CARDIOVASCULAR OUTCOMES IN CEREBRAL PALSY
CARDIOVASCULAR EVENTS AND THEIR RISK FACTORS IN ADULTS WITH CEREBRAL PALSY

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree of Master of Science

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Abstract

Background

Adults with cerebral palsy (CP) may have special health care considerations related to an increased prevalence of risk factors for chronic diseases. In particular, disability-related sedentary time may increase the risk of cardiovascular disease and the related major adverse cardiovascular events (MACE) in this population.

Methods

Part I: A systematic review of major databases, trial registries, and conference abstracts identified randomized trials and observational studies exploring the prevalence and evaluating the prevention of MACE and risk factors for MACE in adults with CP. Title and abstract, data extraction, and quality of reporting assessment were completed in duplicate.

Part II: A secondary analysis of Canadian census data evaluated the crude and adjusted risk of stroke in adults with CP and compared the crude risk with other Canadian adults with spinal cord injury, acquired brain injury, and epilepsy. All risks were reported as an odds ratio (OR) with 95% confidence intervals.

Results

Part I: 2281 unique articles were screened to provide 10 cross-sectional studies. No studies evaluated any interventions for MACE or risk factors for MACE. The most common risk factor studied was obesity. Two studies showed an increased in death due to circulatory diseases.

Part II: Crude risk of stroke to CP was OR=12.5 (12.2-12.9). Mediation effects or multicollinearity was not observed. The adjusted risk of stroke was OR=7.9 (1.8-34.2). Elevated crude risk of stroke was also noted in patients with acquired brain injury (OR=16.2 [16.0-16.5]), spinal cord injury (OR=6.1 [6.0-6.3]), and epilepsy (OR=6.2 [6.0-6.3]).

Conclusions

This thesis provides a preliminary overview of the risk of MACE in adults with CP and hypothesis generating evidence for further research in this population. A prospective cohort study is urgently needed assess the implications of these findings. Adults with CP should minimize exposure to modifiable risk factors as much as possible.
Acknowledgements

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A special acknowledgement to my dear wife, Angelina, who so generously shared her first year of marriage with my academic responsibilities. Always appreciated, always thankful, always yours.
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List of Abbreviations and Symbols

AACPDM..........................American Academy for Cerebral Palsy and Developmental Medicine
ABI..................................Acquired Brain Injury
BMI..................................Body Mass Index
CeVD...............................Cerebrovascular Disease
CENTRAL...........................Cochrane Central Register of Controlled Trials
CCHS...............................Canadian Community Health Survey
CI ..................................Confidence Interval
CINAHL............................Cumulative Index to Nursing and Allied Health Literature
CVD.................................Cardiovascular Disease
CP .................................Cerebral Palsy
DS .................................Daily Smoker
EMBASE .........................Exerpta Medica
GMFCS .............................Gross Motor Function Classification System
HD .................................Heart Disease
HDL.................................High-Density Lipoprotein
HR .................................Hazard Ratio
HT .................................Hypertension
IHD.................................Ischemic Heart Disease
LDL:.........................Low-Density Lipoprotein
MACE..............................Major Adverse Cardiovascular Event
MEDLINE/ PUBMED ..........Medical Literature Analysis and Retrieval System
MeSH..............................Medical Subject Heading
NASPEM ..........................North American Group of Pediatric Exercise Medicine
OR .................................Odds Ratio
PWP.................................European Group of Pediatric Work Physiology
PRISMA ...........................Preferred Reporting Items for Systematic Reviews and Meta Analyses
SMR:..............................Standardized Mortality Rate
TChol:............................Total Cholesterol
TG: ...............................Triglycerides
HC: ...............................Hip Circumference
RCT ...............................Randomized Controlled Trial
RDC ...............................Research Data Centre
RR .................................Relative Risk
SCI.................................Spinal Cord Injury
SCORE: ..........................Systematic Coronary Risk Evaluation
SMART.............................Second Manifestations of Arterial Disease
SMR.................................Standardized Mortality Ratio
ST .................................Sedentary Time
STROBE.........................Strengthening the Reporting of Observational Studies in Epidemiology
WC/ Waist cir ..................Waist Circumference
WHO...............................World Health Organization
WHOICTRP........................World Health Organization International Clinical Trials Platform
Declaration of Academic Achievement

Student contribution to work:

Both sections of this thesis will be submitted for publication and below outlines the contributions to the paper.

Under the supervision of Dr. Gorter, with various discussions with Dr. Hanna, Dr. Rosenbaum, and Dr. Mbuagbaw, I carried out both studies in this thesis. The systematic review was performed with the assistance of Patrick McPhee and in consultation with a Research Librarian at McMaster University. I designed and carried out the secondary analysis of the Canadian Community Health Survey after applying for and obtaining access to the survey microdata from Statistics Canada. I performed all data searching, statistical analyses, and drafted the manuscript for both studies.
Overarching Introduction
Cerebral palsy (CP) is a term used to describe a group of disorders of the development of motor and postural control that affect approximately 2-3 per 1000 live births, making it the leading cause of physical neurodevelopmental disability in North America (1, 2). This condition is caused by a neurological insult occurring prior to, during, or shortly after birth resulting in a lifelong physical disability (3, 4). Although the underlying neurological insult is non-progressive in nature, CP is associated with impairments which may require medical care and may also progress to produce a negative impact on already limited functional ability (5). The varying physical abilities of people with CP are categorized by the validated and clinically meaningful Gross Motor Function Classification System (GMFCS) which describes a range of functional ability, from walking with some difficulties (GMFCS I) to increasing levels of disability through Levels II and III, independent mobility with assistive equipment (e.g. powered wheelchairs; Level IV), and culminating in a total loss of any form of independent mobility, even with specialized equipment (Level V) (6, 7).

Improvements in health care and clinical understanding of CP have resulted in increasing numbers of people surviving into adulthood and participating in society (8, 9). Survival to adulthood in this population is dependent on the severity of disability. While recent research in Sweden has found that 96% of children with CP survive into adulthood (10), the subgroup of children classified as a GMFCS Levels IV-V were found to have a decreased survival compared to their peers with 60% of them surviving past the age of 18 (9, 10).
However, researchers have been slow to follow these improvements in survival and clinical care. The vast majority of research on the population with CP has treated it as a paediatric condition only. As a result, few health outcomes have been explored in the cohort of adults with CP. Although there is considerable understanding of pediatric CP, what has been learned may not translate into a good understanding of chronic conditions and age-related health outcomes. Further, the particular health care challenges associated with the pediatric population with CP may not be reflective of those experienced in an adult population.

In addition to the above challenges, children and youth in Canada usually transition into the adult health care system around the age of 18. As a result, they lose access to many essential services which focus on maintenance of physical function and prevention of secondary conditions (11). Thus adults with CP and their families are often poorly served within the ‘adult’ health care system: they no longer qualify for some essential services, yet they represent an emerging population with special physical health care needs (12, 13).

These special health care needs may be directly associated with CP or be related to an increased prevalence of risk factors for negative cardiovascular outcomes in the population of adults with CP. When we consider the risk of a major adverse
cardiovascular event (MACE)\(^1\) in the general adult population of North America, we should be able to extrapolate these risks to the population of adults with CP (14). For example, it is understood that behavioural and environmental factors can result in a highly sedentary lifestyle and decreased physical fitness which are closely related to an increased risk of a MACE (15). However, people with neuromotor impairments may represent a subgroup at particularly increased risk by experiencing a sedentary lifestyle exacerbated by the level of disability and secondary conditions such as fatigue and pain (16-21).

Recent work by van der Slot et al. (2013) has helped to quantify the risk associated with various risk factors for MACE. In this study they investigated the prevalence of classical risk factors for cardiovascular diseases (CVDs) in a sample of individuals with CP. They used the Systemic Coronary Risk Evaluation to quantify the ten-year risk of CVD occurrence. This tool measures the prevalence of cardiovascular risk factors, including hypertension, increased BMI, reduced physical activity, and smoking behaviour and, based upon current evidence, quantifies a ten-year cardiovascular risk. In this younger cohort of individuals (mean [SD] age = 36 [6] years), these risk factors were already present to varying degrees, but demonstrated no elevated ten-year fatal cardiovascular risk compared with the general population (22).

However, there are some indications in the literature that cardiovascular risk factors play

\(^1\) MACE includes: stroke, ischemic heart disease (angina pectoris, cardiac ischemia, myocardial infarction), cardiovascular death
a significant role in mortality outcomes in the population of adults with CP. In 1999, Strauss et al. reported a two to four-fold greater mortality due to ischemic heart disease in adults with CP than was found in the general California population (23). Thus it can be hypothesized that cardiovascular disease and MACE for people with CP may represent major causes of morbidity and mortality in this population.

Current evidence does not provide systematic insight into common cardiovascular events and risk factors specific to adults with CP (9). Although there have been several studies investigating health outcomes in this population, there remain major gaps in our knowledge surrounding MACE and related cardiovascular risk factors. These gaps represent areas in need of careful research, especially as this population begins to age and re-enter the health care system with chronic diseases and age-related illnesses that may be attributed to their disability (24), their age (20), or their lifestyle (25). In other words, given the increased mortality observed by Strauss et al. it is necessary to examine the prevalence of MACE, its associated risk factors, and their association to a population of adults with CP.

In this thesis, I have begun to address some of the gaps identified here. I do so by exploring two broad questions regarding cardiovascular health outcomes in adults with CP using two methodological approaches described in each chapter. Each question is answered separately and the results described as a whole in the final discussion.
Part I: *What is the prevalence of MACE and risk factors for MACE in the adult population with CP and what are the management strategies specific to these events and risk factors in this population?*

This question is addressed through a systematic review of the literature and is explored with the following objectives:

1. To describe the prevalence of MACE and risk factors for MACE (hypertension, heart disease, arterial disease, diabetes, smoking, increased body mass, sedentary lifestyle, and various laboratory/clinical risk factors) among adults with CP.
2. To identify any strategies used in the management of MACE and risk factors for MACE in adults with CP in the published scientific literature.

Part II: *What is the risk of stroke and cardiovascular risk factors in Canadian adults with CP?*

Statistics Canada recently (2010-2011) explored the prevalence of various neurological conditions (including CP) along with various other outcomes of interest including a self-report of previous stroke. Although only one of the MACE of interest, this dataset provides a unique opportunity to explore the link between a major cardiovascular outcome and CP within a population dataset. As a result, this question addresses the risk of stroke as one of the MACE of interest and explores its relationship to various risk
factors for stroke and CP.

This question is explored with the following objectives:

(1) To determine the risk of stroke in Canadian adults with CP.
   i. To assess the potential mediating effect of risk factors for stroke (hypertension, heart disease, diabetes, smoking behaviour, increased body mass, and sedentary lifestyle) on risk of stroke in adults with CP.
   ii. To explore the effect of CP on risk of stroke adjusted for all above-mentioned risk factors.

(2) To compare the relationship of stroke and CP with the relationship of stroke to other populations with neurological impairments (spina bifida, spinal cord injury, acquired brain injury, and epilepsy).
Prevalence of major adverse cardiovascular events and their risk factors in adults with cerebral palsy: A systematic review

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<table>
<thead>
<tr>
<th>Author</th>
<th>Contributions</th>
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<tbody>
<tr>
<td>SN</td>
<td>Study design, search design, search, study screening, data extraction, data analysis, and preparation of manuscript</td>
</tr>
<tr>
<td>PM</td>
<td>Search, study screening, data extraction, and review of final manuscript</td>
</tr>
<tr>
<td>LM</td>
<td>Study design, study screening, data extraction, and review of final manuscript</td>
</tr>
<tr>
<td>JWG</td>
<td>Conceptualization of study idea, study design, data validation, review of final manuscript, mentorship</td>
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<tr>
<td>SH</td>
<td>Review of final manuscript, mentorship</td>
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<tr>
<td>PR</td>
<td>Review of final manuscript, mentorship</td>
</tr>
</tbody>
</table>
Abstract

Background
Cardiovascular diseases (CVDs) are a leading cause of death and hospital admissions worldwide and a major contributor to the global burden of disease. Common risk factors for CVDs are known to include modifiable factors such as a sedentary lifestyle. However, special populations such as individuals with cerebral palsy (CP) are known to have greatly increased sedentary lifestyle which may contribute to an increased risk of CVDs compared with healthy peers.

Objectives
(1) To describe the prevalence of major adverse cardiovascular events (MACE) and their risk factors (hypertension, heart disease, arterial disease, diabetes, smoking, increased body mass, sedentary lifestyle, and various laboratory/clinical risk factors) among adults with CP.
(2) To identify any strategies reported in the published scientific literature used in the management of MACE and their risk factors in adults with CP.

Data Sources
A systematic review was performed using MEDLINE, EMBASE, CINAHL, and CENTRAL. No limits were placed on language, date, or study design.

Study Eligibility Criteria
Randomized Controlled Trials (RCTs) and observational studies which explore the prevalence of and interventions for cardiovascular health outcomes in adults with CP were included in this review.

Participants
Adults (aged 18+) with CP were included in this review. Studies which made use of a non-CP control arm were also included.

Study Appraisal and Synthesis
Title and abstract, data extraction, and quality of reporting assessment were completed independently by two raters. Data were synthesized qualitatively and reported in tables.

Results
We identified 2281 unique articles in the search, of which eight studies and two abstracts fulfilled criteria for final inclusion. All articles were cross-sectional surveys, half of which were performed using registry data.

No studies identified any MACE outcomes. Risk factors associated with MACE were reported in only three studies. The most commonly studied lifestyle risk factor noted was obesity (n=5). Three studies reported cause of death, two of which showed an increase in deaths due to circulatory diseases. No studies detailed any management strategies for MACE or risk factors for MACE in this population.
Conclusions & Implications
Little is reported about cardiovascular health outcomes or risk factors in adults with CP. Further longitudinal research is necessary to determine the prevalence and causation of these outcomes in this population. Clinicians should be aware that there are many unanswered questions and that there is potentially high risk of CVD among aging adults with CP.

Registration
The protocol is registered on Prospero (CRD42013004923).
Background:

The World Health Organization (WHO) estimates that 30% of all global deaths are due to cardiovascular diseases (CVDs), making this the number one cause of death worldwide (26). In 2008 an estimated 17 million people died from CVDs (27), a number that is projected to increase to 23 million deaths worldwide by 2030 (28). Each year approximately 10 million deaths are attributed to hypertension alone, accounting for 17% of all deaths worldwide (27).

Traditional risk factors for CVDs are identified as poor diet, sedentary lifestyle, smoking, stress, family history, diabetes, and obesity (29-31). As the population ages, the incidence and prevalence of CVDs increases and the development of these CVDs is often associated with an interaction between an aging body and prolonged exposure to traditional risk factors (32).

Risk factors for CVD may be exaggerated in populations with physiological factors which inherently predispose to major cardiovascular events (MACE) such as stroke and heart attack. Adults with cerebral palsy (CP) may represent one such population. CP is caused by a non-progressive neurological insult occurring prenatally, perinatally, or in the early months after birth and results in a life-long limitation of daily activity (3, 33). As a result, people with CP may be more likely to remain sedentary for longer periods of time during a day, exposing them earlier in life to a lifestyle risk factors (6, 34, 35). Furthermore, CP is a neuromotor disability, with implications for both neurological and motor systems.
It is conceivable that the presence of such a condition affecting neurological control of both voluntary and involuntary musculature may stress the cardiovascular system (14, 37). This stress may lead to the development of various CVDs.

Further, as postulated by Peterson *et al.* it is possible that this group ages more quickly than their healthy peers, resulting in an earlier onset of CVDs (20). In their review, Peterson and colleagues give an overview of CP and the risk factors found in these people. They note that body mass index (BMI) was not predictive of cardiovascular health in this population and postulate that people with CP are more likely to age at a greater rate based on their shorter lifespan and their cardiovascular health (20). Thus it is plausible that people with CP may be at higher risk for CVDs which is not reflected by some commonly-accepted risk factors such as BMI.

Despite the hypotheses regarding the likelihood of CVDs as a clinically relevant concern in adults with CP, little information is available on the prevalence or management of cardiovascular events and traditional risk factors in this population. Indeed, the evidence above presented suggests that traditional screening and management strategies for CVDs and MACE may demonstrate decreased efficacy in this population. This postulation forms the basis of the secondary objective of this study and provides clinical relevance for the overall purpose of this thesis.
The purpose of this work is to inform clinicians, promote evidence-based healthcare, and provide researchers with epidemiological insights into the burden and risk of CVDs in this population. In light of this, we seek to describe the reported prevalence and management of cardiovascular disease in adults with CP in this first section. We addressed this goal with the following two objectives:

1. To describe the prevalence of MACE and risk factors for MACE among adults with CP.
2. To evaluate any strategies used in the management of MACE and risk factors for MACE in adults with CP in the published scientific literature.
Methods:

Eligibility Criteria

We sought to include all randomized controlled trials (RCTs) and observational studies which explored major adverse cardiovascular events and cardiovascular risk factors within the population of adults with CP.

Case studies, “n of 1” studies, and editorial comments were excluded as these reports provide no generalizable evidence. All reviews were excluded from the final selection but retained for additional reference searching.

No limits were placed on year or language of publication.

Information Sources

A comprehensive search was conducted using the following major search terms and their medical subject heading (MeSH) equivalents: cerebral palsy, cardiovascular disease, cerebrovascular disease, stroke, myocardial infarction, peripheral arterial disease, cardiac ischemia, mortality, angina, hypertension, heart disease.

These search terms were compiled into a search strategy in consultation with a research librarian, Faculty of Health Sciences library, McMaster University and based upon the search methodology of several other reviews (38, 39) for the following major electronic databases:
1. Cumulative Index to Nursing and Allied Health Literature (CINAHL)

2. Cochrane Central Register of Controlled Trials (CENTRAL)

3. Exerpta Medica Database (EMBASE)

4. Medical Literature Analysis and Retrieval System (MEDLINE/ PUBMED), including all In-Process and Other Non-Indexed Works

See Appendix A for full search strategy (EMBASE).

Reference lists of identified publications and reviews were hand searched to identify other studies not located in the initial search. In addition, we searched trial and protocol registries (WHO International Clinical Trials Platform [WHOICTRP], clinicaltrials.gov) and the 2010-2013 abstracts and proceedings of the American Academy for Cerebral Palsy and Developmental Medicine (www.AACPDM.org), North American Association of Pediatric Exercise Medicine (www.NASPEM.org), European Group of Pediatric Work Physiology (PWP), and the proceedings of the 2011 and 2012 International Conference on Cerebral Palsy (www.CP2011.co.za and www.CP2012.it) to identify current developments. Grey literature abstracts without a published manuscript were included if the abstract contained sufficient information or the authors provided additional information relevant to this study.
Study Selection and Data Collection

Titles, abstracts, and full texts were reviewed independently by two authors (SN, PM) using standardized screening forms (Appendix B). The relevance of each study was established based upon the following characteristics:

- **Study design**: RCTs and observational studies evaluating interventions and preventions of CVDs and observational studies exploring the prevalence of MACE and their risk factors.
- **Types of participants**: This review was focused only on adults (aged >18) with CP. Results including children were excluded. Intervention studies with a non-CP control arm and studies with a CP subgroup were included.
- **Outcome measures**: All outcomes described below as a MACE or risk factor were included (Table 1).

Table 1: Included outcomes by class

<table>
<thead>
<tr>
<th>Major Adverse Cardiovascular Events (MACE)</th>
<th>Stroke, ischemic heart disease (angina, ischemia, myocardial infarction), mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factors</strong> associated with cardiovascular conditions</td>
<td>Hypertension, heart disease, arterial disease</td>
</tr>
<tr>
<td><strong>Risk Factors</strong> associated with lifestyle</td>
<td>Diabetes, smoking, overweight/increased body mass, sedentary lifestyle</td>
</tr>
<tr>
<td><strong>Risk Factors</strong> associated with laboratory/clinical measures</td>
<td>Laboratory/clinical risk factors (e.g. LDL cholesterol)</td>
</tr>
</tbody>
</table>
A measure of agreement (kappa (40)) was taken following title, abstract, and full text screening. Acceptable levels of agreement were defined as moderate (kappa=0.41-0.60), substantial (kappa=0.61-0.80), and almost perfect agreement (kappa=0.81-0.99). Any disagreement between the two data abstracters was resolved by discussion or by consulting a third author (LM). A final reference list was sent to a fourth author and content expert in the field of management for people with CP to identify any additional studies (JWG). Data were extracted independently using standardized forms (SN, PM). Authors once again discussed their results and all disagreements were resolved by consensus and/or in consultation with a third party author (LM).

Following data extraction, outcome measures were classified according to the subtype of outcome as defined previously (MACE or risk factor) and reported descriptively according to the classification of outcome.

**Data Items**

The total population and mean age of participants within each study, the population and mean age with CP, the subgroups within each population, and the disability descriptors of each population were extracted from each study along with the relevant time period and location of the study. Following this, outcomes of interest were extracted from each study.

Patient-important outcomes included MACE (stroke (32), myocardial infarction, angina
pectoris, cardiac ischemia, and cardiovascular-related mortality) (41-43). Cause of death statistics do not provide evidence for causation, prevalence, or incidence of MACE, but they do provide indications of mortality due to these outcomes.

Secondary outcomes of interest are traditional risk factors for MACE and include stand-alone medical conditions such as hypertension (44, 45), coronary artery disease (41) and heart disease. These risk factors also include risk-increasing behaviours (e.g. smoking (30), increased sedentary time (30)), chronic disease states (e.g. diabetes, obesity) and clinical/laboratory measures of cardiovascular health (e.g. arterial stiffness, low-density lipoprotein profile, aerobic capacity, time-to-fatigue (46-49)).

**Quality of reporting**

Quality of reporting was assessed using the STROBE guidelines (50). Although the STROBE checklist evaluates the quality of reporting and not the quality of the study itself, this assessment provides a basis for comment upon the scientific rigour of each study included.

**Summary Measures and Synthesis of Results**

Data were not pooled and thus no summary measures were taken. Data were reported descriptively in tables summarizing each study’s relevant output.

**Additional Analyses**
Sensitivity analyses or explorations of subgroup effects could not be performed.
Results

Study Selection:

We identified 2645 articles of which 2290 were unique studies. Of these, 2234 were removed after screening of title and abstracts for reasons of design, population, or outcomes with near perfect overall agreement (kappa=0.89, [95% CI: 0.81-0.97]). A further nine articles and abstracts were identified based on a hand search of included studies (51-54) and grey literature (49, 55-58). Fifty-six studies were reviewed in full text, 33 of which were excluded based upon study design, population, and outcomes, with almost perfect overall agreement kappa=0.9, [95% CI, 0.78-1.03]). Figure 1 is a PRISMA diagram that describes the flow of studies from search to final inclusion.

Three studies and potential abstracts were excluded after contact with the authors of those papers. One study did not provide a population breakdown to study those with CP alone (55), one abstract was an early publication of an already included study (56), and one study did not report the risk factors of interest in the context of CP (as was done in the conference

Figure 1: PRISMA flow diagram
Two unpublished abstracts (49, 57) were included upon review with a third author (LM) prior to inclusion.

A total of ten studies (eight manuscripts and two abstracts) were included in this review. Of note is that the studies by Brooks et al. (57) and Strauss et al. (23) may have been performed in the same database. However, these studies explored different population outcomes and thus do not duplicate results.

**Study Characteristics:**

No RCTs or longitudinal studies were identified in this search. All included studies were cross-sectional analyses of registry data or surveys of a specific population (Table 2).

<table>
<thead>
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<th>Date</th>
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<td>2008</td>
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<td>Hemming (62)</td>
<td>2006</td>
<td>Cross-sectional analysis of registry</td>
</tr>
<tr>
<td>Henderson (63)</td>
<td>2009</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Peterson (64)</td>
<td>2012</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Strauss (23)</td>
<td>1999</td>
<td>Cross-sectional survey of registry</td>
</tr>
<tr>
<td>van Der Slot (49)</td>
<td>Unpublished</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Wang (65)</td>
<td>2007</td>
<td>Cross-sectional survey</td>
</tr>
</tbody>
</table>

The population of CP in each study ranged from n=43 to n=45,292 and reported data collection occurred between 1951 and 2004. Given this timeline, only two studies (49, 64) described their population in terms of a modern, reliable clinical classification such as the
GMFCS, especially within the larger registry studies. However, the registry studies (57, 59, 60, 62, 66) included those with a general diagnosis of CP and did not select specific subgroups of this population (see Table 3).
Table 3: Population characteristics of included studies

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Date</th>
<th>Population</th>
<th>n&lt;sub&gt;tot&lt;/sub&gt;</th>
<th>Mean Age (SD)</th>
<th>Subgroups</th>
<th>n&lt;sub&gt;CP&lt;/sub&gt;</th>
<th>Disability Descriptors</th>
<th>Age&lt;sub&gt;CP&lt;/sub&gt; (SD)</th>
<th>Location</th>
<th>Relevant Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair</td>
<td>2001</td>
<td>Children and adults with CP</td>
<td>2014</td>
<td>IQ</td>
<td>Hemi/diplegic, other</td>
<td>151</td>
<td>Reported in ranges</td>
<td>Reported in ranges</td>
<td>Australia</td>
<td>1997</td>
</tr>
<tr>
<td>Bottos (61)</td>
<td>2001</td>
<td>Adults with CP</td>
<td>72</td>
<td>IQ, Syndrome</td>
<td>(Mild, moderate, severe)</td>
<td>72</td>
<td>Reported in ranges</td>
<td>33 (9.2)</td>
<td>Bologna, Padua,</td>
<td>1998-1999</td>
</tr>
<tr>
<td>Brooks (57)</td>
<td>grey</td>
<td>Adults with CP</td>
<td>12515</td>
<td>BMI</td>
<td>Ambulation, Cognition</td>
<td>12515</td>
<td>28 (N/R)</td>
<td>Reported in ranges</td>
<td>Australia</td>
<td>1983-2002</td>
</tr>
<tr>
<td>Hemming (62)</td>
<td>2006</td>
<td>Children and adults with CP</td>
<td>65</td>
<td>IQ, Syndrome</td>
<td>Reported in ranges</td>
<td>65</td>
<td>(Severe, not severe)</td>
<td>N/R</td>
<td>Bristol, UK</td>
<td>1951-1964</td>
</tr>
<tr>
<td>Peterson (64)</td>
<td>2012</td>
<td>Adults with CP</td>
<td>43</td>
<td>Gender</td>
<td>GMFCS</td>
<td>43</td>
<td>37.3 (13.2)</td>
<td>Reported in ranges</td>
<td>Michigan, USA</td>
<td>2012</td>
</tr>
<tr>
<td>Strauss (23)</td>
<td>1999</td>
<td>Children and adults with CP*</td>
<td>45292</td>
<td>Gender</td>
<td>(Severe, not severe)</td>
<td>45292</td>
<td>36.6 (6)</td>
<td>Reported in ranges</td>
<td>California, USA</td>
<td>1986-1995</td>
</tr>
<tr>
<td>van Der Slot (49)</td>
<td>grey</td>
<td>Adults with CP</td>
<td>43</td>
<td>Gender</td>
<td>GMFCS</td>
<td>43</td>
<td>36.6 (6)</td>
<td>Reported in ranges</td>
<td>Rotterdam, NL</td>
<td>2011</td>
</tr>
<tr>
<td>Wang (65)</td>
<td>2007</td>
<td>Adults with Intellectual Disabilities</td>
<td>1129</td>
<td>D Syndrome, CP, Epilepsy, Community/Institution</td>
<td>67</td>
<td>ADL, Greater Rochester Area Health Status Survey</td>
<td>N/R</td>
<td>Taiwan</td>
<td>2002-2003</td>
<td></td>
</tr>
</tbody>
</table>

*Study reported ages from 0-34, 35-54, >54; results included for ages >34.

D Syndrome = Down Syndrome, IQ= Intelligence Quotient, ID = Intellectual Disability, BMI = Body Mass Index, GMFCS = Gross Motor Function Classification System, ADL=Activities of Daily Living, N/A=Not Applicable, N/R=Not Reported
Quality of Reporting of Studies

Nine of ten studies included (the exception was one abstract (57)) provided adequate reporting for many items included in the STROBE checklist (50). Areas of poor reporting were noted in the definitions of variables (n=7), failure to identify or discuss potential biases (n=6), and the statistical methodologies for examining subgroups (n=5), missing data (n=10), accounting for sampling strategies (n=8), and sensitivity analyses (n=3; Table 4). See Appendix C for STROBE checklist (50).
Table 4: Summary of STROBE assessment for included studies

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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<td>Title and Abstract</td>
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<tr>
<td>1b</td>
<td>Abstract</td>
<td>9</td>
<td>1</td>
<td>0</td>
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<td></td>
<td><strong>Introduction</strong></td>
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<td></td>
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<td>Background/Rationale</td>
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<td>Setting</td>
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<td>Participants</td>
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<td>Variables</td>
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<td><strong>Discussion</strong></td>
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<td></td>
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<td>Key Results</td>
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<td>19</td>
<td>Limitations</td>
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<td>20</td>
<td>Interpretation</td>
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<td>21</td>
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<td></td>
<td><strong>Other</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Funding</td>
<td>6</td>
<td>4</td>
<td>0</td>
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</table>
Results of Individual Studies

No studies explored incidence or prevalence figures regarding MACE. All included studies explored the prevalence of cardiovascular risk factors (n=8) or cause of death statistics (n=3) in adults with CP. No studies explored or even discussed prevention strategies for MACE or CVDs in this population. See Table 5.

Table 5: Summary of outcomes explored by study

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Study</th>
<th>Date</th>
<th>n</th>
<th>MACE</th>
<th>Outcome Classification</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhaumik</td>
<td></td>
<td>2008</td>
<td>20</td>
<td></td>
<td>Cardiovascular risk factor</td>
<td>BMI</td>
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<td>Blair</td>
<td></td>
<td>2001</td>
<td>151</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bottos</td>
<td></td>
<td>2001</td>
<td>72</td>
<td></td>
<td>“Cardiac Problems”</td>
<td></td>
</tr>
<tr>
<td>Brooks</td>
<td>grey</td>
<td>12515</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemming</td>
<td></td>
<td>2006</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Henderson</td>
<td></td>
<td>2009</td>
<td>177</td>
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<tr>
<td>Peterson</td>
<td></td>
<td>2012</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strauss</td>
<td></td>
<td>1999</td>
<td>45292</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Der Slot</td>
<td>grey</td>
<td>43</td>
<td></td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>2007</td>
<td>67</td>
<td></td>
<td></td>
<td>“Cardiovascular Disease”</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body Mass Index
SMR: Standardized Mortality Rate
HDL: High-Density Lipoprotein
LDL: Low-Density Lipoprotein
TChol: Total Cholesterol

TG: Triglycerides
HC: Hip Circumference
WC: Waist Circumference
SCORE: Systematic COronary Risk Evaluation
Cardiovascular-related causes of death were mentioned in three studies. In adults with CP over 55 years of age, Strauss (23) observed 24 age- and sex-standardized deaths due to other heart disease compared to 8.2 deaths expected in the general population. Similarly, 11 deaths due to cerebrovascular disease were observed (compared to 0.9 expected) in those aged 0-34 years of age. This elevated trend, however, was not reproduced in the smaller cohort of higher functioning people with CP (n=151) studied by Blair et al. (60) who noted no deaths due to cardiac organ failure in the study. It must be noted, however, that the study by Blair et al. was a registry analysis which was only able to explore 144 deaths in adults with CP. Most recently, Hemming (62) found that respiratory disease was the most common cause of death of individuals with CP between ages 20 and 40 (50%), whereas the majority of deaths of adults with CP occurring above age 40 were related to cardiovascular causes (21%). In reference to the UK population, these cardiovascular-related deaths were nearly the same proportion from 20-29 years of age (6% vs. 5%) and nearly double the reference population between 30-39 years (17% vs. 9%). The proportion of deaths due to circulatory diseases was approximately equal between the CP and reference populations in the 40-49 year age groups. In people older than 50, the reference population had a more elevated proportion of deaths due to circulatory disease (see Table 6). It must be noted that these trends are based on 65 deaths across all four ten-year categories.

Three studies reported an outcome associated with a chronic cardiovascular condition. One reported that 3% (n=2) of their 72 participants with CP had “cardiac problems” (21).
This study is a cross-sectional survey of adults with CP which did not include a reference population. Wang et al. performed a survey of 1128 caregivers of which 67 were supporting adults with CP. They report a non-significant relationship between CP and cardiovascular disease adjusting for age, institution, gender, Down syndrome, intellectual disability, and seizures (65). However, they note that caregivers report increasing cardiovascular impairments as age progresses. The third (unpublished) study reported a 30% versus 15% and 19% versus 8% prevalence of hypertension among male and female adults with CP, respectively (49) (see Table 6).

Half of the studies (n=5) reported obesity or BMI as a risk factor of interest (49, 57, 59, 63, 64). Studies reporting a BMI measure in this population noted a prevalence of obesity or weight gain that was consistently elevated within this population (see Table 2). Van der Slot et al. (49) noted a high-risk waist circumference in 15% of males (>102 cm) and 25% of females (>88 cm). They also found that 26% of males and 2% of females in their cohort were current smokers (lower than the Dutch reference population of 39% for both genders; see Table 6).
### Table 6: Cardiovascular outcomes by classification

<table>
<thead>
<tr>
<th>Author</th>
<th>Hypertension</th>
<th>CVD</th>
<th>Smoking</th>
<th>Obesity</th>
<th>Lab/ Clinical Measures</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhaumik (59)</td>
<td></td>
<td></td>
<td></td>
<td>5% (BMI &gt; 29.9)</td>
<td></td>
<td>0% cardiac organ failure deaths.</td>
</tr>
<tr>
<td>Blair (60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottos (61)</td>
<td></td>
<td></td>
<td></td>
<td>2.7% (2) &quot;cardiac problems&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brooks (57)</td>
<td></td>
<td></td>
<td></td>
<td>38.9/33.4%F/M (BMI&gt;24.9)</td>
<td>Gain+0.39 (0.37-0.41) kg/year</td>
<td></td>
</tr>
<tr>
<td>Hemming (62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henderson (63)</td>
<td></td>
<td></td>
<td></td>
<td>55% (BMI&gt;24.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peterson (64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strauss (23)</td>
<td>M:30% (8) F:19% (3)</td>
<td></td>
<td>M:26% (7) F:13% (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van der Slot (49)</td>
<td>M:30% (8) F:19% (3)</td>
<td></td>
<td>M:26% (7) F:13% (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang (65)</td>
<td>CP association with CVD=0.17+/-0.55, p&gt;0.05*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- BMI = Body Mass Index; SMR = Standardized Mortality Ratio; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; TChol = Total Cholesterol; TG = Triglycerides; Waist cir = Waist Circumference; SCORE = Systematic Coronary Risk Evaluation, IHD = Ischemic Heart Disease, HD = Heart Disease, HT = Hypertension, CeVD = Cerebrovascular Disease
- *Measures standardized by age and gender.
- *Adjusted for Age, Gender, Residence, Down Syndrome, Intellectual Disability, Seizures.
Narrative Synthesis of Results

i. Objective 1: Description of MACE prevalence

No studies reported a measure of MACE. Risk factors for MACE (hypertension and heart disease) were vaguely reported and added little to the evidence here presented. Measures of body weight and composition represented the most explored risk factor and the majority of these studies found an increased BMI and waist circumference in their samples. Higher than average sedentary activity was noted in one study (49).

Mortality was investigated (using cause of death statistics) in three studies (60, 62, 66). Two noted that elevated causes of death included diseases of the circulatory and respiratory systems (23, 62) while the other noted no deaths due to cardiac organ failure within their cohort of highly functioning people with CP (60).

ii. Objective 2: Identification of Management Strategies

No intervention trials or strategies were identified that explored the management (including prevention) of CVDs in adults with CP. As such, this objective could not be addressed within this review.
Discussion

Summary of Evidence

The cross-sectional data summarized in this review detail nothing about MACE outcomes and little about risk factors for MACE in adults with CP. High risk conditions such as heart disease and hypertension are barely noted within the literature reporting the population of adults with CP. However, risk factors associated with behavioural habits such as body weight/composition and sedentary activity were addressed more frequently and were mostly found to be elevated in this population. Strauss et al noted a 2-4 fold increased mortality due to diseases of the circulatory system (23) compared with the general population, whereas other smaller studies reported little to no relationship to cardiovascular-related mortality in this population.

This review provides several clinical messages of interest. First, little evidence exists in this area of research. The few studies identified in this review were cross-sectional in nature and mostly focused upon a few risk factors for MACE. As such, this review can make only limited synthesis of such preliminary evidence suggesting elevated prevalence of risk factors for MACE as well as cardiovascular-related mortality. The state of the evidence in this area of research suggests that much more research is necessary. As a result, both clinicians and patients should be aware that these individuals face many unknown cardiovascular health risks. As such, adults with CP and their care-givers may benefit from increased awareness, as preliminary findings indicate an increased risk for MACE and related risk factors.
Limitations

This search did not identify any RCTs or longitudinal studies and returned a total of eight studies and two abstracts (all cross-sectional in nature). Although cross-sectional, these few studies do provide a preliminary description of the point prevalence of MACE and their risk factors in adults with CP. However, the evidence could not be pooled to obtain an overall effect and showed weaknesses in the quality of reporting (especially around sources of bias). As a result, the evidence summarized in this review should be considered preliminary and hypothesis generating.

Furthermore, the elevated mortality rates due to CVDs compared with reference populations noted in the large registry studies do provide some evidence that this population requires further study. Indeed, since all included studies were published after 1997, the few studies identified may be more indicative of an emerging area of research than a bias within the reporting of the published articles.

Future Research Directions

Health researchers are beginning to explore health outcomes in adults with CP for the first time. The cross-sectional studies summarized here provide a source of data which represents foundational research necessary to inform future studies (67). Such future studies should inform both the incidence and prevalence of MACE and its risk factors. Although there is yet no evidence to support a resource-heavy prospective cohort study, a
well-designed population-based cross-sectional study using hospital admissions records linked to death registries could provide extensive insights into these outcomes.

**Conclusion:**

The prevalence of MACE is still unknown in this population. Further, risk factors for MACE are addressed only to some extent within the literature. Interestingly, the largest registry study reported a 2-4 fold increased age- and gender-standardized mortality due to CVDs in adults with CP, representing a source of evidence which support a hypothesis of increased MACE in adults with CP (23).

Since research evidence is limited, effective preventions and interventions have not yet been determined for this population and consensus has not been reached that these are even necessary. Thus, policy and practice should not change at this time. However, awareness should be advocated regarding the possibility of a high-risk special population. Finally, researchers should explore this large gap in our current understanding of health outcomes in adults with CP and work to provide necessary evidence for effective evidence-based decision-making in both practice and policy.
Stroke and risk factors for stroke in adults with cerebral palsy: a cross-sectional secondary analysis of the Canadian Community Health Survey 2010-2011

Stephen Noorduyn
Steven Hanna
Peter Rosenbaum
Jan Willem Gorter
Abstract

Background
Stroke is known to be associated with many risk factors and disease conditions. These risk factors may be elevated in adults with cerebral palsy (CP). However, little research has been done in this area and no work has focused on a population-based cohort. In 2010 and 2011, the Canadian Community Health Survey (CCHS) included a module which identified adults with CP and explored various health outcomes in this population.

Objectives
This study addressed two objectives using the 2010 and 2011 cycles of the CCHS. First, we determined the risk of stroke in Canadian adults with CP. In so doing, we assessed crude risk of stroke in adults with CP and explored the mediating effect of risk factors for stroke (hypertension, heart disease, diabetes, smoking behaviour, increased body mass, and sedentary lifestyle) on this risk of stroke. We also estimated a risk of stroke adjusted for the above-mentioned risk factors.

Secondly, we compared the relationship of stroke and CP with the relationship of stroke to other populations with neurological impairments (spina bifida, spinal cord injury, acquired brain injury, and epilepsy).

Methods
The 2010 and 2011 survey cycles were merged to create a combined dataset for analysis in Stata 12. Unadjusted odds ratios (ORs) and their 95% confidence intervals were reported for each risk factor. Mediating and moderating effects were tested in logistic regression models. Unrelated risk factors were entered into a large logistic regression model more representative of the clinical reality of multiple risk factors contributing to a difference in risk of stroke. Bootstrap weights were used to provide population-representative data and accurate variance estimates.

Results
A clear difference was found in mean age between the CP and non-CP group (5-10 years younger), providing reasons to adjust all analyses by age. Males accounted for 81% of stroke patients in the CP group and 50% in the non-CP group. Crude risk of stroke is strongly associated with CP (OR=12.5 [12.2-12.9]) with no evidence of mediating effects by classical risk factors for stroke. When adjusted for all risk factors, the risk of stroke is still strongly associated with CP (OR=7.9 [1.8-34.2]). The crude elevated risk of stroke seen in adults with CP is also noted in patients with acquired brain injury (OR=16.2 [16.0-16.5]), spinal cord injury (OR=6.1 [6.0-6.3]), and epilepsy (OR=6.2 [6.0-6.3]).

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2This research and analysis is based on data from Statistics Canada and the opinions expressed do not represent the views of Statistics Canada.
Conclusions

This preliminary study shows a strong relationship between CP and risk of stroke. This observation, and the risk of stroke found in other neurological conditions, raise many questions about the causation and pathology of this risk of stroke. Further exploration is needed in prospective cohort studies to expand the findings of this study and provide evidence to inform clinicians, patients, and policymakers. Adults with CP and their caregivers should be aware of the risk of stroke and minimize exposure to modifiable risk factors such as an increased BMI and a sedentary lifestyle.
Introduction

The World Health Organization reports cardiovascular diseases to be a major cause of mortality and morbidity worldwide (30). Central to this group of diseases are the Major Adverse Cardiovascular Events (MACE), which are responsible for the deaths of nearly 320 million people yearly across the globe. These MACE events are comprised mainly of ischemic heart disease (angina, ischemia, and infarction), cerebrovascular disease (stroke), and cardiovascular death (30). The prevalence of these MACE in developed nations is expected to continue to rise even though they are often regarded as preventable outcomes (68).

As a result, clinical focus often rests on the primary prevention of MACE such as stroke (69). These strategies have been informed by ground-breaking epidemiological research such as the Framingham cohort studies (70) and the more recent SMART program of research (71). In both of these cohorts, major risk factors for stroke were associated with lifestyle (e.g. increased sedentary time and regular smoking behaviour), demographics (e.g. increasing age and male gender) and health status (e.g. diabetic, increased body mass index, hypertensive, or has heart disease) (44, 48, 70, 71). Although the main focus of these studies was to identify risk factors for stroke, Wolf et al. delineated an average 10-year probability of stroke in the Framingham cohort ranging from 3% in the fifth decade of life to nearly 25% in the early 80s (70). These numbers have been supported and expanded since then and the Canadian surveillance data show a prevalence of 1% of
the population in 2009 and an annual incidence of stroke approaching 50000 events (32, 72, 73).

It must be noted that the Framingham and SMART studies have been performed in large cohorts considered representative of the general population in developed nations. As a result, the risk of stroke for special populations such as people with cerebral palsy (CP) is not determined, even though it is well known that these individuals often have certain risk factors for stroke such as increased sedentary time from a very young age (25, 74). However, CP has long been considered a pediatric condition and very little research has explored the long-term impact of this condition on cardiovascular health and outcomes (75). Recent paradigm changes have heralded a new awareness of such developmental conditions as a life-long disability which must be approached from a lifetime perspective (76, 77). This attention has increased awareness of the dearth of evidence in the adult population with CP. Since then, much has been postulated about the risk of chronic disease in people with CP.

Cerebral Palsy (CP) is a lifelong condition caused by a non-progressive injury to the brain in the period of early brain development (78). This injury results in a condition of varying physical and mental impairments (1) often associated with limited mobility-associated activities in daily life and reduced physical fitness (25). By virtue of the disability alone, CP is hypothesized to increase the risk of developing secondary health problems such as fatigue, pain, and obesity which may lead to cardiovascular diseases.
later in life (8, 20). Furthermore, it has been postulated, based on evidence from people with spinal cord injury (SCI), that individuals with CP may have unique pathophysiology and exposure to traditional cardiovascular risk factors that ultimately result in an increased risk of MACE compared to the general population (14). However, this has yet to be explored in primary research evidence.

Nevertheless, the hypothesis that there are similarities in health outcomes between people with CP and people with SCI provides the basis for an interesting comparison. A comparable risk of stroke in people with CP would raise further questions about the origin of the postulated risk of stroke. The hypothesis of this comparison is that these two populations represent a comparable neurological pathology and similar level of disability, and thus similar exposure to risk factors for stroke (14). Further to this hypothesis is the postulation that an increased risk is due to the cause of the disability, that is, the neurological involvement in the development of CP. As such, the risk of stroke may be comparable between populations with a neurological injury irrespective of the timing of the injury; one example would be those with CP and those with acquired brain injury (ABI). However, these comparisons have not been made and current research is often restricted to these specific subgroups of the wider population with neurological disabilities.

Despite the lack of data associating CP (and other neurological disabilities) with increased risk of stroke, some evidence for this hypothesis exists. In 1999, Strauss et al.
noted a two-fold increased mortality due to ischemic heart disease, a four-fold increased mortality due to heart disease, and a nearly three-fold increased mortality due to cerebrovascular disease in adults with CP compared with the general population (23). This study analysed death registry statistics and explored causes of excess mortality in California, USA. Although these findings are of great interest, the study by Strauss et al. could not address the burden of illness or prevalence of cardiovascular disease in adult Californians with CP. In the time following that study, little has been done to explore the prevalence of cardiovascular-related diseases in this population and no definitive studies have yet associated a major adverse cardiovascular event such as stroke to CP. (See Part I of this thesis, where these issues are elaborated.)

This paper addresses the risk of stroke in adults with CP using data collected by the Canadian census in the 2010 and 2011 cycles of the Canadian Community Health Survey (CCHS). Both of these survey cycles identified people with CP, SCI, ABI, and epilepsy and also explored various cardiovascular outcomes and risk factors in Canadians. As a result, these data can be used as a cross-sectional snapshot of the Canadian population (including those with CP and other neurological conditions). This paper will use these data to provide a quantification of the risk of stroke in this population and several other developmental and neurological conditions compared with the general population of Canada. This first exploration of the risk of stroke in adults with CP will provide evidence on which to base further research into the burden and management of stroke.
and, by extension, other chronic diseases in adults with CP. The research question explored in this study is as follows:

What is risk of stroke in Canadian adults with CP and how does this compare with risks in other neurological or developmental conditions?

This question explores the issues using the following objectives:

(1) To determine the risk of stroke in Canadian adults with CP.
   a. To assess the crude risk of stroke in Canadian adults with CP.
   b. To assess the mediating effect of risk factors for stroke (hypertension, heart disease, diabetes, smoking behaviour, increased body mass, and sedentary lifestyle) on risk of stroke in adults with CP.
   c. To estimate the risk of stroke in adults with CP adjusted for the above-mentioned risk factors.

(2) To compare the relationship of CP and stroke to the relationship of stroke to other populations with neurological impairments (spinal cord injury [SCI], acquired brain injury [ABI], and epilepsy).
Methods

The cross-sectional Canadian Community Health Survey (CCHS) is designed to support health surveillance programs at a national, provincial, and regional level. This annual survey explores various areas of public health from disease prevalence to high risk behaviour in Canadians older than twelve years. In 2010, a new module exploring the impact of various neurological conditions was introduced which continued until the 2012 survey cycle. This module identified people with various neurological conditions (CP, ABI, SCI, and epilepsy) as well as people who had suffered a stroke and people who were living with several risk factors for stroke (79). Access to the survey microdata was granted for the purposes of this study and this paper describes a secondary analysis of these data.

Population sampling for the CCHS is performed using several different methods which account for socioeconomic status, location, and population density. Individuals are selected from predefined sampling frames using random-digit dialing, area sampling, and targeted telephone list strategies (79). As such it is considered a complex sampling strategy (79) which must be accounted for in statistical analyses. Statistics Canada provides bootstrap weights with each dataset to account for this complex, clustered design and to provide an accurate variance estimate (79). These weights can be modified when merging survey cycles using the validated measures provided by Thomas et al. to remain representative of the Canadian population (80).
The 2010 and 2011 survey cycles were not released as a combined cycle by Statistics Canada since merged cycles usually end with the even year of collection (e.g. 2009-2010). For the purposes of this study, the 2010 and 2011 surveys were combined using SPSS version 20 (81), then imported into STATA version 12 (82). Bootstrap weights were normalized as described by Thomas et al. and all analyses are presented here using the combined 2010-2011 dataset with adjusted bootstrap weights (80). Bootstrapping weights were used in all analyses in this paper and all numbers are reported with weighted variance estimates. All alterations to the raw datasets were performed under the oversight of a Statistics Canada Research Data Centre (RDC) analyst and statistical output vetted for personally identifiable information prior to release from the RDC. Although the research and analyses here presented are based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

The resultant dataset is comprised of a sample of 117,000 people with 1,500 variables, with a response rate of 69.8% for the 2011 cycle. Although the CCHS samples Canadians twelve years and older, only adults (older than eighteen years) were included in these analyses. Survey responses themselves are categorical in nature and include the possibility of non-response or inability to answer. The survey system also flagged some variables as not applicable (based upon previous responses). During data cleaning, participants with incoherent and missing key data were excluded. A proportion of each
sampling frame is expected to fail, or refuse to respond; these missing data are accounted for within the weighting procedures using redundancies within the sampling frame (79).

All regular or derived variables of interest (Table 1) were identified within the dataset and modified into binary variables by extracting the yes or no response into a new binary variable. The two ordinal variables describing sedentary time and smoking behaviour were dummy-coded into binary variables. As such, sedentary time categories were collapsed into ten-hour segments and then dummy-coded into four variables to preserve data integrity: <10 hours, 10-19 hours, 20-29 hours, 30-39 hours, and >40 hours of sedentary time/week.

The combined 2010-2011 dataset was comprised of a sample of Canadian adults including people with CP, SCI, ABI, epilepsy, and people who had suffered a stroke along with several risk factors for stroke (biological and lifestyle). Biological risk factors for stroke were defined as conditions such as hypertension, heart disease, and diabetes. Lifestyle risk factors such as sedentary time and smoking were also included, as were medical conditions such as diabetes and increased body mass. (See Table 1.)

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3 Statistics Canada requires a minimum number of unweighted variables per category. Further, it is in the researcher’s best interest to increase sample size, especially when using weighted data.
Table 1: Outcome variables of interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>CCHS Description</th>
<th>Type of variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Suffers the effect of a stroke</td>
<td>MACE</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Has high blood pressure</td>
<td>Biological risk factor</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>Has heart disease</td>
<td>Biological risk factor</td>
</tr>
<tr>
<td>Smoker</td>
<td>Is a daily/occasional smoker</td>
<td>Lifestyle risk factor</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Has diabetes</td>
<td>Biological risk factor</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Measure of body composition</td>
<td>Lifestyle risk factor</td>
</tr>
<tr>
<td>Sedentary Activity</td>
<td>Hours of sedentary time/week</td>
<td>Lifestyle risk factor</td>
</tr>
<tr>
<td>Age</td>
<td>Age of the participant</td>
<td>Demographic</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender of the participant</td>
<td>Demographic</td>
</tr>
</tbody>
</table>

**Statistical Methods**

Descriptive statistics were reported for the population with and without CP, subdivided by the presence or absence of stroke (see Table 2). Age and Body Mass Index (BMI) were reported as means (standard deviation; SD) and gender was reported as a count (percentage). Gender differences noted in this table prompted the computation of an interaction variable of gender and CP used in the multivariable analysis.

The unadjusted relationship of each risk factor to stroke was tested using chi-squared tests and estimated as odds ratios (OR) with 95% confidence intervals (CI). Similarly, the unadjusted relationship of stroke and cardiovascular risk factors to CP was tested using chi-squared tests and estimated as ORs with 95% CI. P-values are reported for all statistical tests.

The clear age differences between those with and without CP evident in the demographic data provided reason to adjust all multivariate analyses by age (an adjustment based on
the dataset). The gender effect also noted in the demographic data provided reason, corroborated by the literature, to include a gender interaction variable in all models involving gender (70). Multivariable analyses were then used to test possible mediation of the association of CP to stroke by each risk factor and age individually (83)\(^4\). Mediation was tested by first estimating the crude relationship of each predictor to both CP and to stroke. Then the relationship of CP to stroke was adjusted for each predictor. Mediators were defined as those predictors positively related to CP and positively associated with risk of stroke which resulted in a large change in the relationship of CP to stroke.

All predictors were then tested for multicollinearity using a correlation matrix and considered collinear if they were more than 80% correlated (84). All noncollinear variables were entered into a larger model adjusting the effect of CP for each predictor. This larger model accounts for the clinical reality that an increased risk of stroke is a result of the effect of multiple risk factors and their interactions in a patient’s risk profile (85).

\(^4\) Mediation effects are found when a variable associated with both the independent (cause) and dependent (outcome) variables occurs along the causal pathway. This variable causes variation in the outcome variable and is also varied by the causal variable. In a regression analysis, this relatedness will have effects on predictors, noted by a drop in regression estimates and possible loss of significance in the postulated predictor (83). An example relevant to this paper would be a link between CP, BMI, and risk of stroke. If CP is closely related to an increased BMI and an increased BMI is closely related to an increased risk of stroke, it is possible that the increased BMI (and not CP) would be the cause of an increased risk of stroke. However, since CP is highly associated with an increased BMI, it can be misconstrued that the presence of CP alone results in an increased risk of stroke.
A comparative bivariate analysis of the relationship of stroke to different conditions was also performed. In this analysis, the unadjusted relationship of CP and stroke was compared with those associated with other diagnoses (ABI, SB, SCI, epilepsy). All risks were tested as with a chi-square test and estimated as ORs with 95% confidence intervals (see Figure 1).

**Figure 1: Statistical Plan**

- **Merged Dataset**
  \[n_{\text{weighted}} = 25,756,938\]

- **Baseline Statistics**
  - Descriptive Statistics of age, BMI, and gender divided by CP and stroke status.

- **Bivariate Analyses**
  - Chi squared test of correlation between:
    1. Risk of stroke, risk factors for stroke and CP.
    2. Risk of stroke and risk factors for stroke, including CP.

- **Regression Analyses**
  - Logistic regression exploring:
    1. Association of CP to risk of stroke; adjusted for age and potentially mediating risk factors.
    2. Association of CP to risk of stroke; adjusted for all risk factors (overall clinical model).

- **Comparative Analysis**
  - Chi squared test of correlation between other populations (acquired brain injury, epilepsy, and spinal cord injury) and risk of stroke.
Results

The merged datasets provided a sample size of approximately 117,000 records. After applying the bootstrap weights provided by Statistics Canada, each sample is weighted to provide a dataset numerically and demographically representative of the population of Canada. Once weighted, the sample represented a population of approximately 25 million Canadians 18 years and older. An unweighted sample of 179 persons represents the 35,295 persons with CP, approximately 0.15% of the population dataset. This prevalence estimate is corroborated within the literature for industrialized nations (from 0.15-0.3%) (12).

Demographic Data

Respondents with CP were younger than the general population albeit similar in BMI estimates and gender distribution. When divided by stroke outcomes, those with CP who reported to have suffered a stroke were younger (mean [standard deviation; SD]=59.3 [11.0] years), at a lower BMI (mean [SD]=20.6 [5.3]), and are more likely to be male (82% vs. 52%) than the general population. See Table 2.

Table 2: Descriptive statistics and demographics

<table>
<thead>
<tr>
<th>Has CP</th>
<th>Does not have CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke +</td>
<td>Stroke -</td>
</tr>
<tr>
<td><strong>Age</strong>&lt;br&gt;mean (SD) years</td>
<td>59.3 (11.0)</td>
</tr>
<tr>
<td><strong>BMI</strong>&lt;br&gt;mean (SD) kg/m²</td>
<td>20.6 (5.3)</td>
</tr>
<tr>
<td><strong>Gender=M</strong>&lt;br&gt;# (%)</td>
<td>3 812 (81.8)</td>
</tr>
</tbody>
</table>
**Crude relationship of CP to stroke and risk factors.**

The unadjusted (or crude) OR (95% CI) for stroke and CP is 12.5 (12.2-12.9). The relationship of hypertension and heart disease to CP estimates were OR=1.1 (1.1-1.2) and OR=1.5 (1.4-1.5), respectively. Smoking behaviour (OR=0.6 [0.6-0.6]) and diabetes (0.6 [0.6-0.7]) were negatively associated with CP. Of the sedentary time categories, only the categories of 20-29 hours/week (OR=1.4 [1.4-1.5]) and >40 hours/week (OR=4.7 [4.6-4.9]) were positively related to CP (unadjusted for other variables). Table 3 reports these effects with their 95% CI.

**Table 3: Crude relationship of stroke and risk factors for stroke to CP**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (events)</th>
<th>CP (n=35 295)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>4 663</td>
<td><strong>12.5</strong> (12.2-12.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 343</td>
<td><strong>1.1</strong> (1.1-1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>2 693</td>
<td><strong>1.5</strong> (1.4-1.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non/Occasional Smoker</td>
<td>31 611</td>
<td><strong>1.7</strong> (1.6-1.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>3 684</td>
<td><strong>0.6</strong> (0.6-0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedent. Time &lt;10 hrs*</td>
<td>1 235</td>
<td><strong>0.3</strong> (0.3-0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedent. Time 10-19hrs</td>
<td>2 129</td>
<td><strong>0.3</strong> (0.3-0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedent. Time 20-29hrs</td>
<td>5 249</td>
<td><strong>1.4</strong> (1.4-1.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedent. Time 30-39hrs</td>
<td>1 488</td>
<td><strong>0.8</strong> (0.8-0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedent. Time &gt;40hrs</td>
<td>5 871</td>
<td><strong>4.7</strong> (4.6-4.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 567</td>
<td><strong>0.6</strong> (0.6-0.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>35 295</td>
<td>r=0.0032</td>
<td></td>
</tr>
</tbody>
</table>

*reference category
Unadjusted relationship of stroke to CP and risk factors for stroke.

All hypothesized risk factors, with the exception of gender and BMI, were associated with an increased risk of stroke. CP maintained the strongest univariate relationship with stroke (OR=12.5 [12.2-12.9]) followed by heart disease (OR=10.9 [10.8-11.0]), hypertension (OR=6.7 [6.6-6.7]), and diabetes (OR=4.7 [4.7-4.8]). Increasing sedentary time also increased risk. Positive associations were noted between risk of stroke and sedentary time at 30-39 hours/week of sedentary time (OR=1.3 [1.3-1.4]) and > 40 hours/week (1.9 [1.9-1.9]), in reference to <10 hours/ week of sedentary time (see Table 4).

Table 4: Crude relationship of CP and risk factors for stroke to risk of stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>weighted</th>
<th>Stroke</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy (CP)</td>
<td>4 663</td>
<td>12.5</td>
<td>(12.2-12.9)</td>
</tr>
<tr>
<td>Hypertension (HT)</td>
<td>194 905</td>
<td>6.7</td>
<td>(6.6-6.7)</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>117 180</td>
<td>10.9</td>
<td>(10.8-11.0)</td>
</tr>
<tr>
<td>Non/ Occasional Smoker</td>
<td>262 751</td>
<td>0.7</td>
<td>(0.8-0.9)</td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>60 621</td>
<td>1.2</td>
<td>(1.2-1.2)</td>
</tr>
<tr>
<td>Sedentary Time (&lt;10 hrs/ week)</td>
<td>31 515</td>
<td>0.9</td>
<td>(0.9-0.9)</td>
</tr>
<tr>
<td>Sedentary Time (10-19hrs/ week)</td>
<td>44 005</td>
<td>0.8</td>
<td>(0.8-0.8)</td>
</tr>
<tr>
<td>Sedentary Time (20-29hrs/ week)</td>
<td>36 636</td>
<td>0.8</td>
<td>(0.8-0.8)</td>
</tr>
<tr>
<td>Sedentary Time (30-39hrs/ week)</td>
<td>23 432</td>
<td>1.3</td>
<td>(1.3-1.4)</td>
</tr>
<tr>
<td>Sedentary Time (&gt;40hrs/ week)</td>
<td>30 806</td>
<td>1.9</td>
<td>(1.9-1.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>81 394</td>
<td>4.7</td>
<td>(4.7-4.8)</td>
</tr>
<tr>
<td>Gender=M</td>
<td>159 111</td>
<td>1.0</td>
<td>(1.0-1.0)</td>
</tr>
<tr>
<td>Interaction CP*Gender</td>
<td>3 812</td>
<td>0.9</td>
<td>(0.8-0.9)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>r=0.0157</td>
<td></td>
</tr>
</tbody>
</table>
Relationship of stroke to CP adjusted for age and risk factors for stroke.

All logistic regression models were adjusted for the age difference previously noted in Table 2. Age was associated with risk of stroke but remained a small predictor (approximate OR=1.1 [95%CI: 1.1-1.1) in all regression models. All models included CP as a large predictor (OR>15) associated with risk of stroke with the exception of the gender model. Bootstrapped variance estimates resulted in wide confidence intervals in most predictors.

The relationship of CP to risk of stroke adjusted for hypertension (OR=2.7 [2.2-3.3]) and age was OR=20.0 (4.9-85.8). Heart disease also maintained a large unique effect (OR=4.1 [3.3-5.0]) but did not impact the strong association of CP to stroke (OR=20.6 [5.5-78.0]; see Table 5.) Models adjusting BMI and diabetes showed that CP was a substantial risk factor independent of these risk factors among people who have had a stroke. The adjusted relationship to stroke in adults with CP was OR=15.5 (4.3-56.0) adjusted for BMI (OR=1.0 [1.0-1.1]) and age. When adjusted for diabetes (OR=2.2 [1.8-2.7]) and age, the association of stroke to adults with CP remained strong (OR=22.7 [5.9-87.3]). (See Table 5.)

Models adjusting for lifestyle or behavioural risk factors and age also demonstrated a strong association between stroke and CP. CP remained strongly associated with stroke (OR=23.1 [6.1-87.2]) when adjusted for smoking behaviour (OR=1.8 [1.5-2.2]) and age. The association of CP to stroke was strong (OR=15.6 [4.4-57.7]) when adjusted for a
sedentary lifestyle and age. This model demonstrated an association between 30-39 hours/week (OR=1.1 [1.1-2.5]) and >40 hours/week (OR=1.7 [1.1-2.5]) of sedentary time and risk of stroke (with <10 hours/week as reference). (See Table 5.)

The final model adjusted the relationship of CP to stroke by age, gender, and an interaction of gender and CP. When adjusted for age, gender, and a gender*CP interaction term, the association of stroke to CP dropped to 6.2 (0.9-45.5). The interaction variable of gender and CP showed a no effect (OR=7.2 [0.5-101.2]). Age remained a small, significant predictor. (See Table 5.)

The pseudo R\(^2\) values for each model varied from 0.12-0.16 as reported in Table 5. Of these models, those that adjusted the relationship of CP to stroke with hypertension (pseudo R\(^2\)=0.15) and heart disease (pseudo R\(^2\)=0.16) (and age) were the best fit models followed by the diabetes-adjusted model (pseudo R\(^2\)=0.14). Sedentary time, smoking behaviour, and gender were the poorest predictive models of stroke (pseudo R\(^2\)<0.14).

Mediation effects were not noted in any models in Table 5. Despite the strong relationship of CP to >40 hrs/week sedentary time (Table 3; OR=4.7 [4.6-4.9], this relationship is not strongly associated with risk of stroke (OR=1.9 [1.9-1.9]). No other variables were closely related to both CP and stroke and impacted the relationship of CP to stroke.
Table 5: Logistic regression analyses testing possible mediation effects

<table>
<thead>
<tr>
<th>Model (Stroke)</th>
<th>OR</th>
<th>95% CI</th>
<th>Model Fit</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>20.6</td>
<td>4.9</td>
<td>85.8</td>
<td>0.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.7</td>
<td>2.2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>20.6</td>
<td>5.5</td>
<td>78.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>4.1</td>
<td>3.3</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>15.6</td>
<td>4.4</td>
<td>54.7</td>
<td>0.00</td>
</tr>
<tr>
<td>Sedentary 10-19 hrs</td>
<td>0.8</td>
<td>0.5</td>
<td>1.4</td>
<td>W. Chi²=384.5</td>
</tr>
<tr>
<td>Sedentary 20-29 hrs</td>
<td>0.7</td>
<td>0.5</td>
<td>1.0</td>
<td>Pseudo R²=0.12</td>
</tr>
<tr>
<td>Sedentary 30-39 hrs</td>
<td>1.1</td>
<td>1.1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Sedentary &gt;40 hrs</td>
<td>1.7</td>
<td>1.1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>6.2</td>
<td>0.9</td>
<td>45.5</td>
<td>0.00</td>
</tr>
<tr>
<td>Gender</td>
<td>1.1</td>
<td>0.9</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Interaction (CP*Gender)</td>
<td>7.2</td>
<td>0.5</td>
<td>101.2</td>
<td>W. Chi²=819.2</td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>15.5</td>
<td>4.3</td>
<td>56.0</td>
<td>0.00</td>
</tr>
<tr>
<td>BMI</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>23.1</td>
<td>6.1</td>
<td>87.2</td>
<td>0.00</td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>1.8</td>
<td>1.5</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>22.7</td>
<td>5.9</td>
<td>87.3</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2</td>
<td>1.8</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

Bolded values represent a significant (p<0.05) predictor.
Multicollinearity was explored in the correlation matrix detailed in Appendix D and showed low correlations among most risk factors for stroke. The greatest relationship observed was that of CP and its interaction variable with Gender ($r=0.7$), within the categories of sedentary time ($r=0.5-0.7$), and between BMI and sedentary time ($r=0.5-0.6$). These correlations were expected based upon the nature of each interaction. No correlations were deemed sufficiently strong to warrant removal from a larger model. (See Appendix D.)

The large clinical model adjusted the relationship of CP and stroke with hypertension, heart disease, smoking behaviour, diabetes, age, BMI, gender, and gender*CP interaction. In this model, the CP was associated with risk of stroke (OR=7.9 [1.8-34.2]; see Table 6). The unique effect of heart disease was large and similar to the effect of CP (OR=3.8 [2.9-5.2]. The adjusted effect of hypertension was OR=2.13 (1.4-3.2. Smoking behaviour was also associated with risk of stroke (OR=1.9 [1.3-2.7]). The effect of sedentary time was unrelated to risk of stroke in every category with a small magnitude of effect (using <10 hours/week sedentary time as a reference category). Gender was not associated with risk of stroke, and the added risk to males with CP (interaction term) showed no effect (OR=4.1 [0.4-45.5], p=0.25). Diabetes and BMI were not associated with risk of stroke. Overall, the large model adjusting for more individual risk factors was statistically significant (p<0.001) and demonstrated a slightly higher fit than previous, smaller models (pseudo R$^2=0.17$).
Table 6: Crude and adjusted ORs for risk of stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>n_{weighted}</th>
<th>Crude</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Adjusted</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy (CP)</td>
<td>4663</td>
<td></td>
<td>12.5</td>
<td>(12.2-12.9)</td>
<td>&lt;0.01</td>
<td>7.9</td>
<td>(1.8-34.2)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Hypertension (HT)</td>
<td>194905</td>
<td></td>
<td>6.7</td>
<td>(6.6-6.7)</td>
<td>&lt;0.01</td>
<td>2.1</td>
<td>(1.4-3.2)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>117180</td>
<td></td>
<td>10.9</td>
<td>(10.8-11.0)</td>
<td>&lt;0.01</td>
<td>3.8</td>
<td>(2.9-5.2)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Non/ Occasional Smoker</td>
<td>262751</td>
<td></td>
<td>0.7</td>
<td>(0.8-0.9)</td>
<td>&lt;0.01</td>
<td>1.0</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>60621</td>
<td></td>
<td>1.2</td>
<td>(1.2-1.2)</td>
<td>&lt;0.01</td>
<td>1.9</td>
<td>(1.3-2.7)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (&lt;10 hrs/ week)</td>
<td>31515</td>
<td></td>
<td>0.9</td>
<td>(0.9-0.9)</td>
<td>&lt;0.01</td>
<td>1.0</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (10-19hrs/ week)</td>
<td>44005</td>
<td></td>
<td>0.8</td>
<td>(0.8-0.8)</td>
<td>&lt;0.01</td>
<td>0.8</td>
<td>(0.5-1.4)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (20-29hrs/ week)</td>
<td>36636</td>
<td></td>
<td>0.8</td>
<td>(0.8-0.8)</td>
<td>&lt;0.01</td>
<td>0.7</td>
<td>(0.4-1.0)</td>
<td>0.07</td>
<td></td>
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<tr>
<td>Sedentary Time (30-39hrs/ week)</td>
<td>23432</td>
<td></td>
<td>1.3</td>
<td>(1.3-1.4)</td>
<td>&lt;0.01</td>
<td>0.9</td>
<td>(0.6-1.5)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (&gt;40hrs/ week)</td>
<td>30806</td>
<td></td>
<td>1.9</td>
<td>(1.9-1.9)</td>
<td>&lt;0.01</td>
<td>1.2</td>
<td>(0.8-2.0)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>81394</td>
<td></td>
<td>4.7</td>
<td>(4.7-4.8)</td>
<td>&lt;0.01</td>
<td>1.7</td>
<td>(1.3-2.3)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Gender=M</td>
<td>159111</td>
<td></td>
<td>1.0</td>
<td>(1.0-1.0)</td>
<td>&lt;0.01</td>
<td>0.8</td>
<td>(0.6-1.0)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Interaction CP*Gender</td>
<td>3812</td>
<td></td>
<td>0.9</td>
<td>(0.8-0.9)</td>
<td>&lt;0.01</td>
<td>4.1</td>
<td>(0.4-45.5)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>r=0.0157</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>(1.0-1.0)</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

Bolded values represent significant predictors
---- denotes a dummy-coded reference variable

Wald chi$^2 = 696.5$
p = 0.00
Pseudo R$^2 = 0.17$
Comparison across populations and health outcomes.

We also explored the relationship of stroke to other developmental and acquired health conditions similar to CP. People with ABI, SCI, and epilepsy all demonstrated increased odds of experiencing a stroke. Of these groups, people with CP and ABI both demonstrated the highest risk of stroke (OR=12.5 and 16.2, respectively). People with epilepsy and SCI also demonstrated a strong relationship to stroke (OR=6.2 and OR=6.1, respectively). (See Table 7.)

Table 7: Crude risk of stroke in neurological conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>n_{weighted}</th>
<th>n_{events}</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>35 295</td>
<td>4 663</td>
<td><strong>12.5</strong></td>
<td>(12.2-12.9)</td>
</tr>
<tr>
<td>ABI</td>
<td>131 458</td>
<td>20 531</td>
<td><strong>16.2</strong></td>
<td>(16.0-16.5)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>117 405</td>
<td>8 038</td>
<td><strong>6.2</strong></td>
<td>(6.0-6.3)</td>
</tr>
<tr>
<td>SCI</td>
<td>136 037</td>
<td>9 322</td>
<td><strong>6.1</strong></td>
<td>(6.0-6.3)</td>
</tr>
</tbody>
</table>
**Discussion**

*Summary of results*

**Objective I**

In this study we explored the relationship between CP and risk of stroke. Before accounting for the effect of other risk factors, CP was strongly and significantly related to stroke (OR=12.5 [12.1-12.9]). When the effect of CP was adjusted for these risk factors, the strength of this relationship changed depending on the risk factor of interest, but demonstrated no effects indicative of mediation (83). In these models, CP remained strongly related to stroke (OR>15) with the exception of the gender-adjusted model. The effect of gender was non-significant, such that any moderation effect is undetermined. The overall clinical model adjusting the effect of CP on risk of stroke for all other risk factors demonstrated a strong unique effect of CP (OR=7.9 [1.8-34.2]). Thus CP appears to be a significant predictor and source of elevated risk for stroke in Canadian adults.

**Objective II**

Of further interest is the relationship of stroke to other developmental and acquired conditions. Risk of stroke was found to be strongly associated with people with ABI (OR= 16.2 [16.0-16.5]), SCI (OR=6.2 [6.0-6.3]), and epilepsy OR=6.1 [6.0-6.3]). In the first objective, we explored the relationship of CP to stroke and determined that CP is strongly associated to increased risk of stroke. When this risk is compared with the risk demonstrated in these other neurological populations, it seems that risk of stroke is elevated irrespective of the timing of the injury (developmental or acquired). Further, the
elevated risk in all of these conditions leads to the conclusion that the increased risk of stroke may be linked to the neurological nature of each condition. However, a causal link has not yet been determined and all associations here detailed must be interpreted with care.

**Interpretation**

There is a lack of evidence available regarding the risk and prevalence of stroke within the population of adults with CP. This study represents one of the first to make a direct link between risk of stroke and a developmental disability such as CP in a large population survey. When the results of this study are compared with the accepted literature surrounding cardiovascular disease, we can see similarities with the risk factors here presented.

Not surprisingly, hypertension and heart disease remained significantly related to stroke in this study. This finding is supported by the results of the earlier Framingham studies where the risk associated with each risk factor was elevated (hypertension: relative risk [RR]=1.9 [M], 1.7 [F], heart disease: RR=1.7 [M], 1.5 [F]) (70, 74).

In this study, smoking was not associated with having CP (OR=0.6 [95% CI=0.6-0.6). However, in the overall clinical model which accounts for risk of stroke across the entire sample of Canadians, daily smoking behaviour is significantly related with stroke (OR=1.9 [1.3-2.7]). This risk is comparable to that described in the Framingham
It is interesting to note that increased sedentary time was univariately related to risk of stroke and CP but lost statistical significance in the adjusted analysis. In the literature, an increasingly sedentary lifestyle is associated with an increased prevalence of hypertension and thereby an increased risk of stroke (74, 86). However, in this dataset results were positively associated with risk of stroke, but showed high variance when adjusted for the effect of CP and other risk factors. (See Table 6, adjusted analysis.) Although this finding does not affirm the study hypothesis, it does uphold our current multifactorial understanding of risk of stroke. In this dataset, it appears as though the risk of stroke is not related as strongly to a sedentary lifestyle as it is to other, stronger risk factors such as hypertension and heart disease.

Diabetes and BMI were both significantly related to risk of stroke in the Framingham and the SMART studies. In our study we found a significant relationship with increased risk of stroke in people with diabetes. This risk is similar to that found in the Framingham (relative risk [RR]=1.4 [M], 1.7 [F]) and SMART studies (hazard ratio [HR]=1.8) and thus verifies their findings in the Canadian population (70, 87). Increasing BMI, however, did not prove to be related to risk of stroke (OR=1.0 [1.0-1.0]; see Table 8.) This directly contradicts most medical literature, including the findings of the Framingham and SMART studies. This is an interesting finding which may be more related to the challenges and limitations of this dataset and the analyses performed in this study than a comment on the Canadian population itself. For example, it is possible that the adults with CP who responded fell within a narrow range of BMI, nullifying a relationship
found more clearly when outliers are included in the analysis. Further comment is provided in the limitations section following.

It is already established that male gender modifies the risk of many common CVDs including stroke (88) in the general population. Interestingly, the effect of gender alone was not associated with stroke in the univariate or multivariable models (OR~1.0). However, the extent to which gender affects the relationship of CP to stroke is as yet unexplored within the literature. In the model testing this, introducing the gender interaction term had a large effect on the magnitude of the relationship of CP with risk of stroke compared with the univariate analysis. However, this effect remained non-significant and therefore attributable to chance in both the mediation and the clinical models. Given the small number of weighted events in this dataset, this result should not be disregarded completely. Rather, based on the increased risk of stroke in males in the general population, this effect should be further explored based upon the contradictory evidence provided by large, well-designed epidemiological research such as the Framingham and SMART studies.

Special Considerations:

The relationship of CP to stroke compared with the relationship of other populations to stroke provides evidence for an interesting comment. It is clear that there is also an increased risk of stroke in other populations with neurological conditions. ABIs usually occur later in childhood than the conditions that are associated with the genesis of CP, yet
the effects of the injury may mimic those of CP (89). This raises the question whether the pathology of the brain injury, in itself, occurring at birth or during adulthood, is linked to an increased risk of stroke.

A further perspective would be that which views this increased risk of stroke as risk of recurrent stroke. Given that CP is a brain injury, sometimes analogous to a stroke, occurring very early in life, it can be postulated that this population may be at high risk for further cerebrovascular events due to their historical neurological condition. This increased risk of stroke noted in people with CP in this study is similar in magnitude to the risk of recurrent stroke found in the literature. Burn et al. note that the risk of recurrent stroke is especially elevated one year following stroke in older adults, approaching 15 times the risk attributable to the general population. This risk decreases to just under 9 times the background risk by 5 years (90). This similarity raises the question of the efficacy of primary prevention strategies in this population and demonstrates the need for further research into the arterial health of adults with CP.

Limitations

This study is an early exploration of risk of stroke in Canadian adults with CP. Given the secondary nature of this analysis, there are several limitations to the interpretation of these findings.

i. Self-Response
The CCHS relies upon self-response and voluntary participation. Medical diagnoses claimed within the survey responses are unverified and are accepted at face value. As a result, this is an imperfect measurement tool fraught with potential weaknesses which may bias the results.

Beyond medical diagnoses, smoking, sedentary behaviour, and BMI are extremely hard to quantify accurately in a survey setting. It has been demonstrated that socially stigmatized statuses such as smoking or obesity are often underreported or downplayed in survey responses (67). As a result, the relationship of smoking and BMI with risk of stroke may be underestimated in this model. Further, sedentary time was calculated based on self-recalled activity over the past month, a method which is questionable at best (67). Although this variable provided some basis for a comment on sedentary time, this risk factor for many cardiovascular outcomes was weakly measured and it is unclear whether this bias may over- or under-estimate the risk seen.

**ii. Responders**

Of interest to note is the selection of responders. Although the Statistics Canada sampling methodology is rigorous and designed to produce a sample highly representative of the Canadian population, it is not designed to provide a sample highly representative of a specific subgroup within the Canadian population (adults with CP). As a result, selection bias may be present. It is probable that those who are more highly functioning (GMFCS levels I-III) were selected for participation while those with higher levels of disability
more likely to require assisted living arrangements (GMFCS level IV-V) were unaccounted for in this survey. As a result, the association of several classical risk factors to stroke such as an increased BMI and sedentary lifestyle may have been under-represented in adults with CP. However, without the use of a discriminatory classification tool like the GMFCS and independent BMI measurement, it is impossible to ascertain the presence or effect of this possible bias.

*Strengths*

*i. Weighting*

Methodologically, this study represents a rigorous approach within the constraints of the dataset. However, it must be noted that the entire sample of those with CP remains somewhat small (n=179). Although representative of the population of adults with CP in an industrial nation (12), weighting a small sample may mask or exaggerate some trends. An example of this can be seen in the seeming non-linearity of the relationship of CP to sedentary time. It is possible that smaller numbers of individuals were present in some categories than others and each individual was weighted differently in order to be representative of the population. Thus, it is possible that the use of data weights in a small sample resulted in the non-linear trends here noted. Howbeit, the weighted data remain a strength which enables a small, complex sample to become representative of the Canadian population and provides a powerful dataset from which to perform epidemiological analyses.
ii. *Generalizability*

The CCHS is designed to be representative of the Canadian population and weighted estimates of the prevalence of CP were comparable to the prevalence estimated for developed nations. Thus these findings should be generalizable to people with CP found in developed nations around the world.

Further, the increased risk of stroke in CP was also noted in other neurological conditions. Although people with CP remained the focus of this thesis paper, it may be of particular value to explore the risk of stroke across neurological conditions with different diagnoses as subgroups of interest. This approach would explore the large-scale implications of a neurological condition or injury on risk of stroke.

*Future Directions & Conclusions*

This study represents a preliminary level of cross-sectional evidence that should provide an impetus for further study in the field. The findings detailed here are thought-provoking and challenge the status quo of risk factors for stroke in the general population. Furthermore, these results raise questions about the causation and temporality of this risk of stroke.

Such questions should be addressed, particularly when faced with such strong effect sizes. Ideally, future studies would follow the lead of the Framingham cohort and build a similar, large-scale sample of people with multiple types of neurological conditions and
injuries. Such a prospective cohort design would provide an enormous benefit to this field of research, but would also be tremendously costly. More realistically, observational studies may be undertaken to access electronic medical records (EMRs) to conduct cross-sectional studies using retrolective data. Such studies cannot, however, pinpoint causality in a relationship and should be used to inform further research.

That said, these findings have some implications for policy, patients, and practice. Since this is a preliminary level of evidence, policy makers are encouraged to remain aware of the gathering evidence and monitor this new area of research for possible policy opportunities. Funders should be joined by clinicians to advocate for further study in this area, particularly around the need for a long-term prospective cohort study to inform cardiovascular and other chronic disease and age-related health outcomes in this population. Clinicians should also become aware of a potentially new patient group at high risk of stroke. Further, they should realize that the primary prevention of stroke in these patients may not be as effective as found in the general population. Finally adults with CP and their caregivers should maintain high awareness of the risk of stroke in this population and take care to minimize exposure to modifiable risk factors such as an increased BMI and a sedentary lifestyle. At this time, with this preliminary evidence, risk of stroke seems to be highly related to CP.
Overarching Discussion and Conclusion
Thesis overview

This work explored the prevalence of CVDs and MACE as well as the risk of stroke in adults with CP. Although little is currently known of these health outcomes, together these two papers provide a clearer picture of the understanding of CVDs and MACE in this population.

The systematic review of the literature found very little published evidence and described the prevalence of MACE and risk factors for MACE without providing a pooled estimate of effect. This review was able to demonstrate some of the large gaps in the knowledge base, particularly around the lack of evidence linking MACE and adults with CP. Further gaps encompassed the entire second objective exploring interventions and prevention strategies of CVDs and MACE in this population. As a result, this review highlights the paucity of evidence in this area and demonstrates many of the gaps associated with cardiovascular risk factors and outcomes in this population.

The secondary analysis of the Canadian Community Health Survey 2010-2011 began to address one of these gaps. This study linked a MACE (stroke) and several risk factors for MACE to adults with CP for the first time. Although a secondary analysis using imperfect survey data, this study provides evidence of the need for future research exploring the causation and implications of stroke in individuals with neurological conditions. These areas of interest should be addressed more completely in future
research, ideally from a long-term prospective cohort study investigating the chronic disease and age-related health outcomes in this population.

Current state of the evidence

Our systematic review found that studies only began focusing upon the population of adults with CP in 1998. Since that time, 10 studies have been undertaken which met the inclusion criteria of the review. Between 1999 and 2006, 3 of 4 of the studies made use of population registries to estimate mortality and cause of death (60, 66, 91). Following 2006, publications (n=6) began to focus upon cardiovascular risk factors such as obesity, albeit in smaller population studies.

Chronological trends and subjective impressions from these studies show a growing interest in CVDs and their risk factors within adults with CP. Early studies mostly focused upon cause of death (23, 60, 62) with a few recent studies more closely examining several lifestyle risk factors (mostly obesity) and a few reporting some outcomes of chronic cardiovascular conditions (49, 61, 65).

The work detailed by this thesis as well as that of the Stay-FIT program of research underway at the CanChild Centre for Childhood Disability Research (Hamilton, Canada) is a good first step to provide a much clearer clinical understanding of cardiovascular health outcomes in persons with CP beginning during childhood and adolescence. Such a
lifespan perspective is essential to explore the impact of childhood disability upon the adult beginning to age with that disability.

*Future directions*

The cross-sectional studies summarized and detailed within this thesis represent foundational research necessary to inform future studies (67). However, long-term cohort studies are needed to establish a more concrete link between CVDs and MACE in adults with CP. Given the costs associated with such a study, it is prudent to approach this using an alternative observational design. One such method is a cross-sectional study using retrolective patient data. In this study design, patient records would be identified based upon diagnoses of CP and reviewed over the course of their patient history to identify CVDs and MACE within this population.

Concurrently, studies should explore the relationship of traditional risk factors for these outcomes in this population. Biomarkers of disease such as LDL cholesterol profile or arterial stiffness may provide a more accurate picture of cardiovascular health than traditional risk factors (such as BMI) in this population (64). It is essential that a clear understanding of the risk factors specific to this population be formed in order to provide adequate patient care to form the basis of further clinical research.
Conclusion

In conclusion, this evidence provides a rationale for accelerating further research in this domain. Although there is growing interest in this population, it is essential that researchers begin to explore both the prevalence and prevention of CVDs and MACE and their risk factors in this population. Policy makers should be aware of a special group with emerging health needs and remain ready to support emerging evidence with appropriate policies and funding. Finally, clinicians and adults with CP should be aware that there are many gaps in our current clinical understanding of health outcomes associated with chronic disease and aging with developmental disabilities. Further, clinicians should advocate for this vulnerable group. Their advocacy should recognize that preliminary evidence demonstrates that cardiovascular health outcomes may represent a dramatic cause of excess mortality and morbidity in adults with cerebral palsy. As such, community members, clinicians, researchers, and policy makers should work carefully (yet speedily) to ask the right questions, perform high quality research, and inform both clinicians and patients of the risk and management strategies of CVDs and MACE in adults with cerebral palsy.
Appendix A: Search Strategy

MEDLINE
1 cerebral palsy.mp. or exp Cerebral Palsy/ 18034
2 Spina bifida.mp. or exp Spinal Dysraphism/ 8936
3 1 or 2 26729
4 exp Disabled Persons/ or Disabled Person*.mp. 43722
5 disability.mp. 138912
6 psychomotor disorders/ or neuromuscular manifestations/ 4590
7 developmental disabilit*.mp. or exp Developmental Disabilities/ 15294
8 exp Movement Disorders/ or Movement Disorder*.mp. 102001
9 exp Musculoskeletal Diseases/ or musculoskeletal disorder.mp. 787593
10 4 or 5 or 6 or 7 or 8 or 9 1044061
11 diplegi*.mp. 1756
12 quadriplegi*.mp. 8323
13 quadriplegi*.mp. or exp Quadriplegia/ 8323
14 exp Paraplegia/ or paraplegi*.mp. 16790
15 Hemiplegi*.mp. 13682
16 hemiplegi*.mp. or exp Hemiplegia/ 13682
17 dyskinesi*.mp. or exp Dyskinesias/ 68871
18 11 or 12 or 13 or 14 or 15 or 16 or 17 105501
19 "Gross Motor Function* Classification System".mp. 688
20 GMFCS.mp. or exp Disability Evaluation/ 36776
21 19 or 20 37033
22 exp Adult/ or Adult*.mp. 5590762
23 exp Middle Aged/ or Middle Aged*.mp. 3097090
24 Aged*.mp. or exp Aged/ 3764184
25 exp Aging/ or Aging*.mp. 251158
26 exp Middle Aged/ or Middle Aged*.mp. 3097090
27 22 or 23 or 24 or 25 or 26 5810869
28 chronic disease risk among adults with cerebral palsy.m_titl. 1
29 (adult outcomes and lifespan issues for people with childhood-onset physical disability).m_titl. 1
30 prevalence of risk factors for cardiovascular disease stratified by body mass index.m_titl. 2
31 greater daily leisure time physical activity is associated with lower chronic disease risk.m_titl. 1
32 28 or 29 or 30 or 31
33 10 or 18 or 21
34 1 and 27 and 33
35 exp Cardiovascular Diseases/ or Cardiovascular DiseasE*.mp.
36 exp Cerebrovascular Disorders/ or Cerebrovascular Disorder*.mp.
37 (coronary* adj2 (BYPAS* or GRAFT* or DISEASE* or EVENT*)).mp.
38 (Myocardial* adj2 (infarct* or Re?vascular* or Isch?emi*)).mp.
39 (morbid* adj2 (heart* or coronary* or isch?em* or myocard*)).mp.
40 (vascular* adj2 (peripheral* or disease* or complication*)).mp.
41 (heart* adj2 (disease* or attack* or bypass*)).mp.
42 exp Coronary Artery Disease/ or coronary artery disease*.mp.
43 exp Myocardial Infarction/ or Heart Attack*.mp.
44 Angina*.mp.
45 Angina Pectoris.mp. or exp Angina Pectoris/
46 exp Stroke/ or Stroke*.mp.
47 Arterial Stiffness.mp.
48 Vascular Stiffness.mp. or exp Vascular Stiffness/
49 exp Hypertension/ or Hypertension.mp.
50 Blood Pressure.mp. or exp Blood Pressure/
51 exp Chronic Disease/ or Chronic DiseasE*.mp.
52 exp Obesity/ or Obesity.mp.
53 exp Waist Circumference/ or Waist Circumference*.mp.
54 Body Mass Index.mp. or exp Body Mass Index/
55 Dyslipidemia.mp. or exp Dyslipidemias/
56 exp Adiposity/ or Adiposity*.mp.
57 exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or Diabetes Mellitus*.mp. or exp Diabetes Mellitus/
58 exp Sarcopenia/ or Sarcopenia*.mp.
59 exp Risk Factors/ or Risk Factor*.mp.
60 exp 'Quality of Life'*/ or Quality of Life*.mp.
61 exp Life Expectancy/ or Life Expectancy*.mp.
62 Mortality.mp. or exp Mortality/
63 Death*.mp. or Death/
64 exp 'Cause of Death'*/ or Cause of Death*.mp.
65 exp Metabolic Diseases/ or Metabolic Disease*.mp.
66 Prognosis.mp. or exp Prognosis/
67 Survival Analysis.mp. or exp Survival Analysis/
35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or
68 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or
65 or 66 or 67

69 34 and 68

946
Appendix B: Full Text Screening Form

Study Design – include most, flag some.
- Include all:
  - RCTs
  - Observational Studies
  - Cross-Sectional Studies
- Case studies & letters to the editors are not to be included
- (Systematic) Reviews are to be flagged for reference searching but not included in the final text search.
- NOTE: All non-intervention studies reporting statistics and prevalence rates are to be flagged for Objective 2 using the “Population Stats” flag.
- NOTE: All grey literature (including free paper abstracts, presentations, and conference abstracts) are to be flagged using the “Include (Unpublished/ Grey Literature)” flag.

Study Population – include CP only.
- The study population should be CP.
- The comparator should also be CP, but do not exclude based upon a different comparator.
- Flag others that include only spinal cord injury, spina bifida, etc for reference searching and background material.
- No “n of 1” studies.

Study Intervention – include all.
- Must target a cardiovascular disease, event, or risk factor.

Study Outcomes – must include a measure of interest as dictated here:
- Must measure an outcome that fits the chart below.
- NOTE: measuring a construct of something similar (e.g. blood glucose level for diabetes) is a criteria for inclusion.
- NOTE: all outcomes not associated with these outcomes are to be excluded.

<table>
<thead>
<tr>
<th>Major Adverse Cardiovascular Events (MACE)</th>
<th>Risk factors associated with cardiovascular conditions</th>
<th>Risk Factor associated with lifestyle/clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>Condition</td>
<td>Factor</td>
</tr>
<tr>
<td>Stroke (Cerebrovascular Accident - CVA)</td>
<td>Hypertension</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Heart Attack (Myocardial Infarction - MI)</td>
<td>Peripheral Artery Disease (PAD)</td>
<td>Smoking</td>
</tr>
<tr>
<td>Cardiac Ischemia (CI)</td>
<td>Heart Disease (HD)</td>
<td>Obesity (BMI/Waist-Hip)</td>
</tr>
<tr>
<td>Angina Pectoris (AP)</td>
<td></td>
<td>Arterial Stiffness</td>
</tr>
<tr>
<td>Death (CVD-related mortality)</td>
<td></td>
<td>Lab Measures of CV Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedentary Time</td>
</tr>
</tbody>
</table>
### Appendix C: STROBE Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Title and abstract** | 1  
  (a) Indicate the study’s design with a commonly used term in the title or the abstract  
  (b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** |  
  Background/rationale | 2  
  Explain the scientific background and rationale for the investigation being reported |
|  | Objectives | 3  
  State specific objectives, including any prespecified hypotheses |
| **Methods** |  
  Study design | 4  
  Present key elements of study design early in the paper |
|  | Setting | 5  
  Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
|  | Participants | 6  
  (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
  Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
  Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants  
  (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed  
  Case-control study—For matched studies, give matching criteria and the number of controls per case |
|  | Variables | 7  
  Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
|  | Data sources/measurement | 8*  
  For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
|  | Bias | 9  
  Describe any efforts to address potential sources of bias |
|  | Study size | 10  
  Explain how the study size was arrived at |
|  | Quantitative variables | 11  
  Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
|  | Statistical methods | 12  
  (a) Describe all statistical methods, including those used to control for confounding  
  (b) Describe any methods used to examine subgroups and interactions  
  (c) Explain how missing data were addressed  
  (d) Cohort study—If applicable, explain how loss to follow-up was addressed  
  Case-control study—If applicable, explain how matching of cases and controls was addressed  
  Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy  
  (e) Describe any sensitivity analyses |

Continued on next page
**Results**

| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
| | (b) Give reasons for non-participation at each stage  
| | (c) Consider use of a flow diagram  
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
| | (b) Indicate number of participants with missing data for each variable of interest  
| | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount)  
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time  
| | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure  
| | *Cross-sectional study*—Report numbers of outcome events or summary measures  
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
| | (b) Report category boundaries when continuous variables were categorized  
| | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  

**Discussion**

| Key results | 18 | Summarise key results with reference to study objectives  
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence  
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results  

**Other information**

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based  

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
## Appendix D: Correlation matrix of model inputs

<table>
<thead>
<tr>
<th>Item</th>
<th>CP</th>
<th>HT</th>
<th>HD</th>
<th>DS</th>
<th>ST (10-19)</th>
<th>ST (20-29)</th>
<th>ST (30-39)</th>
<th>ST (&gt;40)</th>
<th>Diabetes</th>
<th>Gender</th>
<th>CP*Gender</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.1</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>-0.0</td>
<td>-0.3</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>0.1</td>
<td>-0.3</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (10-19hrs/week)</td>
<td>-0.0</td>
<td><strong>0.6</strong></td>
<td>-0.4</td>
<td>-0.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (20-29hrs/week)</td>
<td>0.0</td>
<td>0.1</td>
<td>-0.3</td>
<td>0.1</td>
<td><strong>0.6</strong></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (30-39hrs/week)</td>
<td>0.1</td>
<td>-0.1</td>
<td>-0.3</td>
<td>0.3</td>
<td><strong>0.5</strong></td>
<td><strong>0.7</strong></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary Time (&gt;40hrs/week)</td>
<td>-0.0</td>
<td>0.0</td>
<td>-0.4</td>
<td>0.1</td>
<td><strong>0.5</strong></td>
<td><strong>0.7</strong></td>
<td><strong>0.6</strong></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.0</td>
<td>-0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>-0.3</td>
<td>-0.1</td>
<td>-0.2</td>
<td>-0.1</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender=M</td>
<td>0.2</td>
<td>-0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>-0.4</td>
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<td>-0.2</td>
<td>0.1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction CP*Gender</td>
<td><strong>-0.7</strong></td>
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<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.3</td>
<td>-0.1</td>
<td>0.1</td>
<td>-0.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.3</td>
<td><strong>-0.6</strong></td>
<td>0.0</td>
<td>0.3</td>
<td><strong>-0.5</strong></td>
<td>-0.2</td>
<td>0.0</td>
<td>-0.1</td>
<td>0.1</td>
<td>0.4</td>
<td><strong>-0.1</strong></td>
<td>1.0</td>
</tr>
<tr>
<td>BMI</td>
<td>0.1</td>
<td>-0.5</td>
<td>0.3</td>
<td>0.1</td>
<td><strong>-0.6</strong></td>
<td><strong>-0.5</strong></td>
<td>-0.4</td>
<td><strong>-0.5</strong></td>
<td>0.2</td>
<td>0.2</td>
<td><strong>-0.0</strong></td>
<td>0.4</td>
</tr>
</tbody>
</table>

CP - Cerebral Palsy  
HT - Hypertension  
HD - Heart Disease  
DS - Daily Smoker  
ST - Sedentary Time
Works Cited:

82. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.