30-min/fasting)]) for early insulin secretion (18). Both indices have been validated against reference methods and are used commonly in epidemiological research. Because of the interdependence between β-cell function and insulin sensitivity, we estimated compensatory β-cell response by calculating (insulinogenic index) * (Matsuda index) at 6 and 18 years and (HOMA-S) * (HOMA-β) at 6, 12, and 18 years (19). Total fat and lean mass and body fat percentages were measured by DEXA. SES was evaluated using the standard of living index (SLI) based on the family's dwelling, land ownership, and assets (20). Higher scores denote higher SES.

Definitions

In adults, underweight was defined as BMI <18.5 kg/m^2 and overweight/obesity as BMI ≥25 kg/m^2 (WHO international cut point); stunting was defined as a height-for-age z score ≤2 SD below the WHO average (<149.8 cm in women and <161.2 cm in men) (21). Central obesity was defined as a waist circumference ≥90 cm in men and ≥80 cm in women (22) and adiposity as a DEXA-derived fat percentage >25% in men and >35% in women. Glucose tolerance in children, fathers, and nonpregnant mothers was classified by American Diabetes Association (ADA) criteria (23) as normal (NGT), prediabetes (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]), or diabetes. IFG, IGT, and diabetes together were referred to as glucose intolerance.

Parental Measurements

Anthropometry and glucose tolerance (75 g OGTT) were measured in both parents during the index pregnancy (~28 weeks' gestation) and at the 6-year follow-up. Gestational diabetes was diagnosed by WHO 1985 criteria (2-h plasma glucose ≥7.8 mmol/L) and treated appropriately. Given the small number of gestational diabetes mellitus cases, for the current analysis we defined glucose intolerance as fasting plasma glucose (FPG) ≥95th centile in this population (5.1 mmol/L), which coincides with current International

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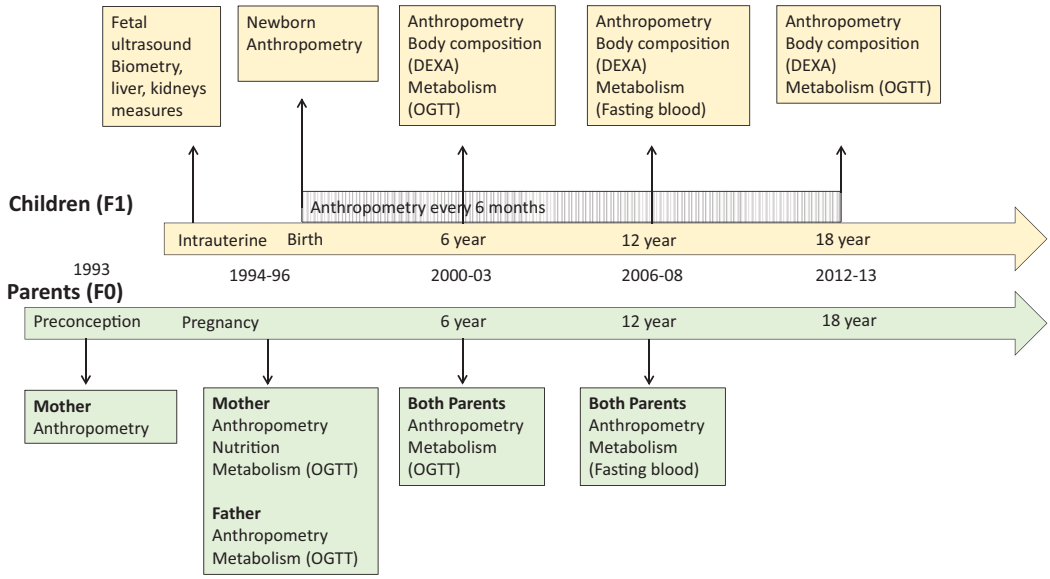

Figure 1—PMNS. Married nonpregnant women were followed up in six villages near Pune, India. Those who became pregnant (singleton fetus <21 weeks) were enrolled during pregnancy. Maternal glucose tolerance was measured at 28 ± 2 weeks' gestation. Babies (F1 generation) were measured at birth and every 6 months thereafter by detailed anthropometry. Comprehensive measurements of body size and composition and glucose-insulin metabolic function were performed every 6 years in the children until age 18 years and in both parents (F0 generation) when the child was age 6 and 12 years. USG, ultrasonography.

Association of Diabetes and Pregnancy Study Groups criteria (24). Anthropometry and only a fasting blood test were available at the 12-year follow-up. Parents were classified as ever underweight or overweight/obese based on their follow-up data. Fathers and mothers were classified as glucose intolerant if they had IFG, IGT, or diabetes at any follow-up.

Replication Cohorts

Pune Children's Study Cohort

The Pune Children's Study Cohort is an urban cohort of children born in the King Edward Memorial Hospital in 1987–1989 (25). Briefly, the children were studied at 8 (n = 477) and 21 years (n = 357) of age. Measurements were the same as those in PMNS, and glucose tolerance at age 21 years was classified by the same ADA criteria.

Extended PMNS Cohort

This cohort included an additional 110 pregnancies, after completing recruitment of the main PMNS cohort, to validate ultrasound protocols for gestational dating. Ninety-two children had glucose tolerance data at 6, 12, and 18 years of age. Given the small numbers in this cohort, we used the upper tertile of 18-year FPG concentration as the outcome.

Statistical Methods

Our purpose was to show a comparative temporal evolution of glucose-insulin relationships and growth in young adults with prediabetes and NGT at 18 years (Table 1). Variables with right-skewed distributions were log transformed; all variables were z standardized, and differences between NGT and glucose-intolerant participants were expressed in z score units with 95% CIs. We used logistic regression for life course predictors of glucose intolerance at 18 years of age (outcome). The predictors included parental body size and glucose tolerance, as well as the F1 participants' birth measurements and childhood and adolescent body size and glucose concentrations, in addition to sex and SES. Thus, our analysis included a combination of traditional and novel risk factors representing the DOHaD paradigm. We used interaction tests to investigate whether associations differed between the sexes. We created receiver operating characteristic curves to show the sensitivity and specificity of these variables in predicting glucose intolerance.

Ethics

The study was approved by village leaders and the KEM Hospital Research Centre Ethics Committee (Pune, India). Parents provided written consent, and children <18 years of age provided written assent and written consent after reaching 18 years.

Data and Resource Availability

Data are available from C.S.Y. for sharing to confirm our findings and for additional analysis by applying to the corresponding author with a 200-word plan of analysis. Data sharing is subject to approval by the KEM Hospital Research Centre Ethics Committee and permission from the Government of India's Health Ministry Advisory Committee.

RESULTS

The analysis included 619 men and women with complete data (86% of the original live births). Mean BMI was 19.7 kg/m^2 in men and 18.7 kg/m^2 in women; 41% of men and 57% of women were underweight, and ~10% were stunted (Supplementary Table 1). Eight percent of men and 4% of women were overweight/obese, while 6% of men and 5% of women were centrally obese. Sixteen percent each of men and women had adiposity (DEXA). A total of 185 (30%) were glucose intolerant: 1 woman had diabetes, and 37% of men and 20% of women had prediabetes. Men had more frequent IFG (27%) than women (9%), but rates of IGT were similar (11% in both sexes). Thirty-one

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Table 1—Comparison of biomarkers between participants with NGT and glucose intolerance at age 18 years

	Men					Women					Sexes combined		
	NGT, median (n = 221)	Glucose intolerant, median (n = 131)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	NGT, median (n = 213)	Glucose intolerant, median (n = 54)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P
18 years													
Height, cm	170.1	169.0	−0.19	−0.40, 0.03	0.09	157.2	157.3	−0.14	−0.44, 0.16	0.35	−0.17	−0.35, 0.00	0.06
BMI, kg/m^2	18.8	19.6	0.29	0.07, 0.50	0.009	18.1	17.4	−0.18	−0.48, 0.12	0.23	0.12	−0.05, 0.30	0.16
Waist circumference, cm	70.5	72.6	0.30	0.09, 0.52	0.006	67.4	66.3	−0.2	−0.50, 0.10	0.19	0.13	−0.04, 0.31	0.14
Fat, %	12.5	14.8	0.37	0.16, 0.59	<0.001	28.1	27.0	−0.03	−0.33, 0.28	0.87	0.24	0.06, 0.41	0.008
SES, SLI score	37	38	0.20	−0.02, 0.41	0.07	36	36	−0.09	−0.39, 0.21	0.55	0.10	−0.08, 0.27	0.27
Fasting glucose, mmol/L	5.2	5.7	1.49	1.35, 1.64	<0.001	5.1	5.6	1.19	0.93, 1.45	<0.001	1.39	1.25, 1.52	<0.001
30-min glucose, mmol/L	7.8	8.9	0.81	0.62, 1.01	<0.001	8.0	9.1	0.95	0.68, 1.23	<0.001	0.86	0.68, 0.99	<0.001
120-min glucose, mmol/L	5.7	7.0	0.92	0.73, 1.12	<0.001	6.0	7.9	1.39	1.14, 1.63	<0.001	1.08	0.93, 1.23	<0.001
Fasting insulin, pmol/L	48.0	66.0	0.57	0.36, 0.78	<0.001	63.0	66.6	0.22	−0.08, 0.53	0.15	0.45	0.28, 0.63	<0.001
30-min insulin, pmol/L	477.0	477.6	0.07	−0.13, 0.31	0.54	578.4	588.3	−0.16	−0.52, 0.09	0.30	−0.01	−0.19, 0.16	0.92
120-min insulin, pmol/L	258.0	352.2	0.51	0.30, 0.72	<0.001	360.0	579.6	0.84	0.56, 1.13	<0.001	0.62	0.43, 0.77	<0.001
HOMA-S	97	69	−0.63	−0.83, −0.42	<0.001	75	70	−0.26	−0.57, 0.04	0.09	−0.51	−0.68, −0.33	<0.001
HOMA-β	92	94	0.04	−0.18, 0.26	0.71	117	110	−0.28	−0.58, 0.03	0.07	−0.07	−0.24, 0.11	0.46
(HOMA-β) * (HOMA-S)	84.2	64.3	−1.25	−1.39, −1.01	<0.001	84.1	71.3	−0.98	−1.24, −0.68	<0.001	−1.16	−1.23, −0.91	<0.001
Insulinogenic index[a]	1.83	1.53	−0.49	−0.70, −0.28	<0.001	1.77	1.53	−0.56	−0.85, −0.26	<0.001	−0.52	−0.69, −0.34	<0.001
Matsuda index[b]	15.4	11.3	−0.70	−0.90, −0.50	<0.001	12.2	9.07	−0.69	−0.98, −0.48	<0.001	−0.67	−0.81, −0.54	<0.001
(Insulinogenic index) * (Matsuda index)[c]	4.56	4.02	−0.55	−0.76, −0.34	<0.001	4.26	3.66	−0.84	−1.13, −0.56	<0.001	−0.63	−0.79, −0.46	<0.001
15 years													
HbA_{1c}, %	5.40	5.50	0.21	−0.03, 0.44	0.082	5.30	5.40	0.18	−0.14, 0.49	0.269	0.19	0.01, 0.38	0.043
HbA_{1c}, mmol/mol[e]	35.51	36.61	0.21	−0.03, 0.44	0.082	34.42	35.51	0.18	−0.14, 0.49	0.269	0.19	0.01, 0.38	0.043
12 years													
Height, cm	138.9	137.4	−0.20	−0.42, 0.02	0.07	139.6	139.1	−0.17	−0.47, 0.14	0.28	−0.19	−0.36, −0.01	0.04
BMI, kg/m^2	14.6	14.7	0.02	− 0.20, 0.23	0.88	14.4	14.2	−0.08	−0.39, 0.22	0.59	−0.02	−0.19, 0.16	0.85
Waist circumference, cm	57.2	57.2	0.02	−0.21, 0.24	0.89	56.0	55.0	−0.36	− 0.67, −0.06	0.02	−0.11	−0.29, 0.07	0.21
Fat, %	13.4	14.5	0.19	−0.04, 0.41	0.10	17.8	17.1	−0.02	− 0.33, 0.3	0.92	0.12	−0.06. 0.30	0.20
Fasting glucose, mmol/L	4.8	4.9	0.40	0.19, 0.62	<0.001	4.7	5.1	0.82	0.54, 1.11	<0.001	0.55	0.38, 0.72	<0.001
Fasting insulin, pmol/L	27.6	30.6	0.10	−0.12, 0.32	0.37	34.0	34.5	−0.01	−0.31, 0.3	0.97	0.06	−0.11, 0.24	0.48
HOMA-S	165	153	−0.12	−0.34, 0.10	0.28	138	134	−0.02	−0.32, 0.28	0.89	−0.09	−0.26, 0.09	0.34
HOMA-β	71	73	−0.06	−0.28, 0.16	0.61	90	80	−0.39	−0.69, −0.09	0.01	−0.17	−0.35, 0.01	0.06
(HOMA-β) * (HOMA-S)[d]	123	112	−0.33	−0.54, −0.11	0.003	122	108	−0.58	−0.88, −0.29	<0.001	−0.41	−0.59, −0.24	<0.001
Pubertal stage[f]	1	1			0.630	2	2			0.136			
Age at menarche, years	—	—	—	—	—	13.5	13.8	0.22	−0.11, 0.56	0.196	—	—	—

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Table 1—Continued

	Men					Women					Sexes combined		
	NGT, median (n = 221)	Glucose intolerant, median (n = 131)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	NGT, median (n = 213)	Glucose intolerant, median (n = 54)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P
6 years													
Height, cm	110.0	110.0	0.01	−0.21, 0.23	0.92	109.4	108.2	−0.38	−0.67, −0.08	0.01	−0.12	−0.30, 0.05	0.17
BMI, kg/m^2	13.4	13.6	0.11	−0.11, 0.33	0.32	13.1	12.9	−0.33	−0.62, −0.03	0.03	−0.04	−0.22, 0.13	0.65
Waist circumference, cm	50.1	50.6	0.13	−0.09, 0.35	0.24	50.0	49.5	−0.38	−0.68, −0.08	0.01	−0.05	−0.22, 0.13	0.60
Fat, %	17.2	17.8	0.14	−0.08, 0.35	0.22	20.4	20.6	−0.01	−0.31, 0.29	0.93	0.09	−0.09, 0.26	0.34
Fasting glucose, mmol/L	4.94	5.16	0.44	0.23, 0.65	<0.001	4.77	4.93	0.31	0.01, 0.61	0.04	0.40	0.22, 0.57	<0.001
30-min glucose, mmol/L	8.21	8.10	0.07	−0.16, 0.27	0.52	8.10	8.55	0.30	−0.03, 0.57	0.05	0.15	−0.05, 0.29	0.10
120-min glucose, mmol/L	5.27	5.49	0.24	0.03, 0.46	0.03	5.57	5.38	0.25	−0.05, 0.55	0.10	0.25	0.07, 0.42	0.006
Fasting insulin, pmol/L	16.80	20.94	0.28	0.07, 0.49	0.01	20.04	18.84	−0.16	−0.46, 0.14	0.29	0.13	−0.05, 0.30	0.15
30-min insulin, pmol/L	138.0	131.7	0.06	−0.19, 0.23	0.60	163.3	153.7	0.06	−0.19, 0.41	0.70	0.06	−0.12, 0.22	0.52
120-min insulin, pmol/L	47.8	58.4	0.20	−0.05, 0.39	0.07	66.1	61.6	0.06	−0.27, 0.33	0.70	0.15	−0.06, 0.28	0.09
HOMA-S	262	218	−0.30	−0.51, −0.08	0.008	225	239	0.13	−0.17, 0.43	0.40	−0.15	−0.32, 0.03	0.10
HOMA-β	48	52	0.06	−0.16, 0.27	0.62	61	48	−0.23	−0.53, 0.06	0.12	−0.04	−0.22, 0.13	0.62
(HOMA-β) * (HOMA-S)	143	119	−0.48	−0.51, 0.08	<0.001	139	140	−0.11	−0.46, 0.15	0.48	-0.35	−0.47, −0.12	<0.001
Insulinogenic index[a]	1.57	1.54	−0.18	−0.40, 0.04	0.11	1.54	1.58	0.18	−0.12, 0.48	0.25	−0.06	−0.23, 0.12	0.53
Matsuda index[b]	58.5	52.5	−0.27	−0.48, −0.05	0.01	46.8	51.5	0.03	−0.27, 0.33	0.83	−0.16	−0.33, 0.01	0.07
(Insulinogenic index) * (Matsuda index)[c]	6.8	6.7	−0.29	−0.51, 0.07	0.008	6.8	6.7	−0.04	−0.35, 0.29	0.77	−0.20	−0.37, −0.03	0.02
2 years													
Height, cm	82.2	82.0	−0.13	−0.35, 0.09	0.24	81.3	79.6	−0.36	−0.66, −0.07	0.02	−0.21	−0.38, −0.04	0.02
Weight, kg	9.9	9.8	−0.06	−0.28, 0.15	0.58	9.2	8.8	−0.45	−0.75, −0.16	0.003	−0.19	−0.37, −0.02	0.03
Birth													
Weight, g	2700	2700	−0.01	−0.23, 0.22	0.99	2550	2500	−0.19	−0.50, 0.11	0.20	−0.07	−0.25, 0.11	0.45
Length, cm	48.2	47.8	−0.17	−0.39, 0.04	0.11	47.4	47.0	−0.41	−0.70, −0.11	0.007	−0.26	−0.43, −0.08	0.004
Head circumference, cm	33.4	33.2	−0.17	−0.39, 0.05	0.12	32.7	32.5	−0.10	−0.40, 0.20	0.50	−0.14	−0.32, −0.03	0.10
Gestation, days	273	272	−0.05	−0.27, 0.16	0.64	273	273	−0.19	−0.49, 0.1	0.20	−0.10	−0.27, 0.07	0.26
Mother	(n = 221)	(n = 130)				(n = 213)	(n = 54)						
Fasting glucose in pregnancy (28 weeks), mmol/L	3.9	4.0	0.14	−0.09, 0.38	0.23	3.8	3.8	0.07	−0.26, 0.40	0.68	0.11	−0.07, 0.30	0.23
	n (%)	n (%)	OR	95% CI	P	n (%)	n (%)	OR	95% CI	P	OR	95% CI	P
Pregnancy glucose intolerance (FPG ≥5.1 mmol/L)	14 (6.3)	15 (11.5)	1.91	0.89, 4.10	0.10	19 (8.9)	9 (16.7)	2.04	0.87, 4.81	0.11	1.97	1.11, 3.48	0.02

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Table 1—Continued

	Men					Women				Sexes combined	
	NGT, median (n = 221)	Glucose intolerant, median (n = 131)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	NGT, median (n = 213)	Glucose intolerant, median (n = 54)	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P	Mean difference (z score), glucose intolerant − NGT	95% CI of mean difference	P
Postnatal glucose intolerance (diabetes + IFG + IGT)	62 (28.1)	52 (39.7)	1.67	1.01, 2.64	0.03	53 (24.9)	17 (31.5)	1.38	0.66, 2.61	0.33	1.58	1.08, 2.29	0.02
Ever overweight/obese	58 (26.2)	23 (17.6)	0.60	0.35, 1.02	0.06	46 (21.6)	8 (14.8)	0.63	0.28, 1.43	0.27	0.60	0.39, 0.96	0.03
Father	(n = 221)	(n = 131)				(n = 212)	(n = 54)						
Ever glucose intolerant (diabetes + IFG + IGT)	113 (52.3)	64 (48.9)	0.91	0.59, 1.41	0.68	77 (36.2)	30 (55.6)	2.21	1.20, 4.04	0.01	1.23	0.87, 1.75	0.24
Ever overweight/obese	81 (36.7)	44 (33.6)	0.87	0.59, 1.54	0.56	71 (33.3)	19 (35.2)	1.08	0.51, 1.90	0.78	0.94	0.65, 1.36	0.75

OR, odds ratio; SLI, standard of living index. [a]ln(insulin[30-min/fasting]/glucose[30-min/fasting]). [b]10,000/√(glucose fasting × insulin fasting × mean glucose [F, 30 min, 120 min] × mean insulin [F, 30 min, 120 min]). Glucose in mmol/L; insulin in pmol/L. [c]Insulinogenic index + ln(Matsuda index) refers to compensatory β-cell response to prevailing insulin sensitivity. [d](HOMA-S × HOMA-β)/1,000 refers to compensatory β-cell response to prevailing insulin sensitivity. [e]HbA_{1c} (mmol/mol) = (10.93 × HbA_{1c} [%]) − 23.5 (NGSP HbA_{1c} converter available at https://www.ngsp.org/convert1.asp). [f]P value calculated using χ^2 test.

percent of glucose-intolerant men and 67% of glucose-intolerant women were underweight. Glucose-intolerant men, but not women, had higher BMI, fat percentage, and waist circumference than NGT participants.

Life Course Evolution of Glucose-Insulin Indices and Comparison of Glucose-Intolerant and NGT Participants

Glucose-intolerant participants had higher FPG than NGT participants at ages 6 and 12 (and 18) years and higher HbA_{1c} at 15 years. Fasting insulin concentrations were similar at 6 and 12 years, but higher at 18 years, in the glucose-intolerant group. In both NGT and glucose-intolerant participants, insulin sensitivity indices (HOMA-S and Matsuda index) were the highest at 6 years of age, and there was a progressive fall from 6 to 18 years. On the other hand, HOMA-β was lowest at 6 years of age in both groups, with a progressive increase from 6 to 18 years of age. Insulinogenic index (insulin secretion) increased from 6 to 18 years of age in the NGT but not in the glucose-intolerant group. Consequently, it was significantly lower in the glucose-intolerant than in the NGT group at 18 years of age. The β-cell indices (HOMA-β and insulinogenic index) in relation to prevailing insulin sensitivity, however, showed a progressive fall from 6 to 18 years in both the NGT and the glucose-intolerant groups and were consistently lower in the glucose-intolerant group (Fig. 2). We interpret this as indicating reduced capacity for insulin secretion in the glucose-intolerant group. Glucose-intolerant men, but not women, had lower HOMA-S and Matsuda index at age 6 years (Table 1).

Glucose-intolerant men and women were shorter at birth, but there were no significant differences in birth weight compared with the NGT group. They continued to be shorter and lighter at 2 years, and women, but not men, continued to be shorter and thinner until 6 years (Supplementary Fig. 2). Glucose-intolerant men, but not women, gained more weight and BMI during adolescence than the NGT group.

Parental Influences

Glucose-intolerant men and women were more likely than the NGT group to have a mother with glucose intolerance in pregnancy or postnatally and a

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mother who was not overweight or obese. Glucose-intolerant women were also more likely to have a father with glucose intolerance. There was no difference in the duration of exclusive or total breastfeeding in the two groups.

Multivariate Modeling of Glucose Intolerance at 18 Years

Significant predictors in both sexes were maternal pregnancy glucose intolerance, a mother who had never been overweight/obese, and higher 6-year and 12-year FPG. Incidence of glucose intolerance was lower in women, and they also had an additional association with paternal glucose intolerance. Apart from smaller length and head circumference at birth, none of the childhood growth variables were significantly related (examined using conditional BMI and height gain through childhood; data not shown in Table 2). Greater adiposity at 18 years was associated with an increased risk only among men. SES was not related to 18-year glucose intolerance.

We examined these associations separately in IFG and IGT groups (Supplementary Tables 2*A* and *B*), aware that this analysis has limited power. Both groups were small at birth and had a reduced β-cell compensatory response from childhood compared with NGT participants.

Childhood and Adolescent FPG as Predictors of Later Glucose Intolerance

We further investigated the associations between FPG at 6 and 12 years and glucose intolerance at 18 years. The prevalence was 2.5 times higher among those in the highest quintile of FPG at 6 years, and 4.0 times higher at 12 years, than among those in the lowest quintile (Fig. 3). Receiver operating characteristic curves (Supplementary Fig. 3*A* and *B*) for 18-year glucose intolerance showed that the area under the curve using FPG was 0.658 at age 6 years and 0.700 at age 12 years (adjusted for sex). These values increased marginally to 0.686 and 0.723, respectively, when the model included all the predictors listed in Table 2.

We replicated this analysis in the two other cohorts. In the Pune Children's Study Cohort (n = 355), 66 (19%) participants were glucose intolerant at age 21 years (type 2 diabetes, n = 5; IFG, n = 40; IGT, n = 21). They had higher BMI and lower insulin sensitivity and insulin secretion than the NGT participants. They also had higher FPG concentrations (4.8 vs. 4.6 mmol/L; P = 0.026) and lower β-cell compensatory response at 8 years (12.9 vs. 15.3; P = 0.026). The prevalence of glucose intolerance at 21 years was 1.7 times higher among those in the highest tertile of 8-year FPG than among those in the lowest tertile (Supplementary Fig. 4*A*). In the extended PMNS cohort, FPG at age 12 years, but not 6 years, was positively associated with higher FPG concentration at 18 years. The likelihood of being in the highest tertile of FPG at 18 years was 3.1 times higher among those in the highest tertile of FPG at 12 years than among those in the lowest tertile (Supplementary Fig. 4*B*).

CONCLUSIONS

We found a high prevalence of glucose intolerance in this young thin rural Indian cohort, higher in men than women. The glucose-intolerant participants had higher glucose in early childhood compared with NGT participants, reflecting an inadequate compensatory insulin response to decreasing insulin sensitivity. Our intergenerational life course analysis revealed novel associations of adult glucose intolerance, including parental glucose intolerance and reduced fetal and infant growth. These findings support an intergenerational DOHaD model of type 2 diabetes, which was first conceptualized in the thrifty phenotype hypothesis, which attributes adult glucose intolerance to a fetus having to be metabolically thrifty to survive intrauterine nutritional deprivation (9). These ideas challenge the prevailing paradigm according to which type 2 diabetes is a disorder of β-cell decompensation

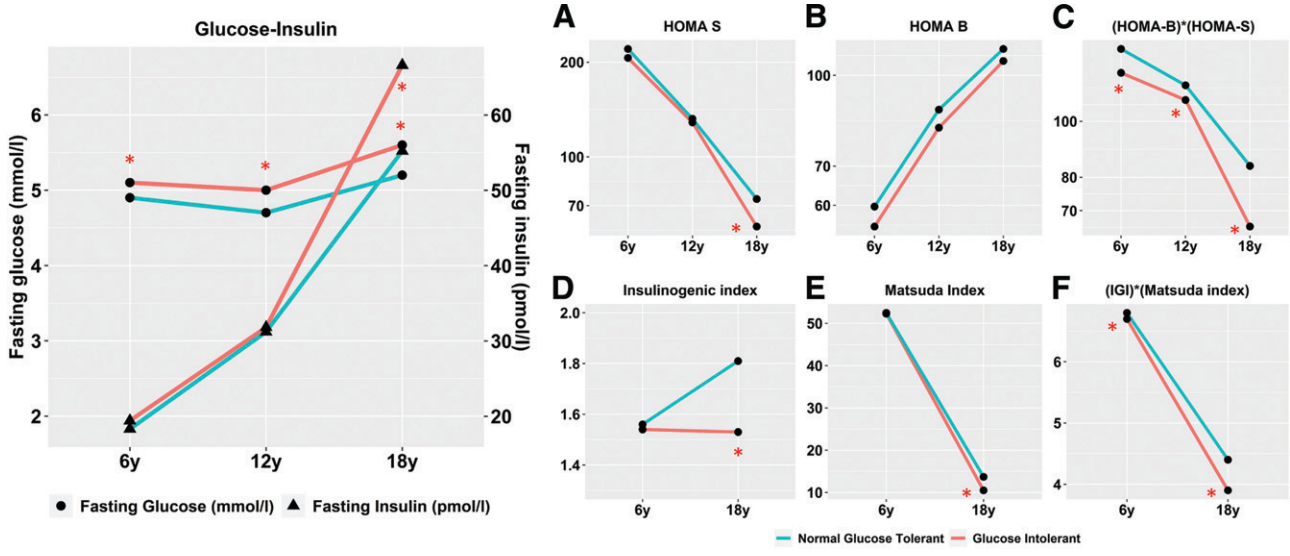

Figure 2—Life course evolution of glucose-insulin metabolism in participants of PMNS (NGT vs. glucose intolerant [GI]). The figure shows the life course evolution of parameters of glucose and insulin metabolism in NGT (dotted line) and GI (solid line) participants. The top panel shows fasting plasma glucose (mmol/L) and fasting plasma insulin (pmol/L). The bottom panel shows HOMA indices (*A*–*C*) and dynamic indices (*D*–*F*). Significant differences between the two groups ($P < 0.05$) are indicated by an asterisk. IGI, insulinogenic index.

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Table 2—Multivariate regression with the outcome of glucose intolerance at age 18 years

Predictor	B	Significance	OR	95% CI
Female sex (yes = 1/no = 0)	−1.689	<0.001	0.185	0.093, 0.365
Mother ever underweight (yes = 1/no = 0)	0.158	0.481	1.172	0.754, 1.821
Father ever underweight (yes = 1/no = 0)	−0.011	0.961	0.989	0.639, 1.531
Mother ever overweight (yes = 1/no = 0)	−0.568	0.045	0.567	0.325, 0.989
Father ever overweight (yes = 1/no = 0)	−0.179	0.454	0.836	0.523, 1.336
Maternal pregnancy glucose intolerance (yes = 1/no = 0)	0.640	0.045	1.896	1.015, 3.540
Father of male child ever glucose intolerant (yes = 1/no = 0)	−0.307	0.222	0.735	0.449, 1.204
Father of female child ever glucose intolerant (yes = 1/no = 0)	0.729	0.028	2.073	1.082, 3.972
Birth length, cm	−0.109	0.014	0.897	0.822, 0.978
Fasting glucose at 6 years, *z* score	0.354	0.001	1.425	1.163, 1.744
Height at 18 years, cm	−0.026	0.122	0.975	0.943, 1.007
Fat % at 18 years (male), *z* score	0.514	<0.001	1.672	1.274, 2.195
Fat % at 18 years (female), *z* score	−0.049	0.767	0.952	0.689, 1.315
SES at 18 years, SLI score	0.020	0.096	1.021	0.996, 1.045
Constant	10.094	0.001		

Maternal postnatal glucose intolerance instead of pregnancy glucose intolerance showed no significant association. Head circumference at birth instead of birth length: B = 0.160, P = 0.023, odds ratio (OR) 0.852, 95% CI 0.742, 0.978. Weight, abdominal circumference, and sum of skinfolds at birth did not show significant associations. 12-year fasting glucose instead of 6-year fasting glucose: B = 0.606, $P < 0.001$, OR 1.833, 95% CI 1.482, 2.266. SLI, standard of living index.

resulting from adult obesity-related insulin resistance (26).

Childhood Glucose Predicts Adult Glucose Intolerance

Higher childhood and adolescent FPG concentrations were strong and graded predictors of future glucose intolerance, which was predicted with 66% and 70% confidence by this measure alone at 6 and 12 years, respectively. These findings provide a simple biomarker for future risk. Our results demonstrate, for the first time in humans, continuous tracking of glycemia from childhood to adulthood and a strong predictive value of childhood FPG for later glucose intolerance. We were able to validate the prediction in two other cohorts in Pune. The Bogalusa and i3C studies hinted at tracking from a single childhood time point, and the Early Bird Study showed tracking from early childhood into adolescence (27–29). These results should

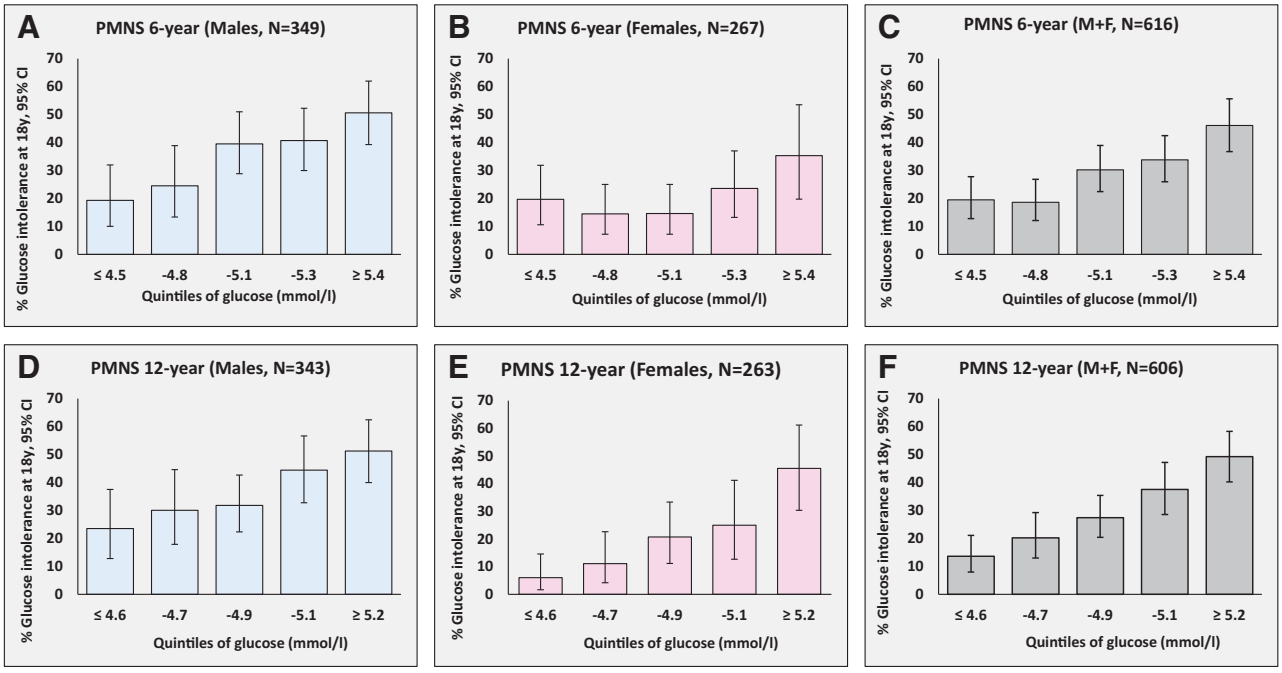

Figure 3—Probability of glucose intolerance at 18 years according to childhood fasting glucose. The prevalence of glucose intolerance at 18 years according to quintile of fasting plasma glucose concentration at 6 years (*A–C*) and 12-years (*D–F*).

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convince pediatricians to measure glucose concentrations in children and policy makers to promote preventive measures at a younger age.

Parental Factors

Intergenerational influences on glucose intolerance seem to reflect a combination of factors. Genetic factors are obviously important, but a specific influence of pregnancy glycemia suggests an epigenetic programming effect. It is intriguing that a lack of overweight/obesity in the mother was associated with glucose intolerance in the child. The parents and grandparents of our cohort grew up in an impoverished drought-prone area. The mothers were short (mean height 1.52 m) and thin (mean BMI 18.1 kg/m^2) and had low macro- and micronutrient intakes and heavy physical workloads in pregnancy (13). Maternal glucose concentrations in pregnancy were relatively low, and few participants had gestational diabetes mellitus, but these concentrations were nevertheless associated with glucose intolerance in their offspring. Our results suggest that the current epidemic of diabetes in young Indians may be rooted in dual teratogenesis (i.e., simultaneous intrauterine exposure to multiple nutritional deficits and [minimally] elevated maternal glucose) (30). Differences in duration of breastfeeding do not seem to have played a role. Sex-specific effects of paternal glycemia suggest a role for imprinting and merit further investigation (31).

Growth and Sex

Rather than low birth weight, short birth length and small head circumference were associated with adult glucose intolerance. While an association of short birth length with later diabetes has been described in another Indian cohort (32), the association with smaller head circumference is a new finding. Human intrauterine growth is governed by the necessity to maintain brain growth (i.e., brain sparing), and our finding of smaller head circumference in the glucose-intolerant participants suggests a relatively severe nutritional challenge. Circulatory adjustments for brain sparing are likely to compromise the development of important abdominal organs (33). Of relevance to glucose intolerance, detrimental effects of intrauterine undernutrition on the structure and function of the liver and pancreas have been well demonstrated in animal models (34,35).

Glucose-intolerant men and women showed different postnatal growth trajectories (Supplementary Fig. 2). Women remained shorter and thinner, and two-thirds of glucose-intolerant women were underweight at 18 years. Glucose-intolerant men gained more body mass during puberty than the NGT group. There were similar findings in the Delhi and Helsinki birth cohorts, which showed that small size in infancy but greater childhood and adolescent weight gain were associated with later glucose intolerance (10,11). It is noteworthy that a third of the glucose-intolerant men were still underweight (low BMI), although with more adiposity (body fat percentage) than the NGT group. These findings support our previous observations of the so-called thin-fat Indian phenotype predisposing to diabetes (33). Becoming heavy relative to oneself (upward centile crossing) is a strong risk factor for diabetes in those who were growth restricted in early life (10, 11,24).

We propose that type 2 diabetes in Indians has its roots in a history of multigenerational undernutrition, leaving a legacy of fetal growth restriction combined with recent rapid nutritional transition, which places increased metabolic demands on developmentally stunted metabolic systems. Between 1830 and 1980, Indians failed to gain height, while Europeans gained up to 15 cm (36). The reasons for the dramatic historical failure of height gain in Indians can only be environmental stresses: famine, undernutrition, and infectious disease. Children in our study, in contrast, are on average 5 cm taller and 5 kg heavier than their parents, suggesting a recent rapid transition. The drivers of such changes in our study area include a reliable water supply from a dam (supporting irrigation and cash-crop farming), a new industrial estate (generating paid employment), and improved literacy rates. The sex difference in glucose intolerance may also partly be due to societal preferences for male children.

Pathophysiology

A typical patient with type 2 diabetes demonstrates both reduced insulin secretion and sensitivity, with varying contributions in different patients. Life course studies are few and predominantly from the more obese Western world, showing that higher childhood FPG, BMI, insulin concentrations, and HOMA-IR (insulin resistance) are predictors of future glucose intolerance; it is noteworthy that HOMA-β and compensatory β-cell response are not mentioned (26,27). The role of reduced β-cell secretion relative to insulin sensitivity was stressed in the Early Bird Study and the ADA statement on youth-onset type 2 diabetes (37,38). Our data highlight that insulin sensitivity progressively decreases from childhood into adulthood, accompanied by an increase in β-cell secretion in the NGT group evident in both fasting and stimulated states. This indicates good β-cell reserve. In contrast, in the glucose-intolerant participants, there was little increase in stimulated insulin secretion between 6 and 18 years of age. As has been pointed out by previous workers, the best approach to understand the dynamics between insulin secretion and sensitivity is to study them in relation to each other. This approach showed a progressive decrease in compensatory β-cell response with increasing age in both NGT and glucose-intolerant groups and showed that β-cell response was consistently lower in the glucose-intolerant group than the NGT group. Taken together, our data point toward underperforming β-cells from early life in the glucose-intolerant group. We believe this is a novel description of the evolution of glucose-insulin physiology from childhood through puberty into young adulthood.

Most previous studies, including some of ours, have considered insulin insensitivity the primary driver of diabetes, probably because of inadequate investigation of insulin secretion. The importance of diminished insulin secretion in the pathophysiology of type 2 diabetes in Indians has recently been highlighted (39). Severely insulin-deficient diabetes was the most common subtype in our young (<45 years) patients with type 2 diabetes (Diabetologia, in press), as well as in the migrant Indians in the U.S. (40). In contrast, in a Swedish cohort, the main subtype was mildly obese diabetes.

Implications

The strong prediction of adult glucose intolerance from childhood glucose

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measurements mandates the monitoring of children's plasma glucose concentrations. Our research will help identify at-risk individuals from childhood and potentially reduce risk by using therapies that improve insulin secretion and sensitivity. Measurement of birth length and head circumference in addition to weight would add to risk prediction. Persistently higher glucose levels in early childhood, even within the normal range, have the potential to epigenetically affect ova and sperm, contributing to a higher risk of diabetes in the next generation (41). Thus, early identification and management of at-risk individuals could benefit future generations. Our findings may be relevant to other developing populations with a history of nutritional deprivation.

Strengths of our study are exceptional follow-up over 20 years (92% of survivors), longitudinal anthropometry from birth, and serial glucose-insulin data from childhood. All measurements used uniform methods throughout, and serial insulin assays were calibrated against the same international reference. Participants included were comparable to those excluded at each stage (Supplementary Fig. 1). The PMNS findings were validated in a rural as well as an urban cohort, increasing their generalizability, although we used a more arbitrary cut point (highest tertile) for glucose intolerance in one validation cohort because of the small numbers of participants with prediabetes. Limitations were that for logistic reasons, we used epidemiological rather than gold-standard measures of insulin action and secretion. However, these are well accepted and used widely in cohort studies. At 12 years, we had only fasting glucose-insulin measurements.

In well-nourished Europeans, experimental starvation causes acute glucose intolerance (42). We took care to avoid any starvation among our participants in the week before the OGTT. In addition, elevated FPG and HbA_{1c} many years earlier suggest ongoing long-term hyperglycemia. The predominance of thin patients with severely insulin-deficient diabetes in our urban diabetes clinics further supports chronic undernutrition as an underlying etiological factor. Therefore, type 2 diabetes in undernourished and transitioning populations may be the new avatar of malnutrition-related diabetes, a previously recognized subclass of diabetes that fell into obscurity because of a lack of prospective data and an increasing focus on obesity-related diabetes (43).

In conclusion, glucose intolerance in thin young rural Indian adults is heralded by slower skeletal and brain growth in utero and impaired compensatory insulin secretion and higher glycemia from childhood. In men, pubertal weight gain aggravated insulin insensitivity and glucose intolerance. Glucose intolerance was seen in women despite continued undernutrition. We describe novel interactions between β-cell secretory capacity and age-related insulin insensitivity in an undernourished population leading to glucose intolerance at a young age. Our findings reveal the pitfalls of cross-sectional studies in adults to postulate antecedent events and stress the importance of prospective life course measurements.

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Author Contributions. C.S.Y. and C.H.D.F. conceptualized the study. S.B., A.B., R.H.W., and C.O. were involved in statistical analysis. P.C.Y., A.P., S.B., K.C., and K.K. contributed to conduct of the study. C.S.Y., S.B.P., C.O., and C.H.D.F. prepared the manuscript. D.S.B. was involved in laboratory measurements. C.S.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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