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Review

Epidemiology of Cerebrovascular Disease among Chinese Canadians with Diabetes

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ABSTRACT

Background: First-generation Chinese Canadians have usually maintained different lifestyles before immigration to North America, and the question of whether Chinese Canadians with type 2 diabetes have a different stroke profile than that of non-Chinese Canadians remains unanswered.
Objectives: To determine whether 1) Chinese Canadians who have had a stroke within the last 15 years are more likely to have diabetes than non-Chinese Canadians and 2) to explore differences in stroke profiles between the 2 cohorts.
Methods: Age- and sex-matched Chinese Canadians (n=70) and non-Chinese Canadians (n=107) were compared on the basis of stroke type, age at stroke onset, stroke etiology and common risk factors. Classifications for disease were done according to professional guidelines. Statistical analysis was done with Student *t* test and odds ratios to confirm differences between groups.
Results: Chinese Canadians with stroke had a higher frequency of diabetes mellitus than non-Chinese Canadians. Chinese Canadians with diabetes were more likely to have small vessel disease, specifically lacunar stroke. Chinese Canadians at high risk for stroke were more likely to have a poor prognosis than non-Chinese Canadians, with near significance.
Conclusion: Chinese Canadians with diabetes who had ischemic strokes were especially susceptible to intracranial small vessel disease compared with non-Chinese Canadians. These results signify that risk factor prevalence and stroke types differ considerably between Chinese Canadians and non-Chinese Canadians residing in Toronto, warranting further study.

Mots clés :
maladie cérébrovasculaire
Sino-Canadiens
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accident vasculaire cérébral

RÉSUMÉ

Introduction : Puisque les Sino-Canadiens de première génération ont généralement eu des modes de vie différents avant leur immigration en Amérique du Nord, on se demande encore si les Sino-Canadiens atteints du diabète de type 2 ont un profil d'accident vasculaire cérébral différent de celui des Canadiens d'origine non chinoise.
Objectifs : 1) Déterminer si les Sino-Canadiens qui ont subi un accident vasculaire cérébral au cours des 15 dernières années sont plus susceptibles d'être atteints de diabète que les Canadiens d'origine non chinoise ; 2) Examiner les différences de profils de l'accident vasculaire cérébral entre les 2 cohortes.
Méthodes : Les Sino-Canadiens appariés selon l'âge et le sexe (n=70) et les Canadiens d'origine non chinoise (n=107) ont été comparés en se basant sur le type d'accident vasculaire cérébral, l'âge au moment de l'accident vasculaire cérébral, l'étiologie de l'accident vasculaire cérébral et les facteurs de risque courants. La classification de la maladie a été faite selon les lignes directrices professionnelles. L'analyse statistique a été réalisée à l'aide du test de t de Student et des ratios d'incidence approché pour confirmer les différences entre les groupes.

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Résultats : Les Sino-Canadiens ayant subi un accident vasculaire cérébral étaient plus souvent atteints de diabète sucré que les Canadiens d'origine non chinoise. Les Sino-Canadiens diabétiques étaient plus susceptibles d'être atteints d'une microangiopathie, particulièrement d'un infarctus lacunaire. Les Sino-Canadiens exposés à un risque élevé d'accident vasculaire cérébral étaient plus susceptibles d'avoir un mauvais pronostic que les Canadiens d'origine non chinoise, et ce, de manière presque statistiquement significative.
Conclusion : Les Sino-Canadiens diabétiques qui ont eu des accidents ischémiques cérébraux étaient particulièrement plus susceptibles d'être atteints d'une microangiopathie intracrânienne que les Canadiens d'origine non chinoise. Ces résultats signifient que la prévalence des facteurs de risque et les types d'accidents vasculaires cérébraux diffèrent considérablement entre les Sino-Canadiens et les Canadiens d'origine non chinoise de Toronto, et justifient des études plus approfondies.

Introduction

Type 2 diabetes is a well-established risk factor for stroke and stroke mortality. Patients who have type 2 diabetes have an increased risk for stroke and stroke-related death compared with their counterparts without diabetes after adjustments have been made for age, sex, cholesterol level, education, smoking history, alcohol consumption and body mass index (1). Previous community studies have concluded that Asians are at higher risk for primary intracerebral hemorrhage and ischemic stroke compared with New Zealanders and Europeans matched for age and sex (2). A previous retrospective study also indicated that Chinese Canadians (CCs) exhibit significant differences in stroke characteristics and risk factors compared with their Caucasian counterparts (3). Although these studies brought to light differences between these cohorts, what remains unclear is whether there are differences in prevalence of diabetes, stroke subtypes and stroke severity. Previous studies have shown that Chinese individuals in Hong Kong have more severe intracranial atherosclerosis and less severe extracranial carotid artery stenosis compared with Caucasians (4). These findings are further supported by angiographic studies, which have demonstrated that Asians tend to have greater rates of intracranial vascular stenosis and Caucasians tend to have higher rates of carotid disease (5–7). Furthermore, there is a high prevalence of undiagnosed diabetes in Chinese patients with ischemic stroke (8).

For this project, we studied first-generation CC immigrants to explore whether their stroke profiles and risk factors differ from those of non-CCs. CCs are identified as first generation if their heritage or ancestry is from China and their place of birth is outside of Canada. Non-CCs are identified as Canadians with a non-Chinese heritage. The objectives were to confirm whether differences exist between CC and non-CC patients with stroke and type 2 diabetes by exploring 1) whether CC patients with stroke more frequently have type 2 diabetes compared with non-CC patients and 2) whether there are differences in stroke profiles between non-CCs and CCs with type 2 diabetes.

Methods

The patient data collected for this study were obtained in part from patient charts of Dr. J. Y. Chu (co-author) within his neurology clinic in Toronto. Additional patient data were obtained from Stroke Prevention Clinic hospital charts with permission from the ethics review committee at the William-Osler Health System (Etobicoke, Ontario, Canada).

Participants

Patients were seen between 2001 and 2011 at a Toronto neurology clinic and at William Osler Health System Stroke Prevention Clinic at Brampton Civic Hospital. Patients were included in the study if they were diagnosed with a stroke. A diagnosis of a stroke was made if a neurologic deficit lasted for more than 24 hours and was caused by a vascular disorder affecting the brain. Type 2 diabetes was diagnosed according to the *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* (9). Hypertension diagnoses were made according to the Canadian Hypertension Guidelines (10). Patients with diagnoses of subdural hemorrhages, subarachnoid hemorrhages, lesions such as brain tumour/abscess on computed tomography scans or transient ischemic attacks only (but not stroke) were excluded from the study. All patients were examined by the lead author (JYC) and had undergone computed tomography scanning and/or magnetic resonance imaging/magnetic resonance angiography scans that confirmed the clinical diagnosis.

Table 1
Classification of acute stroke using modified TOAST criteria

Modified TOAST Classification of Ischemic Stroke Subtypes
Atherosclerosis of great vessels (ATH)
Cardioembolism (excluding cases attributed to patent foramen ovale/atrial septal defect) (CE)
Occlusion of small vessels (lacunar) (OSV)
Ischemic stroke of another etiology (defined) (ISCAN)
Two or more identified causes (2ORMORE)
Cryptogenic ischemic stroke (CRYPT)

CC and non-CC patients with stroke and diabetes were selected by last name and birth country, then matched for age and sex (11). The type of stroke was classified according to the *International Classification of Diseases, 9th revision* (*ICD-9*) (12). Stroke types included in this study are ischemic cerebral infarction (*ICD-9* code 436), lacunar infarction (*ICD-9* code 434.9), embolic cerebral infarction (*ICD-9* code 434.1) and intracerebral hemorrhage (*ICD-9* code 431). Classification of stroke was done according to the modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria by the American Heart Association (see Table 1). Guideline values and prognosis stratification with hypertension severity grade (HSG) were obtained from the World Health Organization (WHO) criteria (grade 1: blood pressure [BP] >140/90, grade 2: BP>160/100, grade 3: BP>180/110) (13). HSG classifies patients' numerical BP values, which could assist in predicting higher risks for other complications. Prognosis was quantified according to a stratification table obtained from the WHO, which outlines prognosis according to the number of risk factors corresponding to HSG (see supplemental chart in Appendix 1) (13–15).

Data collection

Data collection was completed by using Microsoft Excel. Patient data were collected through retrospective chart review, and fields that were collected included age, sex, ethnicity, body mass index, overweight, year last seen, BP, hyperlipidemic profile, smoking history, heart disease history, comorbidity with type 2 diabetes and profile, age at stroke diagnosis, stroke type, stroke severity (based on modified Rankin scale), stroke location, stroke etiology and previous strokes.

Measures

The following measures were obtained: 1) frequency of type 2 diabetes; 2) etiology and stroke type in patients with diabetes mellitus (DM); 3) risk factor differences between CCs and non-CCs with DM; 4) risk for poor prognosis; 5) HSG and 6) BP values.

Analysis

Odds ratios and unpaired 2-sample *t* tests were used to confirm significance.

All calculations were also completed by using Microsoft Excel to calculate associated averages, standard deviations, odds ratios and significance (Welch's Student *t* test).

Results

Mean age of the CC cohort at the time of stroke diagnosis was 69.0 years. Gender stratification yielded mean ages of 69.7 years for women and 68.3 years for men. Mean age of the non-CC cohort was 68.7 years, with gender stratification yielding mean ages of 69.8 years for women and 67.9 years for men.

Significance was confirmed in the following contexts with a p value less than 0.05. In the first portion of the study, patients with stroke without DM were considered to determine incidence of comorbid stroke and DM. Findings showed that CCs had higher DM and stroke incidence than non-CCs (Figure 1). CCs with diabetes more frequently had small vessel disease (SVD), specifically lacunar stroke (Figure 2). Furthermore, SVD frequency dominated large vessel disease in the CCs (Figure 3). In terms of the modified TOAST criteria, significant differences were found in the "Occlusion of Small Vessels," "Atherosclerosis of Large Vessels" and "Two or More Identified Causes" categories. The CC cohort had a significantly greater proportion of patients in the "Occlusion of Small Vessels" category compared with the non-CC cohort. In contrast, the non-CC cohort had a significantly greater proportion of patients in the "Atherosclerosis of Large Vessels" and "Two or More Identified Causes" categories than the CC cohort (Figure 4). Table 3 summarizes the prominent difference in the simultaneous occurrence of SVD and a concurrent risk factor, showing that CCs were more likely be overweight and have hyperlipidemia or hypertension when diagnosed with SVD compared with non-CCs.

The CC cohort was significantly less likely than the non-CC cohort to have a poor prognosis when classified as low risk according to the stratification method outlined by the WHO (14). However, a higher proportion of CCs was found to have poor prognosis than non-CCs when classified as high risk, with near significance ($0.05<p<0.10$). A higher proportion of CCs had a low HSG of 0 compared with non-CCs, whereas a significantly higher proportion of non-CCs had an HSG of 3. HSGs are summarized in Table 2. In terms of BP statistics, non-CC men had significantly higher systolic BP than CC men. The collective systolic BP data for both sexes yielded values near significance ($0.05<p<0.10$). Comparison of diastolic BPs between the 2 groups yielded no significant difference.

Discussion

The mean age at diagnosis of stroke in patients with DM showed no significant variation in the 2 cohorts. Figure 1 shows a significant difference in the proportion of CC and non-CC patients with stroke and DM. The occurrence of stroke and DM is remarkably more frequent in the CC cohort than in the non-CC cohort. ($p<0.05$)

In the literature, it has been suggested that Chinese individuals are especially at risk for stroke, with hypertension being a major risk factor (16). It has also been found that a genetic variation, "rs1799998 (-344C/T)" of the *CYP11B2* (aldosterone synthase) gene, may contribute to the risk for ischemic stroke with moderate effect in the Han Chinese population because of its influence on BP, vasoconstriction, thrombosis and vessel wall damage (17). This is complemented by another study showing that the typical Chinese diet includes more sodium than Western diets (18, 19). On the other hand, findings by Gould et al (20) show that some aspects of SVD can be genetically associated, particularly with *COL4A1*. The mutation of this gene causes a spectrum of cerebrovascular phenotypes that may increase chances of stroke and hemorrhage.

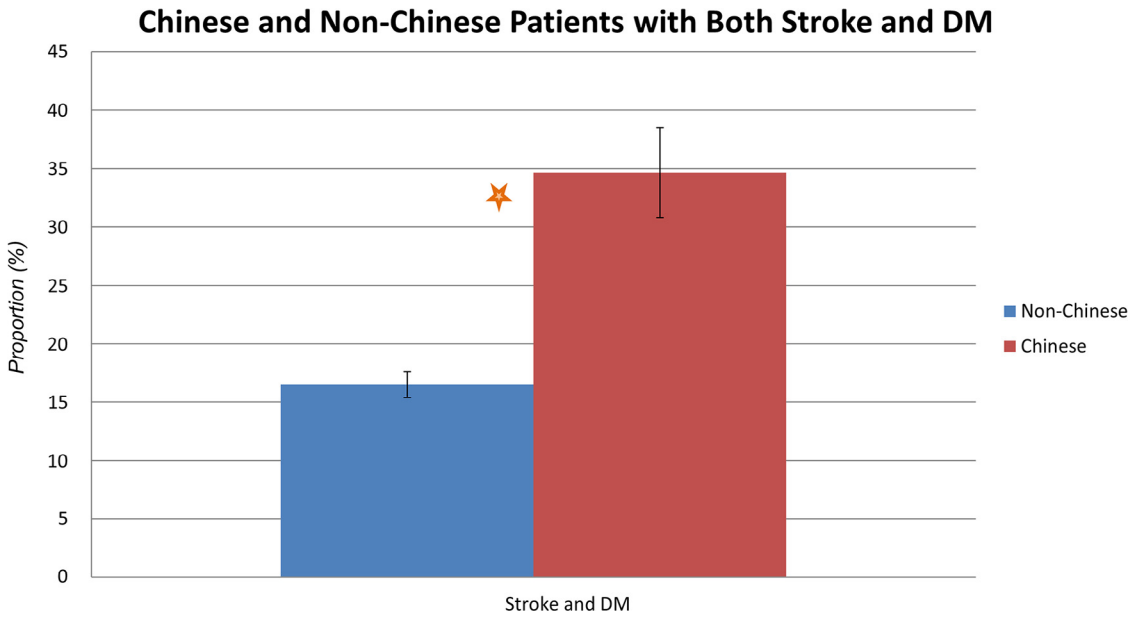

Figure 1. Proportion of Chinese and non-Chinese patients with both stroke and diabetes mellitus (DM) in our database. Data are expressed as proportions (number of patients with stroke and DM/total number of patients of the particular ethnicity). Number of Chinese-Canadian patients with stroke = 101; number of non-Chinese patients = 926. The star represents $p<0.05$.

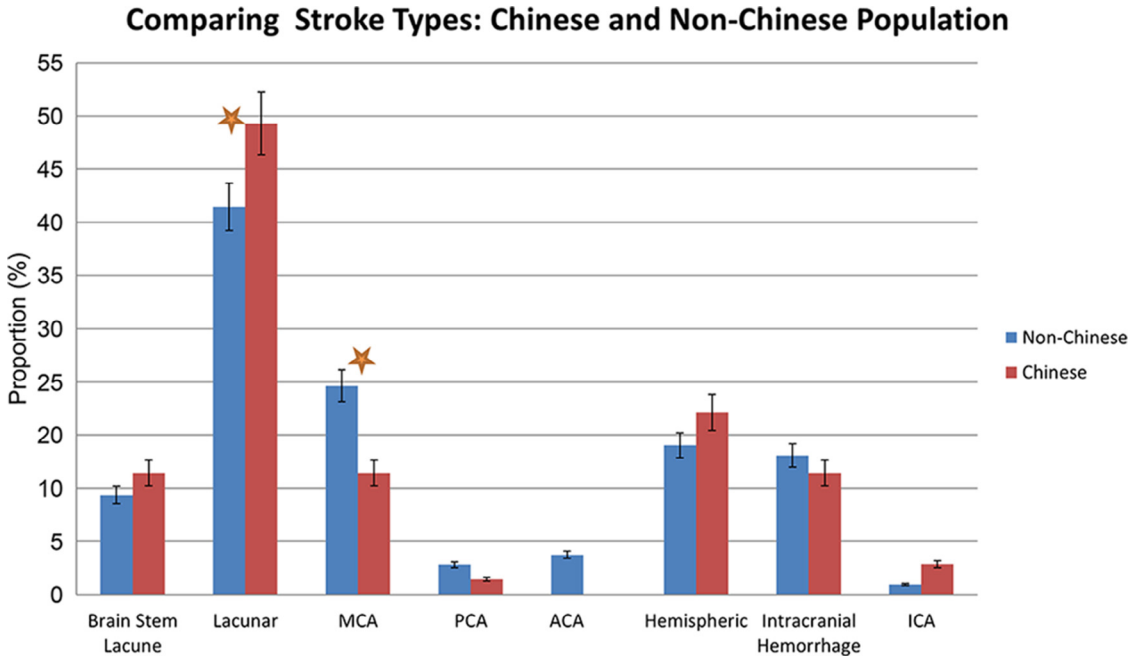

Figure 2. Various stroke types and their corresponding incidences in the 2 cohorts. Data are expressed as proportions (number of patients with stroke type/total number of patients of the particular ethnicity). Number of Chinese-Canadian patients = 70; number of non-Chinese patients = 107. The star represents p<0.05. *ACA*, anterior cerebral artery; *ICA*, internal carotid artery; *MCA*, middle cerebral artery; *PCA*, posterior cerebral artery.

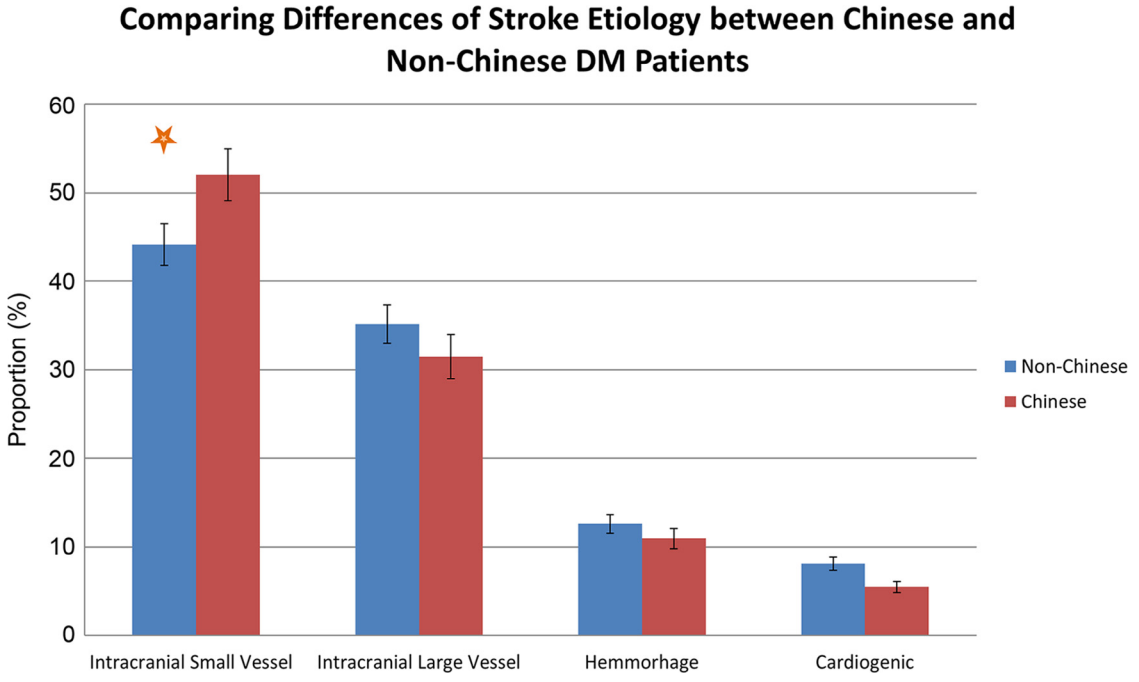

Figure 3. Distribution of varying stroke etiologies from each cohort. Data are expressed as proportions (number of patients with stroke etiology/total number of patients in the 4 categories). Number of Chinese-Canadian patients = 73; number of non-Chinese patients = 111. The star represents p<0.05. *DM*, diabetes mellitus.

Environmental stress enhances this outcome (21). These claims all direct attention to the question of whether the causes of these differences are environmental, genetic or a mixture of both.

Figure 2 shows that a significantly larger proportion of Chinese patients with stroke and DM have lacunar stroke compared with non-Chinese patients, whereas non-Chinese patients have a significantly higher proportion of middle cerebral artery infarctions. This supports our original notion that Chinese patients may be especially vulnerable to SVD and is consistent with findings from a study conducted in Hong Kong indicating that SVD and hemorrhages are more likely than other stroke types (22). Figure 3 shows an analysis of the frequency of SVD versus large vessel disease in our cohorts and indicates the same difference, whereby SVD is more frequent in Chinese patients with stroke and DM than in non-Chinese patients with similar diagnoses. A possible explanation for this is that the effect is due to genetic factors, since Hong Kong and Canadian cultures and environments are substantially different. A relatively consistent observation such as this may indicate an underlying factor

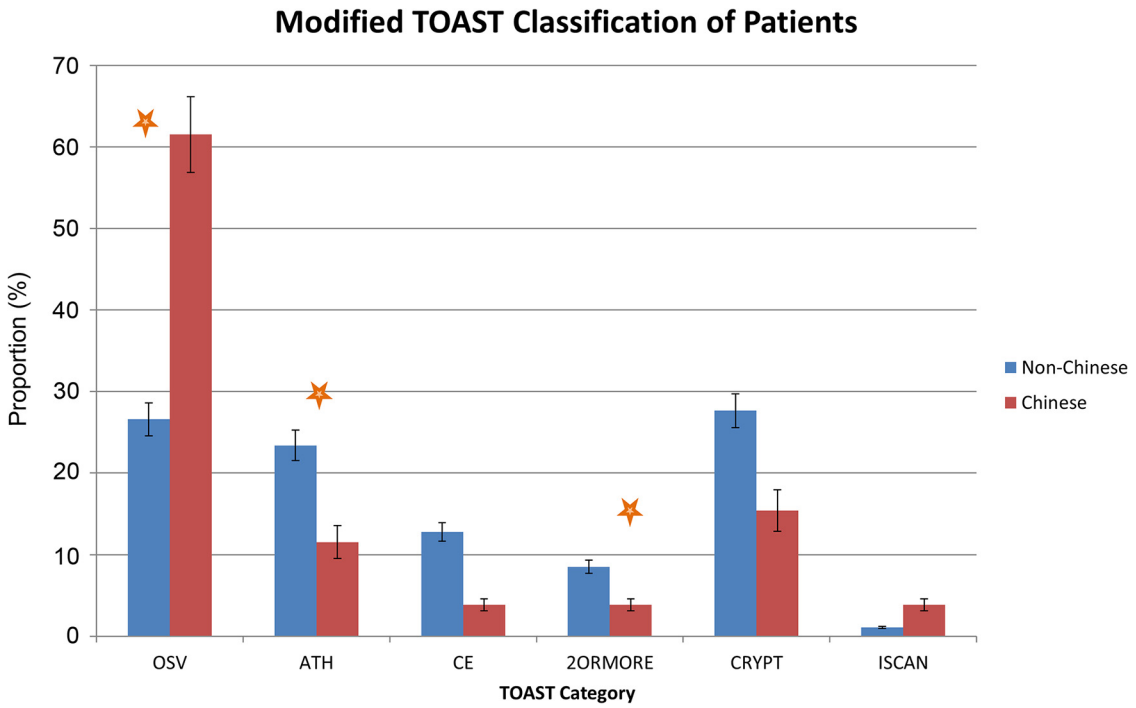

Figure 4. Proportion of patients with stroke within each category of the modified TOAST criteria. Data are expressed as number of patients in that category divided by total number of patients in that cohort. The star represents p<0.05. *2ORMORE,* 2 or more identified causes; *ATH,* atherosclerosis of great vessels: *CE,* cardioembolism; *CRYPT,* cryptogenic ischemic stroke; *ISCAN,* ischemic stroke of another etiology; *OSV,* occlusion of small vessels.

Table 2
Distribution of hypertension severity and odds ratios

Hypertension severity	Non-Chinese proportion	Chinese proportion	Odds ratio, Non-Chinese/Chinese
0	0.3590	0.4857	**0.5929**
1	0.2906	0.3429	0.7851
2	0.2564	0.1143	**2.6724**
3	0.0940	0.0571	1.7123

Odds ratios calculated from the proportion of patients with a particular hypertension severity grade from each cohort. The values in bold indicate odds ratios that are significant (p<0.05) when comparing non-Chinese over Chinese likelihood.

unaffected by the environment, supporting the genetic explanation. It is also important to acknowledge that there are currently no data on how long Chinese immigrants have lived in Canada, and there is also no current reliable resource that would indicate whether these immigrants adopted a Canadian lifestyle and diet.

The data in Figure 4, classified according to the modified TOAST criteria (Table 1), indicate that the CC cohort had a higher incidence of stroke originating from occlusion of small vessels and a lower incidence of stroke originating from atherosclerosis of great vessels. This is consistent with our other data, suggesting that the CC cohort were more susceptible to SVD than the non-CC cohort. Interestingly, a genetic study done to test for polymorphisms in a prostaglandin gene in the Chinese population revealed that the A-1195-G-765 haplotype of *COX-2* is associated with susceptibility to ischemic stroke in the Chinese population, with the effects confined to the subgroup that had small vessel occlusion rather than large artery atherosclerosis (23). This suggests that there may be a specific marker that increases the incidence of small vessel occlusion in the Chinese population. Similar studies have been done to investigate the association of genetics with ischemic stroke in other ethnicities. In large-scale studies in Great Britain and Germany, numerous single nuclear polymorphisms that were associated with ischemic stroke and myocardial infarction in white populations were discovered, although it is not clear whether these polymorphisms are specifically associated with large artery atherosclerosis (24).

More CC patients with type 2 diabetes and hypertension, with a higher HSG, were classified as being at high risk for a poor prognosis. This is in contrast to more non-CC patients with a higher HSG who had a low risk for a poor prognosis. These are interesting findings, because CC patients with higher HSGs fared worse than non-CC patients. Possible explanations for this are that Chinese patients with stroke, type 2 diabetes and hypertension have an alternate pathologic mechanism for disease, leading to poorer prognoses compared with non-Chinese patients with similar diagnoses. It is also crucial to raise awareness of stroke risk factors among both CC and non-CC populations to reduce stroke incidence and mortality (17, 23–29).

Limitations of study

The main limitation is that this is a pilot study in which patient data were obtained from a private neurology clinic and a single, but large, community hospital in the Toronto area. Some referral bias may have occurred in patient selection, and one limitation may be the result of missing some CC women who married non-CCs and did not retain their Chinese maiden names. Additionally, dietary and lifestyle factors will need to be considered and studied systematically in future population-based prospective studies to determine whether genetic or environmental factors influence stroke epidemiology of CCs. The current study is focused mainly on first-generation CCs, and long-term prospective studies of successive generations of CCs who have adopted the Canadian diet and lifestyle may reveal different stroke epidemiology. Such studies may provide further insight into how genetics interact with environmental factors in stroke development.

Table 3
Stroke types and risk factors

	Overweight, SVD	Overweight, LVD	Hyperlipidemia, SVD	Hyperlipidemia, LVD	Hypertension, SVD	Hypertension, LVD
Chinese	**26.9%**	7.7%	**36.5%**	15.0%	**53.8%**	25.0%
OR, SVD/LVD	**4.42**		**3.26**		**3.50**	
Non-Chinese	**16.5%**	7.9%	**23.6%**	15.0%	**33.1%**	26.0%
OR, SVD/LVD	**2.32**		**1.76**		**1.41**	

The table illustrates the proportion of patients in our database who have a certain comorbidity with small vessel disease or large vessel disease. Values in **bold** indicate significant proportions and odds ratios that are different between Chinese and non-Chinese patients with stroke and diabetes. Odds ratios also show the frequency of small vessel disease/large vessel disease with that specific comorbidity.
LVD, large vessel disease; *OR,* odds ratio; *SVD,* small vessel disease.

New contribution to the literature

The results from this study add to the existing literature by providing preliminary evidence that stroke subtypes vary among different ethnicities, in particular between CCs and non-CCs (Table 3). Despite being limited geographically, the significant results of this study call for larger-scale studies to be conducted to confirm these findings. Findings of unique differences in stroke profiles between ethnicities will warrant new tailored approaches to treatment to provide optimal care to various patient populations.

Conclusions

In conclusion, our study has demonstrated that CCs with stroke more frequently have diabetes than non-CCs. CCs with diabetes seem to be especially susceptible to SVD and may have different stroke risk factors compared with non-CCs. CC patients with stroke and diabetes also seem to have poorer prognoses, even though non-CCs are more likely to have high HSGs. These results signify that risk factor prevalence and stroke types differ considerably between CCs and non-CCs within Toronto and call for further large-scale prospective studies.

Author Contributions

Dr. Chu is the lead author in conceptualizing this retrospective study, and Ms. Lam carried out the data collection and analysis. Both Ms. Lam and Dr. Chu participated in the preparation and revision of this manuscript.

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All authors declare no conflict of interest.

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References

1. Hu G, Sarti C, Jousilahti P, et al. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. Stroke J Cereb Circulation 2005;36:2538–43.
2. Feigin V, Carter K, Hackett M, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002–2003. Lancet Neurol 2006;5:130–9.
3. Chu JY, Chu JK, Chung AG. Epidemiology of cerebrovascular disease among Chinese-Canadians: A ten years retrospective case-mix study. Neurol Asia 2006;11:13–18.
4. Leung SY, Ng THK, Yuen ST, et al. Pattern of cerebral atherosclerosis in Hong Kong Chinese: Severity in intracranial and extracranial vessels. Stroke 1993;24:779–86.
5. Brust RW Jr. Patterns of cerebrovascular disease in Japanese and other population groups in Hawaii: An angiographical study. Stroke 1975;65:539–42.
6. Wong KS, Li H, Chan YL, et al. Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large artery occlusive disease. Stroke 2000;31:2641–7.
7. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction: The Northern Manhattan Stroke Study. Stroke 1995;26:14–20.
8. Lam KSL, Ma JTC, Woo E, et al. High prevalence of undiagnosed diabetes among Chinese patients with ischaemic stroke. Diabetes Res 1991;14:133–7.
9. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes 2013;37:S8–11.
10. Stern R. The New Hypertension Guidelines. J Clin Hypertens 2013;15:748–51.
11. Sheth T, Nargundkar M, Chagani K, et al. Classifying ethnicity utilizing the Canadian Mortality Data Base. Ethn Health 1997;2:287–95.
12. International Classification of Diseases. 9th revision. Geneva: World Health Organization, 1978.
13. Project WHOMONICA. WHO MONICA project: risk factors. Int J Epidemiol 1989;18:S46–55.
14. World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) Statement on Management of Hypertension. J Hypertens 2003;21:110.
15. Redon J, Campos C, Narciso ML, et al. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: A prospective study. Hypertension 1998;31:712–18.
16. Palaniappan LP, Araneta MRG, Assimes TL, et al. Call to action: cardiovascular disease in Asian Americans: A science advisory from the American Heart Association. Circulation 2010;122:1242–52.
17. Tu Y, Cui G, Xu Y, et al. Genetic polymorphism of CYP11B2 gene and stroke in the Han Chinese population and a meta-analysis. Pharmacogenet Genomics 2011;21:115–20.
18. Zhai FY, Du SF, Wang ZH, et al. Dynamics of the Chinese diet and the role of urbanicity, 1991–2011. Obes Rev 2014;15:16–26.
19. Gu D, Rice T, Wang S, et al. Heritability of blood pressure responses to dietary sodium and potassium intake in a Chinese population. Hypertension 2007;50:116–22.
20. Gould DB, Phalan FC, van Mil SE, et al. Role of COL4A1 in small-vessel disease and hemorrhagic stroke. N Engl J Med 2006;354:1489–96.
21. Huang CY, Chan FL, Yu YL, et al. Cerebrovascular disease in Hong Kong Chinese. Stroke 1990;21:230–5.
22. Chen G, Shan X, Cheng G, Tao H. Cyclooxygenase-2 genetic polymorphism and stroke subtypes in Chinese. J Mol Neurosci 2013;51:467–73.
23. Yamada Y, Ichihara S, Nishida T. Proinflammatory gene polymorphisms and ischemic stroke. Curr Pharmaceutical Design 2008;14:3590–600.
24. Hegele RA, Breslow JL. Apolipoprotein genetic variation in the assessment of atherosclerosis susceptibility. Gen Epidemiol 1987;4:163–84.
25. Zenker G, Koltringer P, Bone G, et al. Lipoprotein(a) as a strong indicator for cerebrovascular disease. Stroke 1986;17:942–5.
26. Kurtzke JF. Epidemiology of cerebrovascular disease. In: Cerebrovascular disease. Berlin: Springer, 1969, pg. 1–10.
27. McDowell FH, Caplan LR. Cerebrovascular Survey Report 1985 for the National Institute of Neurological and Communicative Disorders and Stroke. 1–34. 1985.
28. Wild SH, Laws A, Fortmann SP, et al. Mortality from coronary heart disease and stroke for six ethnic groups in California, 1985 to 1990. Ann Epidemiol 1995;5:432–9.
29. Jeng JS, Lee TK, Chang YC, et al. Subtypes and case-fatality rates of stroke: a hospital-based stroke registry in Taiwan (SCANIV). J Neurol Sci 1998;156:2206.

Appendix 1:

Supplemental: Stratification of Hypertension Risk to Quantify Prognosis (For details of other risk factors, please visit www.who.int).