PHYSICAL HEALTH IN INDIVIDUALS WITH CEREBRAL PALSY

PHYSICAL HEALTH IN INDIVIDUALS WITH CEREBRAL PALSY: FROM UNDERSTANDING CARDIOVASCULAR DISEASE TO PREVENTION OF MULTIMORBIDITY

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LAY ABSTRACT

Cerebral palsy is the most common child-onset physical disability. The disability can result in low levels of physical activity, obesity, and risk for morbid conditions that get worse over the lifecourse. The studies in this thesis furthered our understanding of cardiovascular disease and cardiovascular disease risk, investigated the relationship between physical activity and cardiovascular health, and evaluated changes in cardiovascular disease risk over time in individuals with cerebral palsy. We investigated three modifiable behaviours in individuals with cerebral palsy, which told us that they have poor sleep quality, do not engage in the recommended amount of physical activity, and could be at risk for poor nutrition. This work suggests that individuals with CP may be at an accelerated risk for cardiovascular disease, and that physical activity, sleep, and nutrition are important and modifiable factors that should be assessed and managed in this population.

ABSTRACT

Cerebral palsy (CP) is no longer just a childhood disability. Children with CP grow up and become adolescents and eventually adults. However their risk of cardiovascular disease (CVD) and multimorbidity, defined as the presence of at least two chronic conditions, is poorly understood. This thesis sought to investigate CVD risk in individuals with CP and identify important health variables to understand and prevent multimorbidity development in this population. First, we discovered that adults with CP have an increased prevalence of CVD and an increased risk of death due to CVD compared to the general population, which raises concerns about CVD in people with CP and warrants further study. We investigated differences in cardiovascular health and moderate-to-vigorous physical activity (MVPA) in ambulatory adolescents and adults with CP between Gross Motor Function Classification System (GMFCS) levels I and II. Our findings suggest individuals who are GMFCS level II may be at increased risk for CVD in comparison to individuals who are GMFCS level I. We then evaluated longitudinal changes in risk factors of CVD in a cohort of individuals with CP. After a time interval of 4.0 ± 1.2 years, we found decreased absolute and relative brachial artery flow mediated dilation as measures of endothelial function, while carotid artery intima media thickness increased. We also discovered that 75% of participants with CP reported poor sleep quality, 80% engaged in less than the recommended 150 minutes of MVPA per week and 14% had poor eating behaviours. Taken together, this research suggests that individuals with CP

experience accelerated aging for disease progression, specifically CVD, and that physical activity, sleep, and nutrition, together, could provide a framework for a lifestyle intervention to reduce and prevent multimorbidity risk in individuals with CP.

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LIST OF ABBREVIATIONS

AACPDM	American academy for cerebral palsy and developmental medicine
AMS	Artery measurement system
ANCOVA	Analysis of covariance
BMI	Body mass index
CDE	Common data element
CENTRAL	Cochrane central register of controlled trials
cfPWV	Carotid femoral pulse wave velocity
CI	Confidence interval
cIMT	Carotid artery intima media thickness
CINAHL	Cumulative index to nursing and allied health literature
COMET	Core outcome measures in effectiveness trials
COS	Core outcome set
COSMIN	Consensus-based standards for the selection of health measurement instruments
CP	Cerebral palsy
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EDACS	Eating and drinking ability classification system
FMD	Flow mediated dilation
GMFCS	Gross motor function classification system
GMFCS-E&R	Expanded and revised gross motor function classification system
HDL-C	High-density lipoprotein cholesterol
ICC	Intraclass correlation coefficient
ID	Intellectual disabilities
LDL-C	Low-density lipoprotein cholesterol
LTPA	Leisure time physical activity
LTPAQ-SCI	Leisure time physical activity questionnaire for persons with spinal cord injury
MAP	Mean arterial pressure
MET	Metabolic equivalent
MVPA	Moderate-to-vigorous physical activity
OMI	Outcome measurement instruments
OR	Odds ratios
PA	Physical activity
PARA-SCI	Physical activity recall assessment for people with spinal cord injury
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PSQI	Pittsburgh sleep quality index
PWV	Pulse wave velocity

RCT	Randomized controlled trial
SBP	Systolic blood pressure
SCORE	Systematic coronary risk evaluation
SD	Standard deviation
SHAPE	Screening for heart attack prevention and education
SPSS	Statistical package for the social sciences
WHO	World health organization

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis, presented in "sandwich" format, includes a general introduction, five independent manuscripts for which the candidate is the first author, and an overall discussion. At the time of the thesis preparation, Chapters 2, 3, and 5 were under review, and Chapters 4 and 6 were in submission. The contributions of the candidate and all coauthors are outlined below for each manuscript:

CHAPTER 2
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CHAPTER 1: INTRODUCTION

1.1 PREAMBLE

Cardiovascular disease (CVD) is the leading cause of death globally (90). Individuals at risk for CVD may present elevated blood pressure, glucose levels, and lipids as well as overweight and obesity (90). On the contrary, physical activity is associated with a reduced risk of CVD (48). Individuals with cerebral palsy (CP) are at an increased risk of CVD likely due to musculoskeletal problems impeding physical activity participation that are secondary to the primary, non-progressive disturbance that occurred to the developing fetal or infant brain (99). Individuals with CP experience joint and muscle pain, contractures, mobility problems, injuries due to loss of sensation, loss of function, and fatigue (52, 62, 117, 125), which lead to decreased physical activity levels, increased sedentary behaviour, and reduction in physical fitness (117). Reductions in the ability to ambulate in individuals with CP contribute to changes in body composition, such as muscle atrophy and increases in body fat, which together highlight a progressive deteriorating process in individuals aging with CP (119).

Traditionally, CVD risk can be categorized by a multitude of factors, including the presence of hypertension, diabetes, or hyperlipidemia (90). However, these traditional risk factors have failed to predict cardiovascular events in close to 50% of cases in the general population (73). More recently, behavioural risk factors of CVD have emerged, including physical inactivity, unhealthy diet, harmful alcohol use and smoking (138). Additionally, novel risk

factors of CVD such as peripheral artery vascular function and structure have been found to strengthen the predictive abilities of CVD (42). However, our understanding of CVD and CVD risk in individuals with CP is poor and not well defined. Recent increases in the survival rate and longevity of persons with CP speak to the advancements of modern medicine (119), but there are no national surveillance programs or longitudinal studies in North America, or for that matter the world, that monitor CP by severity, medical and/or health conditions, or the trajectory of aging that would help provide risk identification of adverse outcomes, such as CVD, in individuals with CP. Identifying which individuals with CP are at risk for CVD would provide a foundation for further research into preventative and management strategies. A systematic review of the literature of CVD, CVD risk, and CVD-related mortality in adults with CP can help advance our understanding of CVD in this population, and potentially identify knowledge gaps that can be addressed and answered through well-tailored research. Moreover, assessing novel risk factors of CVD, such as arterial function and structure, could discern early signs of CVD risk in this population.

Notwithstanding the significant progression of disability that is known to occur in aging individuals with CP, minimal clinical focus on understanding the etiology of comorbid conditions exists (87). Individuals with CP expressing concerns about their future health status generally raise issues that relate to functional capacity (124). Adults with CP may have a limited understanding of CVD risk factors and thus participate in minimal health screening activities (20,

50). Thus the potential risk of multimorbidity, defined as the presence of at least two chronic conditions (27), related to secondary consequences of CP might not be concerning to this population due to a lack of understanding between the risk-disease relationship; however, chronic diseases such as CVD and type 2 diabetes in this population may be attributed to a shared number or modifiable behaviours such as poor diet, physical inactivity, and inadequate sleep (6, 60). Most studies related to aging issues and secondary conditions among adults with CP merely identify health issues or concerns, with few discussing prevention or intervention strategies (122).

Understanding CVD in adults with CP will have a binary effect on this population; it can inform pediatric clinicians of risk factors to monitor and treat early on in life, and can aid in the development of strategies to combat multimorbidity risk later on. Together, these put individuals with CP on a healthy trajectory across the lifespan. The overarching purpose of this literature review will be to forge a connection between CVD and multimorbidity risk in individuals with CP, and to identify and summarize constructs which might be important in multimorbidity preventative strategies (e.g. physical activity, sleep and nutrition). A brief overview of the causes and secondary characteristics of CP will be provided. Details on traditional and novel risk factors of CVD in the context of CP will be provided, as will multimorbidity risk and prevention.

1.2 DEFINITION, PREVALENCE AND CAUSES OF CEREBRAL PALSY

The first definition of cerebral palsy (CP) was documented in 1958 as, "*a persisting qualitative motor disorder appearing before the age of three years, due to non-progressive damage to the encephalon occurring before the growth of the central nervous system is complete*" (61). The definition of CP has remained relatively stable over time (76, 99), with the current definition as follows, "*Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems*" (99). The type and severity of the movement and posture disorder (i.e. motor impairment) is diagnosed from neurologically detectable signs such as increased resistance to passive stretch of a muscle group, abnormal reflexes, or involuntary movements such as dystonic features (111). The impact of the motor impairment ranges from a minimal effect on movement to the complete absence of purposeful movement (111). CP is defined by only clinical description (i.e. there is no definitive test); it is not informative of cause, pathology, or prognosis (111).

Population-based studies in CP report estimates ranging from 1.5 to more than 4 per 1000 live births or children of a defined age range (3, 12, 54, 84, 137). The frequency of CP in Western countries is also expressed as the incidence per

1000 live births and ranges from 2 - 2.5 per 1000 live births (81). The improvements in medical care have been expected to have an impact on the prevalence of CP. One thought is that better management of maternal complications, intensive surveillance during labour, and improved ventilator management of premature newborns would reflect fewer cases of CP. On the contrary, these improvements have been translated into better survival, especially in those with very low birth weights, and the increased survival could reflect a larger number of children, adolescents, and adults with CP (84). Approximately 80000 individuals with CP live in Canada and there are 17 million people with CP worldwide (95). In 2011, approximately 6000 people with CP were over the age of 65, and this number is projected to increase to 15000 in 2031 (95). Cerebral palsy can be acquired during the prenatal, neonatal, or postnatal periods. Postnatally-acquired CP is relatively uncommon in the Western world. Much debate remains in regard to the upper age limit of diagnosing CP (12 months to 36 months) after which motor impairments are no longer considered CP (98).

Freud, in 1895, wrote that a large number of cases of infantile CP are resultant of the same factors that cause cerebral paralysis in adults: when cerebral vessels experience tearing, embolism, and thrombosis (100). In a systematic review, ten risk factors for CP were identified, which included: neonatal infections, hypoglycemia, respiratory distress syndrome, neonatal seizures, birth asphyxia, emergency Caesarean delivery, meconium aspiration,

low birth weight, minor and major birth defects, and placental abnormalities (70). The risk of having a child with CP is four to five times greater for mothers who had a urinary tract infection at some time during pregnancy (91). Finally, perinatal stroke is a common cause of CP and is the most common cause of unilateral or hemiplegic type of CP (78). The risk of perinatal stroke is related to a number of factors related to the history of the mother, including: infections, bleeding, drug abuse, smoking, hypertension and diabetes (57).

1.3 TYPES OF CEREBRAL PALSY AND CLASSIFICATIONS

Traditionally, CP has been described by the level of the impairment, specifically the type of motor impairment and topography (i.e. parts of the body that are affected). Type of motor impairment refers to the predominant characteristics of the motor findings. Type of motor impairment includes the following: spastic, dyskinetic, ataxic, or mixed. Topography includes unilateral involvement (hemiplegia) or bilateral involvement (diplegia, or quadriplegia) for individuals with spastic CP (14, 18, 39). Data from the Canadian Multi-Regional CP Registry have found that 85% of CP is spastic in type, 8% is dyskinetic and less than 5% is ataxic (105). In regard to ambulation, almost 45% of children with CP ambulate independently while approximately 17% are unable to roll and remain entirely wheelchair bound (i.e. unable to independently remove themselves from their chair) (104). However, the levels of agreement between clinicians assessing motor impairment and topography are modest at best (14).

The Gross Motor Function Classification System (GMFCS) was created to address the need for a standardized system to classify the gross motor function of children with CP aged 12 years or less on the basis of functional abilities and limitations (82). It was designed to be quick and easy to use, valid, and reliable. It includes five levels. In 2008, an expanded and revised version of the GMFCS was created for a 12-to 18-year age band. It was developed to include the adolescent period of development and incorporate changes associated with puberty (83). Descriptions of each level of the GMFCS expanded and revised version are found in Table 1. Individuals with less severe functional limitations (i.e. a lower GMFCS level) reach their limits at a later age than individuals with more severe CP (i.e. a higher GMFCS level) (108). Furthermore, there appears to be a peak and decline in gross motor function in GMFCS levels III, IV and V (44). Other studies have shown declines in gross motor function in individuals with more severe CP (29, 44, 134).

GMFCS level	Description
I	Able to walk at home, school, outdoors, and in the community. Able to walk up and down curbs and stairs without assistance or the use of a railing. Able to run and jump but speed, balance, coordination are limited.
II	Walk in most settings. May walk using a hand-held mobility device for safety. May use wheeled mobility to travel longer distances when outdoors and in the community. Walk up and down stairs holding a railing.
III	Capable of walking using a hand-held mobility device. Transported in a manual wheelchair or use powered mobility when outdoors and in the community. Walk up and down stairs holding onto a railing with supervision or physical assistance.
IV	Use wheeled mobility in most settings. Physical assistance from at least one person is required for transfers. Individuals are

	physically capable of operating a powered wheelchair.
V	Transported in a manual wheelchair in all settings. Limited in ability to maintain antigravity head and trunk postures and control arm and leg movements. Physical assistance from at least one person or a mechanical lift is required for transfers. May achieve self-mobility using powered mobility with extensive adaptations.

Table 1: GMFCS-E&R, Expanded and Revised Gross Motor Function Classification System (83).

1.4 SECONDARY CONDITIONS AND CONSEQUENCES IN CEREBRAL PALSY

As is mentioned in the most recent definition of CP, "*The motor disorders of cerebral palsy are often accompanied… by secondary musculoskeletal problems*" (99), secondary conditions are common in individuals with CP. With respect to musculoskeletal problems, these can develop throughout life and are related to physical growth, aging, muscle spasticity and other factors. Examples of these problems consist of muscle/tendon contractures, hip displacement, and spinal deformity (99).

According to Marge et al., secondary conditions, also referred to as comorbidities, are conditions that individuals experience *after* their primary disability (64). Another definition of the term secondary condition states that it is an injury, impairment, functional limitation, or disability that occurs as a *result* of the primary pathology or condition (124). A secondary condition could have a causal relationship to the primary condition, perhaps being preventable, and varying in how and when it is expressed (123). Nonetheless, secondary conditions are in addition to the primary insult in individuals with CP, and impact

the overall health of individuals within this population. Secondary conditions in CP may include a wide array of medical complications, such as arthritis and contractures, psychiatric disorders, like anxiety and depression, and environmental and quality of life issues, such as disability associated with assistive device failures (120). In a study of individuals with intellectual disabilities, participants with CP experienced greater limitations due to secondary conditions than individuals with autism or Down Syndrome (93). Recently it was noted that individuals with CP are at high risk of various secondary health complications that are in conjunction with the primary neurological insult, including orthopedic abnormalities, musculoskeletal fragility, sedentary lifestyles and poor physical fitness (85). Even children with CP, including preschool aged children at GMFCS level I, present with secondary impairments in range of motion, strength, and endurance (53). However, no differences related to age were observed in secondary impairments in this cohort of young children with CP (53).

It is important for clinicians to change their view of CP from being a pediatric disability to being a lifespan condition (32). Adolescents and adults with CP, along with their families and caregivers, should understand that although the primary damage to the brain is static, secondary conditions related to function and ability change over time. In 2009, research was only just beginning to understand the health of adults with CP and to explore how acquiring secondary impairments interacts with the process of aging in this population (117). Adults

with developmental disabilities, including CP, are more likely to live sedentary lifestyles and are at greater risk of having four to five chronic health conditions than the general population (45). Moreover, adults with CP may experience age-related changes earlier in life than their counterparts from the general population (119). A cycle of deconditioning in CP likely exists, where physical function deteriorates due to secondary conditions, followed by a decrease in physical activity, and a cascade of increasing functional decline (25). The regress in function and resultant reduced ability to ambulate may be associated with changes in body composition, muscle atrophy, and increases in body fat which have the potential to extend beyond mobility (119) and may have an impact on cardiovascular disease (CVD) in this population.

1.5 CARDIOVASCULAR DISEASE

Cardiovascular disease is defined by the World Health Organization (WHO) as a group of disorders of the heart and blood vessels, which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thromobosis and pulmonary embolism (138). More people die each year due to CVDs than any other cause. Risk factors of CVD are well documented in the literature. The WHO identifies the following as behavioural risk factors of CVD: unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol (138). Historically, traditional risk factors of CVD were consistent with predictors from the

Framingham Heart Study (77), and included age, gender, total cholesterol and high-density lipoprotein cholesterol (dyslipidemia), smoking, systolic blood pressure (hypertension), and medications to treat hypertension (77). These traditional risk factors were redefined in the guidelines on the assessment of cardiovascular risk, endorsed by a task force of the American College of Cardiology and the American Heart Association, mainly because the traditional Framingham algorithm on 10-year risk for cardiovascular-related disease was derived in an exclusively white sample population, which limited the scope of the outcome. The task force identified the following as risk factors of CVD: total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes (37). Moderate increases in physical activity have shown protective effects against the traditional risk factors of CVD, specifically reductions in systolic blood pressure (73). Some literature suggests that obesity is considered a modifiable behavioural risk factor of CVD (15). Obesity, particularly of the visceral type, has been shown to be associated with inflammation and cardiometabolic changes (67), as well as early death (15), mainly as a result of the development of CVD (21, 22, 141). However, 30-40% of the reduction in CVD risk seen with increased physical activity is not explained by traditional risk factors (42). Structural and functional adaptations to the peripheral arterial wall associated with physical activity, such as reductions in arterial wall thickness, increased elastic properties, the attenuation of collagen progression and increases in endothelial function, may also contribute to physical activity-related

reduction in CVD risk. Together, these structural and functional variables are identified as novel risk indicators of CVD (116).

Decreases in arterial function, notably arterial distensibility, or the arteries ability to expand for a given pressure, of large arteries can independently predict cardiovascular events and all-cause mortality (8, 13, 133). Decreased distensibility is one of the most important contributors to increased cardiovascular risk experienced with aging (59). Carotid artery intima media thickness (cIMT), a measure of arterial structure, has been cited as the most reliable atherosclerotic indicator marking from childhood to adulthood (9). Arterial stiffness is an independent risk factor for CVD (115). It is one of the earliest detectable changes in vascular structure and function that can lead to CVD. Carotid-femoral pulse wave velocity (PWV) has been proposed as the “gold standard” measure of arterial stiffness because of much clinical evidence noting it as an indicator of increased mortality (126). This method of measuring arterial stiffness uses mathematical equations and involves the assumption that blood viscosity remains constant (16). In the general population, a PWV of 10 meters per second is the cut-off value for carotid-femoral PWV after which there is an increased risk for cardiovascular events (126). Another relevant measure of arterial function is that of endothelial function. Endothelial function is commonly measured non-invasively using a flow-mediated dilation (FMD) technique. To quantify FMD, reactive hyperemia after a five-minute occlusion of the brachial artery with a blood pressure cuff stimulates the release of endothelial nitric oxide and causes

an increase in the diameter of the brachial artery (24). A meta-analysis on the prediction of future cardiovascular outcomes by flow-mediated vasodilation of the brachial artery found that a 1% decrease in FMD was associated with a 13% increase in risk of future cardiovascular events (51).

The literature has documented aging as a significant contributing risk factor of CVD, with the presence of underlying hypertension as a catalyst to the aging process (80). Moreover, structural changes to the cardiovascular system are evident as one grows older. For example, elastic properties of the artery wall are reduced, collagen formation increases, and the artery wall itself becomes thicker (114). An abundance of collagen and a thicker artery wall results in a stiffer artery, resulting in a widened pulse pressure and leading to isolated systolic hypertension, a morbid condition affecting more than 30% of adults before they reach the age of 80 (109).

In persons with CP, the presence of heart disease was almost threefold greater in those between the ages of 35 and 55 than it was in the non-disabled population (113). Lipid profiles have been reported in individuals with CP with rather conflicting results. A study from the Netherlands found, in a clinical sample of ambulatory adults with CP, similar cholesterol levels as those in the general population (127). Whereas another study reported modest increases in dyslipidemia in non-ambulatory adults with CP compared to those who were ambulatory (71). In regard to hypertension, studies in adults with CP have reported a prevalence of 20% (103) and 14% (24). In adults with CP, obesity may

exacerbate the severity of functional impairment throughout adulthood, leading to cardiometabolic disease (86). The WHO uses the term metabolic health to include the diseases of diabetes and obesity (138). A more detailed definition of cardiometabolic disease includes a cluster of abdominal obesity, hypertension, dyslipidemia, hyperinsulinemia, and glucose intolerance (30). A study in adults with CP found that waist-to-hip ratio was independently associated with various indices of cardiometabolic risk, including total cholesterol to high-density lipoprotein ratio, high-density lipoprotein cholesterol, and triglycerides (88). Similarly, another study found that waist circumference provided the strongest indication of dyslipidemia in adults with CP, and is a clinically relevant measure to screen for cardiometabolic risk in this population (103). A study using 9 years worth of data from a nationally representative survey of the US population found that adults with CP had significantly greater prevalence rates of diabetes compared to adults without CP (9.2 vs. 6.3%; $p<0.001$) (89).

1.6 PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR

Many of the CVDs can be prevented by addressing modifiable behavioural risk factors, such as physical inactivity (15). Physical activity is commonly defined as any bodily movement produced by skeletal muscles that requires energy expenditure (23). Physical inactivity has been identified by the WHO to be the fourth leading risk factor for global mortality (139). Physical activity challenges the homeostatic environment of the human body and activates acute- and long-term

mechanisms to preserve or re-establish homeostasis (46). Some of these mechanisms include an increase in mitochondrial density, and an increased capacity of the heart to provide increased blood flow, which subsequently result in increased efficiency of energy utilization and enhances the overall endurance capacity of the body (79). Characteristics which might influence the responses to physical activity include baseline level of fitness, age, and nutritional state (79).

Morris et al. made the original hypothesis on the relationship between physical activity and CVD almost 65 years ago. From their research on London Bus Drivers, it was discovered that rates of CVD were much lower in the physically active bus conductors than in the sedentary bus drivers of the London double-decker buses (74). Sedentary behaviour is defined as any behaviour that occurs while one is awake where the body movement is minimal and which the energy expenditure is less than 1.5 metabolic equivalents (METs) (5). Research has shown that a sedentary lifestyle consisting of low daily physical activity levels is associated with a significant increase in CVD and mortality, with these relationships independent of other risk factors for CVD (33). The literature is dense of findings supporting the benefit of engaging in physical activity to reduce CVD risk and mortality. In a prospective longitudinal study of over 1.3 million women, mean age 55.9 ± 4.8 years, the frequency of any physical activity at baseline was associated with a reduced risk of subsequent coronary heart disease, cerebrovascular disease, and venous thromboembolism, with these relationships remaining significant after adjustment for body mass index (BMI),

smoking, and alcohol consumption (2). However, conflicting results on both the intensity and volume of physical activity and the impact on CVD risk are evident in the literature. For example, a study reported that vigorous leisure-time physical activity only, and not total physical activity or less intensive forms of physical activity, was associated with greater reduction in CVD risk (49).

Current physical activity guidelines for adults age 18-64 years old from the general population suggest at least 150 minutes of moderate-intensity aerobic physical activity per week, or at least 75 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity (139). Based on data from over 120 countries, over 30% of adults globally are considered inactive by not meeting these physical activity guidelines (43). It is worth noting that these guidelines are based largely on meta-analyses of studies conceived in the 1980s and 1990s when physical activity was measured by self-report questionnaires (47). There exist many limitations with self-report, including recall bias and misinterpretation of questions (26). Moreover, reported associations with criterion measures (e.g. activity monitor) often have correlations below 0.3, and therefore should be interpreted as low to moderate (92). Over reporting of physical activity is a common measurement issue with self-report questionnaires, which might result in an overestimation of individuals being categorized as physically active. This would suggest that population levels of physical activity derived from self-report questionnaires should be interpreted with caution (112).

1.7 PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR IN CEREBRAL PALSY

Engaging in physical activity is challenging for individuals with chronic neurological disabilities with impaired mobility, such as CP. There is a multitude of barriers to physical activity engagement in individuals with CP and other disabilities, such as transportation, lack of adaptable equipment, and associated fees (i.e. gym membership) (66, 97). A study examining health and physical activity among people with disabilities found that activity level was highly associated with years of survival in CP (25). Changes in function in individuals with CP as they age may be related to a decrease in physical activity and overall fitness in adults in this population (96). Traditionally, physical activity has been measured in a clinical setting to evoke an individual's "capacity", or what they *can* do. Otherwise, assessment of physical activity was made using survey methods such as self- or parent-/caregiver-report. Up until 2009, very few physical activity "performance" measures existed that measured an individual in their natural environment. In 2007, van der Slot et al. were the first to measure physical activity in adults with CP using an activity monitor. They found no differences in physical activity levels between individuals with CP who were GMFCS level I and their age- and sex-matched counterparts (128). This lead to the conclusion that more severely impaired adults, such as those with higher GMFCS levels (i.e. > level I) might have reduced physical activity levels and may be at an increased

risk of poor health. Similarly, decreased levels of moderate-to-vigorous physical activity and increases in sedentary time were associated with risk markers of cardiometabolic disease in adults with CP (102). Taken together, adults with CP are likely not engaging in sufficient physical activity to obtain positive health benefits (117). As a whole, adults with CP spend less time in light, moderate, vigorous and total activity and greater time in a sedentary state than adults without CP (102). Reductions in physical activity may be explained by a greater metabolic inefficiency (i.e. oxygen uptake during activity expressed as a percentage of peak aerobic capacity) during walking, which would explain why some persons with CP typically walk less in daily life and fatigue more quickly than their able-bodied counterparts (107). Predictors of physical activity in individuals with CP include use of walking as the primary means of self-transport, being younger in age, and having positive perceptions of health (63).

Until recently, detailed recommendations for physical activity and sedentary behaviour for children, adolescents, and adults with CP did not exist. In short, these consist of a frequency of at least fives days per week, at an intensity level that is moderate-to-vigorous, and for a duration of 60 minutes. At the minimum, these guidelines suggest 300 minutes of activity per week of moderate intensity for individuals with CP. In regard to sedentary behaviour, individuals with CP should engage in less than two hours per day of sedentary time or break up sitting for two minutes every 30 to 60 minutes (132). It is important to mention that these are merely recommendations based on reviews of the literature, expert

opinion, and extensive clinical experience, and are not evidence-based guidelines. The latter would require the use of a standardized guideline development process combining rigorous methodology, such as a systematic review of research evidence, meaningful engagement of a group of stakeholders to deliberate the research evidence, and pilot testing (36). Given the heterogeneity in CP as it affects motor function, physical activity promotion for the population as a whole is likely a challenge. In a study of 30 adults with CP, Johnson and colleagues characterized total energy expenditure using the doubly labeled water technique, in which they found that that energy expenditure was highly variable in this population. Particularly, they concluded that the contribution of resting energy expenditure and of energy exerted during physical activities contributed to total energy expenditure and this differed between ambulatory and non-ambulatory adults with CP (55). Importantly, activities of daily living might require maximum energy expenditure for some individuals with CP. A recent study in adolescents with CP found that 43% of individuals walked with an oxygen consumption at or above their anaerobic threshold, meaning that they were more easily exhausted with muscles becoming painful due to accumulation of lactate within the exercising muscle cells (7). These findings could contribute to the reduced physical activity levels seen in individuals with CP. Thus it is important for individuals with CP who are beginning to engage in physical activity to be considerate of their physical capacities and to start at a relatively low intensity and for limited duration.

1.8 MULTIMORBIDITY IN CEREBRAL PALSY

Multimorbidity is defined as the presence of at least two chronic diseases or conditions (27). In individuals with CP, this would be considered as two conditions in addition to the presence of CP. The prevalence of multimorbidity in a sample of 435 adults with CP aged 40-60 years was 57.8% (27). The most prevalent combinations of conditions included prehypertension/hypertension and osteopenia/osteoporosis (19.3%), osteoarthritis and osteopenia/osteoporosis (16.7%), and prehypertension/hypertension and osteoarthritis (12.4%). Multimorbidity was significantly more prevalent among individuals who were obese versus non-obese in both GMFCS I-III (75.8% vs. 53.6%) and GMFCS IV-V (79.0% vs. 64.2%). Multimorbidity was also higher for non-obese individuals who were GMFCS IV-V (64.2%) than non-obese individuals who were GMFCS I-III (53.6%). Both obesity status and the GMFCS IV-V category were independently associated with multimorbidity in this sample of adults with CP (27). Recent research has emerged which showed that, among a large population-representative sample in the United States, adults with CP had significantly greater estimates of chronic diseases, including asthma, emphysema, hypertension and cerebrovascular disease compared to adults without CP (89). Importantly, age, physical disability status (i.e. moderate or severe) and physical inactivity were each associated with cardiovascular-related disease in these adults with CP (89). Furthermore, findings from this work

revealed that adults with CP had increased prevalence of both stroke and cardiometabolic-related disease than those without CP. Similarly, in a population-based cohort in Taiwan, patients with CP had a 2.17 fold greater risk for stroke than the general population (140). Interestingly, patients with CP from this study were more prone to stroke at ages less than 50 years than for ages greater than 50. Findings from these studies raise important questions about primary prevention in CP starting in early adulthood and continuing throughout the lifespan.

Currently, there is a divergence between basic research intended to uncover novel etiologic markers and treatments of CP, and that which occurs during transition from adolescence to adulthood to understand the development and impact of secondary conditions unique to this population. Clinical research tends to focus on common symptoms inherent in this population, such as spasticity, gait disorders, pain and fatigue, as well as the efficacy and reported outcomes of respective medical interventions (e.g. surgical procedures). On the other hand, the majority of etiological research in this population is limited to prenatal and perinatal abnormalities and developmental neurology. In the face of the significant progression of disability that is known to occur during the aging process, there has been very little focus on understanding the causes of multimorbidity in adults with CP, independent of those exerted by the primary insult to the developing fetal brain. Traditionally, physical activity promotion and fitness have been the main focus to optimize health in clinical practice and

research in this population, but the long-term health benefits are unknown. It remains to be determined if the promotion of other health behaviours, such as good sleep and adequate nutrition, can aid in multimorbidity risk reduction and prevention in individuals with CP. Recently, the idea of a formula for health and well-being was proposed for individuals with CP, which consisted of physical activity promotion, consistent nutrition, and adequate sleep (130). It is believed that the management of these three components, ideally in a comprehensive manner, will afford a vitally important opportunity to promote the health of individuals with CP across the lifespan.

In 2016, content experts, methodologists, stakeholders, and end-users who followed rigorous guideline development procedures created the *Canadian 24-hour Movement Guidelines for Children and Youth* (121). These were comprised of guidelines for physical activity, sedentary behaviour, and sleep over a 24-hour period for children and youth aged 5-17 years. Following these evidence-based guidelines, which recommend 9 to 11 hours of uninterrupted sleep per night for those aged 5-13years and 8 to 10 hours per night for those aged 14-17 years, at least 60 minutes of moderate to vigorous physical activity per day, and no more than 2 hours per day of recreational screen time per day, is related with better body composition, physical fitness, academic achievement and cognition, emotional regulation, cardiovascular and metabolic health, and overall quality of life (121). Plans for effective interventions and/or the development of 24-hour-like guidelines in individuals with CP remain to be developed.

1.8.1 SLEEP

Sleep is considered an essential biological function with important roles in recovery and energy conservation (31). Good quality and adequate amounts of sleep are critical for good health and quality of life. Self-reported short sleep duration, defined as less than 6 hours of sleep per 24 hour period, has been associated with long-term health-related outcomes such as diabetes, obesity, depression, hypertension and all-cause mortality (19, 34, 40). A policy statement from the American Thoracic Society recommends that the optimal sleep duration for adults for good health is 7 to 9 hours per 24 hour period at a population level (75). Physiologically speaking, sleep is required to replenish glycogen stores in order to provide glucose for activities for the following day. Insufficient sleep could result in elevated blood glucose levels, which over time could lead to hyperinsulinemia and diabetes. The majority of sleep research in CP has been conducted in children. Children with CP are seven to twelve times more likely to experience sleep disorders when compared to their peers (106). Disorders of initiating and maintaining sleep were the most frequently reported complaints of sleep disorders in children with CP (1), with sleep anxiety, night wakings, parasomnias and sleep-disordered breathing being more common in children with CP than in typically developing children (136). A recent review on sleep quantity and quality in children with CP recommends the development of a care pathway for sleep using patient oriented, inductive research and to also identify

strategies to improve sleep in children with CP (129). The literature is nearly void of research on sleep in adults with CP; only three studies have assessed sleep in adults with CP (38, 68, 69), one of which was a case report (68). Two of these studies reported on the effects of intrathecal baclofen, a form of treatment for spasticity, to improve sleep quality, with one study finding no improvements in sleep quality (69) while the other reported improvements with sleep apnea (68). The third study concluded that it was feasible to use the Pittsburgh Sleep Quality Index in seven adults with severe speech and physical impairments, two of who had CP (38).

1.8.2 NUTRITION

Good nutrition is the foundation of health and development for all children (94). Weight gain and growth following predicted age trajectories assure families and healthcare providers that a child is healthy (94). In 2007, a food intake pattern, titled *Eating well with Canada's food guide*, was developed in the Canadian context which promotes a pattern of eating that meets nutrient needs, promotes health, and is consistent with evidence linking diet to reduced risk of chronic disease development (56). Importantly, atherosclerosis is characterized by accumulation of cholesterol along the arterial walls and it is therefore vital to reduce the ratio of saturated to unsaturated fats in the diet (35). An overview of the food intake pattern statements can be found in Table 2.

Food Group	Statement
Vegetables and Fruit	Eat at least one dark green and one orange vegetable each day.
	Choose vegetables and fruits prepared with little or no

	added fat, sugar or salt.
	Have vegetables and fruit more often than juice.
Grain Products	Make at least half of your grain products whole grain each day.
	Choose grain products that are lower in fat, sugar or salt.
Milk and Alternatives	Drink skim, 1% or 2% milk each day.
	Select lower fat milk alternatives.
Meat and Alternatives	Have meat alternatives such as beans, lentils and tofu often.
	Eat at least two Food Guide Servings of fish each week.
	Select lean meat alternatives prepared with little or no added fat or salt.
Oils and Fats	Include a small amount – 30 to 45 mL – of unsaturated fat each day. This includes oil used for cooking, salad dressings, margarine and mayonnaise.

Table 2: Food Intake Pattern Statements (56).

In children with CP, the most significant factor affecting their nutritional status is inadequate intake to meet metabolic demands (110). The ability to swallow food and food processing problems affect 30 to 40% of children with CP and are the main contributors to inadequate food intake (28). Other factors affecting growth and nutrition in children with CP include age, lack of weight bearing and mechanical stresses on bones (94). Feeding problems include oral motor problems, swallowing difficulties and airway protection problems, difficulties with proper positioning, requiring assistance with feeding, and prolonged feeding times (94). There has been debate about the influence of spasticity on the energy requirements of individuals with CP (58), such that spasticity might increase energy expenditure. It appears that there is variability among energy expenditure even when children with CP are matched for motor abilities (4, 135). Studies that have measured nutrition and/or eating behaviours

in individuals with CP are minimal. Two studies from the early 1970s found that malnutrition was a significant contributor to abnormal body composition in 22 children with CP (11), and energy intake was low (66% of the recommended dietary allowance) in 23 children with CP (10). To date, no study has been conducted on the effects of physical activity combined with a targeted nutrition intervention in people with CP (131).

1.9 THE KNOWLEDGE GAP

The prevalence of CVD, risk factors of CVD, and mortality related to CVD is poorly understood in individuals with CP. A recent scoping review on the risk of non-communicable diseases in CP found that adults with CP had higher risks of stroke and other heart conditions compared to the general population (101). However, a systematic review of the literature, including quality assessment of relevant studies, regarding the types of CVD and related risk factors evident in adults with CP remains to be known.

The relationship between physical activity and cardiovascular or cardiometabolic risk in individuals with CP has been studied by few (65, 72, 103, 127). Researchers often dichotomize individuals with CP based on ambulatory versus non-ambulatory abilities to answer questions regarding physical activity, cardiovascular or cardiometabolic health. In adults with CP who were GMFCS levels I-III, moderate activity was significantly negatively associated with waist circumference, systolic blood pressure and diastolic blood pressure (103).

Further risk stratification within an ambulatory population of individuals with CP (i.e. GMFCS levels I and II) might allow for identification of those individuals who could benefit from intensified monitoring and primary preventive strategies.

Endothelial dysfunction is understood to be an early indicator of atherosclerosis and risk marker for CVD, preceding the stiffening of the arteries and considered a nontraditional risk factor of CVD (118). Two studies have assessed endothelial function and parameters of arterial structure and function in individuals with CP (65, 72). However, no study has assessed measures of arterial structure and function longitudinally in this population. Moreover, research examining cardiovascular health in general in individuals with CP over time is non-existent. As recent research has emerged showing the increased prevalence of cardiovascular-related disease (89) and other multimorbid conditions in this population (27), it is important to understand the development of these conditions over time to inform management, intervention, and prevention strategies.

In addition to the importance of physical activity to reduce cardiovascular- and other chronic disease development in both the general population and in individuals with CP, sleep and nutrition are pivotal as well. Of the few studies that have examined sleep and nutrition in people with CP, it appears that a lack of good sleep quality and quantity, and inadequate nutrition is common. Investing in a comprehensive approach to health management in people with CP, consisting of the assessments of physical activity, sleep and nutrition, could be important. However, no one has assessed this triad of health in a sample of individuals with

CP. This is an important first step to inform proper management and intervention strategies in this population.

Multimorbidity has recently emerged as a critical concern for individuals with CP, particularly middle to older adults with CP. Due to advances in medical care, individuals with CP are living to ages comparable to those seen in the general population (17). However, their risk for multiple chronic conditions is high and is related to the presence of underlying obesity and impairments of gross motor function (27). Our understanding of multimorbidity in individuals with CP comes from either retrospective data analyses of patient files or national survey data. Despite the now known risk of multimorbidity in this population, no set of outcomes exist to measure for multimorbidity for individuals with CP, or exist any preventive or management strategies.

1.10 STUDY OBJECTIVES AND HYPOTHESES

The overarching objective of this dissertation is to explore and better understand CVD in individuals with CP and identify important health variables to understand and prevent multimorbidity development in this population. Together, this information can support the idea of a lifecourse health trajectory for people with CP – living longer and living well. The knowledge translation problem to be addressed in this dissertation is a paucity of primary research identifying and understanding CVD prevalence and risk in individuals with CP. A systematic review pertaining to CVD will be performed to summarize the existing research

evidence in this area. From this, different observational studies will be conducted to generate primary knowledge (41) to suggest important risk factors of CVD and outcome measurement instruments (OMIs) to measure morbidities in this population.

In Chapter Two, we perform a systematic review of the literature to investigate the prevalence of CVD, risk factors of CVD, and cardiovascular-related mortality in adults with CP. The premises for this review are that the prevalence of CVD and its associated risk factors might be exaggerated in a population with particular physiological characteristics, such as CP, and that minimal research has explored the long-term impact of this condition into adulthood.

In Chapter Three, we analyze cardiovascular health variables and objective physical activity levels of adolescents and adults with CP who are GMFCS level I versus GMFCS level II. The study hypotheses are: 1. Individuals who are GMFCS level I will have greater physical activity levels and healthier cardiovascular indices compared to those who are GMFCS level II; and 2. Physical activity levels will be inversely associated with cardiovascular health variables.

In Chapter Four, we investigate traditional (blood pressure) and novel risk factors (arterial structure and function) of CVD via a longitudinal study design in a cohort of adolescents and adults with CP inclusive of all five levels of the GMFCS. The objectives of this study are to examine longitudinal changes in CVD

risk factors in individuals with CP, and to investigate the relationships between age and gross motor function with longitudinal changes in these risk factors.

The objective of Chapter Five is to explore and describe physical activity behaviours, sleep quantity and quality, and nutrition in a cohort of individuals with CP and to investigate the influence of gross motor function level and age on these components of health. Understanding whether or not individuals with CP with different functional levels experience different problems related to these health variables is a first step in managing and promoting the health and well-being of individuals with CP across the lifespan.

The objective of Chapter Six is to describe the process of developing a core outcome set (COS) of OMIs for multimorbidity risk in adolescents and adults with CP. This protocol is a component of a program of research aiming to ultimately understand, treat and prevent multimorbidity in adolescents and adults with CP through modifiable behaviours (e.g. physical activity, sleep and nutrition), and to develop an ongoing database that will allow for the harmonization of data and the ability to document changes over time in this population.

The findings from these studies will further our understanding of CVD prevalence and risk in individuals with CP and identify behaviours, in addition to physical activity, that are important to assess and promote in this population to prevent multimorbidity risk across the lifespan.

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CHAPTER 2

Cardiovascular disease and related risk factors in adults with cerebral palsy: a systematic review

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ABSTRACT

AIM: To summarize the literature on the prevalence of cardiovascular disease (CVD), risk factors of CVD, and CVD-related mortality in adults with cerebral palsy (CP).

METHOD: A systematic review was conducted by searching the PubMed, Embase, Medline (Ovid), Cochrane and CINAHL databases. Selection criteria included adults with CP ≥18 years. Methodological quality was assessed using The Newcastle Ottawa Scale for observational studies. Data were reported descriptively.

RESULTS: Nineteen studies met the inclusion criteria. Only one study reported directly on the presence of CVD in adults with CP, which found adults with CP reported greater CVD conditions than adults without CP (15.1 vs. 9.1%, $p<0.001$). The most commonly reported risk factor of CVD in adults with CP was overweight/obesity. Five studies included data on CVD-related mortality in persons with CP, where CVD- and circulatory system-related deaths were elevated and more common at a younger age in adults with CP than in the general population.

INTERPRETATION: The prevalence of CVD and the risk of death due to CVD in this population seem increased, though the knowledge base is fragmented by studies that are small in size and geographically isolated. Further research is required to understand prevalence of risk factors among adults with CP, in particular overweight/obesity.

WHAT THIS PAPER ADDS

- Overweight and obesity are risk factors of cardiovascular disease that are commonly reported in adults with cerebral palsy
- Suggests that cardiovascular- and circulatory system-related deaths are elevated in individuals with cerebral palsy compared to the general population
- Limited knowledge suggests that the prevalence of CVD is increased in adults with cerebral palsy compared to the general population

INTRODUCTION

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition commencing in early childhood and continuing throughout life.[1] The condition itself is the result of non-progressive disturbances to the developing fetal or infant brain, and results in disorders of movement and posture.[2] As CP presents itself early on in life, much research has focused on children with CP. More recently researchers have started to focus on the impact of CP and its secondary disturbances later in life, which is of particular interest given the longer lifespan apparent in most persons with CP.[3] Given the fact that CP is a motor disorder, we and others have shown that individuals with CP demonstrate elevated sedentary behaviour and reduced physical activity as young as preschool that increases throughout adolescence and adulthood, with this trend being particularly prevalent in those who are non-ambulatory.[4; 5] It is conceivable that the presence

of such a condition affecting neurological control of both voluntary and involuntary movements may have implications for the health of the cardiovascular system.[6-9]

The World Health Organization (WHO) estimates that 31% of all global deaths are due to cardiovascular disease (CVD), making it the number one cause of death worldwide.[10] In 2012, an estimated 17 million people died from CVD[11] and CVD-related death is projected to increase to 52 million worldwide by 2030.[11] Ischemic heart disease (ischemia, angina, and myocardial infarction), cerebrovascular disease (stroke), peripheral vascular disease, and heart failure comprise the most common preventable CVDs.[12] Notable risk factors for these CVDs emerged from the Framingham Heart Study,[13] a study which originated in 1948 to identify risk factors for coronary heart disease. These include age, gender, total cholesterol, high density lipoprotein cholesterol (HDL-C), diabetes, systolic blood pressure, and current treatment for high blood pressure.[13] Other non-traditional risk factors of CVD have emerged more recently, including overweight/obesity, carotid artery intima media thickness and arterial stiffness.[14] Arterial stiffness, in particular, has been proven to be an important parameter for the assessment of CVD risk because of evidence demonstrating its association with CVD independent of traditional risk factors, including age, cholesterol, and smoking.[15] The incidence of CVD increases with age in the general population, and these risk factors play a growing role in the development of a chronic cardiovascular condition or acute event requiring medical treatment.[16; 17]

The prevalence of CVD and its associated risk factors may be exaggerated in populations with particular physiological characteristics, such as CP. Cerebral palsy has long been researched only as a pediatric condition and little research has explored the long-term impact of this condition into adulthood, let alone on CVD and CVD risk.[18] Therefore, the aim of this systematic review is to summarize the best evidence regarding the prevalence of CVD, risk factors of CVD, and cardiovascular-related mortality among adults with CP. The results of this review will provide insight into the gaps in our knowledge base regarding types of CVD and related risk factors evident in adults with CP and describe any CVD-related mortality in this population.

METHODS

Eligibility criteria

Outcomes were grouped into two classes of interest. The first consists of CVD and CVD risk factors. Cardiovascular diseases are defined as a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, and peripheral arterial disease.[10] We chose to include risk factors of CVD that were consistent with the Framingham Heart Study[13] and other emerging non-traditional risk factors[14] in an attempt to synthesize the literature on what is known about these risk factors in adults with CP, to compare risk in adults with CP to the general population, and to understand whether these risk factors are weighed the same in adults with CP.

The second class of interest is CVD-related mortality. Cardiovascular disease-related mortality, which included cause of death statistics, was classified within its own category. Studies were excluded if the authors did not distinguish persons with CP from persons with a physical disability or if the authors did not separate adults with CP from children with CP, except for CVD-related mortality where a combination of children and adults with CP were included to discern whether or not CVD-related mortality occurs at a younger age in individuals with CP compared to the general population.

Search strategy

A comprehensive literature search was conducted in the following electronic databases: PubMed, Embase, Medline (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). These databases were searched from their inception up to December 2016. A search strategy was developed in consultation with a research librarian around the following major themes: ‘cerebral palsy’, ‘adult’, and ‘cardiovascular disease’. Key terms within the search strategy were aligned to medical subject headings in Medline (Ovid) and expanded to include more descriptive terms. The Medline (Ovid) search strategy was translated and applied to the other databases. The complete search strategy for Medline (Ovid) is presented in Appendix S1 (online supporting information). Reference lists of included publications were manually searched to identify other studies that might not have been identified by the initial search. In addition, we searched trial and

protocol registries and abstracts from the American Academy for Cerebral Palsy and Developmental Medicine, the American Academy of Physical Medicine and Rehabilitation, and the American Congress of Rehabilitation Medicine over the year 2016 to identify unpublished (grey) literature.

Selection process

Titles, abstracts and full texts were reviewed independently for eligibility by two authors (PM, EC) using standardized screening forms. Any disagreement was resolved by discussion or in consultation with a third author (SN). Publications selected for inclusion were reviewed by an additional author and expert in the field (JWG) and validated against the inclusion criteria.

Randomized controlled trials (RCTs), longitudinal experimental studies, and observational (including cross-sectional, cohort, and case-control studies) studies exploring CVD, CVD risk factors or cardiovascular-related mortality within the population of adults with CP (≥18 years) were included in the review. Editorial comments and case studies (i.e. n of 1 studies) were excluded. Any reviews identified in the search were excluded from the final selection but reference lists were searched to identify further sources of primary evidence. Published conference proceedings (i.e. abstracts) were searched and included provided they contained information consistent with the outcomes of interest. Studies were required to be written in English.

Data extraction

The data extraction was performed by two independent reviewers (PM and EC) using an adapted screening form (Appendix S2) following guidelines from the Cochrane Collaboration.[19] Any discrepancies between reviewers were resolved by discussion until a consensus was reached. If necessary, a third author (SN) was consulted to resolve any discrepancies.

Levels of evidence and methodological quality assessment of the studies

The levels of evidence were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[20; 21] The Newcastle Ottawa Scale was used to evaluate methodological quality of observational studies.[22] Quality was based on the following criteria: Selection of the cohort; Comparability; and Outcome(s). High quality choices were identified with a star. A maximum of one star can be awarded for each item within the 'Selection' and 'Outcome' categories (totaling 4 and 3, respectively) and a maximum of two stars within the 'Comparability' category.[22] Therefore, a study can achieve a maximum of 9 stars.[22]

Statistical analyses were performed using STATA (version 13.1) statistical software package. For studies that contained a comparator group of which risk ratios or odds ratios were not available, data were extracted and unadjusted odds ratios were calculated. For single-arm studies (i.e. cross-sectional studies without a comparator group), meta-analyses of proportions were performed.[23] We used a random-effects model taking into account the interstudy variation which provided a more conservative effect than the fixed model. Random pooled effect size with

95% confidence intervals (CIs) was obtained. In addition, the statistic I^2 was used to investigate the variation in effect size attributable to heterogeneity across studies.

RESULTS

Search results

The database searches resulted in 1936 studies. After screening titles and abstracts, 1851 studies were excluded. The full texts of the remaining 85 studies were assessed; of these, another 56 studies were excluded since they did not meet the inclusion criteria (Figure 1). The full texts of the remaining 29 studies were reviewed in detail. Of these, ten studies included information about body composition (i.e. waist circumference and/or body mass index (BMI)) as a continuous variable to describe the population and associations with the outcome of interest but did not define them as established risk factors (i.e. overweight and/or obesity), and were therefore removed.

A manual search of the reference lists of the included studies did not identify any additional studies. Nine published conference abstracts were reviewed but were not included in the final selection due to insufficient data (e.g. did not provide values for CVD risk characteristics) or did not distinguish between physical disabilities (e.g. CP vs. spinal cord injury). Therefore, a total of 19 studies were included in the review. The selection process is presented in Figure 1.

Summary of included studies

Of the 19 studies included in the systematic review, no RCTs or longitudinal experimental studies were identified. Fifteen of the 19 studies were cross-sectional;[8; 9; 24-36] three were cohort studies[37-39] and one was a case-control study.[40] Characteristics of the studies that were included in the systematic review can be found in Table I. All 19 studies included adults with CP with sample sizes ranging from 10 to 4028.[31; 37] The studies included in the review were published between 1999 and 2016.[37; 24] A summary of the studies by outcome of interest (i.e. CVD, risk factors of CVD, and CVD-related mortality) is located in Table II. Many of the studies included data on risk factors of CVD, particularly overweight/obesity. Twelve studies reported percentages of individuals with CP that were either overweight or obese based on BMI within their respective sample size.[8; 25; 27; 28; 30; 32-36; 38; 40] One study reported gender differences for percent body fat in adults with CP and included percentages of those who were above clinical cut-offs (i.e. at risk).[35] Other risk factors of CVD were reported: four studies included information on adults with CP who were hypertensive;[8; 25; 33; 34] five studies reported on individuals who were smokers;[8; 25; 33; 34; 38] three studies reported on hypercholesterolemia, HDL-C, high low-density lipoprotein cholesterol (LDL-C), hypertriglyceridemia, hyperglycemia;[8; 32; 34] and other studies reported on intramuscular fat[31] or diabetes.[25] One study explicitly mentioned the prevalence of adults with CP having CVD.[25] Finally, five studies reported mortality related to CVD.[24; 26; 29; 37; 39]

Strength of the evidence

Meta-analyses of proportions revealed significant variation in effect size attributable to heterogeneity for the following risk factors of CVD: hypertension (I^2 = 72.1%, p=0.01), smoking (I^2 = 94.5%, p<0.01), overweight (I^2 = 86.1%, p<0.01), obesity (I^2 = 90.8%, p<0.01), cholesterol (I^2 89.8%, p<0.01) and cardiovascular-related mortality (I^2 = 98.1%, p=0.01). Due to the high degree of calculated and clinical heterogeneity and/or incomparable outcome measures of the studies included, data were presented descriptively. We presented the lowest and highest prevalence numbers from studies for the following risk factors: overweight/obesity, smoking, and hypertension, to allow for interpretation in comparison with prevalence numbers for the general population.

Risk factors of CVD

Hypertension

Within the four studies included in this review, the presence of hypertension ranged from 14%[7] to 30%[25] in adults with CP. Ryan et al. found that 20% of their cohort had hypertension with either a systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg[33]. Peterson et al. found that the presence of hypertension in adults with CP was significantly greater than in adults without CP (30% vs. 22.1% p<0.001), even after controlling for age.[25] In 2013, van der Slot et al. found a similar presence of hypertension in adults with CP, reporting that 28% of participants had hypertension.[34] They also found that 44% of participants were prehypertensive.[34] They found no gender differences for blood pressure in

adults with CP.[34] McPhee et al. found that in a sample of adults with CP, 14% was hypertensive.[8]

Smoking

Within the five studies included in this review, the presence of smoking ranged from 2%[33] - 21%[34]. Twenty-one percent of adults with CP in the study by van der Slot et al., conducted in the Netherlands, were currently smoking (no gender differences in smoking behaviour).[34] Studies by Marciniak,[38] McPhee,[8] and Ryan[33] found 5%, 7%, and 2% of participants were smokers, respectively. Interestingly, Peterson found that 20% of adults with CP were smokers,[25] which was not significantly different from adults without CP.

Overweight and obesity

Overweight (BMI = 25.0 – 29.9kg/m^2) and obesity (BMI >29.9kg/m^2) as risk factors of CVD were reported in 12 of the 19 studies included in this review. Taken together, 17%[38] - 55%[40] of adults with CP were overweight while 5%[28] - 41%[25] were obese. Bhaumik et al. found that 5% of their sample of adults with CP was obese.[28] Henderson et al. found that 55% of adults with intellectual disabilities (ID) and coincident CP were overweight or obese compared to 71% of adults with ID without CP being overweight or obese.[40] Hsieh et al. found that 28% of adults with CP were overweight, 22% were obese and 2% were morbidly obese (BMI >39.9kg/m^2).[30] Marciniak et al. found that 17% of adults with CP were overweight while another 17% were obese based on BMI criteria.[38] McPhee et al. found that 21% of their cohort was obese, with 29% having central obesity

defined as a waist circumference ≥102cm for men or ≥88cm for women.[8] Furthermore, in this study, presence of obesity based on both BMI and waist circumference was greater among participants who were GMFCS levels III-V than those who were GMFCS levels I-II. Approximately 52% of 112 adults with CP were overweight as discovered by Peterson et al.[27] Of those, 23.5% were classified as obese. Peterson et al., in a different study found that 31% of 1015 adults with CP were overweight, which did not differ significantly from adults without CP; however, they also found that 41% of these overweight adults with CP were obese, which was significantly greater than those without CP (29.7% $p<0.001$).[25] The unadjusted odds ratio for obesity was 1.67 (95% CI 1.47 – 1.90), $p<0.001$. Ryan et al., in a study of 41 adults with CP who were found that 42% were overweight while 37% had central obesity as measured via waist circumference.[32] In another study by Ryan in 55 adults with CP, 33% were overweight, 7% were obese, and 36% had central obesity.[33] In this study, central obesity was defined as a waist circumference ≥94cm for men and ≥80cm for women. Van der Slot et al. found that 6 out of 16 ambulatory adults (38%) with hemiplegic CP were obese in comparison to 50% of control participants being obese.[35] The unadjusted odds ratio for obesity was 0.60 (95% CI 0.12 – 3.06), $p=0.72$. In a second study by van der Slot, 19% of 43 adults with CP were overweight, 12% were obese and 26% had central obesity.[34] Finally, Yoon et al. found that 7 of 38 adults (20%) with CP were overweight.[36]

Other CVD risk factors and CVD risk

Other studies have looked at different risk factors of CVD in adults with CP, such as cholesterol levels. McPhee et al. found that 39% of adults with CP had hypercholesterolemia, 24% had low HDL-C, 39% had high LDL-C, 24% had hypertriglyceridemia, and 51% were hyperglycemic.[8] Similarly, Ryan et al. discovered that 31% of adults with CP in their cohort had hypercholesterolemia, 16% had low HDL-C, 27% had high LDL-C, 13% had hypertriglyceridemia and 6% were hyperglycemic.[33] Noble et al. discovered that ambulatory adults with CP had elevated levels of intramuscular fat compared to typically developing peers, ranging from 2.3 to 34.4%.[31] Peterson et al. showed that 9.2% of adults with CP had diabetes which was significantly greater than the 6.3% of adults without CP that had diabetes.[25] McPhee et al. reported that 7% of adults with CP within their cohort were at increased risk for stroke and other CVDs based on the thickness of the carotid artery wall (i.e. arterial structure).[9] Finally, van der Slot et al. reported that adults with spastic bilateral CP had a Systematic Coronary Risk Evaluation (SCORE) of <1%, translating to a low 10-year risk of fatal CVD.[34] However, adults with CP with a higher waist circumference or who were male were more likely to have a higher 10-year risk SCORE.[34]

Prevalence of CVD

Peterson et al. discovered, via files from a Medical Expenditure Survey, that adults with CP reported significantly greater age-adjusted prevalence rates of conditions inclusive of CVD, myocardial infarction, angina, and other cardiovascular conditions than adults aged 18 and over without CP (15.1 vs.

9.1% p<0.001). Adjusted odds ratios (95% CIs; adjusted for education, income level, marital status, race/ethnicity, type of health insurance, metropolitan statistical area, and geographic location) for these conditions were 1.40 (1.12-1.76).[25]

Mortality related to CVD

Hemming et al. found that, compared with the general UK population, cardiovascular-related deaths in the CP population were the highest relative risk between 30-39 years (17% vs. 9%).[39] Pilla et al. examined cause of death in decedents with CP in South Australia and found that 9 of 48 died due to CVD, with ischemic heart disease accounting for 8 of the 9 deaths.[24] Strauss et al. investigated cause of death in a Californian population of individuals with CP n=4028 of whom died between 1986 to 1995.[37] Forty-one percent of these individuals were categorized as 'not severe' CP (mild, moderate, or unspecified) while the other 59% were reported as 'severe' CP. Mortality due to the diseases of the circulatory system was significantly elevated in comparison to the general population. Standardized mortality ratios were calculated as the ratio of observed deaths in individuals with CP to those expected in the general Californian population for the same distribution by age. For diseases including ischemic heart disease, other heart disease, and cerebrovascular disease, standardized mortality ratios were 5.5, 13.5, and 11.5 for the not severe group and 13.5, 21.8, and 38.5 for the severe group, respectively in ages 0-34.[37] Two other studies reported cause of death statistics related to the circulatory system: Durufle-Tapin

et al. found that the third most common cause of death among individuals with CP was due to diseases of the circulatory system (15% of total observed deaths);[26] while Maudsley et al. found that 1.4% of deaths in people with CP were related to the circulatory system.[29]

Methodological quality

Quality assessments as per the NOS of each study can be viewed in Table III. The quality of the studies varied from one star to three stars (maximum 4 stars) with regard to the selection and representativeness of the cohort. Studies that were awarded one star might not have described the derivation of the sample and/or did not have a control group. The comparability and factors controlled for in the studies ranged from zero stars to two stars (maximum 2 stars). Studies were awarded zero stars if the study design did not control for variables (e.g. confounders or covariates) that could influence the primary outcome variable. Finally with regard to outcome and follow-up, included studies were either awarded zero stars or one star (maximum 3 stars). Studies were given zero stars if they did not describe the assessment of outcome and did not include a follow-up period.

DISCUSSION

The objective of this review was to summarize the evidence from studies that investigated CVD and related risk factors in adults with CP, as well as studies that reported on CVD-related mortality. As adults with CP engage in less physical

activity than the general population,[41] it is often hypothesized that adults with CP will be at increased risk of developing CVD and that development of these conditions will occur at an earlier age. We found 19 studies in the area of CVD research for adults with CP. These studies were observational in nature and mostly focused upon risk factors for CVD. Thus, this review can make limited synthesis of inconsistent evidence regarding the prevalence of risk factors for CVD among adults with CP and whether the prevalence of risk factors is different in this population in comparison to the general population needs to be studied further. Indeed, the review did identify two large population based studies that found an increased prevalence of CVD[25] and an increased risk of death due to CVD[37] in adults with CP compared to the general population, respectively, which should raise concerns about CVD in this population and prompt further study.

In regard to risk factors of CVD, hypertension[8; 25; 33; 34] was noted within the literature pertaining to adults with CP. However, other risk factors of CVD such as overweight and obesity were addressed most frequently and may be of concern in this population.[8; 25; 27; 28; 30; 32-36; 38; 40] Of the limited evidence gathered from this review, inconsistent results make it challenging to discern whether or not the prevalence of overweight / obesity is greater in adults with CP in comparison to the general population. Although twelve of the nineteen studies reported on overweight or obesity in adults with CP, only two studies made comparisons to the general population. Van der Slot found obesity was more prevalent in a sample of controls from the general population than in a small sample of adults

with CP,[35] while Peterson found obesity to be more prevalent in adults with CP compared to the general population.[25] The study conducted by van der Slot et al. included adults with CP from the south-west region of The Netherlands. Conversely, the study by Peterson et al. included data from a large nationally representative survey of the US civilian population. Approximately half of adults with CP in this study reported having a minor or no disability. This suggests that adults with CP in the community are more likely to be ambulatory and self-sufficient, whereas those in care facilities who were less likely to be represented are more heavily impacted by their CP and quite possibly at even higher risk for CVDs or related risk factors. Nonetheless, the findings by Peterson et al[25] are particularly alarming as the dangers of obesity are unknown in adults with CP, and could have varying impacts associated with the level of severity or complexity. Overall, our understanding of overweight and obesity remains fragmented by observational studies that are typically geographically isolated with small sample sizes, or do not capture the population in its entirety due to selection bias of self-report surveys.

The presence of hypertension in adults with CP ranged from 14%[7] to 30%.[25] Research by Peterson et al. was the only study to report that hypertension in adults with CP was greater than in adults without CP.[25] Within adults with CP themselves, mobility impairment was positively associated with hypertension, inferring that those with CP who were more severely affected by the disability had greater instances of hypertension than those less affected. However, like our

understanding of obesity in this population, our understanding of the prevalence of hypertension is again limited to observational studies, identifying a void in the knowledge on this topic. From the current body of evidence it appears that smoking is relatively low in adults with CP, ranging from 2%[33] to 21%[34]. Although minimal data pertaining to smoking in adults with CP exist, the results should be interpreted cautiously. Despite a lack of evidence, it should be noted that it is important to always include blood pressure assessments and smoking as part of the history taking and for counseling in adults with CP as these risk factors should not be treated differently than the general population.

Studies have also reported on the presence of cholesterol-related risk factors of CVD, with McPhee et al.[8] and Ryan et al.[33] reporting on similar variables. Interestingly, both reported elevated levels of LDL-C in adults with CP compared to reference values, which are a precursor to the development of atherosclerosis.[16] However, McPhee et al.[8] reported elevated LDL-C in non-ambulatory adults (GMFCS III-V) while Ryan et al.[33] reported increased levels in ambulatory adults (GMFCS I-II). These inconsistent findings with regard to GMFCS grouping for elevated LDL-C levels identify an important limitation in our understanding and recommendations pertaining to CVD risk. McPhee et al.[9] measured cIMT, an indicator of atherosclerosis, and discovered that age was the strongest predictor of cIMT, meaning that cIMT increases with increasing age in adults with CP. Taken together, and despite the limited evidence, it is important

for clinicians to routinely check cholesterol levels in adults with CP, regardless of GMFCS level, to prevent the development of atherosclerosis later in life.

It appears CVD- and circulatory-related mortality are elevated in persons with CP compared to the general population at ages up to 39.[37; 39] Moreover, CVD-related mortality appears to be increased in those with severe CP compared to those with non-severe CP.[37] However, our understanding of CVD-related mortality in later adult years in this population is limited by a lack of data: there are no recent or ongoing large data prospective longitudinal studies investigating mortality in adults with CP which would reflect advances in healthcare and subsequent life expectancy in this population. Going forward, longitudinal studies investigating mortality in persons with CP should document all causes of death while reporting the severity (i.e. GMFCS levels) of their cohorts to help our understanding of the pathophysiology and causality of morbidity and mortality in this population.

The studies summarized here identify knowledge gaps in our understanding of CVD and CVD risk in adults with CP. Some evidence exists to show that overweight and obesity could be elevated in adults with CP compared to the general population. Many researchers and clinicians interested in the physical health of persons with CP assert that the physical impairment inherent of CP and restrictions in physical activity participation in this population make these individuals at greater risk for diseases related to inactivity, such as CVD. The aim of this review was to characterize the prevalence of CVD, CVD-related risk

factors, and mortality related to CVD in adults with CP. Overall, the presence of CVD and CVD-related risk factors in this population is fragmented by studies that are small in size and geographically isolated. Future studies should provide information about both the incidence and prevalence of CVD and its risk factors within this population, while considering investigating social determinants of health such as alcohol use, physical inactivity, diet and sedentary behaviour. Although there is limited evidence to support a costly prospective cohort study, a well-designed, population-based study of existing data using hospital admissions or patient records linked to death registries could provide extensive insights into these outcomes. Similarly, a longitudinal multi-centre study, including both ambulatory and non-ambulatory adults with CP, investigating overweight and obesity, hypertension, other CVD risk factors and CVD itself would be insightful as well. A better understanding in this area through well-designed studies could help identify prognostic factors and the pathophysiology of CVD in this population.

Although more research is required to determine whether adults with CP truly have an elevated risk of CVD compared to the general population, some considerations for clinical practice can be given based on this study. The dangers of CVDs are already well documented in the general population. As such, it is critical to monitor and treat common risk factors to prevent the development of CVD in adults with CP, thus clinical researchers and healthcare professionals should not be halted by this lack of evidence in the population of individuals with

CP. In particular, findings from this review could help clinicians focus on more documented risk factors such as overweight/obesity and hypertension, both modifiable and treatable factors. Clinicians should incorporate a holistic approach to monitor and treat these risk factors, by asking patients with CP about other variables of physical health in addition to physical activity, such as sleep and nutrition.[42]

Limitations

This literature search did not identify any RCTs or longitudinal experimental studies and returned a total of 19 studies, all observational in nature. Although not an aim of this systematic review, an RCT or longitudinal experimental study with a comparator group could provide information about the risk of, and change in, CVD and risk factors of CVD between adults with CP and a control group. Another limitation in this study was that the evidence identified could not be pooled to obtain an overall effect. As a result, the evidence summarized in this review should be considered preliminary, hypothesis generating, and a resource to guide future research based on identified knowledge gaps.

Conclusion

The evidence for prevalence of CVD-related health outcomes remains limited in this population. Additionally, risk factors for CVD from the Framingham Heart Study and other emerging risk factors are only somewhat addressed within the literature. Healthcare providers should be aware of the evidence around adult CVD-related outcomes in those with CP. Researchers should explore this large

gap in our current understanding and work to provide necessary evidence first via epidemiological studies and then via intervention studies for effective evidence-based decision-making in clinical practice. Although evidence pertaining to CVD risk factors is accumulating in this population (i.e. obesity and hypertension), how it translates to CVD itself or CVD-related mortality remains unknown.

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Table I. Characteristics of the studies included in the systematic review

Source (year), type of study	Country	Individuals with CP (N)	Age, years (sex)	Severity of CP
Bhaumik 2008,[27] cross-sectional	England	20	>20	NA
Durufle-Tapin 2014,[25] cross-sectional	USA and France	3031	<1 – 95 (58% male)	NA
Hemming 2006,[38] cohort	England	65	>20	NA
Henderson 2009,[39] case-control	USA	179	33 - 79	NA
Hsieh 2014,[29] cross-sectional	USA	167	18 - >60 (50% male)	NA
Marciniak 2015,[37] cohort	USA	42	22.4 – 73 (57% male)	GMFCS II-V
Maudsley 1999,[28] cross-sectional	England	282	<1 - ? (63% male)	NA
McPhee 2015a,[8] cross-sectional	Canada	42	18 – 75 (50% male)	GMFCS I-V
McPhee 2015b,[9] cross-sectional	Canada	42	18 – 75 (50% male)	GMFCS I-V
Noble 2014,[30] cross-sectional	England	10	18 – 27 (70% male)	GMFCS I-III
Peterson 2014,[26] cross-sectional	USA	112	34 ± 13.4 (56% male)	GMFCS I-V
Peterson 2015,[24] cross-sectional	USA	1015	58 (57 – 60) (66% male)	Minor, moderate and severe disability
Pilla 2016,[23] cross-sectional	Australia	48	<1 – 80 (60% male)	NA
Ryan 2014a,[31] cross-sectional	Ireland	41	18 – 62 (46% male)	GMFCS I-III

Ryan 2014b,[32] cross-sectional	Ireland	55	18 -65 (56% male)	GMFCS I-V
Straus 1999,[36] cohort	USA	4028	<1 - >55	Non severe and severe
van der Slot 2013,[33] cross-sectional	The Netherlands	43	25 – 45 (63% male)	GMFCS I-IV
van der Slot 2007,[34] cross-sectional	The Netherlands	16	25 – 35 (44% male)	NA
Yoon 2012,[35] cross-sectional	Korea	38	20 – 59 (48% male)	NA

GMFCS = Gross Motor Function Classification System; NA = not available.

Table II. Summary of studies by outcomes of interest (i.e. cardiovascular disease, cardiovascular disease related risk factors, mortality)

	CVD / Risk Factor / Mortality					
Study	CVD	Hypertension	Smoking	Overweight / Obesity	Other	Cause of Death
Bhaumik, 2008				5% (BMI >29.9)		
Durufle-Tapin, 2014						1.7% due to diseases of the circulatory system
Hemming, 2006						Circulatory Deaths % vs ref. % (age group) 6% vs. 5% (20-29) 17% vs. 9% (30-39) 19% vs. 19% (40-49) 21% vs. 27% (50-59)
Henderson 2009				55% (BMI>24.9)		
Hsieh, 2014				28% (BMI>24.9) 22% (BMI>29.9) 2% (BMI>39.9)		
Marciniak 2015			5%	17% (BMI>24.9) 17% (BMI>29.9		

				)		
Maudsley, 1999						1.4% died of circulatory-related disease
McPhee, 2015		14%	7%	21% (BMI>29.9) 29% centrally obese	39% hypercholesterolemia 24% Low HDL-C 39% High LDL-C 24% hypertriglyceridemia 51% hyperglycemia	
McPhee, 2015	7% risk of CVD					
Noble, 2014					2.3 to 34.4% elevated levels of intramuscular fat compared to typically developing adults	
Peterson, 2014				23.5% (BMI >29.9)		
Peterson, 2015	20%	30%	20%	31% (BMI>24.9) 41% (BMI>29.9)	9.2% diabetic	
Pilla, 2016						18.8% died of CVD
Ryan, 2014				42% (BMI>24.9) 37% (central obesity)		

Ryan, 2014	20%	2%	33% (BMI>24.9) 7% (BMI>29.9) 36% (central obesity)	31% hypercholesterolemia 16% low HDL-C 27% high LDL-C 13% hypertriglyceridemia 6% hyperglycemia	
Strauss, 1999					8.6% died of diseases of the circulatory system
van der Slot, 2013	26%	21%	12% (BMI>29.9) 26% (central obesity)	7% elevated total cholesterol 12% low HDL-C	
van der Slot, 2007			38% (percentage body fat >25%(M) and >32%(F))		
Yoon, 2012			20% (BMI>25)		

Table III. Methodological quality of the studies

Study	Selection	Comparability	Outcome
Bhaumik 2008	★	★★	★
Durufle-Tapin 2014	★		★
Hemming 2006	★	★★	★
Henderson 2009	★	★★	★
Hsieh 2014	★★★	★★	
Marciniak 2016	★★		★
Maudsley 1999	★★		★
McPhee 2015[a]	★★★		
McPhee 2015[b]	★★★	★★	★
Noble 2014	★★★		★
Peterson 2014	★★	★★	★
Peterson 2015	★★★	★★	★
Pilla 2016	★★		
Ryan 2014[a]	★★★	★★	★
Ryan 2014[b]	★★★	★★	★
Strauss 1999	★★		★
van der Slot 2007	★★★		★
van der Slot 2013	★★★	★	★
Yoon 2012	★★★		★

McPhee 2015[a]: [8]
McPhee 2015[b]: [9]
Ryan 2014[a]: [32]
Ryan 2014[b]: [33]

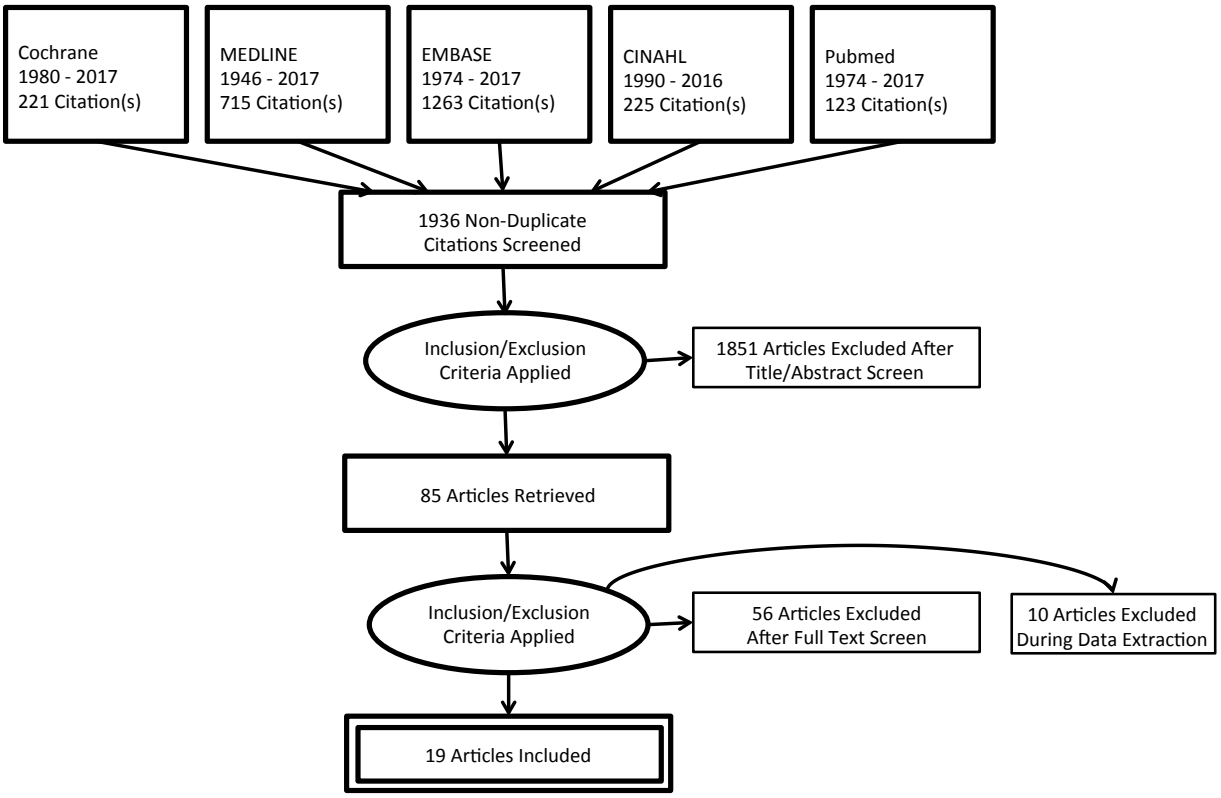

Figure 1. Flow diagram detailing study selection process

Appendix S1. Search Terms

#1 Search (young adult OR adult* OR elderly OR senior* OR retire* OR pensioner* OR mid* age*)

#2 Search (cerebral pals* OR little* disease OR diplegia*)

#3 Search (cardiovascular disease* OR CVD OR cerebrovascular disorder* OR endocarditis OR arrhythmia* OR (cardiac adj 2 (disease* OR arrest* OR attack* OR bypass* OR aneurysm* OR defect* OR failure* OR neoplasm* OR rupture*)) OR (coronary* adj2 (BYPAS* OR GRAFT* OR DISEASE* OR EVENT*)) OR (morbid* adj2 (heart* OR coronary* OR isch?em* OR myocard*)) OR (vascular* adj2 (peripheral* OR disease* OR complication* OR fistul* OR neoplasm* OR system injur*)) OR (heart* adj2 (disease* OR attack* OR bypass* OR defect* OR aneurysm* OR arrest* OR failure* OR neoplasm* OR rupture*)) OR coronary artery disease* OR angina OR angina pectoris OR stroke OR arterial disease* OR embolism* OR ischemi* OR vasculitis OR aneurysm* OR metabolic disease* OR (ventricular adj2 (dysfunction* OR outflow obstruction*)))

#4 Search (arterial stiffness OR vascular stiffness OR prehypertension OR hypertension OR blood pressure OR chronic disease* OR obesity OR waist circumference OR (body mass index OR BMI) OR dyslipidemi* OR adiposit* OR diabetes OR sarcopeni* OR varicose)

#5 Search #3 OR #4

#6 Search #1 AND #2 AND #5

Appendix S2. Screening Form

Articles answered "yes" or "unclear" to all criteria should be included in full text screening.

1. Is this article about humans?
If no → EXCLUDE
If yes or unclear → go to next question

2. Is this article about adults (≥18years of age)?
If no → EXCLUDE
If yes or unclear → go to next question

3. Is this article about people with cerebral palsy?
If no → EXCLUDE
If yes or unclear → go to next question

4. Is this article about cardiovascular disease(s) (cerebrovascular disorder, endocarditis, arrhythmia, cardiac disease, cardiac arrest, cardiac attack, cardiac bypass, cardiac aneurysm, cardiac defect, cardiac failure, cardiac neoplasm, cardiac rupture, coronary bypass graft, coronary disease, coronary event, vascular disease, peripheral vascular disease, peripheral artery disease, vascular complication, vascular fistful, vascular neoplasm, vascular systemic injury, heart disease, heart attack, heart failure, heart bypass, heart defect, heart aneurysm, heart arrest, heart neoplasm, heart rupture, coronary artery disease, angina, angina pectoris, stroke, arterial disease, embolism, ischemia, vasculitis, aneurysm, metabolic disease, ventricular dysfunction, outflow obstruction
AND/OR
other cardiovascular health outcomes / risk factors for CVD - arterial stiffness, vascular stiffness, prehypertension, hypertension, blood pressure, chronic disease, obesity, waist circumference, body mass index, dyslipidemia, adiposity, diabetes, varicose, smoking, risk factor, inactivity, heart rate reserve, energy expenditure, fatigue.
If no → EXCLUDE
If yes or unclear → go to next question

5. Is this study a randomized controlled trial, longitudinal study or observational / cross-sectional study?
If no → EXCLUDE
If yes or unclear → go to next question / include in nest step / review

CHAPTER 3

Differences in cardiovascular health variables in ambulatory adolescents and adults with cerebral palsy after adjusting for age

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ABSTRACT

Objective: To compare cardiovascular health variables and physical activity levels of adolescents and adults with cerebral palsy who are Gross Motor Function Classification System (GMFCS) level I and II.

Methods: Eleven adolescents (mean 13.1 (2.1) years) and fourteen adults (mean 31.7 (10.4) years)) with cerebral palsy were included, grouped by their GMFCS level (level I (n=12); level II (n=13)). Assessments of cardiovascular health, body composition and physical activity levels were performed. Cardiovascular variables included resting blood pressure and carotid artery intima media thickness. Body composition included height, weight, body mass index, and waist circumference. Physical activity was measured using accelerometry.

Results: Adjusting for age between GMFCS levels (GMFCS I=17.3 ± 5.2; GMFCS II=29.3 ± 14.1 years, *p*=0.011), significant differences were evident for moderate-to-vigorous physical activity (MVPA) per day (GMFCS I=45.8 (32.4, 75.1); GMFCS II=16.4 (13.0, 25.0) (IQR; 25-75 percentile) minutes/day, *p*=0.011), height (GMFCS I=1.63 ± 0.14; GMFCS II=1.56 ± 0.12 meters, *p*=0.010), mean arterial pressure (MAP) (GMFCS I=84.6 ± 7.8; GMFCS II=89.4 ± 8.5 mmHg, *p*=0.030), and carotid artery intima media thickness (cIMT) (GMFCS I=0.431 ± 0.057 ; GMFCS II=0.489 ± 0.104, *p*=0.026).

Conclusion: Individuals with CP who were GMFCS level I had a lower MAP, a thinner cIMT, and engaged in a greater amount of MVPA per day than those who were GMFCS level II. Clinicians should acknowledge that ambulatory individuals

with CP could have differing cardiovascular health profiles and should monitor these cardiovascular variables and discuss physical activity during health care visits, regardless of age.

Key-words:

Cerebral palsy

Adolescent

Adult

Physical activity

Cardiovascular health

Body composition

INTRODUCTION

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition commencing in early childhood and continuing throughout life (1). The condition itself is the result of non-progressive disturbances to the developing fetal or infant brain, and the resulting motor disorders can be accompanied by secondary disturbances affecting cognition, communication, and behaviour, to name a few (2). As CP presents itself early on in life, much research has focused on children with CP. However, recently researchers have started to also examine the impact of CP and its secondary disturbances later in life, which is of particular interest given the longer lifespan now apparent in most persons with CP (3).

A prominent concern from clinicians and researchers regarding persons with CP, regardless of their age, is a lack of physical activity (PA) (4). Low levels of PA seen in persons with CP can partly be explained by the condition itself, as well as accompanying perceptions of physical pain and fatigue that worsen with aging (5, 6). Studies in both children and adults with CP have shown that persons with CP engage in significantly less PA than the general population (4). While this finding is most evident in non-ambulatory individuals with CP (4), it also has been reported in the most functional, ambulatory individuals (i.e. individuals classified as Gross Motor Functional Classification System (GMFCS) (7) level I or II) (8). Compared with adolescents and adults in GMFCS level I, adolescents and adults in level II have limitations walking long distances and balancing, may use wheeled mobility when traveling long distances outdoors and in the community, require the use of a railing to walk up and down stairs, and are not as capable of running and jumping (7).

Research is starting to reveal relationships between reductions in PA and increased risk for cardiometabolic and cardiovascular disease (CVD) (9, 10) and co-morbidity (11) in persons with CP, with these relationships becoming more prevalent later on in life in this population (12). Descriptive data from our previous work showed that non-ambulatory adults with CP (GMFCS levels III-V) may be at greater risk for CVD compared to those who are ambulatory (GMFCS levels I, II) (13). A Medical Expenditure Panel Survey of over 200 000 adults (of which 1015 had CP) reported that adults with CP were at greater risk for cardiovascular-

related diseases such as diabetes (unadjusted odds ratios (OR); 2.63), hypertension (unadjusted OR; 3.13) and stroke (unadjusted OR; 4.08) compared to the general population (11). Importantly, age, physical disability status (i.e. moderate or severe) and self reported PA were associated with cardiovascular-related disease in these adults with CP (11). Similarly, in a population-based cohort in Taiwan, patients with CP had a 2.17-fold greater risk for stroke than the general population (14).

While it is apparent that non-ambulatory (GMFCS level III-V) individuals with CP have an increased susceptibility to physical inactivity and cardiovascular risk (12), the companion risk relationship for ambulatory individuals with CP is understudied. A secondary objective in a study by Ryan and colleagues was to examine the relationship between PA, measured by accelerometry, and cardiometabolic risk in adults with CP who were GMFCS levels I-III (9). They found that moderate activity was negatively associated with waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Indeed, previous research within our group revealed that adolescents with CP who were GMFCS levels I and II did not differ from their age- and sex-matched counterparts in measures of arterial health (15). However, a limitation of this study was that GMFCS I and II were combined and limited to adolescents only. Further risk stratification within an ambulatory population (GMFCS level I vs. GMFCS level II) would permit identification of those individuals who would benefit from intensified monitoring and preventative management. Therefore, the primary

objective of this exploratory study was to compare cardiovascular health variables and objectively measured PA levels of adolescents and adults with CP who are GMFCS level I versus those who are GMFCS level II. A secondary objective was to assess the relationships between objectively measured PA and cardiovascular health variables in this sample of persons with CP who are ambulatory. It is hypothesized that those who are GMFCS level I will have increased PA levels and healthier cardiovascular indices compared to those who are GMFCS level II. Secondly, it is hypothesized that PA levels will be inversely associated with cardiovascular health variables in this study sample.

METHODS

Data from the Stay-FIT Program of Research (https://www.canchild.ca/en/stay-fit), a multi-step research program whose objectives are to understand physical health and encourage a healthy active lifestyle in children, adolescents and adults with CP, were reviewed for study eligibility. Specifically, adolescents and adults with CP who were GMFCS levels I or II were included in the present study. This resulted in a sample consisting of 11 adolescents (13.1 ± 2.1yr [mean ± SD]) and 14 adults (31.7 ± 10.4yr) with CP. Data were previously collected in the Vascular Dynamics Laboratory at McMaster University, Hamilton, Ontario, Canada with recruitment occurring between the years 2010-2012 (15) and 2012-2014 (12), respectively. The Hamilton Integrated Research Ethics Board granted study approval.

Methods for body composition data collection and non-invasive arterial structure and function measures are described elsewhere (12, 15). Physical activity was measured using an ActiGraph GT1M or GT3X accelerometer (ActiGraph, Pensacola, FL) worn on the hip of each participant during all waking hours, with the exception of any water activities, over 7 consecutive days. All data were collected in 3-second sampling intervals, or epochs. The average minutes of moderate-to-vigorous physical activity (MVPA) per day (mins/day) were determined using age-appropriate cut-points, as previously described (16, 17). Accelerometer data were only included in the analysis if the participant wore the device for a minimum of five hours on at least four days (18).

Participants included in the study had data pertaining to the following variables: age, height (cm), weight (kg), body mass index (BMI) (kg/m^2), waist circumference (cm), heart rate (beats per minute), SBP (mmHg), DBP (mmHg), mean arterial pressure (MAP) (mmHg), carotid artery distensibility ($mmHg^{-1}$), carotid artery intima-media thickness (cIMT) (mm), absolute brachial artery flow mediated dilation (FMD) (mm), relative FMD (%), and MVPA per day. GMFCS level was recorded for each participant using a self-report version of the GMFCS-E&R (7). Participants were separated into two groups based on their GMFCS level (i.e. GMFCS level I or GMFCS level II).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 20. IBM, Armonk, NY, USA). Descriptive summary statistics were calculated as means and standard deviations for continuous

variables and as percentages for nominal data (i.e. sex). Assumptions pertaining to the t-test for independent means were tested. Continuous variables were assessed for normality using the Shapiro-Wilk descriptive test in each GMFCS level. T-tests for independent means were performed for each continuous variable. An analysis of covariance (ANCOVA) was performed where age, a continuous variable, was included as a covariate when examining between group differences for body composition, cardiovascular variables, and MVPA per day. Age was chosen as a covariate due to the fact that it has been identified as a salient predictor of CVD in the general population (19), and was recently shown to be a significant predictor of cIMT and other non-traditional markers of CVD risk in adults with CP (12). Separate Pearson correlations were performed between MVPA per day (independent variable) and BMI, waist circumference, heart rate, SBP, DBP, MAP, carotid artery distensibility, FMD (both absolute and relative), and cIMT (dependent variables). A minimum criterion alpha level of $p \leq 0.05$ was used to determine statistical significance.

RESULTS

Data collection

One adolescent who was GMFCS level I did not have an FMD assessment performed and therefore was not included in the between group analysis for absolute or relative FMD. Another adolescent who was GMFCS level II was not included in the between group analysis for cIMT due to data acquisition

error. Finally, four adolescents and one adult (four GMFCS level I, one GMFCS level II) did not have MVPA values as a result of missing data files. On average, participants wore the accelerometer for 6.5 ± 0.9 days equaling a total average wear time of 77.4 ± 15.5 waking hours.

Comparison between GMFCS level I and II

Participant characteristics and descriptive summary statistics are presented in Table 1. Carotid artery distensibility (p<0.001) and MVPA per day (p=0.001) were not normally distributed, therefore natural log transformations of the data were performed prior to hypothesis testing. These transformations resulted in normal distributions of the data. Independent samples t-test revealed significant differences for age (p=0.011, 95% CI -20.9 to -3.0) and MVPA per day (p=0.037, 95% CI 2.2 – 57.9) between GMFCS levels I and II (Table 1), with the GMFCS level II group being older in age and engaging in less MVPA per day than the GMFCS level I group.

With age included as a covariate, ANCOVA revealed statistically significant differences in height, MAP, cIMT and MVPA per day between individuals who were GMFCS level I compared to those who were GMFCS level II. More specifically, the GMFCS level I group was taller than the GMFCS level II group ($F_{1, 23}$ = 5.68, p=0.010). The GMFCS level I group had lower MAP ($F_{1, 23}$ = 4.11, p=0.030) and smaller cIMT ($F_{1, 22}$ = 4.34, p=0.026) than the GMFCS level II group. Finally, the GMFCS level I group engaged in more MVPA per day than the GMFCS level II group ($F_{1, 18}$ = 6.027, p=0.011) (Table 1).

Relationships between MVPA per day and cardiovascular health variables

Log transformed values of MVPA per day and carotid artery distensibility were used in the Pearson correlations. Moderate-to-vigorous PA per day was inversely associated with waist circumference (r = -.608, p=0.004), BMI (r = -.593, p=0.006), and cIMT (r = -.563, p=0.010) in this sample of persons with CP (Figure 1). There were no significant relationships between MVPA per day and heart rate, SBP, DBP, MAP, carotid artery distensibility, and FMD.

DISCUSSION

As research continues to investigate the relationship between physical (in)activity and CVD risk in the general population (20), the alarming evidence has led to queries of how persons with CP, who have an inherent physical disability, may be at increased risk of CVD by virtue of engaging in less PA than the general population. Our previous work recently identified age as an important predictor of cardiovascular-related disease risk in adults with CP (12). Given this, as well as the fact that age was significantly different between GMFCS levels I and II in the present study, we adjusted for age differences by including age as a covariate in subsequent between group analyses of body composition, PA and cardiovascular-related variables. We found that after adjusting for age, the GMFCS level I group had lower MAP, smaller cIMT and engaged in greater amounts of MVPA per day than the GMFCS level II group.

In agreement with our primary hypothesis, our exploratory findings revealed that individuals who were GMFCS level I engaged in more MVPA than those who were GMFCS level II. These findings are in line with two previous studies, one in adolescents and another in adults, which reported higher levels of MVPA in GMFCS level I compared with GMFCS level II (9, 21). Our research is unique in that we have analyzed a sample that combined adolescents and adults with CP whereas the aforementioned studies included participants who represented only one or the other group. Our study is also the first to report a negative relationship between MVPA per day and cIMT in persons with CP.

After adjusting for age, we found significant differences in cardiovascular health between groups such that individuals who were GMFCS level I had lower MAP and reduced cIMT than those who were GMFCS level II. These differences in MAP and cIMT are in agreement with our hypothesis that those who were GMFCS level I would present healthier cardiovascular variables compared to those who were GMFCS level II. Research has shown that increased cIMT in adults is a significant predictor for developing CVD (22). Specifically, the risk of having a myocardial infarction or stroke increased with intima-media thickness in individuals without a history of CVD, even after adjusting for traditional risk factors of CVD (23). This may be particularly important for persons with CP, as recent studies showed that persons with CP were at increased risk for stroke compared to the general population (11, 14) particularly at ages equal to or less than 50 years (14). Given that the average age in both groups was less than 50

years and that cIMT was elevated in the GMFCS level II group, our findings highlight the importance of early screening for cardiovascular health, including cIMT assessment, particularly in individuals who are GMFCS level II. In the general population, a cIMT ≥ 1mm is considered to be at high risk for atherosclerosis (24). Of the individuals with CP in the present study, no one presented with a cIMT at or above this risk value. However, an important implication from our findings is that it should no longer be assumed that it is acceptable to combine GMFCS levels I and II when investigating cardiovascular and/or cardiometabolic disease risk in persons with CP.

The difference in MAP between GMCFS levels is also interesting. Previous research has shown that increases in MAP are related to increased CVD risk (25). Furthermore, increases in blood pressure are also related to cIMT (26). This combination of elevated MAP and cIMT seen in those who were GMFCS level II could identify a group that is at increased risk for the development of CVD in comparison to those who are GMFCS level I, which again alludes to the importance of separating individuals with CP who are GMFCS levels I and II in these investigations. Regarding body composition, research has shown that individuals with CP are significantly shorter in stature than age-matched controls due to a reduced growth development experienced during childhood in those with CP (27). Research in the general population revealed an inverse relationship between height and cardiovascular health, such that individuals who were shorter had poorer cardiovascular health (28). The results

from our exploratory study may suggest a similar relationship even within persons with CP, particularly as individuals in GMFCS level II were statistically significantly shorter, had increased MAP, and increased cIMT compared to the GMFCS level I group.

Consistent with findings from Ryan and colleagues (9), we found an inverse relationship between MVPA per day and waist circumference in our sample of persons with CP. We also reported inverse associations between MVPA per day and BMI, as well as MVPA per day and cIMT. The latter is particularly interesting as this is the first study to reveal a significant relationship between PA and cIMT in individuals with CP, thereby indicating a strategic target of PA interventions for CVD risk reduction in this population. In the general population, increased PA has been shown to be related to a decreased progression of intima-media thickness in adolescents (29). Future studies investigating the effect of PA/exercise interventions in people with CP should consider measuring changes in cIMT and body composition (i.e. waist circumference and BMI) as outcome variables of interest while adjusting for age and gender.

Limitations

There are both technical and logistical limitations that should be considered. Different assessors collected data for non-invasive measures of arterial structure and function. However, assessors employed similar techniques that are comparable to studies that reported test-retest reliability for the FMD assessment

(30) and cIMT (31) measures of 0.90 and 0.97, respectively. Additionally, PA measurement via accelerometry may have been underestimated for some participants due to the device's sensitivity to water. Swimming is a preferred activity for individuals with CP and any time spent swimming would not have been recorded by the device. Furthermore, accelerometer cut points are commonly population and age specific (32). A limitation in the present study was the adoption of two sets of cut points, one validated for children and adolescents with CP, and another developed for the general adult population (17). While there are no data to suggest whether these cut points are comparable, the fact that they were used consistently between the two GMFCS levels in the present study allows for a more meaningful comparison between groups. Also, other noteworthy limitations include our small sample size, lack of statistical power analysis, and lack of a comparator group from the general population. However, the findings from this study should be considered knowledge building and should be explored in a larger sample of ambulatory individuals with CP, including those who are GMFCS level III.

In conclusion and in support of recent research identifying an increased risk of stroke in persons with CP compared to the general population, our findings identify important differences in both MVPA levels and CVD health variables between GMFCS levels I and II. Particularly, a combination of elevated blood pressure (MAP), increased cIMT, and lower levels of MVPA in individuals who were GMFCS level II could put this group at risk for CVD in comparison to

individuals who were GMFCS level I. Therefore, we recommend clinicians to acknowledge that ambulatory individuals with CP could have differing cardiovascular health profiles and should monitor cardiovascular variables, including resting blood pressure, during regular clinical visits for persons with CP, regardless of age.

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Table 1. Participant characteristics

	GMFCS I	GMFCS II	Unadjusted CIs	Age adjusted CIs
N	12	13		
Sex (males), %	66.7	61.5		
Age, years	17.3 ± 5.2	29.3 ± 14.1*	-20.8 to -3.0	
Height, m	1.63 ± 0.14	1.56 ± 0.12	-.04 – .17	.04 - .25*
Weight, kg	55.7 ± 25.5	58.6 ± 18.3	-21.3 – 15.5	-10.8 – 27.8
BMI, kg/m^2	20.2 ± 6.2	23.5 ± 5.1	-8.0 – 1.4	-6.0 – 4.2
Waist circumference, cm	72.1 ± 15.9	80.6 ± 15.7	-21.6 – 4.5	-16.4 – 12.3
Heart rate, bpm	72.0 ± 11.8	73.4 ± 10.3	-10.5 – 7.8	-14.7 – 6.3
SBP, mmHg	112 ± 13.8	119 ± 12.9	-17.6 – 4.5	-14.3 – 10.6
DBP, mmHg	65.2 ± 7.3	70.8 ± 10.5	-13.2 – 1.9	-8.1 – 7.2
MAP, mmHg	84.6 ± 7.8	89.4 ± 8.5	-11.6 – 1.94	-7.9 to -1.2*
Carotid distensibility, $mmHg^{-1}$ [a]	0.004 (0.003, 0.007)	0.006 (0.004, 0.008)	-.003 - .003	-.005 - .002
Carotid IMT, mm	0.431 ± 0.06	0.489 ± 0.04	-.13 - .01	-.09 to -.01*
Absolute FMD, mm	0.316 ± 0.150	0.309 ± 0.179	-.13 - .15	-.18 - .15
Relative FMD, %	9.88 ± 5.83	9.46 ± 6.41	-4.8 – 5.6	-6.8 – 5.3
MVPA, min/d [a]	45.8 (32.4, 75.1)	16.4 (13.0, 25.0)*	2.2 – 57.9*	5.4 – 49.1*

Note: BMI percentiles for adolescents for each GMFCS level were calculated according to CDC criteria for age and reported as follows: GMFCS level I (4 males; 3 females) = 20.4 ± 16.3; GMFCS level II (4 males) = 70.5 ± 24.2
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; IMT, intima-media thickness; FMD, flow mediated dilation; MVPA, moderate-to-vigorous physical activity; CI, confidence interval.
* $p<0.05$
[a] Variable not normally distributed, data presented as median (IQR; 25-75 percentile)

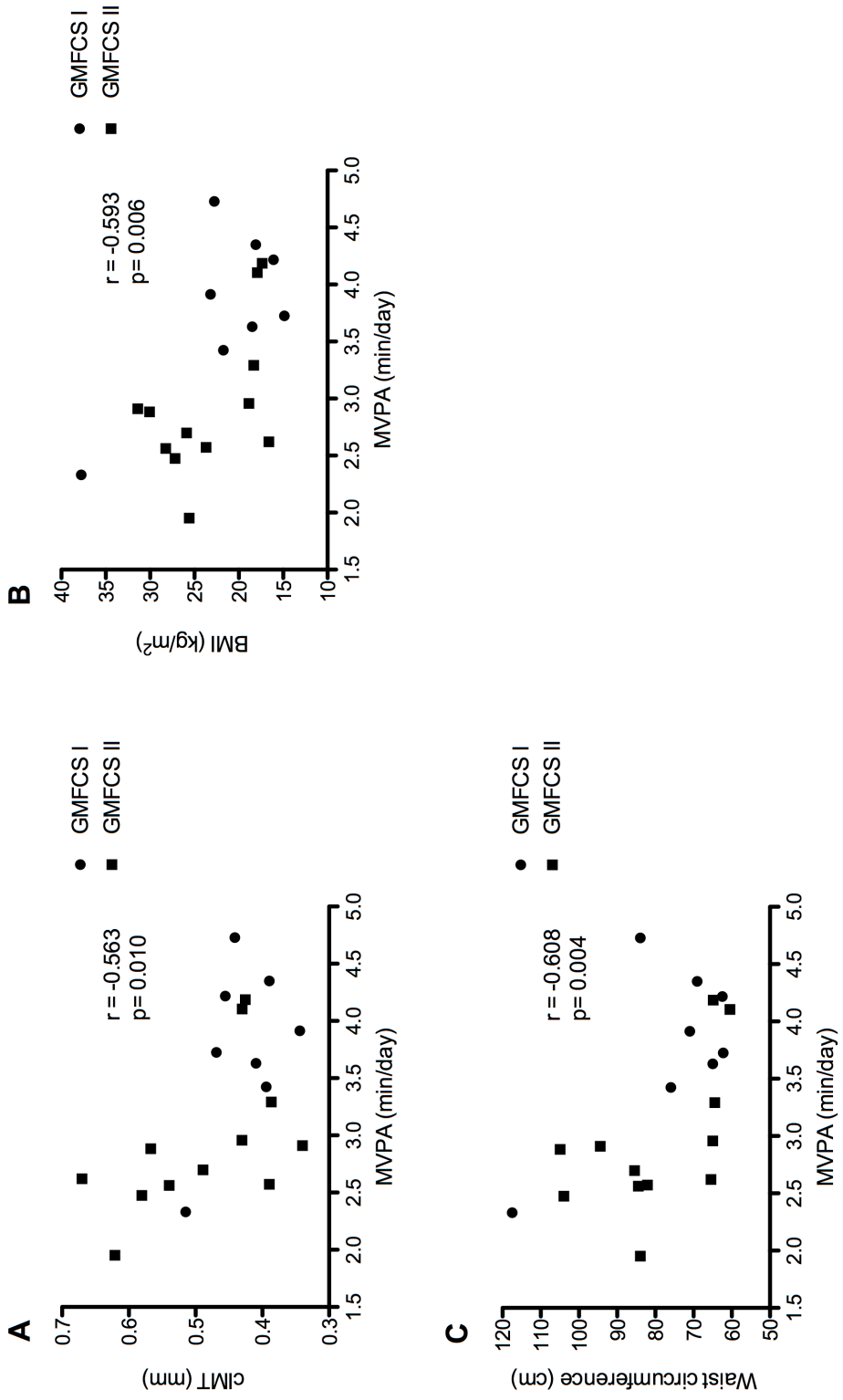
A
cIMT (mm)
0.7
0.6
0.5
0.4
0.3
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
MVPA (min/day)
r = -0.563
p= 0.010
GMFCS I
GMFCS II
B
BMI (kg/m2)
40
35
30
25
20
15
10
r = -0.593
p= 0.006
C
Waist circumference (cm)
120
110
100
90
80
70
60
50
r = -0.608
p= 0.004

Figure 1. Pearson correlations between moderate-to-vigorous physical activity per day and carotid artery intima media thickness, body mass index, and waist circumference

CHAPTER 4

Evidence for accelerated aging through longitudinal evaluation of traditional and non-traditional risk factors of cardiovascular disease in individuals with cerebral palsy

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ABSTRACT

Background and aims: 1) To examine longitudinal changes in traditional and non-traditional risk factors for cardiovascular disease (CVD) in individuals with cerebral palsy (CP); and 2) to investigate relationships between age, gross motor function and CVD risk factors.

Methods: A longitudinal cohort study was conducted within a University laboratory. Participants were individuals with CP (*n*=28; Gross Motor Function Classification System (GMFCS) levels I-V); follow-up mean age = 35.1 ± 14.4, min-max 16-78 years. Traditional risk factors included waist circumference and systolic blood pressure. Non-traditional risk factors included carotid artery intima media thickness (cIMT) and distensibility, carotid-femoral pulse wave velocity (cfPWV), and flow mediated dilation (FMD). Repeated measures analysis of variance was performed to compare variables at baseline and follow-up. Multiple linear regressions were performed to investigate the relationship between age and GMFCS on change scores of traditional and non-traditional CVD risk factors.

Results: The average time between assessments was 4.0 ± 1.2 years. Absolute (0.31 ± 0.13 vs. 0.22 ± 0.08 mm, *p*=0.045, 95%CI .040, .151) and relative FMD (9.9 ± 4.7 vs. 7.5 ± 2.6 %, *p*=0.049, 95%CI .464, 4.42) decreased while cIMT (0.52 ± 0.17 vs. 0.67 ± 0.33 mm, *p*=0.041, 95%CI -.242, -.074) increased from baseline to follow-up, while no other risk factor changed significantly. Age at baseline was a significant independent predictor of cIMT change (R-squared = 0.261 *p*=0.031).

Conclusions: Individuals with CP experience significant changes in non-traditional CVD risk factors over four years, in the face of no changes in traditional risk factors. These non-traditional risk factors should be considered sensitive measures in this population. Importantly, age was strongly associated with changes in cIMT in this cohort and this relationship should guide surveillance and management of CVD in young adults with CP and continue throughout the lifespan.

Keywords

Cerebral palsy

Cardiovascular disease

Risk factor

Cohort

Endothelial function

Arterial stiffness

INTRODUCTION

Cerebral palsy (CP) is the most common childhood physical disability.[1] The severity of the physical disability ranges from a minimal effect on movement to the complete absence of purposeful movement.[2] The implications of disability severity are associated with survival rates for individuals with CP; mortality has been reported to be lowest in individuals with unilateral spastic CP (also known as hemiparesis), while individuals with bilateral spastic CP with tetraparesis have

significantly higher mortality.[3] However, the scientific community knows very little about the effects of aging on individuals with CP. It is hypothesized that individuals with CP experience an accelerated aging process that might be linked to an increased prevalence of secondary conditions, such as reduced range of motion, muscular strength, and aerobic endurance.[4] Undeniably, adolescents and adults with CP have been reported as overweight and/or obese,[5] sedentary,[6] engaging in low levels of physical activity,[7] and hypertensive,[8] all of which contribute to an increased risk of developing cardiometabolic disease,[9] cardiovascular disease (CVD),[10] and multimorbidty.[11]

CVD remains the leading cause of death globally, meaning more people die annually from diseases related to the cardiovascular system than any other cause.[12] The World Health Organization acknowledges that many CVDs can be prevented by modification of behavioural risk factors, such as unhealthy diet, obesity, and physical inactivity. A recent review examined the risk of non-communicable diseases in CP and revealed that adults with CP had increased risks for stroke, ischemic heart disease, and other cardiac conditions compared to the general population.[13] Associations between reduced physical activity levels and physical disability status with chronic conditions, such as stroke, hypertension, and other cardiac conditions, in adults with CP have been reported from a large nationally representative survey of the US population.[14]

However, a knowledge gap exists in the understanding of CVD risk, and progression of CVD, in individuals with CP due, in part, to a lack of well-designed

longitudinal studies. Indeed, Peterson et al. recently examined age-related trends in cardiometabolic disease in adults with CP from a de-identified nationwide claims database and reported that age was a strong predictor of type 2 diabetes, hypercholesterolemia, hypertension, cardiac dysrhythmias, and atherosclerosis, such that mean disease-free survival rates were significantly less for middle-aged (40-<60y) and older (≥60y) compared to young adults (18-<40y).[15] Despite this being the first longitudinal cohort study to investigate cardiometabolic disease in adults with CP, other important risk factors such as gross motor function and physical activity were unavailable for consideration in the analysis and may have influenced the disease-free survival trends. Moreover, measures of arterial structure and function have emerged as novel (i.e. non-traditional) independent risk factors of CVD and could add prognostic value to the assessment and treatment of CVD in this population.[16] We previously showed the feasibility of assessing non-traditional risk factors of CVD, including arterial stiffness and endothelial dysfunction through cross-sectional studies of adolescents[17] and adults with CP.[10] A longitudinal research study examining both traditional and non-traditional risk factors of CVD in individuals with CP is lacking. A better understanding and detection of changes and progression of CVD risk throughout adulthood could assist in developing interventions to prevent cardiovascular and cardiometabolic disease development in this population, as well as inform physicians who see adults with CP about the importance of CVD risk screening. The objectives of this study are to examine longitudinal changes in both

traditional and non-traditional CVD risk factors in individuals with CP, and to investigate the associations between age and gross motor function with longitudinal changes in these risk factors.

MATERIALS AND METHODS

This study is a component of the Stay-FIT program of research at *CanChild*, Centre for Childhood Disability Research. The purpose of the Stay-FIT program of research is to promote physical activity and encourage an active lifestyle for youth with CP. However, we know that youth with CP eventually grow into adults, thus it is equally important to promote physical activity and understand health-related variables in adults with CP as well. Adolescents and adults with CP (n=53), who previously participated in cross-sectional studies[10, 17] within the Stay-FIT program including cardiovascular health assessments, were invited to participate in this longitudinal study. All individuals with CP were eligible for the present study, regardless of intellectual ability and gross motor function. Participant or parent/caregiver written consent was obtained prior to study commencement. This study received proper research ethics board approval (Hamilton Integrated Research Ethics Board Project #12-110).

Participant characteristics

All participants were invited to a research laboratory within a University setting to undergo a battery of cardiovascular health assessments. All participants arrived to the laboratory having abstained from food, caffeine and

vigorous physical activity at least 12 h prior to data collection. The visit began with measures of height and body mass. Supine height was measured on a testing table to the nearest 0.5cm using a Gulick tape measure. For individuals with contractures, height was measured segmentally. All participants, regardless of Gross Motor Function Classification System (GMFCS) level, had their body mass (kg) measured on a digital wheelchair scale (Detecto Scales, FHD Series, Webb City, Missouri, USA). For participants using a manual or powered wheelchair, the mass of the wheelchair was subtracted from the combined mass of the participant and wheelchair to give an estimate of the individual's body mass to the nearest 0.1 kg. Together, body mass and height were used to calculate body mass index (BMI, kg/m^2). Waist circumference was measured to the nearest 0.5 cm at the end of a normal expiration 4 cm proximal to the umbilicus with the participant in the supine position. Supine systolic, diastolic, and mean arterial blood pressures were measured using an automated blood pressure device (Dinamap PRO 100 series). Four measures of blood pressure were recorded; the first measure was used for calibration purposes while the remaining three were averaged to give a composite blood pressure for each participant. These assessments were performed by a clinical researcher who has >5 years experience collecting these measures in individuals with CP and spinal cord injury (first author [PM]). For the purpose of this study, waist circumference and systolic blood pressure (SBP) were included as traditional CVD risk factors.

The Expanded and Revised version of the GMFCS[18] was used to determine level of gross motor function via self-report by participants.

Non-traditional cardiovascular disease risk factors

Non-traditional risk factors and details pertaining to their data collection and analysis techniques are below. All measures were performed with the participant in a supine position following 10 minutes of supine rest. A data acquisition system (Powerlab model ML795; ADInstruments, Colorado Springs, CO, USA) and software program (LabChart 8; ADInstruments, Colorado Springs, CO, USA) were used to acquire continuous heart rate and blood pressure during data collection. Heart rate was obtained using electrocardiography and blood pressure was obtained using finger photoplethysmography (Finometer MIDI, Finapres Medical Systems; Amsterdam, The Netherlands).

Carotid distensibility

Carotid distensibility was acquired as an indicator of local carotid artery stiffness. This technique required a combination of brightness mode ultrasound with a 12 MHz probe (Vivid Q; GE Medical Systems, Horten, Norway) and applanation tonometry (model SPT-3-1; Millar Instruments, Houston, TX, USA). Simultaneous images and tonometer signals were acquired for 10 consecutive heart cycles. Brightness mode ultrasound images were stored offline and subsequently analyzed using Artery Measurement System software (AMS; AMS Image and Data Analysis; Gothenburg Sweden). Distensibility was calculated as follows:

Distensibility ($mmHg^{-1}$) = $(\pi(dmax/2)^2 - \pi(dmin/2)^2) / PP * \pi(dmin/2)^2$

where d_{max} is the average maximum arterial lumen diameter, d_{min} is the average minimum arterial lumen diameter, and PP is the average pulse pressure of the carotid artery (difference between systolic and diastolic pressure) calculated from signals acquired using the applanation tonometer.

Carotid artery intima media thickness

The same brightness mode ultrasound images that were collected for carotid distensibility were used to calculate carotid artery intima media thickness (cIMT). cIMT was measured offline using AMS as the distance (mm) from the lumen-intima to the media-adventitia interface of the carotid artery wall at 100 sites along the arterial wall in the end diastolic frame for each of the 10 heart cycles and reported as an average for each participant.

Carotid-femoral pulse wave velocity

Carotid-femoral pulse wave velocity (cfPWV) is a regional measure of arterial stiffness. It is a measure of the velocity of the arterial pulse between the carotid and femoral arterial sites.[19] cfPWV was determined from 20 continuous heart cycles and arterial pressure waveforms at the areas of greatest pulsation from the common carotid and superficial femoral arteries, and was calculated as follows:

cfPWV (m/s) = distance (m) / pulse transit time (s)

Distance was measured via the subtraction method as the distance from the sternal notch to the femoral site minus the distance from the sternal notch to the carotid site.

Brachial artery flow-mediated dilation

Noninvasive assessment of endothelial function can be measured using the flow mediated dilation (FMD) technique performed on the brachial artery. Ultrasound was used to acquire images of the brachial artery approximately 10 cm proximal to the antecubital fossa. A baseline image of the brachial artery was acquired for 30-sec prior to instantaneous inflation of a blood pressure cuff to 200mmHg on the forearm of the participant. After five minutes of cuff inflation, the pressure in the cuff was released and images of the brachial artery were recorded for three-minutes. Reactive hyperemia, increased blood flow resulting in a change in brachial artery diameter (i.e. peak diameter), occurs during the post occlusion phase. The FMD technique functions on the premise that increases in shear rate (a surrogate for shear stress in the absence of blood viscosity) cause vasodilation through an upregulation and/or production of nitric oxide, which causes a relaxation of the smooth muscle layer of the arterial wall, and a subsequent increase in arterial diameter. Absolute and relative FMD values are calculated and reported using the following equations:

Absolute FMD (mm) = (peak diameter(mm) – baseline diameter(mm))

Relative FMD (%) = (absolute FMD / baseline diameter)*100

Statistical analysis

Statistical analyses were performed using STATA (version 13.1) statistical software package. Descriptive summary statistics for participants were calculated as means and standard deviations for continuous variables and as percentages for categorical data (i.e. sex and body mass index (BMI) categories). Assumptions pertaining to repeated measures analysis of variance and multiple linear regression analysis were tested.

To examine longitudinal changes in traditional and non-traditional risk factors of CVD in individuals with CP, repeated measures analysis of variance was performed. Dependent variables of interest included waist circumference, SBP, cIMT, carotid artery distensibility, cfPWV, and both absolute and relative FMD, while time point (baseline and follow-up) was the independent variable. Difference in age in months between baseline and follow-up assessments was entered as a covariate to control for the differences in time between assessments for participants.

To investigate the relationships between age and gross motor function with longitudinal changes in traditional and non-traditional risk factors of CVD, multiple linear regression was performed. Analysis began with graph matrices and separate scatter-plots of the independent variables with the dependent variable to inspect the data for non-linear relationships. Dependent variables consisted of waist circumference, SBP, cIMT, carotid artery distensibility, cfPWV, absolute and relative FMD. Variation inflation factor analyses were performed to assess for collinearity. The regression models included both age at baseline (as a

continuous variable) and GMFCS (dichotomous indicator variable; ambulatory (GMFCS I-II) vs. non-ambulatory (GMFCS III-V) as independent variables and were subsequently tested for heteroskedasticity via the Breusch-Pagan/Cook-Weisberg test. These independent variables were chosen as previous research in cardiovascular and cardiometabolic health in individuals with CP found age to be associated with cIMT, cfPWV[10] and disease-free survival,[15] while GMFCS or disability status were associated with resting heart rate[10] and chronic disease prevalence.[14] A leverage-versus residual squared plot was generated to determine data points of high influence (i.e. outliers) followed by calculating Cook's Distance to confirm data points of high influence, with those having a score ≥ .1 removed. Statistical significance was set at an alpha criterion (0.05).

RESULTS

Descriptive characteristics

Descriptive characteristics of the study participants are presented in Table 1. Twenty-eight of the 53 eligible participants agreed to participate in the follow-up assessments. It was conceivable that individuals who participated in the follow-up component of this study might be a selection of more healthy participants in comparison to those who did not participate; however, two sample t-tests performed for age, and traditional and non-traditional risk factors of CVD at baseline between participants who participated in the follow-up and those who did not revealed no significant between sample differences for all variables (i.e.

p>0.05). GMFCS distribution was as follows: I = 6; II = 7; III = 5; IV = 7; V = 3. The average time interval between baseline and follow-up assessments was 4.0 ± 1.2 years. Eighteen of the 28 participants had an increase in waist circumference relative to their baseline assessment. Fourteen participants had an increase in SBP, while the other 14 participants experienced a decrease in SBP relative to baseline assessment. cfPWV was missing for four participants from baseline, and was not obtained for one participant at follow-up; therefore, cfPWV was reported for 23 participants. cfPWV increased in 16 of the 23 participants. Interestingly, three participants at follow-up had cfPWV values that were above the clinical value (i.e. 10m/s) deemed at risk for future cardiovascular events, whereas only one participant was at risk at baseline. In regard to brachial artery FMD, 23 of 27 participants experienced a decrease in both absolute and relative FMD at follow-up. One participant did not have the assessment performed at follow-up due to an inability to transfer from a seated to supine position. Twenty-five of 27 individuals experienced an increase in cIMT. One participant did not have a cIMT assessment at baseline. Carotid artery distensibility decreased in 16 of 27 participants compared to baseline. One individual did not have a distensibility measurement at baseline. With age in months included as a covariate, repeated measures analysis of variance revealed statistically significant differences in absolute FMD (0.31 ± 0.13 vs. 0.22 ± 0.08 mm, p=0.045 95%CI .040, .151), relative FMD (9.9± 4.7 vs. 7.5 ± 2.6%, p=0.049, 95%CI .464, 4.42), and cIMT (0.52 ± 0.17 vs. 0.67 ± 0.33 mm, p=0.041, 95%CI -.242, -.074)

between baseline and follow-up assessments. Absolute and relative FMD decreased while cIMT increased from baseline to follow-up.

As a result of the different time intervals between the two sets of assessments between participants, changes in traditional and non-traditional risk factors were divided by time for each participant and reported as rates of change for the regression analyses. Multiple linear regression analysis for rate of change in cIMT revealed an R-squared of 0.294, p=0.015 with age at baseline being a significant predictor of change in cIMT. From Cooks Distance calculation, participant 19 (age = 58; GMFCS III; change in cIMT = 1.07mm) was identified as an outlier with a residual of .14. The regression analysis was performed without this data point, resulting in an R-squared of 0.261, p=0.031 and again with age at baseline being a significant predictor of change in cIMT (Table 2). Age at baseline and/or GMFCS grouping were not significant predictors of rates of change for waist circumference, SBP, carotid artery distensibility, cfPWV, and both absolute and relative FMD (Table 2).

DISCUSSION

The objective of this study was to examine the longitudinal changes in traditional and non-traditional risk factors of CVD in a cohort of individuals with CP to better understand the development of CVD in this population. An important finding from this study was that while both traditional and non-traditional risk factors for CVD increased in at least 50% of participants with CP relative to

baseline over approximately a 4-year time period, there were some non-traditional indices that seemed to have higher sensitivity for detecting changes over time. Specifically, we discovered that the traditional risk factors SBP and waist circumference increased in 50% and 64% of participants respectively, while non-traditional risk factors cfPWV and cIMT increased in 70% and 93% of participants, and brachial artery FMD and carotid artery distensibility decreased in 85% and 59% of participants, respectively. However, after controlling for the varying time intervals between baseline and follow-up assessments among participants, significant changes in these variables were only apparent for the non-traditional risk factors absolute FMD, relative FMD, and cIMT. Importantly, this tells us that non-traditional measures may detect changes in CVD risk in individuals with CP when not revealed by tracking traditional risk factors.

Concerning traditional risk factors for CVD, obesity and hypertension have shown a strong association with the non-traditional risk factors arterial stiffness and endothelial dysfunction. In fact, some non-traditional risk factors are considered negative prognostic factors of hypertension.[20, 21] The increases in waist circumference and significant changes in FMD and cIMT within this cohort of CP underscore the importance of monitoring and managing CVD risk in this population to prevent the development of hypertension.

As this was the first longitudinal cohort study to investigate changes in non-traditional CVD risk variables in individuals with CP, it is important to understand these findings in the context of the general population. A longitudinal

study completed in older adults (mean age 60 ± 9 years) assessing relationships among different tonometry measures, including cfPWV, found that cfPWV increased from 9.6 to 10.4 m/s in a four to six year time period.[22] Comparably, we found a modest increase in cfPWV from 6.2 to 6.9 m/s in a similar time period (i.e. four years) but in a much younger cohort of individuals with CP (mean age 31.2 ± 15.0 at baseline). These findings provide initial support for the argument that individuals with CP experience accelerated ageing for disease progression, specifically CVD, in comparison to the general population. Additionally, there is well established literature demonstrating that advancing age is the strongest predictor of increases in cfPWV,[20, 23] and we previously found age to be significantly associated with cfPWV in a cross-sectional analysis of 42 adults with CP.[10] However, our current multiple regression analysis did not reveal age to be associated with rate of change in cfPWV in the present study, which might be explained by a combination of the small magnitude of observed changes in cfPWV and the small sample size. Similarly, cIMT increases with age due to changes to the structural components of the arterial wall, particularly thickening of both the intima and media layers; in the general population, cIMT increases by approximately 3-fold between the ages of 20 and 90 years[24]. Carotid plaque is defined as the presence of a cIMT greater than 1.5mm which protrudes into the lumen area of the carotid artery.[25] A consensus statement from the American Society of Echocardiography proposed that the presence of carotid plaque or a cIMT greater than or equal to the 75th percentile for an individual's age, sex, and

ethnicity are indicative of increased CVD risk.[26] Moreover, the 1st Screening for Heart Attack Prevention and Education (SHAPE) Program identified an individual to be at high risk for subclinical atherosclerosis when a cIMT ≥ 1mm is present.[27] Considering the information in the SHAPE guideline, two individuals in the present study were at high risk for subclinical atherosclerosis from cIMT alone. A study in a cohort of 70-year old Swedish adults found that cIMT significantly increased from 0.88 to 0.95 mm over a 5-year period.[28] In the present study, we found a larger relative increase in cIMT compared to the Swedish cohort. It is worth mentioning, however, that one participant in the current study had an increase in cIMT that was considered an outlier and was removed from multiple linear regression analysis. Still, age remained a strong significant predictor of cIMT change in our study, which is consistent with what is known in the general population and further supports our findings from cross-sectional work.[10]

Few studies have examined longitudinal changes in brachial artery FMD from adolescence to adulthood. A study in children and adolescents with type I diabetes mellitus observed a significant decrease in FMD in approximately a 3-year follow-up period;[29] whereas no significant change in FMD was observed after a 5-year follow-up study in older adults.[28] The latter study observed a significant inverse relationship between change in FMD and change in LDL-cholesterol[28] whereas the former study observed an inverse relationship between glycemic control and FMD.[29] It is plausible that metabolic markers

could be associated with change in FMD in individuals with CP; however, we did not measure these in the current study. At the very least, we know that age and gross motor function were not significantly associated with change in FMD in the present cohort. Given the recent work by Peterson *et al*.[14] and Ryan *et al*.[30] pointing towards adolescents and adults with CP having elevated risk of cardiometabolic disease, it is important for future work to include cardiometabolic markers to advance our understanding of the regulation of endothelial function in this population. Indeed, we did observe a [non-significant] increase in waist circumference, however our modest sample size limited our ability to include waist circumference as an independent predictor in linear regression analysis. Finally, we observed a significant decrease (1.1E-3 $mmHg^{-1}$) in carotid artery distensibility between baseline and follow-up assessment in our cohort. In a large cohort of men and women free of CVD (45-84 years old), carotid artery distensibility decreased by 0.41E-3 $mmHg^{-1}$ over a mean period of 9.4 years, and SBP was associated with accelerated stiffening.[31] We observed a larger decrease in distensibility that was not associated with age or gross motor function.

Strengths/limitations

There are important limitations to address in this cohort study. Firstly, we did not include a direct comparative group as this was not the primary objective of the study. Instead, we referenced studies that have investigated changes in traditional and non-traditional risk factors of CVD in the general population to

characterize the relevance of our findings. However, a matched cohort group of typically developing adolescents and adults undergoing the same assessments of CVD risk using the same techniques would provide subsequent support for altered risk patterns in this population. Due to our small sample size, we were unable to determine whether other factors (e.g. waist circumference) may have been associated with the observed changes in CVD risk variables. Finally, we adopted BMI cut-points from the adult population in this study despite four participants at baseline and one participant at follow-up being under 18 years of age. Despite these limitations, this study has key strengths. Most importantly, this is the first study to provide longitudinal evaluation of traditional and non-traditional CVD risk factors in individuals with CP. The findings will be used to inform future studies to further understand cardiovascular health in individuals with CP and to improve the health of individuals ageing with child-onset disabilities. This is particularly important as persons with CP represent a population that is living longer than ever before, yet changes to their clinical health remain to be determined.

CONCLUSIONS

Changes in CVD risk factors, both traditional and non-traditional, were observed in the majority of individuals with CP at a relatively young age over a relatively short period of time (i.e. four years). Age was a significant independent predictor of cIMT change in this population. These findings add to our knowledge on the effects of aging on individuals with CP across the lifespan and will inform

future large-scale studies on multimorbidity in this population. Key implications from this study include evidence for the importance of clinical screening for CVD risk, particularly measuring cIMT and brachial artery FMD, to assess changes over time in individuals with CP as young as early adulthood.

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PM conceived and designed the research study, recruited the participants, acquired the data, analyzed and interpreted the data, drafted the manuscript, and critically revised the manuscript.

MM conceived and designed the research study, analyzed and interpreted the data, and critically revised the manuscript.

JC acquired the data, analyzed and interpreted the data, and critically revised the manuscript.

ED acquired the data, analyzed and interpreted the data, and critically revised the manuscript.

JWG conceived and designed the research study, recruited the participants, analyzed and interpreted the data, and critically revised the manuscript.

The authors have stated that they have no conflicts of interest.

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Table 1. Descriptive characteristics and measures of CVD risk factors in individuals with CP at baseline and follow-up.

	Baseline	Follow-up	Δ ± SD
Descriptive characteristics			
Age (years), mean ± SD	31.2 ± 15.0	35.1 ± 14.4	4.0 ± 1.2
Age range (years), min - max	10 – 75	16 - 78	
Male, %	46.4%	46.4%	
Traditional CVD risk factors			
BMI, kg/m^2	24.8 ± 8.2	26.1 ± 8.1	1.3 ± 4.2
Underweight (BMI <18.5)	28.6%	17.9%	
Normal weight (BMI 18.5-	35.7%	32.1%	
Overweight (BMI 25-29.9)	14.3%	21.4%	
Obese (BMI ≥30)	21.4%	28.6%	
Waist circumference, cm	81.0 ± 16.9	84.0 ± 19.7	3.0 ± 7.4
SBP, mmHg	120.3 ± 14.9	118.9 ± 16.6	-1.4 ± 12.6
DBP, mmHg	71.0 ± 8.7	69.5 ± 8.2	-1.5 ± 8.2
MAP, mmHg	90.1 ± 9.5	88.2 ± 9.9	-1.8 ± 8.1
Non-traditional CVD risk factors			
cfPWV, m/s	6.2 ± 1.4	6.9 ± 1.9	0.4 ± 1.2
Absolute FMD, mm	0.31 ± 0.13	0.22 ± 0.08	-0.1 ± 0.1
Relative FMD, %	9.7 ± 4.7	7.5 ± 2.6	-2.4 ± 5.1
cIMT, mm	0.52 ± 0.17	0.67 ± 0.33	0.2 ± 0.2
Distensibility, $mmHg^{-1}$	4.4E-3±2.2E-3	3.4E-3±1.7E-3	-8.6E-4±2.3 E-3

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; cfPWV = carotid femoral pulse wave velocity; FMD = flow mediated dilation; cIMT = carotid artery intima media thickness

Table 2. Multiple linear regression analyses

cIMT	Coef.	p value	95% Conf. Interval	
GMFCS grouping	-.009	0.507	-.035	.018
Age (baseline)	.001	0.010	3.4E-4	.002

N = 27

cIMT = Carotid artery intima media thickness; GMFCS = Gross Motor Function Classification System

Waist circumference	Coef.	p value	95% Conf. Interval	
GMFCS grouping	1.01	0.231	-.690	2.71
Age (baseline)	.015	0.659	-.054	.084

N = 28

GMFCS = Gross Motor Function Classification System

SBP	Coef.	p value	95% Conf. Interval	
GMFCS grouping	.292	0.825	-2.41	2.99
Age (baseline)	.127	0.066	-.011	.220

N = 28

GMFCS = Gross Motor Function Classification System; SBP = Systolic Blood Pressure

Distensibility	Coef.	p value	95% Conf. Interval	
GMFCS grouping	2.5E-4	0.169	-1.1E-4	6.2E-4
Age (baseline)	1.3E-5	0.086	-1.9E-6	2.7E-5

N = 27

GMFCS = Gross Motor Function Classification System

cfPWV	Coef.	p value	95% Conf. Interval	
GMFCS grouping	-.053	0.724	-.360	.255
Age (baseline)	.009	0.119	-.003	.022

N = 23

cfPWV = carotid femoral pulse wave velocity; GMFCS = Gross Motor Function Classification System

Absolute FMD	Coef.	p value	95% Conf. Interval	
GMFCS grouping	-.011	0.523	-.047	.025
Age (baseline)	1.6E-4	0.784	-.001	.001

N = 27

FMD = Flow mediated dilation; GMFCS = Gross Motor Function Classification System

Relative FMD	Coef.	p value	95% Conf. Interval	
GMFCS grouping	-.461	0.486	-1.80	.882
Age (baseline)	.006	0.796	-.039	.050

N = 27

FMD = Flow mediated dilation; GMFCS = Gross Motor Function Classification System

CHAPTER 5

The formula for health and well-being in individuals with cerebral palsy: cross-sectional data on physical activity, sleep, and nutrition

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ABSTRACT

AIM(S): To determine physical activity, sleep, and nutrition patterns in individuals with cerebral palsy (CP) and to investigate the effects of Gross Motor Function Classification System (GMFCS) and age on these health components.

METHOD: A cross-sectional study was conducted in an outpatient setting. Participants included adolescents and adults with CP (*n*=28; GMFCS level I-V; mean age 35.1y, standard deviation [SD] 14.4y). An Exercise Questionnaire or Leisure Time Physical Activity Questionnaire was used to measure physical activity in adolescents and adults, respectively. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). An adapted version of the PrimeScreen questionnaire was used to assess nutrition.

RESULTS: The average total physical activity was 29.2 (30.0) mins/day. Twenty-one participants had poor sleep quality (PSQI score >5). Seventy-one percent reported “fair” eating behaviours; none reported “excellent” eating behaviours. Neither GMFCS nor age were associated with PSQI score, PrimeScreen score, or total physical activity. A negative correlation existed between sleep quantity (hours/night) and PSQI score ($r=-0.66$, $p<0.01$).

INTERPRETATION: The triad of health, consisting of physical activity, sleep, and nutrition, should be assessed and managed in all individuals with CP, regardless of disability severity, across the lifespan.

WHAT THIS PAPER ADDS

- Seventy-five percent of individuals with CP had poor sleep quality and over 50% get less than 7 hours of sleep per night
- Almost 80% of participants engaged in less than the recommended 150 minutes of moderate-to-vigorous physical activity per week
- No participants reported *excellent* eating behaviours and are at risk for poor dietary habits
- Severity of CP was not associated with physical activity, sleep, or nutrition
- Questionnaires assessing the triad of health are easy to implement in practice

INTRODUCTION

Cerebral palsy (CP) is the most common pediatric physical disability, with an estimated prevalence ranging from 2.6-3.1 cases per 1000 live births.[1; 2] Although the majority of individuals with CP can expect similar life expectancies as the general population, except for those with greater severity and complexity,[3] the vast majority of research in this population is focused on clinical symptom management in childhood and adolescence. Preventive medicine has become an emerging area given that individuals with CP experience significant progressive functional declines, fatigue, diminished musculoskeletal mass and quality, excess adiposity, chronic physical inactivity, and increased risk for cardiovascular disease; all of which increases with age.[4-7] Collectively, these factors place individuals with CP at a greater risk for secondary chronic conditions that further

contribute to disability, diminished quality of life, loss of independence and diminished life expectancy.[8]

There is an increasing interest in chronic disease surveillance and promotion of behaviour modification interventions for people with CP, including physical activity, sleep, and nutrition.[9] However, there have been no systematic observational studies that have examined all three of these factors comprehensively in a cohort of individuals with CP. Physical activity has been studied most extensively, where individuals with CP have been reported to be less physically active than their typically developing peers,[10; 11] and ambulatory individuals with CP engage in more physical activity and decreased sedentary time compared to those non-ambulatory.[12] Moreover, among ambulatory adults with CP, being younger in age was associated with a higher odds of being physically active.[13]

Sleep issues are also a common occurrence among children with CP,[14] which may be a product of intrinsic and extrinsic factors such as muscle spasms or other forms of musculoskeletal pain and use of devices (e.g. orthosis, night worn splints, postural equipment), respectively.[14] Increasing awareness of the presence and the broad range of causes and consequences of inadequate sleep in people with CP across the lifespan is critical.

Moreover, few studies have examined nutrition status or dietary habits in individuals with CP. One early study found that inactivity and malnutrition were relevant causes of abnormal body composition in 22 children with CP.[15] More

recent research in 103 adolescents and young adults with CP without severe learning disabilities found that 27% indicated problems with nutrition.[16] To date, no studies have examined nutrition in a broader age range of adults with CP.

Managing physical activity, sleep, and nutrition, in a comprehensive fashion underscores the opportunity to encourage and promote the health and well-being of individuals with CP across the lifespan.[9] To guide clinicians, an important first step towards this goal is to observe and understand these behaviours in individuals with CP and determine if individuals with different functional levels experience different problems. Therefore, the objectives of this study were to describe physical activity behaviours, sleep quantity and quality, and nutrition patterns in a cohort of individuals with CP and to investigate the influence of disability severity and age on these components of health.

METHODS

This study is part of a larger on-going research investigation to examine cardiovascular health and physical activity levels in adolescents and adults (age range 16-78 years) with CP. More details pertaining to this program of research can be found at www.canchild.ca/STAY-FIT. A total of 53 individuals with CP who participated in previous studies[17; 18] from the Stay-FIT program of research were contacted to participate in this study. All individuals with CP were eligible for inclusion provided they were able to respond to questionnaires about physical activity, sleep and nutrition with some degree of independence. The study design

was explained to participants and their caregivers prior to obtaining written consent. Participants were asked to complete the questionnaires on their own but assistance from a caregiver was allowed if needed. Approval from the Hamilton Integrated Research Ethics Board was obtained for the study.

Demographic variables

All subjects were invited to the Vascular Dynamics Laboratory at McMaster University to perform assessments of cardiovascular health as a component of the on-going research program. During this visit, supine body height, body mass (digital wheelchair scale; Detecto Scales, FHD Series, Webb City, Missouri, USA) and waist circumference were measured by the first author [PM]. Body mass index (BMI) was calculated by dividing the subject's weight (kg) by their height squared (m^2) (kg/m^2). Waist circumference (cm) was measured supinely at the end of a normal expiration and at a site 4 cm proximal to the umbilicus.[5] Gross Motor Function Classification System (GMFCS) level[19] was collected by self-report, and type of motor impairment (spastic, dyskinetic, or mixed) and topographical distribution (unilateral or bilateral) were classified according to the Surveillance of Cerebral Palsy in Europe Guidelines.[20]

Physical activity

Physical activity was quantified via selected questionnaires following the protocols within the ongoing Stay-FIT program for adolescents and adults with CP, respectively.[17; 18] For adult participants, physical activity was measured using the Leisure Time Physical Activity Questionnaire for persons with Spinal Cord

Injury (LTPAQ-SCI).[21] Leisure Time Physical Activity (LTPA) is defined as intentional activities that people choose to do during their *free* time, such as exercising, playing sports, gardening, etc., whereas necessary physical activities such as physiotherapy, grocery shopping, and/or wheeling for transportation were not considered LTPA.[21] Criterion validity and test-retest reliability have been reported for the LTPAQ-SCI in individuals with SCI.[21] Mild, moderate and heavy intensity physical activity measured by the LTPAQ-SCI were associated with those captured using the Physical Activity Recall Assessment for people with SCI (PARA-SCI).[22] While the PARA-SCI has been validated for use in adults with CP,[12] the LTPAQ-SCI was chosen for the present study due to its lower time requirement (<5 minutes vs. 20 to 30 minutes).[21] Subjects were asked to report the number of days and the number of minutes each day that they engaged in mild-, moderate-, and/or heavy-intensity LTPA over the previous seven days. Subjects were asked to provide information on both aerobic and strength training activities. The primary outcome of this questionnaire was the total number of minutes of LTPA at each intensity performed over the previous seven days. These totals were combined and divided by 7 to give the average amount of physical activity performed per day (i.e. mins/day). Also calculated was the average number of minutes per day of moderate-to-vigorous physical activity (MVPA).

For adolescent participants, physical activity was measured using the Exercise Questionnaire adopted from Brunton and Bartlett.[23] In this

questionnaire, exercise was defined as activities that involved stretching, strengthening, or physical exertion.[23] The Exercise Questionnaire was developed in part from activities within the Previous Day Physical Activity Record, with the addition of activities that were appropriate for youth with CP from consultation with an expert group.[23] These additional items were confirmed by a pilot study of youth with CP, which supported the content validity of the Exercise Questionnaire.[23] The questionnaire was designed to be completed by the adolescent with or without help from parents.[23] This questionnaire measures frequency, duration, and intensity of physical activity performed in the previous week. Total weekly duration (minutes) of physical activity at all intensities (light, medium, or hard) was calculated and divided by 7 to give an average amount (minutes) of physical activity performed per day. Test-retest reliability of the Exercise Questionnaire revealed no significant difference between two time points.[23]

Sleep

Sleep was measured using the Pittsburgh Sleep Quality Index (PSQI).[24] The PSQI consists of 19 self-rated questions in seven component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction). Each component is scored from 0-3, and the sum provides a global PSQI score (maximum score 21) where higher scores indicate worse sleep quality. Scores >5 indicate poor sleep quality.[24] The PSQI takes 5-10 minutes to complete, and

approximately 5 minutes to score. The PSQI has a high degree of internal consistency (Cronbach's α 0.83),[24] and good test-retest reliability (ICC 0.85).[24] Regarding validity, the PSQI identifies between good and poor sleepers, and compares favorably with the criterion standard of sleep disorder diagnosis through polysomnography (T tests showed no difference for sleep latency between the two measures).[24]

Nutrition

An adapted version of the PrimeScreen questionnaire was used to measure eating behaviours and food choices over the previous 6 months.[25] The questionnaire consists of 21 questions about the average frequency of consumption of specified foods and food groups during this time period. The questionnaire highlights intake of fruits, vegetables, whole and low-fat dairy products, whole grains, fish, poultry and red meat as well as other foods that are major contributors to the intake of fats.[25] The questionnaire includes examples of the most frequently consumed foods that pertain to a certain food group. For example, one specific question asks, "*How often do you eat… dark green leafy vegetables (spinach, romaine lettuce, mesclun mix, kale, turnip greens, bok choy, swiss chard)*". Frequency of consumption is categorized as: less than once per week, once per week, 2-4 times per week, nearly daily or daily, or twice or more per day with scores ranging from 0 to 4 for 11 questions, 0 to -4 for 9 questions, and -2 to 2 for 1 question. Scores from the 21 questions are totaled and eating behaviours are classified based on the following scores: 35 or more – Excellent;

16-34 – Good; 1-15 – Fair; and 0 or less – Poor.[25] The PrimeScreen has been shown to have adequate reproducibility when compared to the semi-quantitative food frequency questionnaire (131 items), with an estimated correlation coefficient of 0.59.[25] Participants found that the PrimeScreen was easy to understand and complete, with 87% of participants requiring less than 10 minutes to complete the questionnaire.[25]

Statistical analysis

Statistical analyses were performed using STATA (version 13) statistical software package. Descriptive statistics were calculated and presented as means, standard deviations, minimum, lower quartiles, medians, upper quartiles, and maximum values for continuous variables, and as frequencies for dichotomous and categorical variables. All continuous variables were tested for normality using Shapiro-Wilk descriptive tests. Linear regression was performed to investigate the relationship between GMFCS level (dichotomized into community ambulatory (GMFCS I-II) and community non-ambulatory (GMFCS III-V)) (independent predictor) and total physical activity (mins/day), PSQI score, and PrimeScreen score, each as a dependent variable in separate models. Linear regression was also performed to investigate the association between age as a continuous variable (independent predictor) and total physical activity (mins/day), PSQI score, and PrimeScreen score, again as dependent variables in separate models. Other correlations examined included BMI and PrimeScreen score, waist circumference and PrimeScreen score, and sleep quantity (hours/night) and

PSQI score. A minimum criterion α level of 0.05 was used to determine statistical significance.

RESULTS

Subjects

Physical activity, PSQI, and PrimeScreen questionnaires were completed by 28 individuals with CP (mean age 35.1y [SD 14.4y]; min-max 16-78) from a database of 53 eligible subjects.[17; 18] Two sample t-tests for age, BMI, and waist circumference between the 28 participants that engaged in the present study and the 25 individuals that did not revealed no significant between sample differences (i.e. $p>0.05$) (data not shown). Table I displays the subject characteristics. It was not possible to obtain waist circumference measurements at the site 4cm proximal to the umbilicus in four subjects, which was impeded by the presence of an intrathecal baclofen pump or enteral feeding tube. For three of these subjects, waist circumference was instead measured at the border of the right anterior superior iliac crest. One subject was unable to have their waist circumference measured due to the inability to transfer from wheelchair to testing bed.

Age, BMI, total physical activity, MVPA, and sleep (hours/night) were not normally distributed (Shapiro-Wilk test $p <0.05$). The variables age, BMI and sleep were log transformed to assume normality, with these transformed variables used in subsequent statistical analyses. Visual interpretation of the

variables total physical activity and MVPA appeared to be normally distributed and therefore were included in statistical analyses as original values.

Physical activity

The mean (SD) total physical activity for subjects was 29.2 (30.0) mins/day and 13.5 (18.8) mins/day for MVPA. Overall, mean total physical activity (mins/day) values by GMFCS level are displayed in Figure 1. Twenty-two (78.6%) subjects engaged in less than 150 minutes of MVPA per week.

Sleep

Using the PSQI questionnaire, participants reported an average score of 7.6 (3.7). Twenty-one (75%) subjects had PSQI scores greater than 5, indicating poor sleep quality, and 16 (57%) obtained less than 7 hours of sleep per night. Mean PSQI scores and hours of sleep per night by GMFCS level are presented in Figure 2 (A and B). Ten (36%) subjects indicated that they were using medication to assist with sleeping.

Nutrition

Average scores for nutrition using an adapted version of the PrimeScreen questionnaire were 8.0 (6.8), which is in the fair range (score of 1-15). Only 4 (14%) subjects had “good” eating behaviours (score >15), while 4 (14%) subjects had “poor” eating behaviours (score of 0 or less). Mean PrimeScreen scores by GMFCS level are presented in Figure 3.

Predictors of sleep, nutrition and physical activity

GMFCS was not an independent predictor of PSQI score (β=0.35, p=0.81, 95% CI -2.55, 3.25), PrimeScreen score (β=-0.93, p=0.72, 95% CI -6.28, 4.42), or total physical activity (mins/day) (β=-20.5, p=0.07, 95% CI -42.9, 1.79).
Similarly, age was not an independent predictor of PSQI score (β=1.74, p=0.35, 95% CI -.065, .137), PrimeScreen score (β=-1.63, p=0.64, 95% CI -.242, .132), or total physical activity (mins/day) (β=-17.5, p=0.25, 95% CI -1.17, .485). We did not see any correlation between BMI and PrimeScreen score (r=0.15, p=0.44) or waist circumference and PrimeScreen score (r=0.03, p=0.89). A negative correlation existed between sleep quantity (hours) and PSQI score (r=-0.66, p<0.01).

DISCUSSION

Results from this study suggest that physical activity behaviours, sleep quantity and quality, and nutrition require attention from clinicians across the lifespan. Importantly, severity (GMFCS I-II versus III-V) and age were not significantly associated with any component of health, proposing that these three health variables should be managed in all people with CP, regardless of GMFCS level or age.

Clinicians working with individuals with CP often presume that patients with higher functioning experience less problems with their health than those with lower functioning. Indeed, there is empirical evidence to support this presumption in regard to physical activity and sedentary behaviour, as we have previously

shown that adults with CP who are higher functioning engage in more habitual physical activity than those with lower functioning.[12] Regardless, overall PA is lower in adolescents,[26] and adults[11] with CP compared to the general population. This is reflected in the present study, where almost 80% of subjects reported engaging in less than 150 minutes of MVPA per week-, the current recommendation by the World Health Organization for adults aged 18-64 years.[27] Importantly, individuals classified as GMFCS levels IV and V reported some involvement in light intensity activities, which is a great starting point that may lead to health gains.[28] However, individuals with GMFCS level V engaged in zero minutes of MVPA. Although some literature exists regarding a negative association between age and physical activity in adults with CP,[13] age was not associated with physical activity in this study, and may likely be attributable to our small sample size. Acknowledging the challenges and difficulties for those with excessive mobility limitations to engage in MVPA, proper nutrition and sleep management might also be critical.[9] Results from the present study illustrate, at the very least, assessment techniques for clinicians to capture and discuss with patients with CP the equally important variables of sleep and nutrition.

It is well-known that sleep is an essential biological function with important roles in recovery, conservation of energy, and survival.[29] Insufficient sleep or patterns of sleep that interfere with physical and mental well-being can result from deprivation of sleep or decreased sleep quality. In the present study, 75% of subjects had poor sleep quality, indicated by a PSQI score greater than 5.

Moreover, greater than half of the subjects were getting less than the recommended 7 hours of sleep per night for adults.[29] We found a significant negative association between sleep quantity (hours/night) and PSQI score, which suggests that low sleep quantity is related to increased PSQI score. A simple solution may be to increase sleep quantity, but this approach minimizes the complexity of factors that potentially influence the hours of sleep per night for individuals with CP. For example, someone with spastic CP might awaken in the night frequently due to muscle spasms, which in turn would affect sleep duration. There is some evidence in children and adults with CP that injections with botulinum toxin serotype A or oral baclofen, respectively, reduces spasticity and improves sleep.[30; 31] However, it is important for clinicians to be mindful of the use of spasticity medications to assist with sleep, given that a component of the global PSQI score is use of sleeping medications. A person with CP might associate medical treatment of spasticity with assisting with sleep, and in turn, score higher in that component of the PSQI. Thus, clinicians should interpret global PSQI scores cautiously, particularly among individuals with CP who receive prescription medication for spasticity. Of the 10 subjects in the present study who used medication to assist with sleeping, 8 had poor sleep quality with a PSQI score greater than 5.

There were no individuals with CP who reported excellent nutritional intake, again highlighting the important opportunities to improve in this area. We were able to use the feasible PrimeScreen questionnaire in adolescents and

adults with CP in the present study to identify persons with suboptimal diets. The questionnaire has been shown to be easily understood and can be completed by most participants in less than 10 minutes,[25] and can be readily applied in clinical settings. Although we did not see significant associations between BMI or waist circumference and PrimeScreen scores, future research may include the use of the PrimeScreen in combination with the Eating and Drinking Ability Classification System (EDACS).[32] The EDACS is a system which describes functional eating and drinking ability in people with CP from 3 years of age and older.[32] It affords an opportunity to be used in population studies to assess its association with nutrition and other health concerns, and investigate the stability, progression, or regression of eating and drinking ability for individuals with CP.[32]

Taken together, the triad of physical activity, sleep, and nutrition assessed in a comprehensive manner can allow clinicians to both prevent risk and promote health and well-being in adolescents and adults with CP. Although GMFCS was not a significant predictor of any one of the three components, recommendations can be made for clinical care. Individuals who were GMFCS level I reported, on average, the greatest amount of physical activity, the lowest PSQI score, but the second lowest PrimeScreen score. These initial findings tell us, albeit in a small sample of subjects with CP, those individuals with GMFCS level I should consider dietary counselling to improve their overall health. On the other end of the spectrum, individuals with GMFCS level V had the highest PrimeScreen score, the second lowest PSQI score, but the lowest total physical activity levels. This

suggests that while physical activity should be promoted in this group, given the challenges to engage in physical activity for individuals with severe mobility limitations,[28] clinicians might also strongly encourage continued good sleep and nutrition.

Future research investigating these health components in persons with CP should do so in a prospective method, with a larger sample across multiple sites which will allow for better generalizability of the findings.

Limitations

We present results for the triad of health in our study across all five levels of the GMFCS. Our findings should be interpreted with caution as a result of the small number of participants. The use of subjective questionnaires to assess the components of health could have resulted in social desirable response bias.[33] Additionally, subjects volunteered to participate in this study and therefore could be more health conscious than a random sample from the community. Another limitation in this study was the use of two questionnaires to assess physical activity. A notable difference between these questionnaires is that the Exercise Questionnaire asks participants whether or not they participated in specific exercises and their intensities in the last seven days. However, there is an opportunity for participants to mention other exercises that they might have participated in that were not included in the questionnaire.[23] The LTPAQ-SCI asks participants about the frequency and duration of light, moderate, and heavy intensity activity performed in the previous seven days.[21] Despite this difference,

both afford an opportunity to quantify total and moderate to heavy (i.e. vigorous) physical activity, allowing for a meaningful aggregation of responses from the two questionnaires.

Conclusion

The triad of health, consisting of physical activity, sleep, and nutrition, has been observed in a group of adolescents and adults with CP inclusive of all five levels of the GMFCS. Severity or age was not predictive of any component of health, emphasizing the importance of assessing the triad of health in all individuals with CP, regardless of GMFCS, across the lifespan.

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Table I. Subject characteristics

		Total (*n*=28)
Sex, *n* (%)		
	Males	13 (46)
	Females	15 (54)
Type, *n* (%)		
	Spastic	23 (82)
	Dyskinetic	2 (7)
	Mixed	3 (11)
Distribution, *n* (%)		
	Unilateral	13 (46)
	Bilateral	15 (54)
GMFCS, *n* (%)		
	I	7 (25)
	II	6 (21)
	III	5 (18)
	IV	7 (25)
	V	3 (11)

	Mean	SD	Min.	Lower Q	Median	Upper Q	Max.
Age, y$^{\Psi}$	35.1	14.4	16.0	24.5	33.0	40.5	78.0
BMI (kg/m^2)$^{\Psi}$	26.1	8.1	15.7	19.2	24.3	33.1	42.6
Waist circumference (cm)*	84.0	19.7	56.0	68.0	79.0	99.5	135.0
Total PA (mins/day)	29.2	30.0	0	8.57	19.3	42.5	125.0
MVPA (mins/day)	13.5	18.8	0	0	2.9	22.1	60.0
PrimeScreen	8.0	6.8	-4.0	3.0	8.0	12.0	21.0
PSQI	7.6	3.7	1.0	5.5	8.0	9.5	16.0
Sleep (hours/night)$^{\Psi}$	7.1	1.9	4.0	6.0	6.5	8.0	12.0

$^{\Psi}$ Data not normally distributed and therefore log transformed to assume normality. Raw values presented.

* N = 27

BMI = body mass index; GMFCS = Gross Motor Function Classification System; MVPA = moderate-to-vigorous physical activity; PA = physical activity; PSQI = Pittsburgh Sleep Quality Index.

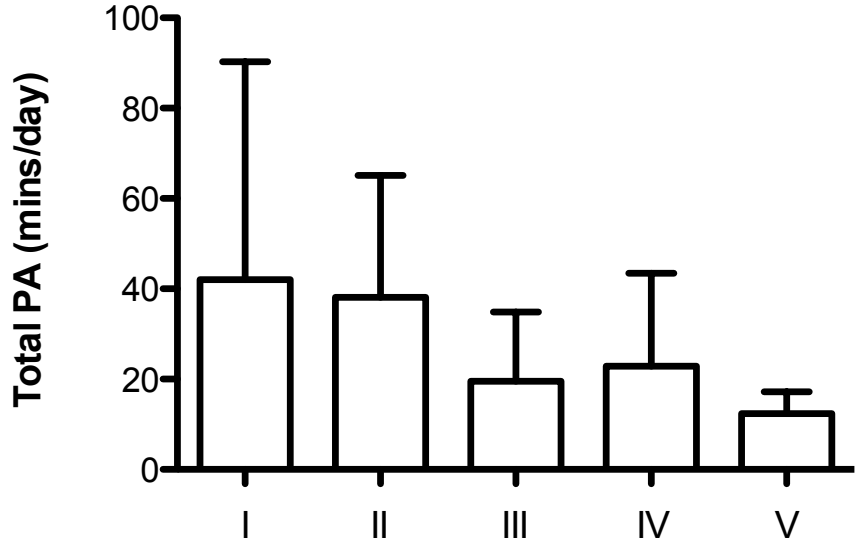

Figure 1.
Average total physical activity (mins/day) for each GMFCS level. Error bars indicate SD.

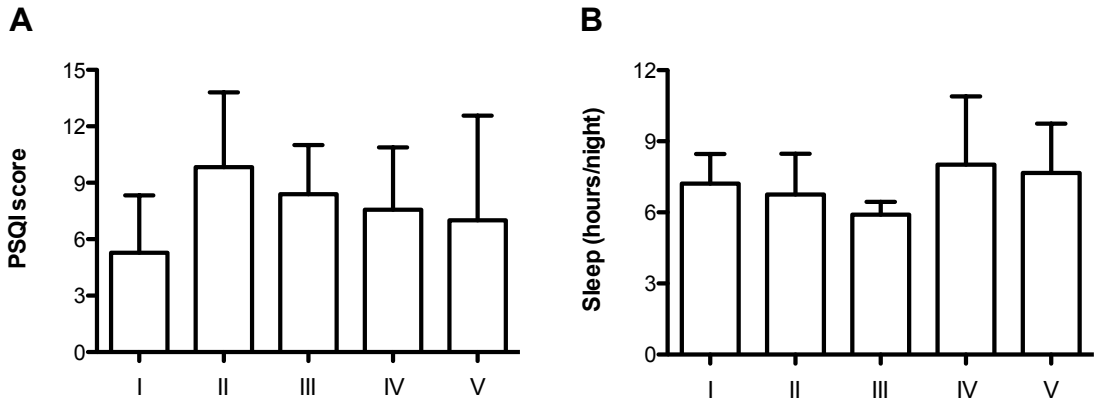

Figure 2.
A. Average Pittsburgh Sleep Quality Index score for each GMFCS level. Error bars indicate SD.
B. Average sleep hours per night for each GMFCS level. Error bars indicate SD.

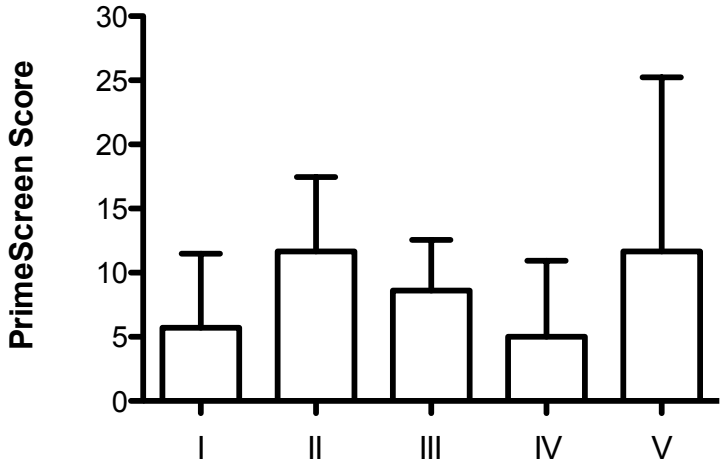

Figure 3.
Average PrimeScreen score for each GMFCS level. Error bars indicate SD.

CHAPTER 6

Multimorbidity risk assessment in adolescents and adults with cerebral palsy: a protocol for establishing a core outcome set for clinical research and practice

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ABSTRACT

Background: Adults with cerebral palsy (CP) have high estimates of multimorbidity, defined as the presence of at least two chronic conditions, some of which are attributable to modifiable behaviours. In order to develop and evaluate effective interventions to optimize lifelong health in individuals with CP, an established assessment protocol evaluating multimorbidity risk is needed. The aim of this protocol paper is to describe the development of a core outcome set (COS) for multimorbidity risk in adolescents and adults with CP to be used in clinic and research.

Methods: The expert consortium will first define the target population and outcomes to be measured. Through a process of literature review and an international Delphi survey with expert clinicians and researchers, we will then determine which outcome measurement instruments (OMIs) can best measure those outcomes. The resulting OMIs will be used in a feasibility study with adolescents and adults with CP from an international clinical research network. Finally, a face-to-face stakeholder meeting with adolescents and adults with CP, their families/caregivers, and researchers and clinicians who are experts in CP, will be organized to reach final agreement on the COS.

Discussion: This COS will guide clinicians and researchers in assessing multimorbidity risk in adolescents and adults with CP. The inclusion of experts and individuals with CP from international locations for establishing the COS lends strong support for its generalizability. Evidence of its feasibility and

approval from all stakeholders will enable implementation in clinical practice, and guide future research using the COS in individuals with CP.

KEYWORDS

Cerebral palsy

Adolescents

Adults

Health

Core outcome set

Multimorbidity

COMET

COSMIN

BACKGROUND

Cerebral palsy (CP) is a well-recognized neurodevelopmental disability commencing in early childhood and continuing throughout life, and is the most common motor disability in childhood.[1] The disability itself results from non-progressive disturbances to the developing fetal or infant brain, and the resultant motor disorders are often accompanied by disturbances of cognition, behaviour and communication, to name only a few.[2] Population-based studies report prevalence estimates of CP ranging from 1.5 to greater than 3 per 1000 live births.[3-7] As CP presents itself early in life, much research has focused on children with CP; however, given the longer lifespan apparent in most persons

with CP,[8] clinicians and researchers have started to focus on the impact of CP and associated health issues with a lifespan approach.

A prominent concern for individuals with CP is their physical behaviour and reduced cardiorespiratory endurance. Physical behaviour is defined as the behaviour of a person in terms of body postures (e.g. sitting and standing), movements (e.g. walking and cycling) and/or daily activities (e.g. sports and gardening) in his/her own environment, and therefore consists of both physical activity and sedentary behaviour.[9] Cardiorespiratory endurance is the capacity of the body to perform physical activity, which is dependent mainly on the aerobic or oxygen-requiring energy systems.[10] Adolescents and adults with CP have reduced cardiorespiratory endurance,[11] which is a risk for cardiovascular disease and cardiovascular-related mortality.[12] Also, children, adolescents and adults with CP engage in significantly less physical activity and increased sedentary behaviour compared to typically developing peers.[13-17] Low levels of physical activity and increased sedentary behaviour can partly be explained by reduced mobility following from the condition itself, as well as accompanying physical pain and fatigue that progressively worsen with aging.[18] Among individuals with CP, differences exist in physical activity levels[19] and obesity prevalence [20], which are contingent upon the functional status of individuals, as determined by the Gross Motor Function Classification System (GMFCS).[21] Reduced cardiorespiratory endurance and physical activity, and increased sedentary behaviour, are associated with risk for cardiovascular (i.e. coronary

heart disease, cerebrovascular disease, peripheral arterial disease) and cardiometabolic (i.e. diabetes and obesity) disease in persons with CP,[15, 22, 23] which may become higher later in life.[24, 25] Recent research in middle-aged adults with CP revealed high-estimates of multimorbidity, which were significantly more prevalent among obese versus non-obese persons with CP.[26]

Multimorbidity has been defined as the presence of at least two chronic conditions.[26] Among individuals with CP, chronic conditions apart from CP itself, such as hypertension, dyslipidemia, hyperglycemia, insulin resistance, and obesity are emerging in the literature.[15, 22, 24] Results from a population-representative sample of adults with CP showed that this population had significantly greater age-adjusted prevalence of hypertension (30.0% vs. 22.1%) and obesity (41.4% vs. 29.7%) compared to adults without CP.[27] Despite the significant progression of disability that is known to occur during the aging process in CP,[18] there has been a lack of attention devoted to understand the pathophysiology to develop multimorbid conditions in adolescents and adults with CP, beyond those stemming from the primary brain injury in infancy. Multimorbidity risk could be attributed to a shared number of modifiable behaviours such as physical inactivity and/or sedentary lifestyles, poor diet, and inadequate sleep.[28] This highlights the importance of screening for, and understanding of risk exposures for multimorbidity in individuals with CP.

Over the last decade, a number of generic and CP specific instruments and protocols assessing multimorbidity risk factors have been developed. As a result, studies evaluating these risk factors in adolescents and adults with CP are using a variety of outcome measurement instruments (OMIs) (e.g., self-report questionnaires, accelerometry-based activity monitors, biomarkers and performance-based tests), which might possibly be measuring the same outcome, and thus causing difficulty synthesizing knowledge from the published literature and when generalizing findings.[29] Moreover, the psychometric quality (i.e. reliability, validity, sensitivity) of OMIs tends to vary and/or published evidence is lacking. Altogether making it inconvenient for clinicians and researchers to select the most appropriate OMIs for the outcome of interest. In order for clinicians and researchers to work with individuals with CP on plans for effective interventions – including advice pertaining to physical behaviour, nutrition and sleep– to reduce multimorbidity risk, it is vital to reach consensus on the outcomes to assess, the ways to assess them, and ultimately leading to routine clinical practice.

Lately, there is an increasing recognition for identifying core sets of outcomes that enable comparison of clinical trials for a particular condition. Moreover, establishing a core outcome set (COS) may be useful for routine health screening. Currently, there is no established COS for adolescents and adults with CP for the purpose of evaluating multimorbidity risk factors. A search of “cerebral palsy” through the Core Outcome Measures in Effectiveness Trials

(COMET) database resulted in six matches, all of which focus on children with CP.[30] Common Data Elements (CDEs) exist for CP through a joint effort between the CP CDE Working Groups and the National Institute of Neurological Disorders and Stroke.[31] Within the CDEs is a summary of core and supplemental recommendations that is highly recommended as a start-up resource for clinical research in this population. Although this set of CDEs was recently developed (2016), it only applies to children and adolescents aged 0 to 18 years and does not specify instruments specific to adults with CP or measures that assess multimorbidity risk.[32]

The aim of this protocol paper is to describe the process of developing a COS of OMIs for multimorbidity risk in adolescents and adults with CP. This work includes: (1) identifying what outcomes should be measured; (2) determining how to best measure those outcomes; and (3) measuring these outcomes in an international cohort of individuals with CP. The final COS will be made in consultation with individuals with CP and their families and caregivers, and representatives of the clinical and research community who are working with people with CP. The inclusion of adolescents and adults with CP, as well as their families and caregivers, is critical, to ensure that OMIs are meaningful, appropriate, and acceptable to inform decisions about assessment of multimorbidity risk in this population. We will include adolescents with CP in the assessments of multimorbidity risk, as this will capture a pivotal transition period, and may highlight the importance of engaging in positive behaviours early on to

attenuate multimorbidity risk later in life. This study is part of a program of research aiming to ultimately understand, treat and prevent multimorbidity in adolescents and adults with CP through modifiable behaviours (e.g. physical behaviour, sleep and nutrition), and to develop an international database that will allow for harmonization of data and the ability to document changes over time in this population.

METHODS

This study protocol is registered with the COMET Initiative (http://www.comet-initiative.org/studies/details/1130) and follows recently published guidelines from a collaboration between the COMET Initiative and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN).[29] Slight adjustments were made to the original flowchart,[29] as we chose to include a pilot testing phase (Fig. 1). Phase 1 has begun, and the target population and outcomes to be measured have already been defined.

Investigators and co-investigators

Four authors (PM, JB, MR, JWG) will have an investigating role in the COS development. After deciding on the conceptual considerations in consultation with co-investigators (MP, EH, WS, AB, OV, RB), they will first perform a review of the literature and extract relevant OMIs. Secondly, they will carry out a consensus procedure with experts to obtain agreement on selected OMIs to be included in the COS. Third, they will coordinate a cross-sectional feasibility study in which

the COS will be tested in an international cohort of adolescents and adults with CP at four sites. Finally, they will organize a stakeholder meeting to review and finalize the COS of OMIs for multimorbidity risk.

Phase 1: Selecting relevant OMIs

Step 1: Conceptual considerations

We defined a target population and outcomes to be measured, in line with the COSMIN-COMET guideline.[29] This was done via an in-person meeting with the co-investigators from four research centres (Hamilton, Canada; Ann Arbor, USA; Rotterdam and Utrecht, The Netherlands), at the 29th European Academy for Childhood Disability conference (2017). During this meeting, the target population was defined as adolescents (14-18 years) and/or adults (>18 years) with CP. Furthermore, the following outcomes were decided to be important for assessing multimorbidity risk in the target population: physical behaviour, nutrition, sleep, cardiorespiratory endurance, body composition, blood pressure, and lipids/glucose. Including risk behaviours (i.e. physical behaviour, nutrition, and sleep) is important to identify which patients require intervention. Measuring cardiorespiratory endurance, body composition, blood pressure and lipids/glucose will allow clinicians and researchers to observe the benefits of improved risk behaviours.

Step 2: Finding existing OMIs

In order to find all existing OMIs addressing the defined outcomes, we will use three sources of information, including: (1) existing systematic reviews, (2)

literature searches, and (3) additional sources (e.g., conference proceedings).[29] Additional sources are considered optional since it is unlikely that one will find OMIs of good quality that were not already identified from a systematic search of the literature.[29]

The COSMIN database of systematic reviews of OMIs will be consulted to see if systematic reviews, describing our target population and any of the seven outcomes, exist. Candidate OMIs for each outcome will further be identified by electronic searches of the following databases: EMBASE and Medline (Ovid), PsycINFO, and Pubmed. The electronic searches will be carried out by two researchers with experience in conducting systematic reviews (PM, JB). We will develop a search strategy which will include the following major themes: ‘cerebral palsy’, ‘adolescent OR adult’, and each outcome on their own. Key terms within the search strategy will be aligned to medical subject headings and expanded to include more descriptive terms. Searches consistent with ‘measurement properties’ will not be included in the search strategy, since evidence on measurement properties of relevant OMIs is expected to be limited in our target population, exposing a risk of missing relevant studies. Eligible publications will be randomized controlled trials, longitudinal (including experimental and cohort studies) and observational (including cross-sectional, cohort, and case-control studies) studies. Studies will be grouped by outcome and repeated where appropriate (i.e. if there is >1 outcome within a single study). The two researchers will screen titles and abstracts independently and select references using a

predetermined set of inclusion/exclusion criteria (see Additional file 1). If there are any discrepancies, these will be resolved by consulting other investigators (JWG, MR). Upon agreement on the final selection of studies, the two researchers will record each OMI for each outcome used in an eligible study. We will also extract characteristics of the study sample (i.e. sample size, mean age, sex, type of CP, and GMFCS level(s)). Data extracted will be crosschecked for accuracy between the two researchers.

A group of experts that will be consulted during the second phase of the COS development process will serve as additional sources for finding OMIs. The group will be requested to provide any additional OMIs that are considered relevant to an outcome but were not identified in existing systematic reviews or in the literature searches.

Step 3: Quality assessment of the OMIs

A quality assessment of the OMIs that result from Step 2 will be performed in accordance with the COSMIN-COMET guideline.[29] The quality assessment will include two parts: (1) evaluating the methodological quality of the studies included from the literature searches, and (2) evaluating the quality of the OMIs (i.e. their measurement properties). Since the literature search will not be limited to studies on measurement properties of OMIs, we will use a combination of the COSMIN checklist and the McMaster critical review form.[33, 34] The COSMIN checklist will be applied for evaluating the methodological quality of studies on measurement properties of OMIs,[33] while the McMaster critical review form will

be applied to assess the methodological quality of the other study types (e.g., clinical trials and observational studies).[34] The quality of the OMIs will be evaluated by applying criteria for good measurement properties.[35] We will first evaluate the content validity of the included OMIs and where applicable the remaining measurement properties.[29] Both researchers (PM and JB) will perform the OMI evaluation, and will crosscheck each other's quality assessments to ensure accuracy and completeness. Evaluations of the methodological quality of the studies and the quality of the OMIs will be combined into a best evidence synthesis, grading the body of evidence for each OMI.[29] Feasibility aspects of the OMIs including applicability (for the target population), patient feasibility, assessor/clinician feasibility, and practical feasibility will be considered in the next phase of the study.

Phase 2: Consensus procedure: Delphi survey

Step 4: Select an OMI for each outcome included in the COS

We will use the Delphi survey method[36] as a consensus procedure to obtain agreement on the selected OMIs included in developing a COS using experts in the area of multimorbidity risk in adolescents and adults with CP. In a Delphi procedure, interactions between experts occur via a series of individual surveys, preserving both anonymity and balance in participation from the experts.[37] In contrast to an in-person consensus method, a Delphi procedure can be conducted via email survey and is therefore accessible to participants regardless of location and involves no cost.[38]

Experts

To remain consistent with the international aspect of the protocol, we will include a group of 8 experts that consist of clinical and research experts in this field. The experts will be from Canada (*n*=2), US (*n*=2), and The Netherlands (*n*=4; two locations). The investigators (PM, JB, MR, JWG) discussed and confirmed *a priori* that each international location must consist of at least one clinical and one research expert. To be considered a clinical expert, the individual must have worked with adolescents and/or adults with CP for at least 5 years. To be considered a research expert, the individual must have published one or more articles related to an identified outcome of multimorbidity risk in this population (adolescents and/or adults with CP).

Delphi survey

The initial stage of the Delphi survey will be a pre-round to obtain a list of OMIs that is as complete as possible. Based on the results from the literature searches performed by the two researchers, a list of studies with OMIs will be identified and divided into the seven defined outcomes: (1) physical behaviour, (2) nutrition, (3) sleep, (4) cardiorespiratory endurance, (5) body composition, (6) blood pressure, and (7) lipids. Experts, via e-mail, will be provided the results from the literature searches and requested to provide any additional OMIs that are relevant to an outcome but are not identified in the literature searches. These could include OMIs that are being used in clinical practice, ones used by a colleague, and/or ones that were read in an abstract or article or in a student's

thesis. Any proposed OMIs will be required to have a reference or abstract attached to allow the two researchers to evaluate the quality of both the study and the OMI as per Step 3.[29]

In round 1 of the Delphi survey, experts will receive an updated list of OMIs pertaining to each of the seven outcomes, which will be delivered by e-mail. The investigators will provide the experts with a spreadsheet consisting of seven tabs, one for each outcome. Every tab will include all associated OMIs that were obtained during Step 2 and the Delphi pre-round, accompanied by a brief note of the methods/equipment used, a short description of the samples in which the OMI was used, and graded evidence of the OMI resulting from Step 3. A detailed description of the characteristics for each included study will be provided separately to assist experts in reviewing the OMIs. Study characteristics will include author and year of publication, the outcome(s) studied, the sample characteristics extracted in Step 2, and the methodological quality of the study evaluated in Step 3. Experts will be given detailed instructions and an instructional video outlining how to score each OMI on a 1-10 scale (1=lowest, 10=highest) for five different aspects of feasibility: applicability, patient feasibility, clinician feasibility, practical feasibility, and overall rating. A comment box will be provided to allow experts the option to provide additional information to the researchers (i.e. explain responses or raise concerns), or to indicate that they are ignorant or uncertain. Experts will have two weeks to score the OMIs for feasibility. Reminder e-mails will be sent after 1 week as well as 1 day before the

end of the two-week period. After receiving and aggregating expert scores, mean and median scores will be calculated. Moreover, we will examine differences between clinician and researcher scores and describe these results.

In subsequent rounds of the Delphi survey, experts will be presented the results from the previous round. All experts will see aggregated scores for each OMI, as well as a synopsis of the comments made by each expert (if applicable). Experts will be asked to consider the feedback (i.e. aggregated scores and comment synopsis) and again score the feasibility aspects with an option to provide their rationale in a comment box. In these rounds, experts also will be asked to identify their preferred OMI for each outcome and to explain why. Similar to round 1, experts will have two weeks to score the OMIs for feasibility with reminder e-mails provided at the same time points.

The investigators will attempt to identify a provisional COS pertaining to the seven outcomes from the scores after two rounds. This will be based on aggregated scores (mean and median), expert opinion (i.e. rationales and additional information from the comments), and the quality of the studies and OMIs. The provisional COS will be presented to all experts, who will be asked whether they agree or disagree with the OMI for each outcome in the COS. If an expert disagrees with the suggested COS, they will be asked to provide their comments and reasons for disagreement.[39] From the decisions and comments made by the experts, a final provisional COS will be presented and evaluated for

final agreement. The COS will only become final after feasibility testing (Phase 3) and stakeholder engagement (Phase 4) (see below).

Phase 3: Feasibility study

Step 5: Feasibility test of the COS in the target population

After developing a COS for multimorbidity risk assessment for use in clinical research and practice, the next stage will be to test the feasibility of the COS in a cohort of adolescents and adults with CP. Aspects of feasibility to be assessed from the perspectives of the clinicians and researchers will include ease of assessment, time required for completion, and their confidence in the COS to assess multimorbidity risk. Regarding feasibility from the patient perspective, time requirement and interpretation of results will be assessed (see below).

Participants

The feasibility study will focus on adolescents and adults with a diagnosis of CP aged 14 years and over. We will include individuals with CP across all GMFCS levels (levels I-V), from three different international locations: Hamilton, ON, Canada; Ann Arbor, MI, US; Rotterdam and Utrecht (combined), The Netherlands. The knowledge to be gained from this multinational study will be far superior to the minimal information that would be gained if we were to conduct the study at a single site, which has constrained the generalizability of research in this area.[40]

Recruitment strategy

Individuals with CP will be recruited during clinical visits to an adult rehabilitation centre or a child and youth clinic in Hamilton, ON, Ann Arbor, MI, and Rotterdam and Utrecht, The Netherlands. During clinical visits, a physician (JWG, EH, or WS) or a study coordinator (PM or JB) from our research team will introduce the study to the patient, at which point the patient will have an opportunity to consent to participate in the study. Members of our team have used a similar recruitment strategy successfully in the past,[24] and we are confident in achieving a total sample size of 75 (25 per geographical region) for testing the feasibility of the COS. As feasibility testing of the COS will be cross-sectional in nature, we will not include a control group at this time. We plan for a future grant application to fund an intervention study using the findings of our feasibility study, which will incorporate a control group.

Sample size

An *a priori* criterion for success of this feasibility study is that a subsequent intervention trial would be feasible if the outcome variables are collected for ≥ 70% of participants. Using a 95% confidence interval (CI) for the proportion of eligible participants who complete the assessment, a margin of error of 0.05, a lower bound CI of 0.70, and an expected completion rate of 75%, the required sample for the feasibility study will be at least 75 participants. We aim to recruit five participants per GMFCS level per location (i.e. 5 participants * 5 GMFCS levels * 3 locations), for a total of 75 participants. As this is a cross-sectional study (i.e. single time commitment), we will not factor in attrition rate.

Assessments

Eligible participants who have provided written consent to participate in the feasibility study will be assessed. Participants will be invited to visit the relevant setting, in which we will execute the OMIs selected for the COS. Assessments will be conducted by the clinicians and researchers involved, where applicable with support from research/laboratory assistants. Based on the outcomes that have been identified in Step 1, we estimate that it will take 3-4 hours to conduct the total set of OMIs. Naturally, the collected data itself will provide insight into the risk profile of the individual participant. A qualitative evaluation will be carried out to examine the acceptability of the COS as a whole, by both the participants and clinicians/researchers. After the measurements, participants will be asked about their experience of the COS via a short survey. Upon completion of all measurements, we will question the clinicians and researchers who conducted the assessments regarding the ease of assessment, completion time, and their confidence in the COS, also via a short survey. Together with the collected data, the feedback from the participants, clinicians and researchers will provide a clear indication of the feasibility of the COS for future use in clinical research and practice.

Phase 4: Patient and family/caregiver engagement

Step 6: Final agreement on the COS among stakeholders

As a final step and after taking into consideration the quantitative and qualitative evaluations from study participants, clinicians and researchers, we will organize a

face-to-face stakeholder meeting to reach final agreement on the COS. Adolescents and adults with CP and their families and/or caregivers, as stakeholders for this project, will be recruited with support from the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) family/participant education forum. The AACPDM education forum is held annually at the AACPDM conference. Prior to the meeting, we will work with the AACPDM administrative leaders to have an advertisement positioned on their website asking for adolescents and adults with CP (and their families/caregivers) to participate in a meeting to help review and finalize a COS for multimorbidity risk. We will invite four adolescents and four adults with CP of varying GMFCS levels, whom did not participate in the feasibility study, and their families and/or caregivers (if applicable) to take part in the meeting, which will occur during the AACPDM 2018 conference (October 9-13 2018).

Dissemination

Details of the finalized COS will be disseminated through publication in a scientific journal, presentation(s) at international scientific conferences, and research rounds at clinics and academic institutions at each international location.

DISCUSSION

The aim of this project is to develop and test the feasibility of a COS to assess multimorbidity risk in adolescents and adults with CP. Ultimately, the COS will be

used to understand, treat and prevent multimorbidity in this population, while being utilized in a clinical and/or research setting. The development of this COS is expected to have the potential to generalize to other types of child-onset neurodevelopmental disabilities.

A strength of the proposed work is the inclusion of clinical and research experts in this field (COS development), and individuals with CP (feasibility study), from international locations. The knowledge to be gained from an international study will be significant and meets a major limitation in multimorbidity risk research in this population (i.e. studies of small sample sizes that are geographically isolated). If we are able to conduct the feasibility study successfully, and receive positive feedback from individuals with CP, their families/caregivers, and clinicians and researchers, our next step will be to apply for funding to conduct an intervention study in this population aiming to prevent multimorbidity risk. In the meantime, the development of a COS for adolescents and adults with CP will improve the consistency of CP research moving forward. Ultimately, we aim to utilize the COS in clinic to work towards developing a database that will allow for harmonization of data and the ability to document changes over time, which will enhance and accelerate our understanding of multimorbidity risk and presentation in this population, and will help to overcome the issues of current small-scale studies. As well, performing the COS assessment in clinic will obtain a risk profile for the patient, which can help inform an individualized treatment plan.

A challenge we faced with this protocol was selecting when to engage individuals with CP and their families/caregivers as key stakeholders in COS development. Ideally, we would have included these stakeholders throughout the study, from the very beginning to the end. However, due to the focus on knowledge synthesis in the Delphi survey with research rigor and the terminology involved in quality assessments of studies and OMIs, we decided it would be more pragmatic to develop a provisional COS amongst clinicians and researchers, and then bifurcate to feasibility testing and a stakeholder meeting, to incorporate perspectives from individuals with CP and their families/caregivers and come to a final agreement on the COS. A former study attempting to develop a COS with patient perspectives from the onset of the idea reported it as challenging.[41]

Despite an effort to include expert clinicians and researchers working with adolescents and adults with CP who are knowledgeable of multimorbidity, none of these individuals considered themselves as experts in the outcomes nutrition and sleep in CP. This identifies an important gap in clinical research in this population; if nutrition and sleep are to be considered important components of multimorbidity risk prevention in people with CP,[42] clinicians and researchers need to be trained in these outcomes in order to assess and manage these components of health.

Trial status

At the time of submission, we have included experts for the Delphi survey. Recruitment for the feasibility study will start in June 2018 subject to the ethics approval from all institutions involved.

LIST OF ABBREVIATIONS

AACPDM American Academy for Cerebral Palsy and Developmental Medicine

CDE Common Data Elements

COMET Core Outcome Measures in Effectiveness Trials

COS Core Outcome Set

COSMIN COnsensus-based Standards for the selection of health Measurement INstruments

CP Cerebral Palsy

GMFCS Gross Motor Function Classification System

OMI Outcome Measurement Instrument

DECLARATIONS

Ethics approval and consent to participate

Consent from the clinical and research experts invited to participate in the Delphi procedure will be implied through completion of the surveys. We will seek ethics approval from each participating institution (McMaster University, Hamilton, Canada; University of Michigan, Ann Arbor, US; Rijndam Rehabilitation and Erasmus University Medical Center, Rotterdam, The Netherlands; De Hoogstraat

Rehabilitation Centre of Excellence, Utrecht, The Netherlands) for the feasibility study involving patients. Consent from the patients to participate in the feasibility study will be documented prior to the measurements; consent for the face-to-face stakeholder meeting will be documented prior to the AACPDM conference.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors (PM, JB, AB, OV, RB, EH, MP, WS, MR, JWG) made substantive contributions to the conceptualization of the research project. PM, JB, MR and JWG elaborated the study protocol in detail; co-authors critically reviewed it for important intellectual content. PM and JB drafted the manuscript. MR and JWG critically reviewed it for important intellectual content. All co-authors read and approved the final manuscript to be published and agreed to be accountable for all aspects of the work.

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FIGURES, TABLES AND ADDITIONAL FILES

Fig. 1 Main steps in the COS development including roles of all involved at each step Schematic outline of the different phases and steps included in the development of a COS for multimorbidity risk assessment in adolescents and adults with cerebral palsy. Roles of all involved at each step are indicated. COS, core outcome set; OMI, outcome measurement instrument; CP, cerebral palsy.

Additional file 1 Article screening form including inclusion/exclusion criteria

PDF 76kb

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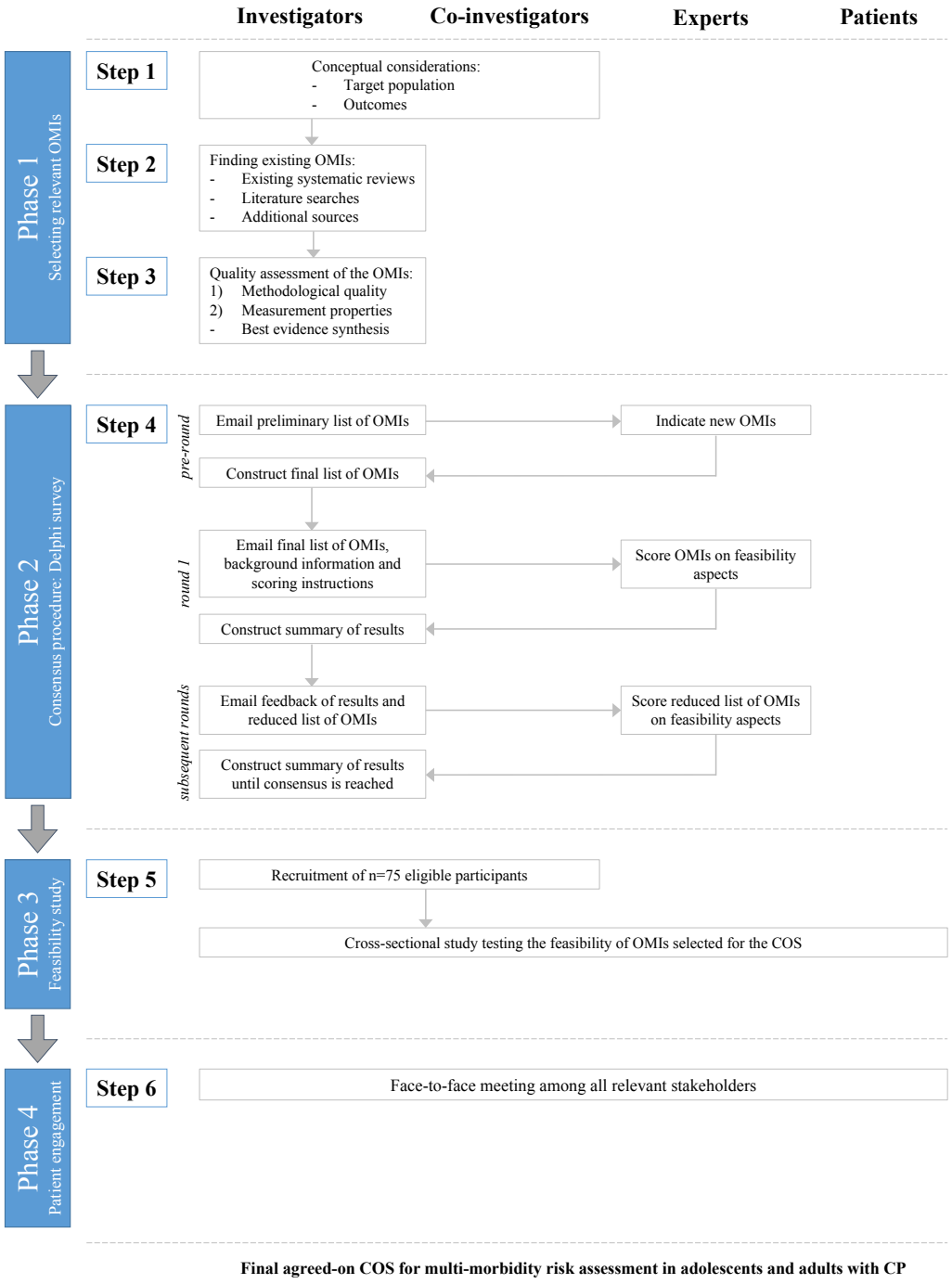

Figure 1. Main steps in the COS development including roles of all involved at each step

Additional file 1

Article screening form including inclusion/exclusion criteria

Articles answered "yes" or "unclear" *to all criteria* should be included.

1. Is this article about humans?

If no → EXCLUDE

If yes or unclear → go to next question

2. Is this article about people with cerebral palsy?

If no → EXCLUDE

If yes or unclear → go to next question

3. Is this article about adolescents (≥14years of age) or adults (≥18years of age)?

If no → EXCLUDE

If yes or unclear → go to next question

4. Is this article about…

Physical activity, physical inactivity, sedentary lifestyle, sitting, energy expenditure, motor activity, accelerometry

OR

Anthropometric parameters, body composition, BMI, adiposity, obesity, overweight, height, fat distribution, adipose distribution, waist circumference, hip circumference, waist-to-hip ratio

OR

Sleep, sleep disorder, dyssomnia, hyposomnia, hypersomnia, insomnia, parasomnia, sleeplessness, sleepiness, tiredness, sleep disturbance, sleep paralysis

OR

Blood pressure, blood pressure monitoring, abnormal blood pressure, blood pressure measurement, hypertension, blood pressure monitor, artery pressure, hypotension, hypertension, prehypertension, normotension

OR

Dyslipidemia, hyperlipidemia, hypolipemia, cholesterol, triacylglycerol, lipid profile

OR

Nutrition, feeding behavior, dietary intake, feeding, diet, diet survey, nutrition survey, diet assessment, nutrition assessment, diet state, nutrition state, diet status, nutrition status, food, feed, energy, calorie, nutirient, food uptake, food intake, food consumption, energy uptake, energy intake, energy consumption, calorie uptake, calorie intake, calorie consumption, dietary uptake, dietary intake, dietary consumption, nutrient uptake, nutrient intake, nutrient consumption, feeding behavior, feeding habit, feeding pattern, eating behavior, eating habit, eating pattern, drinking behavior, drinking habit, drinking pattern, alimentary behavior, alimentary habit, alimentary pattern, nutrition behavior, nutrition habit, nutrition pattern

If no → EXCLUDE

If yes or unclear → go to next question

5. Is this study a randomized controlled trial, intervention study, longitudinal study or observational / cross-sectional study?

If no → EXCLUDE

If yes or unclear → include

2

Appendix 1. Article screening form including inclusion/exclusion criteria

CHAPTER 7: DISCUSSION

7.1 DISCUSSION OVERVIEW

The purpose of this thesis was to investigate and better understand cardiovascular disease (CVD) in individuals with cerebral palsy (CP) and to identify important health variables to measure and prevent multimorbidity and promote long-term health and a healthy lifecourse trajectory in this population. A common assumption in research and clinical practice is that individuals with CP are at increased risk for the development of CVD because of low levels of physical activity attributed to their physical disability. However, a key knowledge gap is our actual understanding of CVD, its risk factors and natural course or disease progression in individuals with CP.

To address this knowledge gap, our work began by conducting a systematic review to better understand the prevalence of CVD, traditional and novel risk factors of CVD, and CVD-related mortality in adults with CP (Chapter 2). Searching for these outcomes specifically in adults with CP could help inform healthcare strategies for individuals with CP at an earlier age, to ultimately prevent, or at the very least attenuate, the progression of CVD development in this population. Specifically, colleagues and myself identified only one large US study that investigated the prevalence of CVD in adults with CP, which found that adults with CP were 1.67 times more likely to develop CVD than the general population (32). By investigating cardiovascular health variables in adolescents and adults with CP who were Gross Motor Function Classification System (GMFCS) level I versus those who were GMFCS level II, we discovered that,

after adjusting for age, the GMFCS level I group had a lower mean arterial pressure (MAP), smaller carotid artery intima media thickness (cIMT), and engaged in greater amounts of moderate-to-vigorous physical activity (MVPA) per day than the GMFCS level II group (Chapter 3). Through a longitudinal evaluation of CVD risk factors and progression of cardiovascular health in individuals with CP, we reported that brachial artery flow mediated dilation (FMD), a measure of endothelial function, decreased while cIMT increased in individuals with CP over a four-year time interval (Chapter 4). Moreover, age was independently associated with rate of change of cIMT in this study.

Physical activity, sleep and nutrition have only recently been recognized as important components of the formula to promote long-term health in both the general population and in persons with CP. For the first time we showed, in a comprehensive fashion, that individuals with CP reported poor sleep quality, at best *fair* eating behaviours, and engaged in less than the 150 minutes of recommended MVPA per week (Chapter 5). In parallel with these findings, we proposed a protocol for the development of a core outcome set (COS) to guide clinicians and researchers in assessing multimorbidity risk in adolescents and adults with CP (Chapter 6). The ultimate goal in developing this COS is to identify individuals at risk for multimorbidity and encourage healthy behaviours such as adequate sleep, good nutrition, and physical activity promotion to prevent multimorbidity development. This general discussion aggregates the main findings of my thesis and provides an overarching interpretation on this topic

while supplementing what is currently available in the literature. Limitations from these studies are addressed and outstanding knowledge gaps and future directions for advancing this field of work are provided.

7.2 ADVANCING OUR UNDERSTANDING OF CVD RISK IN CP

Despite CP being a permanent physical disability that presents in early childhood and remains throughout the lifespan, implications of the disability and its association with CVD development through adulthood have only been researched in the last 15-20 years. Indeed, recent research has shown an increase in cardiovascular- and cardiometabolic disease in children, adolescents and adults with CP (28, 31, 32, 40). The terms cardiometabolic disease and CVD are often used interchangeably when describing these morbid conditions in individuals with CP. In the context of this discussion it is important to delineate the meaning and terms associated with each of these diseases. Cardiometabolic disease is essentially a clustering of disorders, including abdominal obesity, hypertension, dyslipidemia, hyperinsulinemia, and glucose intolerance, which together lead to the development of CVD and type II diabetes (10). On the contrary, cardiovascular diseases are a group of disorders of the heart and blood vessels (52). Risk factors of CVD, however, overlap with many of the disorders identified in cardiometabolic disease. For example, the World Health Organization (WHO) recognizes hypertension, diabetes, and hyperlipidemia as important risk factors for the development of CVD (52). Taken together, and in

light of our findings from our systematic review in combination with a recent review of noncommunicable disease development in individuals with CP (36), individuals with CP are on a trajectory for the development of both cardiovascular- (Chapter 2) and cardiometabolic disease (36). In Chapter 2, we identified an increased prevalence of CVD and an increased risk of circulatory system-related mortality in adults with CP compared to the general population. Interestingly, CVD risk factors consistent with the Framingham Heart Study (51) were not commonly reported in studies involving adults with CP. On the other hand, overweight and obesity were identified in a multitude of studies; however, the majority of these studies was cross-sectional and lacked a comparator group, making it impossible to perform a relative risk analysis to determine whether or not adults with CP were at greater risk for overweight/obesity than the general population. Other non-traditional risk factors of CVD might better our understanding of CVD development in individuals with CP.

To our understanding, only two other studies have measured non-traditional risk factors of CVD, such as arterial stiffness and endothelial dysfunction, in individuals with CP (14, 15). Both of these studies were components of the Stay-FIT program of research within *CanChild*, Centre for Childhood Disability research (more details pertaining to this program can be found here: www.canchild.ca/Stay-FIT). Key implications of assessing arterial stiffness and endothelial function are that they can detect sub-clinical atherosclerotic development and risk of having a future cardiovascular event (4,

16). Measures of arterial stiffness and/or endothelial function have been conducted in many clinical populations, including stroke (45), spinal cord injury (19), and multiple sclerosis (33) and have been reported as reliable and sensitive to detect change over time (17, 54). In Chapter 3, we hypothesized that those who were GMFCS level I would have healthier cardiovascular indices than those who were GMFCS level II. Scientists investigating cardiovascular- and cardiometabolic-related research questions in individuals with CP often separate this population based on severity of disability (i.e. GMFCS levels) (38, 50), ourselves included (15). Our findings illustrated that individuals who were GMFCS level I had a lower MAP and decreased cIMT than those who were GMFCS level II. These findings have both research and clinical implications: researchers should consider differences in cardiovascular related variables between the higher functioning GMFCS levels when deciding whether or not to group these functioning levels for statistical analysis purposes; and clinicians should implement monitoring and preventative management for CVD development in individuals who are GMFCS level II.

Chapter 3 also revealed that individuals in GMFCS level II engaged in less MVPA than those who were GMFCS level I, which supports the already conceived idea that individuals who are GMFCS level I engage in the most physical activity relative to the rest of the GMFCS (6, 11). The majority of physical activity research in CP includes individuals who only walk independently or walk with the assistance of a walking aid (2, 18, 39). Strong evidence exists to show

that people with CP engage in less physical activity and more sedentary behaviour than the general population (22, 24, 25). Undeniably, physical inactivity is considered a modifiable risk factor of CVD (53) and is associated with other risk factors of CVD, including overweight and obesity, hypertension, and hyperglycemia. In light of this, our results from Chapter 3 were the first to present a negative association between MVPA per day and cIMT in individuals with CP. As MAP and cIMT were elevated in GMFCS level II, and progression of both these risk factors for CVD can be attenuated by physical activity participation, this identifies a strategic target for CVD risk reduction in this subset of CP.

A lack of cohort studies investigating CVD and related risk in individuals with CP provided the impetus for Chapter 4. To our understanding, this was the first study to prospectively investigate longitudinal changes in CVD risk factors in individuals with CP. Notably, we observed within individual changes in non-traditional risk factors that are inline with CVD risk progression. Specifically, decreases in endothelial function and carotid artery distensibility, and increases in carotid-femoral pulse wave velocity (cfPWV) and cIMT identified early stages of CVD risk development in this population. The measurement techniques of these non-traditional risk factors of CVD are sophisticated and require specialized equipment and training. Undeniably, a 1-1.5% change in relative FMD is deemed clinically and physiologically relevant (13); therefore the 2.4 ± 5.1% reduction in relative FMD observed in this cohort of CP is clinically meaningful. However, a limitation in our analysis is that we did not adjust for baseline arterial diameter.

Research has shown that relative FMD responses might be underestimated for larger arteries at baseline while overestimated for smaller baseline arteries (1). A statistical analysis technique can be performed to adjust for differences in baseline diameter, known as allometric scaling, however the clinical meaningfulness of the subsequent FMD values are unknown. Importantly, only the conventional reporting of FMD has been identified as a surrogate measure of coronary artery endothelial function (44) and predictive of future cardiovascular events (55). Similarly, different techniques and devices are available to measure cfPWV. The subtraction method was employed in Chapter 4 to remain consistent with baseline measures and provided an opportunity to compare our findings to the clinically significant and conservative cutoff value of 10m/s, of which we found three individuals with CP to be above. Importantly, our reporting of relative FMD and cfPWV (via the subtraction method) allowed us to compare our findings to other populations to show that individuals with CP might experience accelerated [cardiovascular] aging. We also observed changes in body mass index (BMI) in our longitudinal evaluation. Notably, the percentage of individuals who were underweight or normal weight decreased while overweight and obesity increased. BMI itself has been scrutinized as an insensitive measure of body fat in people with CP (9). Individuals with CP who have a BMI which is in the normal range might have high body fat, therefore potentially underestimating other risk factors of CVD, such as hyperlipidemia. Acknowledging such, we also performed measures of waist circumference, which have previously been shown to correlate

with triglycerides in individuals with CP (30), and which we found increased over time in our cohort. Nonetheless, we observed negative changes in CVD risk factors in a cohort of individuals with CP over a relatively short time period (i.e. 4 years), which appeared to be greater when compared to literature from the general population.

We conducted a systematic review of the literature on CVD in adults with CP, which identified knowledge gaps in our understanding of CVD prevalence and risk in this population. Many studies from our systematic review consisted of a small number of individuals with CP and thus likely did not give a true representation of the prevalence or risk of CVD in this population. We discovered that differences in cardiovascular health indices exist between higher functioning groups of CP and, through longitudinal evaluation, identified significant changes in non-traditional risk factors of CVD. Yet, our understanding of the development of CVD is limited to associations rather than causal data. In particular, a lack of prospective, experimental cohort studies measuring changes in CVD risk factors and the development of occult CVD remains a key knowledge gap in understanding the progression and implications of this disease and its risk factors in this population. Epidemiological studies and surveillance programs can provide essential data to identify and monitor at risk populations and document trends of health across the lifespan. Indeed, patient registries are emerging nationally and internationally to track health-related outcomes and risk factors in persons with CP (12), but these are only in their infancy stages and CVD-related variables

have not been specified as outcomes of interest. These types of studies, along with patient registries and prevention practices which include cardiovascular-related outcomes, can help identify and reduce the risk of CVD in this population.

7.3 IDENTIFYING AND PREVENTING MULTIMORBIDITY RISK IN CP

Only recently has research emerged showing that individuals with CP are at risk for multimorbidity (i.e. the existence of at least two chronic conditions). Researchers in the field of CP have proposed a paradigm such that a combination of decreased mobility, accelerated loss of muscle mass, physical fatigue, and reduced physical fitness and physical activity occurring in young adulthood may put individuals with CP at an increased risk of multimorbidity (29). Our understanding of the prevalence of multimorbidity in adults with CP has been confined to studies conducted in the US (8, 50). Specifically, ~58% of adults with CP had multimorbidity, with hypertension and osteopenia being the most commonly identified combination of chronic conditions (8). Interestingly, there is a direct relationship between physical activity and risk reduction of hypertension, with reductions routinely occurring at levels of 150 minutes of moderate-intensity activity per week (7, 23). In Chapter 5, ~79% of individuals with CP engaged in less than 150 minutes of MVPA per week. Similarly, Ryan et al. showed that only 24% of adults with CP met physical activity guidelines, compared to 54% of adults without CP (37). It is evident that many individuals with CP are not engaging in adequate physical activity to experience risk reductions in

hypertension and other cardiorespiratory health variables (i.e. coronary heart disease, CVD, and stroke). At present, however, opportunities to promote health and prevent disease may be missed by the prescription of physical activity alone. In light of this, we proposed an idea to consider physical activity, sleep, and nutrition comprehensively as the formula for health and well-being in individuals with CP (48). Components of this formula align with the recently developed 24 hour movement guidelines for children and youth, which provide evidence-informed recommendations for a healthy day, consisting of a combination of sleep, sedentary behaviours, light-, moderate-, and vigorous-intensity physical activity (46). These guidelines should be adopted and adapted in the context of a lifespan approach; physical activity, sedentary behaviour and sleep are important for all persons of all ages. In adults, it is recommended that a minimum of 7 hours of sleep be obtained per night (20). Poor sleep has been associated with increased susceptibility to inflammatory related diseases including diabetes and CVD (26). In our study, we observed that nearly 60% of individuals with CP obtained less than 7 hours of sleep per night while 75% reported poor sleep quality. Both sleep quantity and quality were obtained from the Pittsburgh Sleep Quality Index (PSQI), which required subjects to answer 19 self-rated questions. Use of the criterion standard of sleep assessment (i.e. polysomnography) would likely provide a more accurate depiction of sleep behaviour in this population, but would be costly and a burden for the patient to remain in a clinical setting for the measurement. A comprehensive review on sleep quantity and quality in children

with CP discussed the importance of patient reported questionnaires as a good option for initial assessment of possible sleep issues (47). Sleep questionnaires can be performed in parallel with a medical history check and physical examination during a clinical encounter, and can be used again during a subsequent follow-up appointment to assess any changes in sleep behaviour.

Our understanding of the implications of poor sleep behaviour in CP is limited to research in children. Children with CP are seven to twelve times more likely to experience sleep disorders compared to their peers (43), which have been reported to vary by age and gross motor function. Since poor sleep is related to CVD development, and adults with CP are at increased risk for CVD compared to the general population (32), it is important to investigate the role of sleep in attenuating CVD in this population. Although our observations of sleep quantity and quality in Chapter 5 were from a relatively small sample of adolescents and adults with CP, at the very minimum they provided a first look at sleep problems in individuals with CP inclusive of adolescents and adults. Finally, nutrition is considered a critical component to the formula of health and well-being as malnutrition is elevated in individuals with CP (34). Good nutrition is particularly important for individuals with CP since small muscle mass and muscle atrophy appear at a younger age compared to the general population (49). Decreased muscle mass in non-ambulatory children with CP is related to decreased weight bearing (41) and likely compounded by poor nutrition. To our understanding, and prior to this thesis, no one had investigated nutrition in

individuals with CP across a wide age range comprised of adolescents to older adults. Our findings revealed that nutrition behaviours were diverse in individuals with CP. Like sleep, nutrition was measured via a self-report survey and our results should be interpreted in light of a potential subject bias. However, the PrimeScreen questionnaire, which was used in Chapter 5 to measure nutrition, was previously shown to correlate to both a larger (i.e. 131-item) semiquantitative food frequency questionnaire and plasma levels of nutrients (35). Taken together, an important implication from our results in Chapter 5 was that GMFCS was not significantly associated with any one of physical activity, nutrition, or sleep in individuals with CP. This tells us that all three components of the formula for health and well-being are important to monitor in all individuals with CP of all ages and all severity levels, and could be important contributing factors in maintaining optimal health across the lifespan. Indeed, multimorbidity in adults with CP has been shown to be more prevalent among obese compared to non-obese individuals with CP as well as in GMFCS levels IV-V versus GMFCS levels I-III (8). The formula for health and well-being consists of three themes that are associated with obesity, and combined with proper management and preventative strategies, can reduce obesity and subsequently multimorbidity risk in this population. To our understanding, no research has been conducted on the effects of combining a physical activity program with targeted nutrition and sleep interventions in people with CP.

More individuals with CP are reaching adulthood than ever before due to increases in survival rate as well as prevalence of CP over the lifespan (5, 27). With this, however, comes a greater risk for cardiometabolic disease (31) and multimorbidity (50). Undeniably, young adults with CP have a higher prevalence of multimorbidity compared to their typically developing counterparts, which is more pronounced in those with GMFCS levels IV-V (50). However, our understanding of multimorbidity risk in this population is limited to patient information gathered from electronic medical records (8, 50). Chapter 6 intended to describe the development of a COS to measure multimorbidity risk in adolescents and adults with CP for clinical and research utilization. To the best of our understanding, no COS for adolescents and adults with CP exists. International Classification of Functioning, Disability and Health (ICF) Core Sets have been developed for children and youth with CP and do incorporate sleep functions and eating activities (42). However, describing a protocol to create a COS on an international platform that includes both constructs related to multimorbidity risk as well as modifiable behaviours to combat multimorbidity development has significant implications. Specifically, surveying international CP experts (both clinical and research) allows us to identify the most relevant outcome measurement instruments (OMIs) to measure multimorbidity-related outcomes in this population from an expert's perspective; feasibility testing will allow us to measure clinician and patient feasibility of the COS; and incorporating adolescents and adults with CP in a final stage will encourage final agreement on

the COS. Moreover, assessing modifiable behaviours such as physical activity, sleep, and nutrition provides baseline information from which to improve through lifestyle interventions.

Our intent of developing a COS for multimorbidity risk assessment and prevention comes in light of recognizing that progress for improved and evidence-based clinical care for individuals with CP has been halted by research that is fragmented, with studies with relative small sample sizes, and lack of patient (i.e. stakeholder) engagement. Management of the risk of developing multimorbidity should focus on reduction of its risk factors through primary prevention (3). A priority of primary prevention of multimorbidity is screening individuals with CP while attending primary health care facilities. A goal with the development of the COS in Chapter 6 is for its utility in clinical settings. Upon undergoing a battery of assessments pertaining to the seven constructs within the COS, patients will be presented with an individualized risk report which can be discussed in consultation with their primary care provider. After obtaining and understanding the risk report, primary prevention could entail multi-factorial lifestyle interventions which might include promoting healthy diets, good sleep, and participation in physical activity (3). The WHO supports assessing total disease risk rather than management of single risk factors on their own, which allows for early detection of morbid conditions (21). The collected data from encounters with primary care providers can also go in databases allowing for large data analysis in the future, overcoming the challenges of small fragmented studies in various geographical

settings. Our COS provides a comprehensive approach to assess risk factors related to both cardiovascular- and cardiometabolic-disease, and taken together, multimorbidity.

7.4 CONCLUSIONS AND FUTURE DIRECTIONS

The studies presented in this thesis suggest that individuals with CP are at risk for the development of CVD, and may experience so at an early age, with accelerated aging and disease progressions. Individuals who are GMFCS levels I and II can differ on indices of cardiovascular health, as well as MVPA levels. This work suggests that researchers should be mindful of differences in cardiovascular health and physical activity levels when grouping these two functioning levels for statistical purposes. This will likely require researchers to obtain larger sample sizes to answer research questions that separate subjects based on level of gross motor function. However, conducting research in larger samples of individuals with CP could help address a major limitation in our understanding of CVD, which is that our knowledge of CVD in this population is confined to studies of small sample sizes that are geographically isolated. Longitudinal evaluation of brachial artery FMD and cIMT negatively changed in individuals with CP over a four-year time period. Future longitudinal experimental studies assessing CVD risk which include measures of FMD and cIMT as well as hyperlipidemia and hyperglycemia would be valuable extensions of the current work. While this thesis has contributed to our understanding of cardiovascular health and risk in

people with CP, questions remain, and there would be value in confirmative studies regarding CVD risk factors and CVD related outcomes over time in large sample sizes.

If behaviour modifications or lifestyle interventions are to be effective at reducing the prevalence of multimorbidity risk, proper screening techniques and subgroups of persons with CP who are at elevated risk must be identified, and then implemented in regular care through care pathways. Future research investigating modifiable behaviours in individuals with CP, including physical activity, sleep, and nutrition, should do so prospectively, with large sample sizes across multiple sites to improve generalizability of our knowledge in this area. Lastly, the development of a COS for multimorbidity risk, upon its successful feasibility testing, should be encouraged in clinical settings to establish data registries and monitor and track risk development in this population. Not without its limitations, the combined results of the current work provide substantial understanding of the risk of CVD development and provide evidence that the formula for health and well-being could provide a framework for a lifestyle intervention to reduce and prevent multimorbidity risk in individuals with CP.

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