Cardiometabolic Health in Adults Born Premature With Extremely Low Birth Weight

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abstract

BACKGROUND: Young adults born with extreme prematurity have increased blood pressure and insulin resistance. This study documents their metabolic health as they enter their fourth decade of life. The study objective was to compare body composition, glycemia, lipid levels, and blood pressure in adults born with extremely low birth weight (ELBW) versus age- and sex- matched normal birth weight (NBW) control subjects and to examine related previous and current exposures.

METHODS: The study examines one of the oldest regionally representative cohorts of ELBW subjects (birth weight <1 kg) and NBW individuals born between 1977 and 1982. The primary outcome was dysglycemia (type 2 diabetes or prediabetes) based on results of a 75-g oral glucose tolerance test. Secondary outcomes include body composition, insulin resistance, fasting lipid profile, and blood pressure. Potential predictive factors included birth weight, maternal antenatal corticosteroid exposure, retinopathy of prematurity, growth parameters, and smoking history.

RESULTS: Adults (mean age, 31.8 years) born ELBW (n = 100) had a higher percent body fat (P = .004) and lower lean mass for height (P = .018) but similar waist circumference (P = .54) and BMI (P = .61) compared with NBW control subjects. ELBW adults had a 4.0-fold (95% confidence interval, 1.53–10.66) increased risk of developing dysglycemia. Adults born ELBW also had higher systolic (P = .004) and diastolic (P = .02) blood pressures compared with NBW control subjects, but there were no differences in lipid profile.

CONCLUSIONS: By their fourth decade, these adults born extremely premature had increased body fat, lower lean mass, and a 4-fold increased risk of developing dysglycemia.

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Dr Morrison oversaw the study design, contributed to data acquisition and analysis, and wrote and edited the manuscript; Ms Ramsingh contributed to study design and study conduct, wrote the first draft of parts of the manuscript, and critically reviewed the manuscript; Ms Gunn contributed to data acquisition and data analysis, wrote parts of the manuscript, and critically reviewed the manuscript; Dr Streiner contributed to study design and analysis and critically reviewed the manuscript; Dr Van Lieshout contributed to the conduct of the study and critically reviewed the manuscript; Dr Gerstein contributed to study design and critically reviewed the manuscript; Drs Schmidt and Boyle contributed to study design, conduct of the study, and critical review of the manuscript; Dr Saigal initiated and oversaw the establishment and follow-up of the cohort, contributed to study design and conduct of the study, and critically reviewed the manuscript; and all authors approved the final version of the manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Survivors of extreme prematurity have increased blood pressure and higher insulin resistance by the third decade of life.

WHAT THIS STUDY ADDS: In the fourth decade of life, extremely low birth weight survivors were at increased risk of developing dysglycemia and had higher body fat and lower lean mass for height than normal birth weight control subjects.

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Epidemiologic evidence linking low birth weight to subsequent cardiometabolic disorders has led to the developmental origins of health and disease hypothesis.[1] This hypothesis suggests that developmental stress experienced by an individual either prenatally or in early life encourages compensatory mechanisms that aid survival in the short term but can have deleterious impacts later in the life course. Furthermore, low birth weight as a result of preterm birth (<37 weeks' gestation) is also associated with increased risk of cardiometabolic disturbances in childhood and in adulthood,[2] including insulin resistance and increased blood pressure (BP). In studies utilizing administrative data, preterm birth is associated with a 1.5- to 2-fold increased prevalence of diabetes by late middle age.[3–5] The first generation of extremely low birth weight (ELBW) infants who received neonatal intensive care is now entering their fourth decade of life, and data on their long-term health issues remain scarce. Higher BP and insulin resistance have been reported in children,[6] adolescents,[7] and young adults[8–10] born premature.[11] Little is known of later health outcomes.

The McMaster ELBW cohort is a population-representative cohort of individuals born ELBW between1978 and 1982 and followed up since birth and a matched, normal birth weight (NBW) control group. Periodic assessments of this cohort have contributed a great deal to our understanding of the implications of extreme preterm birth.[12] The objectives of the present study were to evaluate cardiometabolic health in the ELBW survivors compared with the NBW group early in the fourth decade of life and to identify related factors.

METHODS

Participants

This longitudinal cohort included individuals born with ELBW and with NBW. The ELBW group comprised individuals who weighed 501 to 1000 g at birth and were recruited to a population-based study in a geographically defined region of central-west Ontario, Canada, between 1977 and 1982. They have been followed up longitudinally since birth, and health outcomes in survivors have been reported at 3, 5, and 8 years of age; at adolescence (12–16 years of age); and at young adulthood (22–26 years of age). The age-, sex-, and socioeconomic-matched NBW group was identified at 8 years of age. Similar to the ELBW survivors, these children have been studied at 8 years, adolescence, and young adulthood.

Ethics

The study was approved by the joint Research Ethics Board of McMaster University and Hamilton Health Sciences. Participants provided informed, signed consent.

Visits and Measurement

Data collection occurred at a single study visit scheduled in the morning after an 8- to 12-hour fast.

Glucose Metabolism

Participants completed a 75-g oral glucose tolerance test with glucose and insulin measured at baseline and after 120 minutes and analyzed at Hamilton Health Sciences CORE Laboratories (Hamilton, Ontario, Canada). The insulin assay was the Abbott Diagnostics (Mississauga, Ontario, Canada) assay run on an i1000 analyzer (coefficient of variation, 1.9%–2.4%). Glucose metabolism was evaluated according to insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) and glycemic status. HOMA-IR is widely used in clinical and epidemiologic studies to estimate insulin resistance. It is calculated by using fasting glucose and insulin levels with the following formula: HOMA-IR = $G_0 \times I_0/22.5$, where G_0 is the fasting plasma glucose level, I_0 is the fasting plasma insulin value, and 22.5 is a constant. Participants were classified as normoglycemic or dysglycemic based on their fasting and 2-hour blood glucose levels and Canadian Diabetes Association criteria.[13] Dysglycemia included impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG + IGT, or type 2 diabetes (T2DM) (IFG fasting glucose level, 6.1–6.9 mmol/L; IGT, 2-hour blood glucose between 7.8 and11.0 mmol/L; T2DM, fasting glucose ≥7.0 mmol/L and/or 2-hour blood glucose ≥11.1 mmol/L). Those who self-reported the diagnosis of preexisting diabetes and were taking insulin and/or oral hypoglycemic agents did not complete an oral glucose tolerance test and were classified as having T2DM.

Anthropometrics and Body Composition

Standing height was measured by using a Harpenden stadiometer (London, England). Weight was obtained by using an electronic scale. Waist circumference (WC) was measured to the nearest 0.1 cm by using a nonstretchable standard tape measure attached to a spring balance exerting a force of 750 g. The measurement was taken over an unclothed abdomen at the smallest diameter between the costal margin and the iliac crest. Three measurements of height, weight, and WC were taken and averaged. BMI was calculated by using average measurements of height and weight.

Body composition was assessed by using dual-energy radiograph absorptiometry on a GE Lunar Prodigy Advance (Model #8743) scanner (GE Healthcare, Mississauga, Ontario, Canada). The dual-energy radiograph absorptiometry method is quick and of low health risk (radiation exposure <1 μSv or 1/100th of the radiation exposure of a chest radiograph). It provides a whole body scan and measurements of total body fat and fat free mass

(ie, lean mass). Total lean mass for each participant was adjusted for current adult height by calculating the lean mass index (LMI = total lean mass/height). We report body fat as percent fat and as the fat mass index (FMI = total fat mass/height).

Current Health

After anthropometric measurements were taken and before blood sampling, BP was measured by using a BpTRU device (BpTRU Medical Devices, Coquitlam, BC, Canada) with the participant seated and with an appropriate-sized cuff. Categorization of prehypertension (systolic BP of 120–139 mm Hg or diastolic BP of 80–89 mm Hg) and hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) was according to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[14]

Participants completed questionnaires related to lifestyle behaviors (including alcohol intake and cigarette smoking), demographic characteristics (education, marital status, and income), and personal and family health history, including medication use and family history of diabetes and cardiovascular disease. The research staff member conducting the visit was not informed if the participant was ELBW or NBW.

Characteristics at Birth and in Childhood

Birth weight was available for all participants, and additional clinical characteristics were available for the ELBW group. Small for gestational age (SGA) is defined as birth weight <10th percentile based on Canadian standards.[15] NBW subjects were known to be born at term. At 8 years of age, height, weight, BMI, and family socioeconomic status were available.

Statistical Analysis

Statistical analysis was conducted by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). An α of $P \leq .05$ was considered statistically significant. To address our primary questions related to differences in prevalence of dysglycemia and body composition between the ELBW and NBW groups, independent *t* tests for continuous variables and χ^2 tests for categorical variables were used. To examine the influence of being born appropriate for gestational age compared with SGA, a 2-way analysis of variance was used.

Univariate regression analysis was used to analyze the contribution of predictors of insulin resistance and fasting and 2-hour blood glucose. Predictors included age, sex, socioeconomic status (at age 8 years and in adulthood), BMI, WC, total percent body fat, FMI, LMI, birth weight, birth weight group, weight change from birth to 8 years of age, BMI change from 8 years of age to current BMI, presence of retinopathy of prematurity, maternal corticosteroid exposure, and smoking history. Multivariate regression was used to determine the influence of variables significant in the univariate analysis on insulin resistance and glycemia outcomes. Given the non-normality in some variables, log transformations were performed to create normally distributed data for BMI, LMI, HOMA-IR, 2-hour blood glucose, and BMI change from 8 years of age to current findings. To eliminate problems of multicollinearity in the multivariate regression analyses, we chose 1 measure of adiposity (WC) and used birth weight rather than birth weight group. We compared models with each of 3 measures of adiposity (WC, percent body fat, and FMI), with similar results. Logistic regression analysis, controlling for age, sex, and percent body fat, was conducted to determine the risk of prediabetes, T2DM, and dysglycemia in the ELBW group compared with the NBW control group.

Imputation of Missing Data

For individuals who did not attend this visit but were seen at the 24-year visit, the data were also imputed by using the fully conditional specification (Markov chain Monte Carlo) procedure in SPSS version 22. Group membership, sex, height, weight, self-reported diabetes, and estimated household income were used at the 24-year visit (all data were available) to develop the imputed data sets. The following variables were imputed: fasting and 2-hour glucose level from the oral glucose tolerance test and classification of prediabetes (IGT ± IFG), T2DM and dysglycemia status, BP, and socioeconomic status at the time of study visit. The minimum and maximum constraints placed on the imputed values of the following variables were as follows: systolic BP, minimum of 80 mm Hg; diastolic BP, minimum of 45 mm Hg and maximum of 100 mm Hg; socioeconomic status (Hollingshead scale), minimum of 8 and maximum of 66; and fasting and 2-hour glucose levels, minimum of 2.4 mmol/L. Five imputed data sets were created, and we analyzed the pooled estimates and compared these versus the analysis of the original data set.

RESULTS

Study Participants

One hundred of the surviving 148 (67.6%) ELBW subjects participated at this assessment (Table 1). Of the ELBW nonparticipants, we were unable to contact 38 subjects, 5 declined the study, 1 was deceased, and 5 were untestable. More than one-quarter of the included ELBW subjects had a birth weight <750 g, and 25% were born before 26 weeks' gestation. Of the 133 NBW participants recruited at age 8 years and seen at young adulthood, 89 (66.9%) were seen at this visit. We were unable to contact 35

TABLE 1 Characteristics and Cardiometabolic Health Indicators (at Current Visit) of ELBW and NBW Participants

Characteristic	Valid *n*	ELBW (*n* = 100)	Valid n	NBW (*n* = 89)	*P*
Male	100	40 (40)	89	37 (42)	.83
Age, y	100	31.63 ± 1.66	89	31.96 ± 1.42	.15
Married or common-law	96	43 (45)	87	51 (59)	.06
Total household income, median, $	100	40 000–49 999	89	60 000–69 999	
Birth weight, g	100	829.00 ± 130.38	89	3391.30 ± 442.28	<.001*
Gestational age, wk	100	27.10 ± 2.45	—	—	—
Maternal smoking	100	18 (18)	—	—	—
Maternal steroid exposure	93	45 (48)	—	—	—
Retinopathy of prematurity	100	34 (34)	—	—	—
Change in birth weight to 8 y, kg	94	21.37 ± 4.64	89	24.49 ± 5.24	<.001*
Medication					
BP-lowering medication	100	4 (4)	89	4 (4)	.87
Insulin or oral hypoglycemic agents	100	2 (2)	89	1 (1)	.62
Never smoked	100	57 (57)	89	45 (51)	.38
Family history of diabetes	100	54 (54)	89	40 (45)	.27
Family history of early heart disease	100	39 (39)	89	24 (27)	.21
Height, m	95	1.64 ± 0.10	88	1.71 ± 0.11	<.001*
Weight, kg	95	71.90 ± 16.54	88	77.50 ± 18.28	.03*
BMI	95	26.91 ± 6.41	88	26.49 ± 5.08	.63
Change in BMI from 8 y to current	91	11.97 ± 5.82	88	9.77 ± 4.68	.006*
WC, cm	95	85.69 ± 14.64	88	84.63 ± 13.55	.61
Total body fat, %	92	35.45 ± 10.81	80	30.75 ± 10.49	.004*
LMI, kg/m^2	92	15.82 ± 2.40	80	16.71 ± 2.43	.02*
FMI, kg/m^2	92	9.38 ± 4.80	80	7.73 ± 3.51	.012*
Systolic BP, mm Hg	94	113.77 ± 11.93	88	108.86 ± 10.59	.004*
Diastolic BP, mm Hg	94	73.74 ± 10.00	88	70.55 ± 8.27	.02*
Total cholesterol, mmol/L	89	4.77 ± 0.96	80	4.67 ± 0.87	.47
Triglycerides, mmol/L	89	1.38 ± 0.73	80	1.22 ± 1.01	.22
HDL cholesterol, mmol/L	89	1.50 ± 0.46	80	1.50 ± 0.40	.98
LDL cholesterol, mmol/L	89	2.69 ± 0.86	80	2.65 ± 0.76	.76
Total cholesterol/HDL cholesterol	89	3.47 ± 1.26	80	3.31 ± 1.07	.38
Fasting plasma glucose, mmol/L	81	5.17 ± 0.68	73	4.89 ± 0.59	.007*
2-h plasma glucose, mmol/L	78	6.49 ± 2.50	72	5.40 ± 1.77	.003*
Fasting insulin, pmol/L	75	94.79 ± 66.85	72	71.07 ± 64.36	.03*
HOMA-IR	75	1.76 ± 1.22	72	1.30 ± 1.14	.02*

Unless otherwise indicated, data are presented as *n* (%) or mean ± SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein. —, no data for full term cohort.
* $P < .05$.

subjects, 8 declined the study, and 1 is deceased. Male sex predicted nonparticipation in both the ELBW and NBW participants and, among the ELBW, SGA birth predicted increased likelihood of participation. There were no differences in age, sex, or ethnicity between the ELBW and NBW participants at this visit. The current median household income was lower in those born ELBW. Fifty-nine percent of NBW subjects were married or living common-law compared with 45% of ELBW subjects ($P = .06$).

Clinical Outcomes in ELBW Subjects Compared With NBW Subjects

The ELBW survivors had lower height ($P < .001$) as noted at previous visits. Although ELBW subjects had BMI and WC similar to the NBW subjects, their body composition differed. ELBW subjects had lower LMI ($P = .018$) and higher body fat ($P = .004$). ELBW subjects also had higher systolic and diastolic BP levels compared with the NBW control subjects ($P = .004$ and 0.02, respectively) (Table 2). The prevalence of high BP (prehypertension or hypertension) was 35% in the ELBW group and 23% in the NBW group ($P = .07$). ELBW and NBW groups had similar fasting lipid profiles.

As shown in Fig 1, the prevalence of dysglycemia (prediabetes and type 2 diabetes) was higher in the ELBW group than in the NBW group (26% vs 8%; $P = .003$). The ELBW group also had a higher prevalence of prediabetes (14.6% vs 4%; $P = .04$). When we analyzed the data using the 5 imputed data sets, the prevalence of dysglycemia was higher in ELBW subjects (30.2% vs 15.6%; $P = .004$) in the pooled estimates and in 4 of the 5 imputed data sets.

The ELBW adults had a 4.03-fold (95% confidence interval, 1.53–10.66) increased risk of having dysglycemia compared with the NBW group (Table 3). Although adjusting for age, sex, and percent body fat reduced this differential risk (odds ratio, 3.04 [95% confidence interval, 1.01–9.21]) in ELBW adults compared with NBW adults ($P < .049$), it remained significant.

TABLE 2 Prevalence of Prediabetes, T2DM, and Dysglycemia in ELBW Subjects Compared With NBW Subjects by Using Pooled Estimates of 5 Imputed Data Sets

Outcome	ELBW (n = 147)	NBW (n = 131)	z	P
Dysglycemia	30.2 (44.)	15.6 (20.4)	2.90	.004
Prediabetes (IGT ± IFG)	30.2 (44.4)	24.0 (31.4)	1.18	.238
T2DM	26.3 (38.6)	20.3 (26.6)	1.16	.246

Data are presented as % (n).

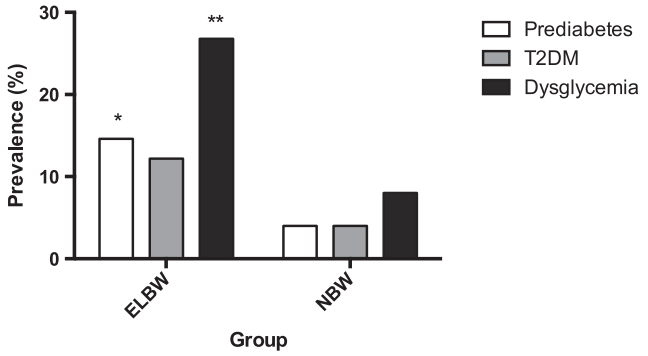

FIGURE 1
Prevalence of dysglycemia (prediabetes and T2DM) in the ELBW group compared with the NBW group. *P < .05, **P < .01.

To understand the life course and current correlates of glucose metabolism, univariate and multivariate models of fasting glucose, 2-hour glucose, and insulin resistance are presented in Table 4. Birth weight was inversely related to insulin resistance, fasting blood glucose levels, and 2-hour glucose levels, and it continued to be independently related to both insulin resistance and fasting blood glucose levels in the multivariate models. Current anthropometric measures (WC, BMI, body fat, LMI, and FMI) were the strongest correlates of all glycemic measures in both univariate analyses and multivariate models. Although the increase in weight from 8 years of age to adulthood was related to all glucose variables in univariate analysis, it was not significant in the fully corrected model. Growth from birth to 8 years of age was unrelated to the glycemic variables.

Influence of Perinatal and Early Childhood Characteristics on Glycemic Variables in Those Born ELBW

The ELBW subjects with dysglycemia had higher weight, BMI, and WC compared with the normoglycemic ELBW group. They also had higher systolic BP levels (118 ± 11.9 mm Hg vs 112 ± 10.5 mm Hg; P = .02) and higher fasting triglyceride levels (1.8 ± 0.58 mmol/L vs 1.2 ± 0.74 mmol/L; P = .001) than the ELBW subjects without dysglycemia. They did not, however, differ in sex, gestational age at birth, birth weight, maternal corticosteroid exposure, or maternal smoking history during pregnancy (Supplemental Table 5). No differences in early growth trajectories were found. The dysglycemic group did, however, have a greater change in BMI from 8 years to adulthood than the normoglycemic group.

In univariate analysis, the presence of retinopathy of prematurity was directly related to 2-hour glucose level. In the fully adjusted model, WC in adulthood was the strongest predictor (standardized β, 0.687; P = .02) but the presence of retinopathy of prematurity remained as an independent predictor (standardized β, 0.23; P = .05) (R^2 = 0.27; P < .001). There were no differences in current clinical health outcomes in the ELBW born SGA compared with those born appropriate for gestational age (Supplemental Table 6).

DISCUSSION

Now in their early thirties, the ELBW survivors in this regionally representative cohort are 4 times more likely to develop dysglycemia than matched, NBW control subjects. They also have higher body fat and lower lean mass than the NBW control group but similar BMI. The ELBW survivors with dysglycemia had higher BMI and WC in adulthood than the normoglycemic ELBW subjects. However, the ELBW subjects with and without dysglycemia had similar gestational ages at birth, prevalence of SGA, weight change from birth to 3 years and birth to 8 years, maternal glucocorticoid exposure, and maternal smoking history.

Hovi et al[8] reported that individuals in their mid-twenties who were born with very low birth weight had increased insulin resistance but no difference in prevalence of dysglycemia. Our cohort was ∼10 years older than the Finnish cohort and had more extreme prematurity because the birth weight cutoff in our study was 1000 g compared with 1500 g. In population-based studies that rely on administrative data for diagnosis of diabetes, there is a 1.5- to 2-fold increased prevalence of T2DM in adults born premature (<35 weeks' gestation)[4,5] by 40 to 60 years of age. A population-based study in adults in a comparable age range to the current study identified a slightly increased risk of diabetes

TABLE 3 Risk of Prediabetes, T2DM, and Dysglycemia in ELBW Subjects Compared With NBW Subjects

Outcome	Unadjusted Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio[a] (95% CI)	*P*
Dysglycemia	4.03 (1.53–10.66)	.005	3.04 (1.01-9.21)	.049
Prediabetes (IGT ± IFG)	3.77 (1.01–14.11)	.049	2.17 (0.53-8.83)	.281
T2DM	3.38 (0.89–12.81)	.073	3.42 (0.676-17.33)	.137

CI, confidence interval.
[a] Adjusted for age, sex, and percent body fat.

TABLE 4 Univariate and Multivariate Regression Analyses Examining Predictors of Insulin Resistance, Fasting Blood Glucose, and 2-Hour Blood Glucose

Predictor	Univariate Analysis		Multivariate Analysis	
	Standardized Parameter Estimate	*P*	Standardized Parameter Estimate	*P*
Insulin resistance				
Sex	0.019	.82	0.028	.80
BMI	0.536	<.001*	—	—
WC	0.530	<.001*	—	—
Percent body fat	0.394	<.001*	—	—
FMI	0.491	<.001*	0.40	.01*
LMI	0.260	.002	0.235	.04*
Smoking history	−0.053	.52	—	—
Birth weight	−0.268	.001*	−0.224	.007*
Group	0.251	.002*	—	—
Change in BMI from 8 y to current	0.538	<.001*	0.028	.86
MODEL			R^2 adjusted, 0.315	<.001*
Fasting glucose				
Sex	0.295	<.001*	0.449	<.001*
BMI	0.231	.004*	—	—
WC	0.342	<.001*	—	—
Percent body fat	0.063	.45	—	—
FMI	0.163	.048*	0.463	.005*
LMI	0.275	.001*	0.091	.43
Smoking history	−0.163	.04*	−0.140	.06
Birth weight	−0.206	.01*	−0.170	.047*
Group	0.215	.007*	—	—
Change in BMI from 8 y to current	0.240	.003*	−0.209	.21
Retinopathy of prematurity	0.167	.17	—	—
MODEL			R^2 adjusted, 0.218	<.001*
2-h glucose				
Sex	−0.011	.90	0.133	.26
BMI	0.328	<.001*	—	—
WC	0.385	<.001*	—	—
Percent body fat	0.334	<.001*	—	—
FMI	0.396	<.001*	0.389	.021*
LMI	0.102	0	0.041	.74
Smoking history	−0.180	.03*	−0.146	.06
Birth weight	−0.275	.001*	−0.164	.07
Group	0.244	.003*	—	—
Change in BMI from 8 y to current	0.375	<.001*	0.028	.87
Retinopathy of prematurity	0.257	.037	—	—
MODEL			R^2 adjusted, 0.210	<.001*

* $P < .05$.

(odds ratio, 1.2) in those born <37 weeks' gestation but very few were born before 28 weeks' gestation.[16] Population-based registry studies are unable to identify prediabetes and may underestimate the prevalence of T2DM because they rely on medication prescription data for diagnosis. Given the importance of prediabetes in increasing coronary artery disease risk[17] and that prediabetes predicts progression to T2DM,[18] our study provides a more complete understanding of glycemic status in adults born with extreme prematurity.

The ELBW survivors had higher body fat and lower lean mass for height despite similar BMI. Previous studies examining body composition in those born prematurely have been inconsistent in their conclusions. Total body fat in children born prematurely has been similar to[19]

or lower than[20] that in term-born control subjects. Young adults born at very low birth weight had reduced lean mass for height but body fat similar to control subjects.[21] In contrast, Breukhoven et al[22] found increased body fat and similar lean mass in a large group of young adults (mean age, 20.1 years) who were born preterm. Because we are reporting on the oldest longitudinal cohort of ELBW survivors, it may be that body composition and metabolic disturbances are only revealed with advancing age. Our findings are consistent with studies in animal models in which prenatal and perinatal stressors resulting in reduced fetal growth enhanced adipogenesis and fat accrual in the offspring.[23] The critical period for adipose tissue development in humans is the third trimester. Because infants born extremely premature are ex utero during this time, it is plausible that they experience disturbances in early adipocyte development that may influence adipose tissue function throughout the life course.

Because the present study involved a longitudinal, prospective cohort, it can also contribute to understanding the association between early life exposures and subsequent health outcomes. Although previous studies have suggested that maternal cigarette smoking[24,25] and more rapid "catch-up" growth in childhood[26] may heighten cardiometabolic risk in those with low birth weight, we found no relationship between these factors and glycemia. Although early exposure to glucocorticoids has been postulated as a key mechanism underlying fetal programming,[27] we identified no relationship between prenatal exposure to synthetic glucocorticoids and glycemia in our study. Interestingly, we did identify a relationship between the presence of retinopathy of prematurity and the 2-hour glucose level, independent of anthropometric findings and birth weight. Perhaps the developing pancreatic β cell, which has low antioxidant defense mechanisms,[28] is also sensitive to disturbances in oxygen exposure that occur in perinatal life in association with extreme prematurity, leading to abnormal vascularization as seen in the retina.[29] Although intriguing, this finding is preliminary, and further study is needed to evaluate cardiometabolic health in those with retinopathy of prematurity in other cohorts.

Although our cohort is one of the largest and oldest prospective studies of those born with ELBW, as with other cohort studies, our results may have been influenced by differential loss to follow-up. We did have similar findings when multiple imputations based on characteristics of the missing participants at their 24-year visit were used. Perinatal care, and parenteral and enteral nutrition practices in particular, has changed since these study participants were born. Increased focus on energy balance and on protein accretion may influence body composition and metabolic health over the life course. It is challenging to predict whether the differences we found in body composition and metabolic health will be seen in more recent cohorts. Our findings underscore the importance of evaluating these newer cohorts.

CONCLUSIONS

Adults born with extreme prematurity have a 4-fold increased risk of developing dysglycemia by their fourth decade of life. They also have increased adiposity and reduced lean mass for height, differences that likely contribute to their metabolic status. In those born ELBW, body fatness is the strongest predictor of dysglycemia. Given the potentially modifiable nature of body fatness, it will be important to develop and evaluate interventions to influence lifestyle behaviors in the preterm population. The age at which such intervention should begin is uncertain, but strong consideration should be given to the early origins literature that suggests beginning early in life may be most advantageous. Although retinopathy of prematurity may identify those at increased risk, these findings should be confirmed in future studies with more direct measures of β-cell function.

This study therefore contributes to our understanding of the implications of extreme perinatal stress to health in adulthood. Given changes in perinatal care since the adults studied in this cohort were born, it is important that future studies examine similar trajectories in metabolic health and body composition in children born more recently. Consideration of mechanism and the development of interventions to address these long-term concerns should be undertaken.

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ABBREVIATIONS

BP: blood pressure
ELBW: extremely low birth weight
FMI: fat mass index
HOMA-IR: homeostasis model assessment of insulin resistance
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
LMI: lean mass index
NBW: normal birth weight
SGA: small for gestational age
T2DM: type 2 diabetes
WC: waist circumference

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