Complications of Type 2 Diabetes Among Aboriginal Canadians: Increasing the Understanding of Prevalence and Risk Factors

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ABSTRACT

Type 2 diabetes mellitus is a highly prevalent condition among Aboriginal Canadians, and a large increase in associated complications is expected to emerge in this population during the next decade. Relatively little information is available, however, regarding the prevalence of, or risk factors for, diabetes complications in Aboriginal Canadians. Data from chart reviews and disease registries have revealed high rates of end stage renal disease (ESRD) and, in some groups, cardiovascular (CV) morbidity, although information regarding the prevalence of retinopathy, neuropathy and risk factors for complications is limited.

This paper presents the methodologic features of an epidemiologic study that was designed to expand existing knowledge regarding the prevalence of diabetes complications and associated metabolic and lifestyle risk factors among Aboriginal Canadians. The protocol involved screening and risk factor assessment techniques that were uncomplicated and acceptable to a broad spectrum of the population, while at the same time demonstrating good reproducibility and validity against gold standard methods. Techniques included standardized questionnaires and body measurements, digital nonmydriatic retinal photography, the assessment of microalbuminuria and glycosylated hemoglobin

RÉSUMÉ

Le diabète sucré de type 2 est très courant chez les Canadiens d'origine autochtone et on s'attend à une hausse importante de la prévalence de ses complications dans cette population au cours des dix prochaines années. On possède toutefois relativement peu de renseignements sur la prévalence des complications du diabète ou sur les facteurs de risque de complications chez les Canadiens d'origine autochtone. Les données provenant de l'analyse de dossiers et de registres sur la maladie révèlent que les taux d'insuffisance rénale chronique au stade ultime (IRSU) et, dans certains groupes, de morbidité cardio-vasculaire, sont élevés, mais les données sur la prévalence de la rétinopathie, de la neuropathie et des facteurs de risque de complications sont limitées.

Ce compte rendu énonce les caractéristiques méthodologiques d'une étude épidémiologique dont l'objet était d'accroître les connaissances actuelles sur la prévalence des complications du diabète et des facteurs de risque métaboliques et liés au mode de vie connexes chez les Canadiens d'origine autochtone. Le protocole comportait des techniques de dépistage et d'évaluation des facteurs de risque qui étaient simples et acceptables pour une grande partie de la population tout en étant reproductibles et valables par rapport aux critères des méthodes de référence. Les techniques étaient les suivantes : questionnaires normalisés et prise des mensurations, rétinographie non mydriatique numérique, mesure de la microalbuminurie et de l'hémoglobine glycosylée (A1C) au moyen d'un analyseur au point de soins, épreuves de dépistage neuropathiques au moyen du *Michigan Neuropathy Screening Instrument* et plusieurs méthodes pour évaluer les facteurs de risque cardio-vasculaire.

L'initiative actuelle des équipes interdisciplinaires de recherche en santé permettra l'expansion et l'évaluation de ce programme dans d'autres communautés autochtones canadiennes, développement qui aura d'importants avantages tant pour la recherche que pour les soins cliniques.

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(A1C) using a point-of-care analyzer, neuropathy testing using the Michigan Neuropathy Screening Instrument (MNSI), and several methods to assess CV risk factors.

The current Interdisciplinary Health Research Teams (IHRT) initiative will allow the expansion and evaluation of this program in other Aboriginal communities in Canada, a development that will have important benefits for both research and clinical care.

INTRODUCTION

Type 2 diabetes mellitus is a public health problem of increasingly serious proportions for Aboriginal Canadians (1). Although extremely rare prior to the 1950s (2), chart reviews conducted only a few decades later revealed high rates of type 2 diabetes in this population compared to non-Aboriginal populations (3-6). In addition, surveillance data highlighted a doubling of the prevalence of type 2 diabetes among Aboriginal people in Saskatchewan, Canada, between 1980 and 1990 (7), and an increase in prevalence of 45% between 1985 and 1994 among the Aboriginal population of the Sioux Lookout Zone in Northwestern Ontario, Canada (8). More recent studies using the standardized oral glucose tolerance test (OGTT) documented that Aboriginal communities in Canada experience prevalence rates of diabetes that are among the highest in the world (9,10). Furthermore, the onset of diabetes in this population occurs at a much younger age than in most other populations (10), and pediatric type 2 diabetes is emerging as an important health issue (11,12). The combination of early disease onset, the advancing age of this demographically young population, and the progression of a disease process that is still in its early stages in most individuals will pose an extremely serious challenge to health systems in Canada in the coming years.

A central aspect of this challenge will arise from the large increase in diabetes complications that is expected to emerge in this population during the next decade. Diabetes is the leading cause of lower extremity amputations and new cases of adult blindness, and it accounts for approximately 35% of incident cases of end stage renal disease (ESRD) (13-15). Individuals with diabetes are also at markedly increased risk for cardiovascular (CV) morbidity. Recent research has demonstrated that the risk of a first myocardial infarction (MI) among subjects with diabetes approximates that for re-infarction among individuals without diabetes who have had a previous MI (16). Finally, despite the clearly demonstrated underestimation of mortality attributable to diabetes (17), this disease is among the most common causes of death for men and women in the majority of developed nations (18).

A distinctive feature of the epidemiology of the complications of diabetes is the wide variation in the prevalence of specific conditions both within and between ethnic groups. For example, Native Americans experience dramatically higher incidence rates of diabetes-related ESRD compared to both black and white Americans (19). Furthermore, the prevalence of diabetes-related ESRD, as well as other complications, is variable across individual tribal groups in the United States (US) (20,21).

Surprisingly little information is available, however, regarding the prevalence of, and risk factors for, the complications of type 2 diabetes among Aboriginal Canadians. This paper will briefly review the existing scientific literature on diabetes complications in First Nations in Canada, and will present the methodologic features of an ongoing study of the prevalence of diabetes complications and associated risk factors in this population. Under the Interdisciplinary Health Research Teams (IHRT) initiative, *Diabetes in the Aboriginal Population: Defining, Understanding and Controlling an Emerging Epidemic*, the protocol will soon be implemented in additional communities in Manitoba, Canada.

LITERATURE REVIEW

Diabetes complications among Aboriginal Canadians: prevalence and associated risk factors

Limited information is available regarding the prevalence of the complications of type 2 diabetes among Aboriginal Canadians. The authors conducted a literature review of the MEDLINE® database using the keywords "diabetes," "complications," "Canada," and either "Aboriginal," "Indigenous," "Native," "First Nations" or "Indian." Additional papers were identified from the reference lists of publications on this topic.

Table 1 presents a summary of the 12 published studies that have examined the prevalence of diabetes complications in this population (22-34). These papers suggest that complication rates are high in this population, particularly for heart disease among Mohawks (23,24), and for ESRD in all groups. Notably, Dyck and Tan reported that the incidence of ESRD among registered Aboriginals in Saskatchewan between 1981 and 1990 was 16 times the rate in the general population (30). Less information is available for rates of retinopathy and neuropathy. Studies published in the 1980s reported similar overall prevalence rates of neuropathy (6%) in the Mohawks of Kahnawake, Quebec, Canada, and the Ojibway and Cree of Northwestern Ontario and Northeastern Manitoba (22-24). Mohawk men, however, appeared to experience a higher disease burden compared to

Mohawk women. Similarly, Montour and colleagues reported higher rates of retinopathy among men compared to women in Kahnawake (24). Very high levels of microalbuminuria (>10 mg/L in 69.4%) were documented among previously diagnosed subjects with diabetes who participated in the baseline survey of the Sandy Lake Health and Diabetes Project (SLHDP) (31,32). In a recent study among the Cree of the James Bay region of Ontario, 21% of subjects with diabetes were reported to have diabetic retinopathy (33).

In 2 cross-sectional studies that employed the OGTT methodology, subjects with type 2 diabetes or impaired glucose tolerance (IGT) were found to have significantly elevated levels of cardiovascular disease (CVD) risk factors compared to subjects without diabetes after adjustment for age, sex and adiposity. Delisle and colleagues reported elevated triglyceride (TG) concentrations in subjects with type 2 diabetes or IGT from 2 Quebec Algonquin communities (35). Harris and colleagues documented elevated TG levels and systolic blood pressure (BP), and reduced high-density lipoprotein cholesterol concentrations among SLHDP participants with type 2 diabetes or IGT (36). In addition, a recent analysis of administrative data in Ontario indicated that, while there was an overall decrease in hospitalizations for ischemic heart disease in the province between 1981 and 1997 (101/10 000 to 82/10 000), rates in Aboriginal communities increased dramatically during this time period (76/10 000 to 186/10 000), a phenomenon that is likely related to foregoing increases in diabetes prevalence (37). Anand and colleagues recently reported that Aboriginal participants in the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP) had significantly more carotid atherosclerosis, a higher frequency of CVD, and higher rates of CVD risk factors compared with participants of European origin (38).

The available information regarding risk factors for diabetes complications among Aboriginal Canadians is also extremely limited (Table 1). Young and colleagues (22) reported that both duration of diabetes and hypertension were significantly associated with the risk of having at least 1 diabetes complication. Body weight, fasting blood glucose concentration and the presence of symptoms of diabetes were not associated with risk. Macaulay and colleagues and Brassard and colleagues found that duration of diabetes was associated with the presence of complications (23,28). In a subsequent analysis, Brassard and colleagues reported that poor glycemic control, increased TG concentration and duration of diabetes were significantly associated with risk of complications (29). In the SLHDP, microalbuminuria (>10 mg/L) was independently associated with concentrations of total and low-density lipoprotein cholesterol and apolipoprotein B, as well as with the T235 variant of the *AGT* gene (31,32). Maberley and colleagues reported that elevated serum cholesterol, lower body mass index and insulin treatment were associated with risk of diabetic retinopathy among the Cree

of James Bay (33). Finally, in a recent paper that utilized data from the Saskatchewan Transplant Program and Canadian Organ Replacement Register, it was reported that young Aboriginal subjects with diabetes-related ESRD had a significantly higher frequency of human leukocyte antigen (HLA) -A2, -DR4 and -DR8 antigens and HLA-A2/DR4 or -A2/DR8 haplotypes compared to older Aboriginal subjects with diabetes-related ESRD or subjects with ESRD not related to diabetes (34).

These available Canadian data (Table 1) on the prevalence and risk factors of diabetes complications have relied largely on hospital records, chart reviews and disease registries. These data sources may underestimate the magnitude of the burden of complications, since they capture only the most severe portion of the disease spectrum. In addition, it is unlikely that standardized methods were used in the documentation of complications or associated risk factors, given variation in recording and diagnostic practices. Finally, the chart review data are based on information from individuals who presented for medical care, and thus may not be representative of the general population of people with diabetes. It would be of value, therefore, to extend this existing knowledge regarding the prevalence of and risk factors for diabetes complications among Aboriginal Canadians. In particular, beneficial information will be gained from studies that attempt to ascertain all subjects with diabetes in the population, and that employ standardized, validated methods to measure both complication outcomes and risk factors. These design features would yield both valid population-based prevalence estimates as well as risk factor associations that are not affected by disease or exposure misclassification.

STUDY OVERVIEW
Determining the prevalence of diabetes complications and associated risk factors in an Aboriginal Canadian community
The objective of this research project was to determine the prevalence of preclinical and clinical microvascular and macrovascular complications among individuals who have type 2 diabetes, and to identify metabolic, lifestyle and genetic factors that are associated with risk for these conditions. This protocol was implemented as part of the SLHDP, an ongoing research partnership between Sandy Lake First Nation and investigators at Mount Sinai Hospital, Toronto, Ontario; University of Toronto, Toronto, Ontario; and University of Western Ontario, London, Ontario, and was funded by a grant from the Canadian Institutes of Health Research (CIHR). Under the IHRT initiative described in this issue of *Canadian Journal of Diabetes* (p. 439), the protocol will soon be implemented in additional communities in Manitoba. Signed informed consent was obtained from all participants, and the study was approved by the Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee.

Table 1. Literature review: studies that have examined prevalence of, and risk factors for, diabetes complications in Aboriginal Canadian populations

Reference	Population	Methods	Results	Risk factors/comments
Young et al, 1985 (22)	Northwestern Ontario, Northeastern Manitoba Ojibway and Cree	Hospital separations, chart reviews, treatment lists, chronic disease lists (n≈190)	Prevalence of DM: 28/1000 (age 0–65 years) Prevalence of ≥1 complication: 30% IHD: 17% CBVD: 7% Neuropathy: 6% Nephropathy: 5%	Duration of DM and hypertension associated with prevalence of complications, but weight and FBG were not
Macaulay et al, 1988 (23)	Kahnawake, Quebec Mohawk	Chart reviews DM: n=82 non-DM: n=94	IHD: 48% CBVD: 13% PVD: 12% Neuropathy: 6% Nephropathy: 5% Hypertension: 71% Cholesterol >7.25 mmol/L: 16%	Positive association between duration of DM and prevalence of complications
Montour et al, 1989 (24)	Kahnawake, Quebec Mohawk	Chart reviews DM: n=82, 34 M/48 F non-DM: n=94	Men (%) / Women (%): IHD 41/54; CBVD 15/13; PVD 12/13; Retinopathy 27/8; Neuropathy 12/0; Nephropathy 6/2; Hypertension 65/75; Cholesterol >7.25 mmol/L 13/19	
Young et al, 1989 (25)	National survey	Documentation of ESRD from the Canadian National Renal Failure Register FN: n=304	Incidence of ESRD, 1981–1996: 13.9–23.1/100 000 Prevalence of ESRD, 1986: 32.0–53.4/100 000 ESRD in FN: 2.5 times the national rate	
Ross et al, 1990 (26)	Southern Alberta Aboriginals and non-Aboriginals	Screening for retinopathy, microalbuminuria, macroalbuminuria and BP	Prevalence data not presented in abstract	Retinopathy higher among insulin users
Wilson et al, 1992 (27)	Moose Factory Zone, Ontario James Bay Cree	Hospital records (n=10)	Prevalence of ESRD, 1989: 139/100 000 (3.2 times the national rate) Incidence of ESRD, 1980–1989: 11.3/100 000 (1.8 times the national rate)	
Brassard et al, 1993 (28) Brassard et al, 1995 (29)	Northern Quebec James Bay Cree	Chart reviews (n=230)	Prevalence of DM: 5.2% (age ≥20 years) Prevalence of complications: 28.7% Microvascular: 19.6% Macrovascular: 14.4% Neuropathy: 9.6% A1C >9.0%: 19.3% TG >1.7 mmol/L: 25%	Prevalence of complications associated with duration of DM, TG level and mode of treatment

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Reference	Population	Methods	Results	Risk factors/ comments
Dyck et al, 1994 (30)	Saskatchewan Registered Aboriginals	Canadian Organ Replacement Register Total FN: n=28 318 FN with ESRD: n=50	Prevalence of DM: 7.4% (age ≥20 years) Incidence of DM-related ESRD, 1981–1990: ≈30/100 000 Prevalence of DM-related ESRD, 1981–1990: ≈250/100 000 ESRD in FN: 16 times rate of general population	Higher ESRD rate not completely explained by higher prevalence of DM
Hegele et al, 1999 (31,32)	Northwestern Ontario Oji-Cree (SLHDP)	n=56 with previous diagnosis of DM; microalbuminuria measured using Micral-Test sticks; genotypes for *AGT* variants	Prevalence of microalbuminuria (>10 mg/L): 69.4%	Microalbuminuria associated with TC and LDL-C, apo B and *AGT* T235
Maberley et al, 2002 (33)	Ontario James Bay Cree	n=157 with previous diagnosis of DM; retinopathy diagnosed by ophthalmologist; exposure data from chart reviews	Prevalence of retinopathy: 21%	Elevated serum cholesterol, lower BMI, and insulin therapy significantly associated with risk of retinopathy
Dyck et al, 2003 (34)	Saskatchewan residents with DM-related ESRD	Aboriginal: n=110 non-Aboriginal: n=524 Canadian Organ Replacement Register and Saskatchewan Transplant Program	Prevalence data not presented	Young Aboriginal subjects with DM-related ESRD had high frequency of HLA-A2, -DR4 and -DR8 antigens vs. older Aboriginal subjects with DM-related ESRD or subjects with non-DM ESRD Younger group also had higher frequency of HLA-A2/DR4 and A2/DR8 haplotypes

A1C = glycosylated hemoglobin
apo B = apolipoprotein B
BMI = body mass index
BP = blood pressure
CBVD = cerebrovascular disease
DM = diabetes mellitus
ESRD = end stage renal disease
F = female
FBG = fasting blood glucose
FN = First Nations
HLA = human leukocyte antigen
IHD = ischemic heart disease
LDL-C = low-density lipoprotein cholesterol
M = male
PVD = peripheral vascular disease
SLHDP = Sandy Lake Health and Diabetes Project
TC = total cholesterol
TG = triglyceride

Subjects and method

All members of the Sandy Lake community with type 2 diabetes were invited to participate in the complications prevalence and risk factor project. Individuals with diabetes were identified using a number of data sources, including health records and lists of patients with chronic diseases maintained at the community clinic, registries of individuals with diabetes, research study databases, and by way of responses to project promotion and recruiting activities (posters, radio shows, information booths at community events, face-to-face contact). Data collection occurred between September 2001 and July 2002, and community response and participation were excellent, with 190 of 250 (76%) eligible subjects with diabetes enrolled.

The combination of remoteness, harsh climate, competing health issues and minimal availability of tertiary care professionals and facilities indicated that a carefully tailored approach was required for the implementation of diabetes complications research in this setting. In particular, it was necessary to identify screening and risk factor assessment techniques that were uncomplicated and acceptable to a broad spectrum of the population, while at the same time showing good reproducibility and validity against gold standard methods. The methods used in the present study are summarized in Table 2, and outlined briefly below (39-45).

Retinopathy

Digital fundus photographs were captured using a nonmydriatic camera (TRC-NW100, Topcon Canada Inc., Waterloo, Ontario), and the photographs were transmitted electronically to a central reading unit, where they were interpreted and graded by the project ophthalmologist. Results were reported to the data coordinating centre, as well as to the individuals responsible for clinical follow-up. Digital fundus photography has been validated against gold standard methods (46,47), including a study that used telemedical technology (48). The camera used in the present study has been validated (kappa=0.65) against dilated 35-mm Early Treatment Diabetic Retinopathy Study (ETDRS) photographs for clinical level of diabetic retinopathy (39). In Ontario, this aspect of the project was carried out through a partnership with NORTH Network, which has implemented a telehealth network to provide medical services to remote areas in the province (49).

Table 2. Summary of complication measurement procedures, SLHDP complication study			
Complication	*Measurement*	*Validation*	*Reference*
Retinopathy	Digital nonmydriatic fundus photographs	kappa=0.65 vs. ETDRS	Bursell et al, 2001 (39)
Neuropathy	MNSI	r=0.77 vs. quantitative neurologic exam and nerve conduction studies	Feldman et al, 1994 (40)
Nephropathy	Urine ACR, DCA® 2000	r>0.95 vs. Dade Behring aca IV® analyzer (Dade Behring Inc., Deerfield, Illinois, US)	Parsons et al, 1999 (41)
Atherosclerosis	Carotid IMT, 2-dimensional and 3-dimensional plaque	Predictive of stroke and MI	Bots et al, 1997 (42)
Peripheral arterial disease	Ankle-brachial BP	Predictive of CVD, Se=0.8 vs. fundoscopic arteriosclerosis	Shinozaki et al, 1998 (43)
Angina pectoris and claudication	Rose questionnaire	Angina pectoris related to thicker carotid walls (p<0.05) Claudication predictive of CVD	Sorlie et al, 1996 (44)
Glycemic control	A1C, DCA 2000	r=0.90–0.98 vs. direct laboratory measures	John et al, 1994 (45)

A1C = glycosylated hemoglobin
ACR = albumin to creatinine ratio
BP = blood pressure
CVD = cardiovascular disease
ETDRS = Early Treatment Diabetic Retinopathy Study
IMT = intima-media thickness
MI = myocardial infarction
MNSI = Michigan Neuropathy Screening Instrument
Se = sensitivity
SLHDP = Sandy Lake Health and Diabetes Project

Neuropathy

The presence of diabetic neuropathy was determined using the Michigan Neuropathy Screening Instrument (MNSI), which includes a brief questionnaire, a visual inspection of the feet and 3 simple tests (40). The tests include the grading of ankle reflexes using a standard reflex hammer, the assessment of vibration perception at the great toe using a tuning fork, and the assessment of sensation using a 10-g Semmes-Weinstein monofilament. The MNSI has been validated (r=0.77) against a quantitative neurologic examination protocol and nerve conduction studies (40).

Nephropathy

The presence of diabetic nephropathy was determined by measuring the albumin to creatinine ratio (ACR) in a single, random, daytime urine sample. This is the recommended screening technique for nephropathy in the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada, and has been validated against timed overnight urine collection methods (50). Subjects with a positive result (>2.8 mg/mmol in females, >2.0 mg/mmol in males) had an overnight urine collection (normal: <20 μg/minute; microalbuminuria: 20 to 200 μg/minute; clinical grade proteinuria: >200 μg/minute). Subjects did not receive the test if they were in the menstrual phase of their cycle. The ACR was determined on location in Sandy Lake using the DCA® 2000 Point-of-Care Analyzer (Bayer Diagnostics, Tarrytown, New York, US). This machine has displayed high levels of reproducibility and has been validated (r>0.95) against laboratory gold standard techniques (41).

CVD risk factors

The presence of CVD risk factors, including carotid artery atherosclerosis, dyslipidemia, hypertension and peripheral arterial disease was determined. Measurements of carotid intima-media thickness (IMT), 2-dimensional plaque area and 3-dimensional plaque volume were performed using a high-resolution duplex ultrasound scanner (HDI 3000, Advanced Technology Laboratories, Seattle, Washington, US) (51). For each carotid artery, IMT was measured as the mean thickness derived from a 10-mm region centred at the bifurcation. Plaque was defined as a local thickening of the intima >1 mm. Total carotid plaque area was measured as described previously (52). Algorithms to measure total carotid plaque volume are under development (R.A.H., oral communication, March 2003). Increased IMT is a prospective risk factor for MI and stroke (42). In addition, subjects whose carotid plaque area is in the upper quintiles have been shown to be at significantly increased risk of both stroke and MI (D. Spence, MD, oral communication, March 2003).

The ankle-brachial BP index, a measure of peripheral arterial disease, was determined using a BP cuff and Doppler stethoscope. Systolic BP was assessed at 3 sites on each side (brachial, posterior tibial and dorsalis pedis). Peripheral arterial disease is associated with atherosclerosis in other vessel beds and has been shown to predict CVD morbidity and mortality (43,53). Fasting blood samples were collected for evaluation of lipid and lipoprotein concentrations, which were determined using standard laboratory procedures. Finally, angina and intermittent claudication were assessed using the Rose (World Health Organization) questionnaire (54), which has shown reasonable repeatability and validity for epidemiologic studies (44).

Determining risk factors for diabetes complications

Concurrent risk factors for diabetes complications were assessed using laboratory and physical measurements, and standardized, interviewer-administered questionnaires. During the examination, subjects provided blood samples for the determination of A1C, which was assessed using the DCA 2000 (r=0.90 to 0.98 vs. direct laboratory measures [45]). Standard SLHDP procedures were used to measure BP, height, weight, percentage of body fat and waist and hip circumferences (55). During the interview, subjects were asked to report their duration of diabetes, smoking status, use of alcohol, level of physical activity, dietary intake, participation in traditional activities, self-perceived mastery (a psychosocial measure related to self-efficacy), language abilities and family history of diabetes and diabetes complications.

CONCLUSION

The high prevalence of type 2 diabetes currently experienced by Aboriginal Canadians is likely to presage a heavy burden of diabetes complications in this population, a development that will pose a significant challenge to individuals, communities and health systems during the coming decades. Fortunately, the complications of diabetes satisfy all 3 criteria for appropriateness for screening: 1) they are important health problems; 2) efficacious treatments are available if the conditions are detected early; and 3) safe and acceptable screening instruments have been developed that have been shown to be valid and reproducible. In addition, recent technological advances (nonmydriatic cameras, point-of-care analyzers) and the availability of simple, valid and reliable instruments make screening for complications highly feasible for First Nations communities, even those in remote locations. Finally, the assessment of risk factors for complications will increase knowledge of the pathogenesis of these conditions and will inform preventive strategies.

The network linkages, knowledge and funding generated under the current IHRT initiative will allow the expansion of this program to other Aboriginal communities in Canada. This is a crucial development that will allow for the evaluation of the feasibility of this protocol in other geographical and administrative settings. Research benefits are also anticipated, including an expanded sample size and the examination of prevalence and risk factor associations across cultural and geographical subgroups.

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