A B S T R A C T

Background: Intrauterine factors have been implicated in the pathogenesis of Type 2 diabetes mellitus (T2DM).

Methods: In a 1:1 matched pairs case-control study, high and low birthweight (HBW, LBW) rates in Saskatchewan Registered Indian (RI) diabetic cases were compared with corresponding rates in RI without diabetes, and non-RI people with and without diabetes.

Results: Birthweights were available for 73% of the 1,366 cases and 3 x 1,366 controls. A greater proportion of RI diabetics were born with HBW (>4000 grams) compared to RI non-diabetics (16.2% vs 10.7%; $p < 0.01$). There was a significant association between HBW (but not LBW [< 2500 grams]) and diabetes for RI people (OR 1.63 [95% CI 1.20, 2.24]), which was stronger for RI females and strengthened progressively from mid to late 20th century.

Interpretation: Certain causes of HBW may predispose to subsequent development of T2DM in Canadian Aboriginal people ("hefty fetal phenotype" ["hefty fetal type"] hypothesis). Programs that optimize healthy pregnancies could reduce T2DM incidence in future generations.

A B R É G É

Contexte : Des facteurs intra-utérins ont été associés à la pathogénie du diabète sucré de type II (DST2).

Méthode : Dans une étude cas-témoin en paires appariées (1:1), nous avons comparé les taux d'insuffisance de poids à la naissance élevés et faibles (IPNÉ, IPNF) dans les cas de diabète chez les Indiens inscrits (Ii) de la Saskatchewan aux taux correspondants chez les Ii non diabétiques et chez les personnes non diabétiques n'étant pas des Ii.

Résultats : Nous avons obtenu le poids à la naissance de 73 % des 1 366 cas et de 3 x 1 366 témoins. La proportion d'Ii diabétiques nés avec une IPNÉ (>4 000 g) était supérieure à celle des Ii non diabétiques (16,2 % c. 10,7 %; $p < 0,01$). L'association entre l'IPNÉ (mais non l'IPNF [$< 2 500$ g]) et le diabète était significative chez les Ii (RC 1,63 [95 % IC 1,20, 2,24]) et plus prononcée chez les femmes; la tendance s'est renforcée progressivement entre le milieu et la fin du 20e siècle.

Interprétation : Certaines causes d'IPNÉ prédisposent peut-être au développement ultérieur du DST2 chez les Autochtones canadiens (hypothèse du « (phéno)type fœtal prononcé »). Les programmes d'optimisation de la santé durant la grossesse pourraient réduire l'incidence de DST2 pour les générations futures.

From "Thrifty Genotype" to "Hefty Fetal Phenotype": The Relationship Between High Birthweight and Diabetes in Saskatchewan Registered Indians

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North American Aboriginal people are experiencing an epidemic of type 2 diabetes mellitus (T2DM) and its complications.¹⁻⁵ Both genetic and environmental factors have been implicated in this epidemic, and the possible diabetogenic role of the intrauterine milieu has attracted increasing attention.

The offspring of Pima women with T2DM and gestational diabetes (GDM) have increased rates of high birthweight (HBW), and a propensity to develop early age onset T2DM.⁶⁻⁸ North American Aboriginal women also have high rates of GDM,⁹⁻¹² an observation that we even found in communities where the prevalence of T2DM was still low.¹³ These reports raise the intriguing possibility that GDM may be one of the earliest manifestations of carbohydrate intolerance in some Aboriginal populations, and an important contributing factor in the initiation and progression of the T2DM epidemic.

A relationship between low birthweight (LBW) and T2DM has also been identified,¹⁴⁻²² possibly due to impaired islet cell development caused by maternal/fetal mal-

nutrition.²³ Since Saskatchewan Aboriginal infants have experienced increased rates of LBW in the past,^{24,25} it is possible that LBW and its causes could also contribute to the Aboriginal T2DM epidemic.

The purpose of this study was to examine the relationship between both HBW (>4000 g) and LBW (<2500 g) and the future development of T2DM among adult Registered Indians (RI) in Saskatchewan. An association between HBW and T2DM would suggest prenatal exposure to T2DM, GDM, or gestational impaired glucose tolerance (GIGT).²⁶⁻²⁹ An association between LBW and T2DM would suggest that poor maternal/fetal nutrition is relevant. If such relationships were observed, the findings could lead to prevention initiatives against intrauterine risk factors that contribute to the epidemic of T2DM in Aboriginal people.

METHODS

Description of research design

This was a 1:1 matched pairs case-control study in which the 1,366 cases were Saskatchewan RI people with diabetes, and the three age- and sex-matched control groups (each with 1,366 subjects) were Saskatchewan RI people without diabetes, and Saskatchewan General Population (GP) people with and without diabetes. Saskatchewan Health identified study subjects in 1996 by linking Saskatchewan Health's physicians services database (DRSV) and the Health Insurance Registration file (HIRF) database. Only subjects born between January 1, 1950 and December 31, 1984 were included because birthweights were not recorded prior to 1950.

The diabetic population was determined from the DRSV database using the first

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TABLE I
Descriptive Analyses of Birthweight (Bwt) and Matched Pair Analyses for HBW

Group	n	% LBW <2500g	% 2500- 4000 g	% HBW >4000g	Bwt (g) Mean (SD)	Pair-wise Comparisons HBW vs. All Other Bwts		
						Groups	n pairs	OR (95% CI)
RI-Dm	846	4.8	79	16.2	3462 (623)	—	—	—
RI-nonDm	882	4.8	84.6	10.7	3371 (544)	RI-Dm + RI-nonDm	679	1.63 (1.20, 2.24)*
GP-Dm	1164	8.6	81.4	10	3304 (586)	RI-Dm + GP-Dm	786	1.84 (1.36, 2.50)*
GP-nonDm	1100	8.2	84.4	7.5	3268 (540)	RI-Dm + GP-nonDm	734	2.36 (1.68, 3.32)*
OVERALL	3992	6.8	82.4	10.7	3342 (577)	GP-Dm + GP-nonDm	965	1.27 (0.92, 1.75)

* statistically significant at $p \leq 0.05$

diabetic service code (ICD9-250 for diabetes and/or ICD9-362 for diabetic retinopathy) between January 1, 1991 and December 31, 1994. Registered Indians were those with a Department of Indian and Northern Affairs number.

A search for birth registration information for all 5,464 subjects (1,366 x 4) was performed by Saskatchewan Health staff. Birthweight, gestational age, number of siblings born alive, type of birth (single or twin), previous sibling stillbirths, and maternal age were recorded. Birth registration information was available for 4,833 (88%) and birthweight was recorded for 3,992 (73%) of those initially identified. Consequently, paired analyses were performed on 50% and 71% of the initial RI and GP target subjects respectively.

Description of analytic strategy

Potential selection bias was evaluated by comparing subjects with and without birthweight. Compared to withdrawals, subjects with birthweights were older in gestational age (39.3 vs 38.3 weeks; $p < 0.01$). They had younger mothers (26 vs 26.9 years; $p < 0.01$), with lower parity (42% vs 56% with parity ≥ 4 ; $p < 0.001$) and more previous stillbirths (6.8% vs 4.1%; $p < 0.01$).

To examine the relationship between either HBW or LBW and the future development of T2DM, total and sex-specific analyses were directed primarily at the two within-population differences (RI diabetic and non-diabetic, GP diabetic and non-diabetic subjects). To identify potential confounders, we compared case and control groups for significant differences ($p < 0.05$) in the birth registration variables.

The association between HBW or LBW and T2DM for each of the matched pairs

TABLE II
Descriptive Analyses of Bwt Over Time

Group by Birth Cohorts	N	% LBW <2500 g	% 2500- 4000 g	% HBW >4000 g	Bwt (g) Mean (SD)
RI-Dm					
1950-59	275	3.6	81.8	14.5	3456 (607)
1960-69	374	5.6	78.6	15.8	3452 (603)
1970-84	197	5.1	75.6	19.3	3489 (677)
RI-nonDm					
1950-59	304	3.0	85.5	11.5	3410 (520)
1960-69	372	5.4	83.9	10.8	3380 (552)
1970-84	206	6.3	84.5	9.2	3298 (558)
GP-Dm					
1950-59	541	10.5	78.7	10.7	3289 (610)
1960-69	403	7.2	82.9	9.9	3311 (575)
1970-84	220	6.4	85.5	8.2	3326 (546)
GP-nonDm					
1950-59	504	8.3	83.1	8.5	3299 (535)
1960-69	382	7.9	85.1	7.1	3244 (556)
1970-84	214	8.4	86.0	5.6	3234 (520)
OVERALL	3992	6.8	82.4	10.7	3342 (577)

was first estimated by the crude odds ratio (OR), followed by determining the adjusted ORs of matched pairs using conditional logistic regression multivariate analysis.³⁰

We wondered if the strength of association between HBW or LBW and T2DM changed over the second half of the last century, since rates of T2DM/GDM/GIGT and maternal/fetal malnutrition are known to have changed during this time. The data were stratified into three numerically balanced birth "cohorts" (1950-59, 1960-69 and 1970-84). Matched pairs in each birth cohort were compared using ORs with 95% CI.

Analyses were performed using SPSS (6.0), Microsoft (5.0) and Epi-Info (6.02).

RESULTS

Subjects with birthweights ranged in age from 10.5 to 44.9 years (mean 31.8) and the overall male to female ratio was 56:100. Mothers of both diabetic groups were significantly older ($p < 0.001$) than mothers of both non-diabetic groups (mean age 26.9 years vs 23.8 years for RI;

27.2 vs 25.3 years for GP). Maternal parity ≥ 4 was most common in the RI diabetic group (56%; $p < 0.001$). There were no differences in type of birth (98.1% were singleton) or gestational age between study groups.

Birthweight and diabetes (Table I)

The highest proportion of HBW was in the RI diabetic group (16.2%) followed by the RI non-diabetic (10.7%), the GP diabetic (10%), and the GP non-diabetic (7.5%) groups. The differences in HBW between the RI cases and control groups were significant ($p < 0.01$) by matched pair analysis. For LBW, no significant differences were found within either the RI or GP populations.

Birthweight and time (Table II)

The mean ages of subjects in each of the birth cohorts was 39.2, 30.6 and 19.8 years respectively. Only the RI diabetic subjects (Figure 1) had progressively increasing rates of HBW over time (14.5% to 19.3%; ns). Matched pair analyses (Table III) also

TABLE III
Matched Pair Analyses of HBW in Three Birth Cohorts
Using All Other Bwts as Denominator

Pair-wise Comparisons	Oldest Age Group 35-44 years		Middle Age Group 25-34 Years		Youngest Age Group 10-24 Years	
	n pairs	OR (CI)	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	169	1.28 (0.66, 2.47)	327	1.47 (0.92, 2.36)	183	2.54 (1.29, 5.08)*
RI-Dm + GP-Dm	241	1.43 (0.79, 2.59)	352	1.73 (1.08, 2.78)*	193	2.83 (1.41, 5.78)*
RI-Dm + GP-nonDm	211	1.60 (0.81, 3.20)	334	2.43 (1.43, 4.17)*	189	3.27 (1.61, 6.82)*
GP-Dm + GP-nonDm	397	1.03 (0.63, 1.68)	358	1.55 (0.88, 2.73)	210	1.50 (0.64, 3.58)

* statistically significant at $p \leq 0.05$

demonstrated a progressive temporal increase in ORs when comparing HBW rates between diabetic RI subjects and each of the three control groups.

Birthweight and sex

Table IV shows that 17% of RI diabetic females had HBW. Matched pair analyses showed a significant relationship between HBW and diabetes in RI females but not in RI males. RI diabetic females were more likely to have HBW than RI non-diabetic females (OR=2.53; CI 1.66, 3.87), GP diabetic females (OR=2.65; CI 1.75, 4.00) and GP non-diabetic females (OR=3.41; CI 2.12, 5.48).

Estimation of adjusted ORs

Crude and adjusted ORs with corresponding 95% CI are shown in Table V. After accounting for potential confounders, the within-population relation-

ship between HBW and diabetes remained significant for RI females. When the ORs for RI females were recalculated using data restricted to singleton births with gestational age 38-41 weeks ($n=2,804$), the crude OR remained significant (OR 2.42; CI 1.42, 4.13) and the maternal age-adjusted OR marginally lost significance (OR 1.71; CI 0.96, 3.06). All LBW relationships that were significant with the complete dataset, lost significance in the restricted dataset.

DISCUSSION

Although a relationship between HBW and T2DM has been demonstrated in animal models³¹ and among Pima Indians,²² this is the first study to show such an association in Canadian Aboriginal people. Common risk factors for HBW are gestational age >42 weeks, male sex, maternal

obesity and pregnancy associated with T1DM/T2DM/GDM/GIGT.^{32,33} We have ruled out the first two; therefore, maternal obesity (also a risk factor for GDM/GIGT) and diabetic pregnancies probably account for the relationship observed in this study. The association between HBW and T2DM strengthened progressively from mid to late 20th century, suggesting that the younger the age of T2DM diagnosis, the stronger its relationship with HBW.

Contrary to other reports,¹⁴⁻²² we did not find an association between LBW and T2DM. This may reflect a survival bias for infants with normal or high birthweights, and a paucity of birthweight data for older RI subjects who had higher LBW rates.^{25,34,35} It is also possible that the relationship between abnormal birthweights and T2DM is population-specific. For example, only McCance³⁶ has shown a relationship between LBW (but also HBW) and T2DM in North American Aboriginal people.

Possible causes of misclassification in this study include Aboriginal status, differentiation between T1DM and T2DM (although most RI with diabetes have T2DM,^{36,37} and diabetes diagnosis; however, these would tend to underestimate the true relationship between HBW or LBW and T2DM, and make the study's findings more conservative.

The association between HBW and T2DM for RI females but not for RI males was likely the result of decreased statistical power owing to the smaller sample of RI males. It is also possible that the expression of intrauterine events predisposing to T2DM could appear in males older than those we studied. Finally, this observation may indicate a true gender difference conceivably due to genetic factors, a sex-specific effect of a diabetogenic intrauterine environment, or differing lifestyles during childhood and early adulthood.

Neel³⁸ first proposed that a "thrifty" genotype conferred a survival advantage on populations subject to periods of nutritional hardship by favouring caloric conservation when food was abundant. He suggested that this had now become a liability because it contributes to obesity and T2DM when combined with nutritional excess and decreased physical activity. We now speculate that the "thrifty" genotype would be particularly advantageous for a population's survival if it

TABLE IV
Descriptive Analyses of Bwt for Males and Females

Group	n	MALES		BWT (g) Mean (SD)	n	FEMALES		BWT (g) Mean (SD)
		% LBW <2500 g	% HBW >4000 g			% LBW <2500 g	% HBW >4000 g	
RI-Dm	292	3.8	14.7	3464 (573)	554	5.4	17.0	3461 (648)
RI-nonDm	311	4.5	16.4	3453 (599)	571	4.9	7.5	3327 (506)
GP-Dm	427	6.1	13.6	3406 (574)	737	10.0	7.9	3244 (585)
GP-nonDm	405	8.1	10.9	3341 (576)	695	8.2	5.5	3225 (514)
OVERALL	1435	5.9	13.7	3410 (581)	2557	7.4	9.1	3304 (571)

increased the likelihood of successful pregnancies. By favouring caloric conservation in women of childbearing age, as well as in their unborn (and possibly female) children, the “thrifty” genotype would optimize fetal nutrition and promote a “healthy” birth-weight. However, with the surfeit of food associated with modern times, it could predispose to maternal T2DM/GIGT/GDM and a tendency towards HBW.

An insulin-resistant state similar to T2DM may be characteristic of normal pregnancy but can result in GIGT or GDM if demands for increasing insulin production are excessive.^{39,40} Pederson⁴¹ proposed that GDM-related hyperglycemia causes fetal hyperinsulinemia, accelerated fuel utilization and macrosomia. Freinkel⁴² suggested that fetal metabolic and anthropometric changes might persist and contribute to the development of insulin resistance in adulthood. Thus, what may have evolved as a survival advantage for newborns and their mothers has now become a metabolic liability for both.

What evidence would support a significant role for GIGT/GDM (and gestational T2DM) in the epidemic of T2DM among Aboriginal people? First, GIGT/GDM would occur as an initial phenomenon in Aboriginal communities experiencing early changes in lifestyle. In three isolated northern Saskatchewan Aboriginal communities, high rates of GDM occurred before the significant appearance of T2DM.¹³ Second, rates of GIGT/GDM in successive generations of Aboriginal women would rapidly increase to levels higher than those observed in the general population. In North America, 3–4% of pregnant women in the general population have GDM,^{43,44} while corresponding rates are much higher among Aboriginal women.^{9–12} Third, levels of HBW among Aboriginal people would increase. In northern Saskatchewan (predominantly Aboriginal),

TABLE V
Summary of Multivariate Analyses Using Conditional Logistic Regression (CLR) for HBW and LBW

Pair-wise Comparisons		Covariates Included†	n pairs	HBW (>4000g) vs. All Other Bwts OR (CI)	LBW (<2500g) vs. All Other Bwts OR (CI)
RI-Dm + RI-nonDm					
All	crude		679	1.63 (1.20, 2.24) *	1.06 (0.66, 1.72)
	adj.	Mat	678	1.33 (0.96, 1.86)	1.00 (0.61, 1.66)
Males	crude		235	0.82 (0.49, 1.36)	0.67 (0.27, 1.63)
	adj.	Mat	235	0.70 (0.41, 1.19)	0.63 (0.25, 1.58)
Females	crude		444	2.53 (1.66, 3.87) *	1.30 (0.73, 2.33)
	adj.	Mat	443	1.99 (1.27, 3.12) *	1.23 (0.67, 2.28)
RI-Dm + GP-Dm					
All	crude		786	1.84 (1.36, 2.50) *	0.56 (0.37, 0.85) *
	adj.	Mat, Par, SB	779	1.66 (1.20, 2.30) *	0.54 (0.34, 0.85) *
Males	crude		277	1.06 (0.66, 1.72)	0.64 (0.28, 1.49)
	adj.	Mat, Par	274	1.13 (0.68, 1.89)	0.51 (0.21, 1.25)
Females	crude		509	2.65 (1.75, 4.00) *	0.53 (0.33, 0.86) *
	adj.	Mat, Par	505	2.19 (1.42, 3.38) *	0.57 (0.34, 0.97) *
RI-Dm + GP-nonDm					
All	crude		734	2.36 (1.68, 3.32) *	0.54 (0.36, 0.82) *
	adj.	Par	730	2.01 (1.41, 2.85) *	0.52 (0.34, 0.80) *
Males	crude		254	1.44 (0.87, 2.40)	0.38 (0.19, 0.80) *
	adj.	Par	251	1.32 (0.79, 2.22)	0.35 (0.17, 0.74) *
Females	crude		480	3.41 (2.12, 5.48) *	0.65 (0.39, 1.08)
	adj.	Par	479	2.76 (1.69, 4.50) *	0.68 (0.40, 1.15)
GP-Dm + GP-nonDm					
All	crude		965	1.27 (0.92, 1.75)	0.97 (0.71, 1.34)
	adj.	Mat, Par	963	1.23 (0.89, 1.72)	1.03 (0.74, 1.44)
Males	crude		355	1.29 (0.83, 2.03)	0.62 (0.35, 1.12)
	adj.	Mat, Par	354	1.34 (0.84, 2.15)	0.61 (0.33, 1.13)
Females	crude		610	1.24 (0.79, 1.97)	1.20 (0.81, 1.77)
	adj.	Mat, Par	609	1.16 (0.72, 1.85)	1.30 (0.87, 1.94)

* statistically significant at $p \leq 0.05$

† only those covariates statistically significant at $p \leq 0.05$, in the presence of all other potential confounding variables, are included in the final CLR model

Covariates: maternal age (Mat), maternal parity (Par), previous stillborn (SB)

HBW rates increased from 12.6% to 19.2% from 1975–1984,⁴⁵ but from only 10.2% to 12.8% in the south (predominantly non-Aboriginal). This is consistent with a Canadian Inuit/Indian survey that reported an increase in HBW rates from 12% to 22% over the period 1962 to 1983.⁴⁶ Fourth, the progeny of women with GDM would experience a higher risk for T2DM as observed in the Pima.^{6–8} Fifth, higher and increasing rates of HBW would be apparent in Aboriginal people with T2DM. We have now shown that Aboriginal people with T2DM are more likely than controls to have HBW and that this relationship has become stronger from the middle to the later part of the last century.

Finally, as suggested by this study and as shown among the Pima^{47,48} and in Manitoba,^{37,49} T2DM would occur in progressively younger Aboriginal people.

We believe that our findings add further support for an instrumental role of intrauterine factors in the epidemic of T2DM among indigenous peoples. While conditions leading to fetal malnutrition and LBW may be important for the subsequent development of T2DM under certain circumstances and in some populations (the “thrifty phenotype”²³ and “surviving small baby genotype”²² hypotheses), they are unlikely to explain the rapidly increasing rates of T2DM in populations experiencing

acculturation. Rather, we believe that there is now compelling evidence that excess fetal nutrition has become the overriding intrauterine factor in the pathogenesis of T2DM among Canadian and possibly other Aboriginal peoples. Accordingly, we speculate that this phenomenon plays a pivotal role in the early stages as well as the perpetuation of the T2DM epidemic in Aboriginal peoples. We now propose a new paradigm, the "hefty fetal phenotype" (or "hefty fetal type") hypothesis, a unifying concept that is consistent with the "thrifty genotype" hypothesis and integrates an expanding and diverse body of information from our own and others' research.

Further work such as longitudinal analyses is necessary to substantiate our findings, and to validate our hypothesis. If confirmed, prevention strategies to target modifiable risk factors for GDM/GIGT as we have recently proposed,⁵⁰ and programs to diagnose and optimally manage diabetes during pregnancy, could play a pivotal role in breaking an exponential cyclic transfer of risk for T2DM in successive generations of Aboriginal peoples.

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