

# The Relationship Between Diabetes and Tuberculosis in Saskatchewan

## Comparison of Registered Indians and Other Saskatchewan People

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### ABSTRACT

**Background:** Saskatchewan Aboriginal people are experiencing epidemics of both type 2 diabetes (T2DM) and tuberculosis (TB). The purpose of this study was to determine if a relationship exists between diabetes and TB in Saskatchewan and to establish whether there is a difference in the degree of any association between Aboriginal and non-Aboriginal people.

**Methods:** Utilizing Saskatchewan Health databases, TB incidence (cases identified from 1986-2001) was compared between four subpopulations identified from 1991-1995: Registered Indians (RI) with and without diabetes, and other Saskatchewan people (OSKP) with and without diabetes.

**Results:** Diabetic women aged 20-59 years had higher average annual incidence rates of TB than non-diabetic women, but within-population rate ratios of TB in diabetic versus non-diabetic women were only significant in those aged 50-59 (2.7 [CI 1.28, 5.72] in RI and 3.9 [CI 1.58, 9.67] in OSKP). No other within-population diabetic subgroup had significantly higher rates of TB. The only male diabetic group that had a higher rate of TB were RI plus OSKP men aged 50-59 years. Overall, diabetes preceded TB in 87/111 individuals with both diseases ( $p < 0.0001$ ).

**Conclusions:** Our results suggest that T2DM is a predictor for TB in Saskatchewan women aged 20-59 but particularly in RI and OSKP women aged 50-59 years. This has implications for TB screening and prevention initiatives.

**MeSH terms:** Diabetes mellitus; tuberculosis; Indians, North American

*La traduction du résumé se trouve à la fin de l'article.*

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**Disclaimer:** This study is based in part on non-identifiable data provided by the Saskatchewan Department of Health. The interpretations and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

**Funding:** Supported by a grant from the Saskatchewan Health Research Foundation.

Canadian Aboriginal people are experiencing epidemics of both type 2 diabetes (T2DM)<sup>1</sup> and tuberculosis (TB).<sup>2</sup> In Saskatchewan (SK), diabetes was absent in 1,500 Status Indians screened in 1937.<sup>3</sup> By 1990, the age-adjusted rate of self-reported diabetes in SK First Nations (FN) adults was 9.7% compared to 6.1% in the general population,<sup>4</sup> and by 2003/2004, diabetes prevalence rates compiled from Saskatchewan Health databases were 19.2% in adult FN and 5.5% in others.<sup>5</sup> TB rates in SK Aboriginal people are also high, with recent incidence rates (43.8/100,000 in 2004) still 50-60 times higher in FN compared to non-Aboriginal people.<sup>6</sup> These differences in rates of diabetes and TB between Aboriginal and non-Aboriginal people suggest that genetic and/or environmental factors related to ethnicity somehow contribute to disease susceptibility.

Is there a link between these two epidemics? Although an association between diabetes and TB has been suggested for more than a thousand years,<sup>7-13</sup> confounding factors such as socio-economic circumstances could lead to independent rate increases of both. There could also be a biological relationship between them. Active TB can lead to glucose intolerance that resolves with TB treatment.<sup>14,15</sup> Alternatively, diabetes is associated with increased susceptibility to infections primarily due to the effects of hyperglycaemia on cellular immunity and phagocytosis.<sup>16-19</sup> Thus, there is a possible biological relationship between TB and diabetes in either, or both, directions.

Defining relationships between T2DM and TB could be valuable in developing TB screening, treatment and prevention initiatives for high-risk groups. We therefore sought to determine if a relationship exists between the two diseases and to establish whether there is a difference in the degree of this association between Aboriginal and non-Aboriginal people. In individuals with both diseases, we also hoped to establish the temporal relationship between the two.

### METHODS

After approval by the University of Saskatchewan Committee on Ethics in Human Experimentation, this descriptive epidemiological study was conducted using

TABLE I

Age-Sex Distribution of Cumulated TB Cases (1986-2001) in Subpopulations (n) Derived from Saskatchewan's 1991-1995 Covered Population – Age Calculated at June 30, 1993

	Registered Indians				Other SK People				Overall Total
	With Diabetes		No Diabetes		With Diabetes		No Diabetes		RI plus OSKP Males plus Females
	Males	Females	Males	Females	Males	Females	Males	Females	
<20	4 (147)	1 (187)	373 (25,601)	406 (24,744)	1 (960)	0 (951)	113 (171,368)	106 (162,547)	1004 (386,505)
20-29	1 (146)	6 (332)	104 (7812)	117 (7787)	0 (762)	2 (1222)	55 (79,732)	54 (75,759)	339 (173,552)
30-39	2 (311)	9 (544)	53 (4968)	54 (5178)	0 (1463)	1 (1732)	57 (88,313)	36 (84,161)	212 (186,670)
40-49	3 (483)	8 (618)	41 (2336)	29 (2417)	1 (2639)	2 (2096)	37 (62,619)	23 (59,201)	144 (132,409)
50-59	5 (449)	16 (570)	25 (1161)	12 (1156)	7 (4037)	6 (2988)	32 (40,549)	21 (40,833)	124 (91,743)
≥60	9 (473)	11 (738)	53 (1326)	33 (1161)	13 (14,606)	3 (13,968)	105 (78,752)	72 (96,275)	299 (207,299)
Total	24 (2009)	51 (2989)	649 (43,204)	651 (42,443)	22 (24,467)	14 (22,957)	399 (521,333)	312 (518,776)	2122 (1,178,178)
Total ≥20	20 (1862)	50 (2802)	276 (17,603)	245 (17,699)	21 (23,507)	14 (22,006)	286 (349,965)	206 (356,229)	1118 (791,673)

de-identified population-based data from the following Saskatchewan Health databases:<sup>20</sup> health insurance registry (REG), physician's services (DRSV), hospital services (HOSP) and tuberculosis (TB).

Sixteen-year TB incidence rates (and average annual TB incidence) were compared between four subpopulations of SK people that totalled Saskatchewan Health's covered population from January 1, 1991 to December 31, 1995. This five-year span coincided with the middle third of the period for which TB cases were available. The subpopulations were: registered Indians (RI) with and without diabetes, and other SK people (OSKP) with and without diabetes. The RI population were Aboriginal people who were ever registered and assigned a registry number under Section 6 of *The Indian Act*. The OSKP population were predominantly non-Aboriginal people but included non-registered Indians and Metis. Subjects with diabetes were identified on the basis of at least one diabetic service code (ICD9-250) on the DRSV or HOSP databases during the five-year period. For diabetic subjects, we also determined the earliest date of an ICD9 250 code before January 1, 1991 to establish if a diagnosis of TB was made before or after a diagnosis of diabetes in those subjects with both diseases. We were unable to differentiate between type 1 diabetes mellitus and T2DM but over 90% of SK people with diabetes have T2DM.<sup>21</sup>

The TB database includes cases reported to Saskatchewan Health as per the *Public Health Act*. Cases born before 1996 and diagnosed between January 1, 1986 and December 31, 2001 were available. The birth year, sex, ethnicity, year of TB diagnosis, diabetic status, and year of death (if applicable) were provided for each TB case.

Analyses were performed using the SPSS program (version 11). Age groups were

collapsed into those <20 and ≥60 years, and by ten-year age groupings in between (age was calculated at June 30, 1993). We determined the 1991-1995 numbers of RI, OSKP and total populations of SK. RI and OSKP populations were then subdivided into those with and without diabetes to generate the four subpopulations. The 16-year (and average annual) incidence rates of TB within the four subpopulations were then determined. The chi square statistic (two-tailed) was used to calculate total as well as age- and sex-specific rate ratios (with 95% confidence intervals and p values) of TB in diabetic versus non-diabetic groups both within and between RI and OSKP populations.

Our null hypothesis was that no biological relationship exists between diabetes and TB. Accordingly, we expected any chronological relationship between the two diseases to reflect possible age differences in their natural occurrence. Using Yate's corrected Pearson's chi square, we then compared observed with expected results to determine if the actual frequency with which one disease preceded the other was significantly different than expected.

## RESULTS

We identified 2,122 TB cases diagnosed from January 1, 1986 to December 31, 2001, including 121 people with TB whose diabetes status could not be determined. They were assumed to be non-diabetic, which would bias results towards the null.

Table I shows the age-sex distribution of TB cases and study subpopulation numbers. Although the five-year crude prevalence of diabetes was only slightly higher for RI than OSKP (5.5% versus 4.4%), almost 12% of RI aged 20 and older had diabetes compared to just over 6% of OSKP.

Of the 2,122 TB cases, 1,375 were RI. Overall, there were equal numbers of TB cases among non-diabetic RI males and females. In contrast, over twice as many TB cases occurred in diabetic RI females than males. Of the 747 TB cases in OSKP, more occurred in OSKP males than females regardless of diabetic status.

Total within-population (RI or OSKP) average annual TB incidence rates were similar in both diabetic and non-diabetic subjects ranging from 93.8-95/100,000 in RI and from 4.4-5/100,000 in OSKP. All between-population differences were statistically significant. The highest overall TB case rate among men was 93.8/100,000 in non-diabetic RI. In contrast, the highest overall TB case rate among women was 106.9/100,000 in diabetic RI.

Tables II, III and IV show the within-population (RI or OSKP) and overall (RI plus OSKP) rate ratios of TB cases in diabetic versus non-diabetic subjects. Overall, SK diabetics aged ≥20 were significantly more likely than non-diabetics to have TB (RR 1.53; CI 1.25, 1.87). However, this was primarily due to higher rates of TB in SK diabetic women between the ages of 20 and 59. Higher rates of TB in diabetic subjects within-populations were only statistically significant for women aged 50-59. Overall, diabetic males aged 50-59 experienced higher rates of TB than their non-diabetic male counterparts. Within RI and OSKP populations, diabetic males plus females aged ≥60 had lower rates of TB than non-diabetics.

TB and diabetes both occurred in 111 subjects. Table I shows that TB case numbers (and incidence) were highest in younger age groups while diabetes prevalence rates increased progressively with age. Despite this, diabetes preceded TB in 87 people (78.4%); this temporal relationship

**TABLE II**  
Rate Ratios (95% Confidence Intervals) of Tuberculosis Cases in Diabetic Versus Non-Diabetic Subjects – Registered Indians

	Males		Females		Total	
	Rate Ratio	CI	Rate Ratio	CI	Rate Ratio	CI
20-29	0.51	(0.07, 3.69)	1.20	(0.53, 2.73)	1.03	(0.49, 2.19)
30-39	0.60	(0.15, 2.47)	1.59	(0.78, 3.21)	1.22	(0.66, 2.27)
40-49	0.35	(0.11, 1.14)	1.08	(0.49, 2.36)	0.68	(0.36, 1.28)
50-59	0.52	(0.20, 1.35)	2.70	(1.28, 5.72)†	1.29	(0.76, 2.20)
≥60	0.48	(0.23, 0.97)*	0.52	(0.27, 1.04)	0.48	(0.29, 0.78)†
Total ≥20	0.69	(0.44, 1.08)	1.29	(0.95, 1.75)	1.02	(0.79, 1.31)

\* p&lt;0.05

† p&lt;0.01

**TABLE III**  
Rate Ratios (95% Confidence Intervals) of Tuberculosis Cases in Diabetic Versus Non-Diabetic Subjects – Other SK People

	Males		Females		Total	
	Rate Ratio	CI	Rate Ratio	CI	Rate Ratio	CI
20-29	–	–	2.30	(0.56, 9.42)	1.44	(0.36, 5.82)
30-39	–	–	1.35	(0.19, 9.85)	0.58	(0.08, 4.16)
40-49	0.64	(0.09, 4.67)	2.46	(0.58, 10.42)	1.29	(0.40, 4.10)
50-59	2.20	(0.97, 4.98)	3.90	(1.58, 9.67)†	2.84	(1.55, 5.21)†
≥60	0.67	(0.38, 1.19)	0.29	(0.09, 0.91)*	0.55	(0.33, 0.92)*
Total ≥20	1.09	(0.70, 1.70)	1.10	(0.64, 1.89)	1.10	(0.78, 1.56)

Blank cell indicates no tuberculosis cases in diabetic population.

\* p&lt;0.05

† p&lt;0.01

**TABLE IV**  
Rate Ratios (95% Confidence Intervals) of Tuberculosis Cases in Diabetic Versus Non-Diabetic Subjects – RI plus OSKP

	Males		Females		Total	
	Rate Ratio	CI	Rate Ratio	CI	Rate Ratio	CI
20-29	0.61	(0.08, 4.33)	2.52	(1.24, 5.11)*	1.9	(0.98, 3.67)
30-39	0.96	(0.24, 3.87)	4.36	(2.27, 8.38)‡	2.71	(1.51, 4.84)†
40-49	1.07	(0.39, 2.91)	4.37	(2.22, 8.59)‡	2.34	(1.35, 4.05)†
50-59	1.96	(1.05, 3.65)*	7.87	(4.59, 13.49)§	3.93	(2.65, 5.83)§
≥60	0.74	(0.48, 1.17)	0.88	(0.51, 1.54)	0.82	(0.58, 1.16)
Total ≥20	1.06	(0.77, 1.45)	2.14	(1.65, 2.78)§	1.53	(1.25, 1.87)§

\* p&lt;0.05

† p&lt;0.01

‡ p&lt;0.001

§ p&lt;0.0001

**TABLE V**  
Proportion of TB Cases Preceded by Diabetes

	Registered Indians		Other SK People	
	Males	Females	Males	Females
<20	2/4	1/1	1/1	0/0
20-29	0/1	3/6	0/0	1/2
30-39	2/2	7/9	0/0	1/1
40-49	2/3	7/8	0/1	2/2
50-59	4/5	13/16	4/7	4/6
≥60	9/9	10/11	11/13	3/3
Total	19/24 (79.2%)	41/51 (80.4%)	16/22 (72.7%)	11/14 (78.6%)

was particularly consistent in older age groups (Table V). If neither disease has any impact on the development of the other, we would have conservatively expected at least half of TB cases to occur before the onset of diabetes. Comparing observed with expected results, the occurrence of most cases of TB after the diagnosis of diabetes was statistically significant (p<0.0001).

## DISCUSSION

A relationship between diabetes and TB has been suspected for more than a 1000 years,<sup>7,8</sup> with modern reports of this association first appearing in the American literature early in the 20<sup>th</sup> century.<sup>7-9</sup> The first comparison of TB rates in matched populations was reported in 1952<sup>10</sup> when those with diabetes were found to have twice the

risk for TB compared to non-diabetics. More recently, reports from both the English and non-English literature cite varying degrees of a relationship between the two diseases.<sup>11-13,22-25</sup>

Our main finding was that diabetic women aged 50-59 years had higher 16-year incidence rates of TB than non-diabetic women regardless of ethnicity. Rate ratios of TB in diabetic versus non-diabetic women in this age group were 2.7 (CI 1.28, 5.72) in RI and 3.9 (CI 1.58, 9.67) in OSKP. No other within-population (RI or OSKP) diabetic subgroup had significantly higher rates of TB. However, when populations were combined (RI plus OSKP), higher rates of TB in diabetic versus non-diabetic women were observed in age groups from 20-59 years. The only combined male diabetic group that had a higher rate of TB were men aged 50-59 years.

The lowest significant rate ratios for TB in diabetic versus non-diabetic adults were observed in both RI and OSKP subjects ≥60 years. Whether this represents a true reduction in TB risk in these diabetic groups, a statistical anomaly due to combining several age groups with small cell sizes, the consequence of differential mortality (those diabetics at most risk for TB may have already died), or another reason is not clear. It is a consistent observation that warrants further investigation.

Why are diabetic females more likely to have TB than diabetic males? There are several possibilities. First, male diabetic subjects with TB may be misclassified as non-diabetics more frequently than women because of less than recommended chronic health care utilization.<sup>26</sup> Second, diabetic women may be more susceptible to TB than diabetic men. Estrogens inhibit cytokines such as gamma interferon and alpha tumour necrosis factor.<sup>27-29</sup> The potential for an immunosuppressive effect might be enhanced by diabetes. Finally, our observations could be due to increased environmental exposure to TB among women. Women may be more likely to be at home as well as in a caregiving role. This could lead to increased exposure to others with TB and pose a particular risk of infection for those with diabetes. Whatever the underlying reason, the fact that higher rates of TB were found in both RI and OSKP diabetic women aged 50-59, and



that there is a reversal in the usual increased male to female ratio of TB in diabetic Mexicans,<sup>25</sup> supports the validity of this observation.

An important finding from our study is that diabetes usually preceded TB. Moreover, some older subjects in whom TB preceded diabetes may have been in a pre-diabetic state (or had undiagnosed diabetes). These observations provide temporal evidence for a possible cause and effect relationship. This is supported by a case-control study that showed that T2DM is an independent risk factor for TB in Hispanic subjects,<sup>13</sup> and by observations that the precise defects in cellular immunity and phagocytosis found with diabetes are those known to predispose to TB.<sup>30</sup> For example, a recent study reported a decrease in alveolar macrophage activity in diabetics with TB.<sup>31</sup>

There are a number of limitations to this study. First, a descriptive study design is limited in its ability to assess cause and effect. Second, OSKP includes some non-registered Aboriginal people, and some subjects in both the non-diabetic and diabetic groups were likely misclassified. However, these limitations will reduce true differences between our four study sub-populations and result in a tendency for our results to be conservative (Type II error). Finally, although all known cases of TB in Saskatchewan are reported to the TB Control Program, formal screening programs are carried out more commonly among RI. This could lead to an under-estimation of TB cases in OSKP; however, this would not affect within-population comparisons of diabetes and non-diabetes groups.

These findings have implications for the screening, treatment and prevention of TB. Diabetes should be considered a risk factor for TB in diabetic women aged 50-59 regardless of ethnicity and a possible predictor of TB in younger adult women as well. However, because of the marked differences in absolute TB rates between RI and OSKP, the greatest concern is for diabetic Aboriginal women. Given the documented efficacy of treating latent TB infection (LTBI),<sup>32</sup> the issue of providing appropriate LTBI treatment to this population will need to be evaluated.<sup>33</sup> For example, it has been suggested that among Oglala Sioux, eliminating TB in those with

diabetes could prevent a significant number of cases.<sup>11,33</sup> If our results are confirmed, such efforts could be applied more specifically on the basis of age and gender.

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## RÉSUMÉ

**Contexte :** Les Autochtones de la Saskatchewan sont aux prises avec des épidémies de diabète de type II et de tuberculose. Dans cette étude, nous avons voulu déterminer s'il existe un lien entre le diabète et la tuberculose en Saskatchewan, et s'il y a une différence entre les Autochtones et les non-Autochtones en ce qui a trait au degré d'association éventuel entre ces maladies.

**Méthode :** À l'aide des bases de données du ministère de la Santé de la Saskatchewan, nous avons comparé la fréquence de la tuberculose (les cas détectés de 1986 à 2001) dans quatre sous-populations définies pour la période de 1991 à 1995 : les Indiens inscrits, diabétiques et non diabétiques, et les autres habitants de la Saskatchewan (AHSK), diabétiques et non diabétiques.

**Résultats :** Chez les femmes diabétiques de 20 à 59 ans, le taux d'incidence annuel moyen de la tuberculose était plus élevé que chez les femmes non diabétiques, mais les ratios des taux de tuberculose entre les femmes diabétiques et non diabétiques dans chaque population n'étaient significatifs que pour les femmes de 50 à 59 ans (IC de 2,7 [1,28 à 5,72] chez les Indiennes inscrites et de 3,9 [1,58 à 9,67] chez les AHSK). Aucun autre sous-groupe de diabétiques à l'intérieur d'une population n'avait de taux sensiblement plus élevés de tuberculose. Le seul groupe d'hommes diabétiques dont le taux de tuberculose était plus élevé se composait d'Indiens inscrits et d'AHSK âgés de 50 à 59 ans. Globalement, le diabète avait précédé la tuberculose chez 87 des 111 sujets ayant les deux maladies (p<0,0001).

**Conclusions :** Nos résultats donnent à penser que le diabète de type II est un prédicteur de la tuberculose chez les femmes de la Saskatchewan de 20 à 59 ans, mais plus particulièrement chez les Indiennes inscrites et les autres habitantes de la Saskatchewan âgées de 50 à 59 ans. Ceci aurait des conséquences pour le dépistage et les mesures de prévention de la tuberculose.

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Received: October 12, 2005  
Accepted: July 14, 2006

## Coming Events / Activités à venir

To be assured of publication in the next issue, announcements should be received by **January 31, 2007** and valid as of **February 28, 2007**. Announcements received after **January 31, 2007** will be inserted as time and space permit.  
Pour être publiés dans le prochain numéro, les avis doivent parvenir à la rédaction avant le **31 janvier 2007** et être valables à compter du **28 février 2007**. Les avis reçus après le **31 janvier 2007** seront insérés si le temps et l'espace le permettent.

9<sup>th</sup> National Metropolis Conference  
*Exploring Canada's Diversity, Today and Tomorrow*  
Hosted by the Joint Centre of Excellence for Research on Immigration and Settlement - Toronto (CERIS)  
1-4 March 2007 Toronto, ON  
Health Plenary (one of six thematic plenaries): *Health and Newcomer Wellbeing: Intersections of Gender, Poverty, and Racialization*  
This panel will debate the impact of migration on the health of immigrants and refugees, with a particular focus on the experiences of newcomers. Discussions will be framed within a social determinants framework and attempts will be made to disentangle the intersections of gender, socioeconomic opportunities and challenges, social integration, and health and social systems' responses to the changing demographics of different waves of migrants.  
Contact: [www.metropolis2007.net](http://www.metropolis2007.net)

*Healthcare Safety Forum 2007*  
Presented by the Canadian Standards Association and the Ontario Safety Association for Community & Healthcare  
5-6 March 2007 Toronto, ON  
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Primary Care Today Education Conference & Medical Exposition  
*Quality Time with Hard-to-Reach GP/FM's and Primary Care Professionals*  
10-12 May 2007 Toronto, ON  
Contact: Primary Care Today  
Tel: (toll free) 1-888-433-6786  
Fax: 905-479-1364  
E-mail: [info@primarycaretoday.ca](mailto:info@primarycaretoday.ca)  
[www.PrimaryCareToday.ca](http://www.PrimaryCareToday.ca)

45<sup>th</sup> International Making Cities Livable Conference  
*True Urbanism: Designing for Social & Physical Health*  
Co-sponsored by The City of Portland & Portland Metro Planning Council  
Co-organized with the University of Notre Dame School of Architecture  
10-14 June 2007 Portland, OR  
Contact:  
Suzanne H. Crowhurst Lennard Ph.D.(Arch.)  
Program Committee Chair  
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Fax: +1- 831-624-5126.  
E-mail: [Suzanne.Lennard@LivableCities.org](mailto:Suzanne.Lennard@LivableCities.org)  
[www.LivableCities.org](http://www.LivableCities.org)

### CALL FOR ABSTRACTS

4<sup>th</sup> International Conference on Children's Health and the Environment  
*Risk-reduced Environments for Children*  
10-12 June 2007 Vienna, Austria  
Organised by the International Network on Children's Health, Environment and Safety (INCHES) and by the Private University for Health Sciences, Medical Informatics and Technology (UMIT) located at the University UMIT, Department of Public Health, Medical Decision Making and Health Technology Assessment, Hall in Tirol, Austria  
Contact:  
Conference Secretariat  
c/o Julia Hellmann  
Dept. of Public Health, Medical Decision Making and Health Technology Assessment, UMIT  
Tel: +43 - 50 - 8648 - 3878  
Fax: +43 - 50 - 8648 - 67 - 3878  
E-mail: [INCHES@umit.at](mailto:INCHES@umit.at)  
[www.inchesnetwork.net](http://www.inchesnetwork.net)  
**Deadline for abstracts: 1 February 2007**

The 19<sup>th</sup> IUHPE World Conference on Health Promotion & Health Education  
*Health Promotion Comes of Age: Research, Policy and Practice for the 21<sup>st</sup> Century*  
International Union for Health Promotion and Education  
11-15 June 2007 Vancouver, BC  
Contact:  
E-mail: [canada2007@iuhpeconference.org](mailto:canada2007@iuhpeconference.org)  
[www.iuhpeconference.org](http://www.iuhpeconference.org)

### CALL FOR ABSTRACTS

International Conference on Physical Activity & Obesity in Children: Science, Policy, Practice  
Organized by the Canadian Fitness and Lifestyle Research Institute (CFLRI)  
24-27 June 2007 Toronto, Ontario  
Contact:  
CFLRI  
Tel: 613-233-5528  
Fax: 613-233-5536  
E-mail: [mcosta@cflri.ca](mailto:mcosta@cflri.ca)  
<http://www.phe.queensu.ca/epi/obesity/index.htm>  
**Deadline for abstracts: 1 May 2007**

Forum 11  
*Equitable Access: Research Challenges for Health in Developing Countries*  
29 October-2 November 2007 Beijing, China  
Global Forum for Health Research  
The annual Forum brings together decision-makers, funders and leaders in research and development to focus on reducing the massive underinvestment in health research for the needs of developing countries.  
Contact:  
[www.globalforumhealth.org](http://www.globalforumhealth.org)