Etiology and Pathophysiology

Chronic disease risk among adults with cerebral palsy: the role of premature sarcopoenia, obesity and sedentary behaviour

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Summary

Premature declines in function among adults with cerebral palsy (CP) are generally attributed to weakness, spasticity and orthopaedic abnormalities, as well as chronic pain and fatigue. Very little research or clinical attention has been devoted to the confluence and consequences of early muscle wasting and obesity as mediators of secondary comorbidity in this population, and perhaps more importantly, to the role of lifestyle to potentiate these outcomes. At present, there are no national surveillance programmes that monitor chronic health in adults with CP; however, mortality records have demonstrated a greater prevalence of coronary heart disease as compared with the general population. Although by definition, CP is a 'non-progressive' condition, secondary factors such as habitual sedentary behaviour, obesity, and premature sarcoepenia may increase the severity of functional impairment throughout adulthood, and lead to cardiometabolic disease, fragility and/or early mortality. Herein we describe the heightened health risk represented in adults with CP, and discuss the hallmark phenotypic features that coincide with ageing, obesity and cardiometabolic disorders. Moreover, we provide discussion regarding the protective role of habitual physical activity to stimulate anti-inflammatory pathways and to ameliorate global risk. Although physical therapeutic modalities are already widely acknowledged as a vital component to improve movement quality in CP, the purpose of this review was to present a compelling case for the value of lifelong physical activity participation for *both* function and cardiometabolic health preservation.

Keywords: Adiposity, cerebral palsy, motor disability, sedentary behaviour.

Introduction

Each year, approximately 3 per 1,000 children are born with cerebral palsy (CP) in the United States (1,2). Considering that the prevalence of CP has been stable or even slightly increasing over the past 40 years (3), evidence suggest that adults with CP represent a growing population and considerable public health burden. Functional loss, especially of mobility, is a major issue in adults with CP.

Various studies have demonstrated that a large percentage of individuals with CP who were once mobile eventually stopped ambulating, mostly because of fatigue, inefficiency of gait and/or joint pain (4). Moreover, among children who walk, but also use a wheelchair, as many as 34% are found to lose the ability to walk by early adulthood (5). It is well documented that high-functioning children with CP are at elevated risk to lose ambulatory skills or turn to assistive devices in adulthood (6,7), which leads to

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substantial declines in functional skills, activities of daily living and/or mobility (8). Opheim *et al* (9) found that 52% reported deterioration in ambulation by the age of 37 years, especially among individuals with bilateral spastic involvement, fatigue and pain. Indeed, functional deterioration has been attributed to both chronic inactivity and secondary conditions common among adults with CP (10). Pain is the most prominent, with 67–84% of patients reporting significant pain (11–13). Moreover, pain is often associated with fatigue (14) and low life satisfaction, as well as declines in activity and function. In conjunction, adults with CP frequently attribute their functional deterioration to losses of strength, balance and diminished physical fitness. The minority of individuals who actually report preservation of mobility throughout adulthood accredit this to regular physical activity (PA) participation, and maintenance of strength, balance and overall fitness (8,9). Functional decline and secondary medical complications can seriously impact employment and social integration (13), as well as participation in exercise and other leisure activities (15). It is therefore critical to gain greater understanding of the modifiable risk factors related to these problems in order to provide better information to the CP population and their caregivers, as well as for future design of targeted, corrective interventions.

Premature sarcopoenia and functional decline

Individuals with CP have permanent neurological impairment, which is known to compromise motor function, mobility and balance. In conjunction with reduced muscle volume (16), these factors may predispose young or middle-aged adults with CP to sustain secondary declines reminiscent of older adults who do not have CP (17). In the geriatrics and gerontology literature, the term 'sarcopoenia' has historically referred to the loss of muscle mass (18), but over time has emerged as a general designation of non-specific vulnerability to weakness, disability, comorbidity and diminished autonomy. Although a robust association indeed exists between chronological age and virtually every symptom of sarcopoenia, ageing *per se* is merely a crude proxy for determining predisposition to these symptoms. More importantly, sarcopoenia and muscular weakness are suggested to translate to acute functional deficit and disability, and this is magnified when the forces required to complete activities of daily living (such as standing and walking) approach/exceed the threshold capacity of muscles. Longitudinal data suggest that muscle strength is a robust predictor of functional decline (19–21), and is an important physiological attribute for maintenance of mobility and movement efficiency. In the non-CP population, strength reaches a peak sometime around the second or third decade of life, and by the fifth decade, begins a gradual decline. This deterioration is attributed to

diminished levels of activity or disuse/immobilization because of disease, and increases in severity after the age of 65 (22).

Secondary to the underlying neurological insult, individuals with CP have a documented inability to maximally recruit target musculature during voluntary activity (i.e. neural inefficiency) (17,23,24), and an over-recruitment and co-activation of antagonist musculature (24). These motor control impairments dramatically reduce gait and movement efficiency, and increase energy expenditure and fatigue during tasks (25–29). Consequently, premature declines in function among adults with CP (5,6,10,30,31) may occur as a result of early sarcopoenia and weakness, beyond that which is expected for typical ageing adults (17). While the specific aetiology of this so-called 'premature ageing (32)' is not fully understood, ample evidence exists to confirm that adults with CP have lower fitness and less muscle mass than individuals without CP, and therefore have significantly reduced functional reserve throughout the span of adulthood. There is thus a circular cause and consequence of events (Fig. 1) that leads towards gradual decreases in activity, further restriction of full participation and a latent, nearly inevitable deterioration of musculoskeletal morphology.

Obesity risk and potential misclassification

Obesity is an independent risk factor for insulin resistance, glucose intolerance, hyperglycaemia, hypercholesterolaemia and hypertension. Left untreated, this combination of pathophysiological factors precipitates increased risk for cardiometabolic disease and early all-cause mortality across populations (33,34). Most research pertaining to obesity in the CP population have been conducted to characterize prevalence (35,36), or to compare and cross-validate anthropometric and body composition strategies (37,38). Several studies have identified a general increased prevalence of obesity among children with CP (35,36), but this has yet to be documented in adults. Along with the hallmark motor impairments, the pronounced sedentary behaviour that occurs in CP (39) has prompted a comparison model of disability to spinal cord injury (40) – a population with significant muscle atrophy, increased adiposity, and elevated risk of type 2 diabetes (41). Although there are no national surveillance programmes that monitor CP, recent data demonstrate that overweight/obese adolescents with CP have a higher prevalence of dyslipidaemia, hypertension, fatigue and early maturation (42). Mortality records have also demonstrated a two to threefold greater prevalence of coronary heart disease among adults with CP as compared with the general population (43). Thus in conjunction with reported increased sedentary behaviour (44,45), it is conceivable that patients with CP are at
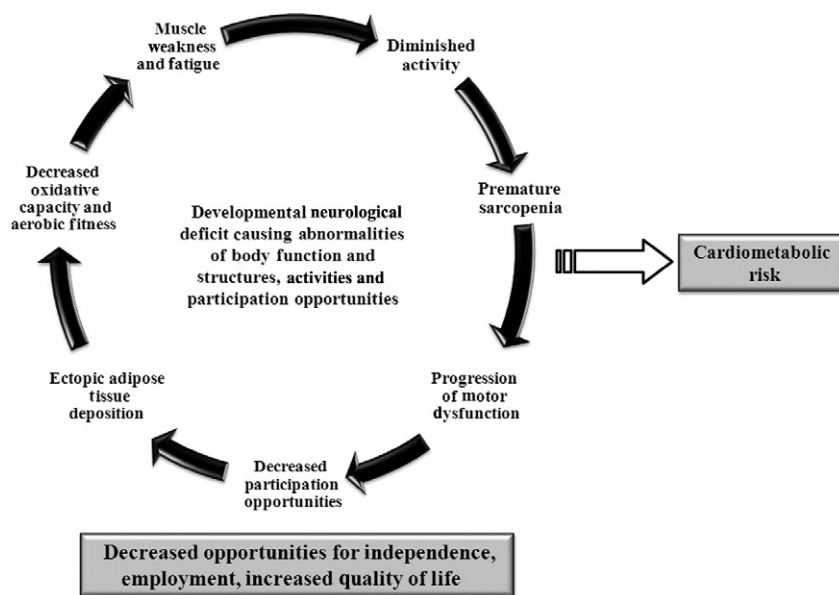
Figure 1 Conceptual model depicting the circular nature of various hallmark causes and consequences of health/functional decline in cerebral palsy (CP).

increased risk for not only exaggerated muscle dysfunction, but also obesity-related cardiometabolic health decline (40).

There has been much discussion on how best to characterize body habitus or 'fatness' in this population. Although body mass index (BMI) is a valid metric for stratifying general population into different risk categories, BMI does not discriminate adipose tissue and muscle, and lacks sensitivity to identify non-obese individuals with excess body fat (46). Whereas most studies have focused on measurement strategies for body fatness or the validation of methods to predict body fat stores among patients with CP (38), findings also reveal significant losses of lean body mass (47) and specific muscle tension (48), and thus highlight the implications of skeletal muscle deterioration. As a result, an individual with muscle atrophy and diminished bone density (another common attribute among adults with CP [49,50]) may likely have a normal BMI, and yet still have excessive body fat, i.e. normal-weight obesity. Indeed, recent data have confirmed that the normal-weight obese phenotype may be present in as many as 30 million Americans, and is strongly associated with cardiometabolic dys-regulation, a high prevalence of metabolic syndrome and an increased risk for cardiovascular mortality (51). Although current statistics are disturbing, they fail to account for individuals with physical and cognitive disabilities, a population in which risk for normal-weight obesity may be significantly higher. Therefore, predetermined BMI cut-points are not only insufficient to delineate the association between fat and muscle, but are similarly inadequate for characterizing cardiometabolic health among individuals with CP (52).

We recently examined the independent association between various anthropometric indicators (BMI, waist circumference [WC], waist-to-hip ratio [WHR] and waist-to-height ratio) and standard clinical markers of cardiometabolic health risk in adults with CP (52). Findings revealed that BMI was significantly lower among individuals with greater motor impairment (i.e. Gross Motor Function Classification System [GMFCS] IV–V) (24.2 ± 6.2 kg m^{-2}) vs. GMFCS I–III (30.1 ± 7.6 kg m^{-2}), and was not associated with any markers of risk. Conversely, WHR was independently associated with various indices of risk, including total cholesterol to high-density lipoprotein (HDL) cholesterol ratio ($r = 0.45$; $P < 0.05$), HDL cholesterol ($r = -0.51$; $P < 0.01$) and triglycerides ($r = 0.40$; $P < 0.05$) – a risk profile similar to what has been identified in the normal population (53,54). Moreover, WHR was not mediated by level of impairment, and thus it may provide a sensitive surrogate marker of visceral adiposity and cardiometabolic risk for this population. As a follow-up case series, we measured body composition in three adults with CP using dual-energy X-ray absorptiometry. Despite having normal BMIs, each of the patients displayed a level of total body fat above the 90th percentile. Moreover, WC and WHR placed all three individuals in the 'high-risk category' (55), which again supports that indicators of visceral adiposity are likely superior for classifying risk for adults with CP (i.e. as compared with BMI).

The role of adiposity in muscle impairment

Emerging data also indicate that localized adipose tissue within and surrounding the muscle are related to acute

weakness and reduced muscle quality (i.e. strength per unit of muscle mass) in the obese and ageing populations (56–58), as well as incident mobility disability (e.g. self-reported difficulty in walking or climbing steps) (59). Specifically, evidence indicate cellular crosstalk between muscle and fat tissue, which may lead to disruption in muscle growth and decreased functional capacity (60). Most research pertaining to the association between muscle mass and strength has demonstrated that physiological cross-sectional area as a robust predictor of force production. In the context of a heterogeneous healthy population, ample evidence exists to support this association, as well as the general belief that increased strength is a direct result of gains in muscle mass. Conversely, from a clinical perspective, there is an increasing interest in defining disparate declines in strength and muscle mass, as a way to explain the health risks of disease, lifestyle and/or ageing. Not surprisingly, nearly all research related to the influence of adiposity to potentiate risk for secondary dysfunction has been conducted among elderly populations. Towards that end, it is now well established that age-related losses of strength cannot exclusively be attributed to the loss of muscle mass (61). As is frequently reported in the ageing literature (57,62,63), if muscle strength deteriorates at a greater rate and to a larger extent than skeletal muscle mass, muscle quality is significantly diminished, placing individuals at heightened risk of gross motor functional decline, falls and early mortality (21,64–66). However, it is also well established that sarcopoenia is paralleled with significant increases in adiposity (i.e. 'sarcopenic obesity') (56,67); the confluence of which represents a robust predictor for subsequent attenuation of muscle strength and quality (56,57), and of course, cardiometabolic disease risk (68,69).

For individuals with CP, neural inefficiency has a well-known effect on voluntary force production (24), and thus is known to influence the association between muscle size and strength. However, to date, secondary mediators of muscle quality, such as altered adiposity partitioning and related cardiometabolic abnormalities, have not been studied in this population. In view of the recent data to suggest an attenuating effect of local adipose tissue deposition on muscular function (56,70), examining this interaction among adults with CP is merited. Particularly relevant to clinical rehabilitation outcomes, evidence have confirmed a definitive link between obesity and reduced functional capacity (59,71,72). This has been attributed to losses of lower extremity-normalized strength (i.e. strength relative to body mass) (73), which manifests as an increased difficulty manoeuvring a larger body habitus. However, in conjunction with general increased skeletal stress and the handicap of lifting/moving greater 'deadweight' fat tissue, the negative impact of adiposity on muscular strength or muscle quality may also contribute to gradual declines in functional status and overall increased disability risk

throughout adulthood. Excessive adiposity would thus represent a dual effect of not just increased mass, but a simultaneous decreased ability for an individual to lift that mass because of diminished muscle quality. The causal mechanism through which adiposity contributes to secondary impairment in CP has yet to be examined. Indeed, further examination of the association between adiposity and muscular function, prior to obesity and cardiometabolic disease presentation, would highlight possible aetiology and/or treatment options for secondary comorbidity and disability among adults with CP.

Altered fat partitioning and chronic inflammation

The accumulation of fatty acids in non-adipose tissues (i.e. ectopic adiposity) is a dynamic, 'lipotoxic' (74) process that occurs as a result of chronic disequilibrium between energy intake and energy expenditure, and is robustly associated with skeletal muscle insulin resistance (75–77). Recent reports pertaining to the impact of ectopic adipose tissue on cardiometabolic health and muscle function have focused on the influence of myosteatosis (i.e. muscle fat infiltration) (78,79). Most often characterized with gross morphological data from ageing adults (e.g. muscle attenuation [78] or localized intermuscular adipose tissue [IMAT] [80]), this infiltration appears as a hallmark of certain disease processes (e.g. Duchenne muscular dystrophy, type 2 diabetes) (81,82), spinal cord injury (83,84) and obesity (85–87), as well as in conjunction with prolonged sedentary behaviour (88).

Ectopic adipose tissue deposition may occur long before an individual meets the BMI criterion for obesity, or is considered at clinical risk for cardiometabolic comorbidity. Previous research has revealed a robust link between IMAT and elevated levels of proinflammatory, adipocyte-derived hormones and cytokines (89,90), which may also lead to attenuated strength capacity (91). Thus, in conjunction with pronounced changes in the hormonal/metabolic milieu, IMAT infiltration could yield a chronic inflammatory state and general, inhospitable physiological environment, which contributes to simultaneous degradation of contractile properties, diminished muscle quality and decreased cardiometabolic health. At the cellular level, increases in skeletal muscle intramyocellular lipid (IMCL) and reductions in mitochondrial size, density and function (92–94) have also been implicated in the aetiology of insulin resistance, the metabolic syndrome and diabetes. Moreover, age-related decreases in mitochondrial function are also linked to accumulation of skeletal muscle lipid, and may thus represent evidence for the hallmark metabolic dys-regulation among many older adults.

Despite the apparent link between increased skeletal muscle fat content, decreased mitochondrial adenosine tri-

phosphate production and insulin resistance (95), there is a well-described 'paradox' (96,97) among trained endurance athletes in which elevated IMCL content is concurrent with high oxidative capacity and insulin sensitivity. Evidence also reveals IMCL increases as a normal adaptive response to chronic aerobic exercise among previously sedentary individuals (98). However, in addition to the mediating role of aerobic activity on lipid accumulation in the muscle, it is also likely that fundamental differences in subcellular localization, ultrastructure and/or proximity of IMCL to mitochondria (99,100) exist between these phenotypes (i.e. and thus no real 'paradox'). Clearly, the trafficking fate of lipid in the muscle is mediated (or determined), to a certain extent, by the type and amount of PA. However, considering the degree of muscle atrophy and sedentary behaviour among individuals with CP, as well as the hallmark fatigability during activity, it is certainly possible that a confluence of several non–CP-specific mechanistic defects may be occurring.

Indeed, secondary factors such as excess deposition of intermuscular adiposity, decreased mitochondrial function or chronic inflammation may serve to exaggerate the severity of functional impairment throughout adulthood, and lead to progressive cardiometabolic disease risk. Among populations with motor disorders such as adults with CP, the influence of altered adipose tissue partitioning on clinical rehabilitation or metabolic outcomes has never been delineated. At present, there has only been a single study to examine myosteatosis in CP. In 2009, Johnson and colleagues (101) demonstrated greater IMAT among children with quadriplegic CP as compared with typically developing children, which was found to be inversely associated with objectively measured PA. Therefore, the extent to which myosteatosis contributes to secondary muscular pathology and/or deterioration of cardiometabolic health is still unknown. However, based on these findings and the abundance of data from the obesity and ageing literature, it is tempting to speculate a strong association between chronic sedentary behaviour , muscle wasting, and risk for metabolic dys-regulation in persons with CP. Recent advances in magnetic resonance imaging technology may prove indispensable to evaluate the progression of muscle pathology in CP and other neuromuscular disorders, and serve as a non-invasive option over biopsy for future bench research (102).

Perhaps more importantly, ageing and obesity are both known to induce a chronic inflammatory milieu that precipitates risk of cardiovascular and metabolic diseases, as well as early mortality. Chronic inflammation in CP may also be linked to a prolonged neurological injury processes (103). However, and despite the extremely well-characterized neuroinflammatory response associated with CP in preterm infants (104,105), there has been no research to examine the potential circular cause and con-

sequence of events with cardiometabolic-induced inflammation in children or adults with CP. We have recently described a potential model of exaggerated risk in this population (106), and speculate that the altered peripheral inflammatory response documented in CP (107) may be at least partially influenced by cardiometabolic dys-regulation, or significantly exaggerated by it. Indeed, obesity stimulates a chronic meta-inflammatory response (108). Moreover, several lines of research now indicate a role for high-fat diet to induce neuroinflammation (i.e. hypothalamic), and a cyclical alteration in the regulatory mechanisms associated with sympathetic drive, satiety and nutrient storage/energy homeostasis (109). Thus, it is likely that chronic and dys-regulated inflammation may have a profound effect on cardiometabolic and neurologic physiology in highly vulnerable populations such as CP, and may thus serve as potential targets for pharmacological or behavioural treatments to improve long-term health in these patients (106).

Physical activity and exercise recommendations

Although by definition CP is a non-progressive condition, muscle pathology is well known to progress concomitantly with age and chronic sedentary behaviour (110). Thus, future work is certainly needed to identify independent mechanistic constituents of the CP phenotype, but also, evidence of overlap with other, modifiable outcomes. Unfortunately, clinical interventions for treating CP-related symptoms have not historically included PA or exercise recommendations for health preservation. In addition to routine outpatient clinical treatments (e.g. Botox injections for spasticity), standard physical/ occupational therapy is prescribed in an effort to assist with gait/mobility deficits, general range-of-motion, issues with pain and fatigue, and to improve muscular strength. However, in combination with these standard clinical procedures, there are various additional interventional strategies that may provide the means to preserve both function and cardiometabolic health in CP. There is thus a critical need to identify predictors of secondary pathology and comorbidity, as well as to evaluate new strategies for maintaining muscle mass and function, enhancing global cardiometabolic health and improving quality of life for adults with CP.

Central to the pathophysiology of muscle dysfunction and related comorbidity, physical inactivity is consistently recognized as a predominant and perennial cause of cardiometabolic decline and sarcopoenia in the general population (111). As muscle atrophy is robustly associated with weakness, frailty and mobility disability (112,113), failure to prevent its progression with behavioural interventions including strategic PA, exercise and lifestyle

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modification may significantly impede optimal quality of life, and lead to early mortality. Several potent behavioural factors are recognized to independently contribute to onset and progression of muscle dysfunction and related comorbidity in the general population, including obesity, physical inactivity, smoking and malnutrition (i.e. both over- and under-nutrition). Of these factors, physical inactivity is perhaps the most detrimental for propagating impairment of function throughout adulthood, and along with insufficient dietary provisions, is the risk component that has received the most research attention for treating age-related atrophy and weakness. Indeed, ample evidence exists to confirm a robust, independent association between sedentary behaviour and disease, disability and shortened lifespan among all adults (114). Despite this rather simplistic and predictable trajectory of health decline, substantial debate persists regarding the optimal strategy to slow or reverse the downward spiral of muscle tissue integrity in CP. At the centre of this debate, there is currently no consensus recommendation for using PA to simultaneously combat secondary muscle pathology and chronic disease risk in this population.

Although several studies have suggested a beneficial role for exercise participation among adults with CP (102,115), implementing PA programmes for this population involves a variety of physical and psychosocial challenges (116). In general, individuals with disabilities who wish to increase their activity levels face widespread problems of accessibility. In many cases, common forms of exercise and activity are not an option, because most fitness facilities do not have specialized or accessible equipment. Moreover, published exercise recommendations often encourage forms of exercise that are not appropriate for non-ambulators (117). Individuals with disabilities often lack knowledge concerning the importance of exercise, or are under the impression that they are unable to participate in PA (39). Ultimately, young adults with paediatric onset disabilities such as CP may have no history or experience with anything more active than standard physical therapy, as many areas have little access to specialized sport programmes. These barriers notwithstanding, recent evidence (118) has revealed that fundamental movement proficiency among children with CP is negatively associated with sedentary behaviour and positively associated with moderate-to-vigorous PA. These results suggest that preservation of functional capacity is important to ensure sustainable activity and participation among children with CP, and that medical rehabilitation should focus on both gross function *and* structured PA recommendations.

Concerns of elevated risk associated with activity for this population have prompted a minimalist paradigm and a general trend of non-progressive, yet safe activity suggestions. However, and as an important point of clarification, 'activity participation' should not be interpreted as merely the inverse of 'inactivity.' Rather, in order to appreciate the extent to which various lifestyle, PA and exercise strategies contributes value to the spectrum of health and physical fitness among adults with CP, the unique attributes of each must be distinguished.

Thus, a clear distinction is made herein between (i) lifestyle strategies to reduce sedentary behaviour and related chronic health risks; (ii) PA strategies that confer preservation of function and basic cardiometabolic health and (iii) structured exercise strategies that are intended to induce specific physiological and morphological adaptations.

Sedentary behaviour is defined as time spent sitting or lying down (119), and is known to be exaggerated in CP (39,44). This modifiable risk factor has received significant attention as a robust predictor of chronic disease and mortality among adults (120,121), and moreover, is acknowledged to accelerate sarcopoenia (122). Importantly, sedentary behaviour should not be regarded as synonymous with the low end of PA, as these factors are each independently associated with diabetogenic and atherogenic profiles (120,121,123). Sedentary behaviour is generally defined as a range of behaviours that coincide with an energy expenditure less than or equal to 1.5× metabolic equivalents (124). In using this definition, it is actually plausible to have a significantly increased risk profile if someone is both physically inactive and also engages in extended bouts of sedentary behaviour. Conversely, it is also possible to become deficient in only one, as these behaviours represent two viable targets of intervention. Although decrements in muscle mass and function have been considered the primary contributing factors of gross motor decline in CP, it is conceivable that such changes are also the principal drivers of increased sedentary behaviour in this population (125). Generally, both weakness and obesity precipitate sedentary behaviour, which ultimately results in a diminished volume and frequency of stimulus to the cardiovascular and neuromuscular systems. Although weakness is considered a readily preventable and treatable condition in CP, it is rarely addressed at early-onset decline, and in turn may lead to decreases in functional capacity, and gradual yet significant muscle wasting over time. Clearly, the associated outcomes of functional deficit and chronic sedentary behaviour may also serve as a contributing risk factor for other chronic disease processes (e.g. the metabolic syndrome [126]). This circular series of events has made the treatment of secondary comorbidity in CP an exceedingly difficult directive; however, a simplistic and yet central preventive strategy from a clinical context is to encourage a lifestyle characterized by increasingly fragmented sedentary behaviour.

Baseline activity is operationalized as the smallest increments of body movements that increases energy above sedentary behaviour (e.g. standing, slow walking, lifting

very light objects, etc.) (127). Consistent with this definition, individuals who do only baseline activity are not sedentary, *per se*, but are *still* considered to be inactive. It is well known that adults with CP are less active than young adults, and this trend is coincident with various secondary effects of the disorder (e.g. pain, fatigue, arthritis, etc.). Recent evidence reveals that increasing or maintaining PA is related to greater survival in older adults in the general population, even among those with obesity or functional limitations (114). Indeed, regular PA is considered necessary for health maintenance, and is recommended to sustain a healthy body composition and/or BMI, lipid/lipoprotein profile, glucose tolerance, blood pressure, ambulatory balance, and psychological well-being (128,129). Lifestyle or leisure-time PA is aerobic in nature, and can take the form of any popular leisure activity (e.g. walking, gardening, biking, etc.). In addition to avoiding sedentary behaviours, some lifestyle PA is certainly better than no activity at all, and for most outcomes there is a dose–response relationship between volume, frequency and intensity of PA, and respective health benefit (128). In remaining consistent with the nomenclature from existing PA guidelines in the general population, moderate-intensity PA may be defined as PA that involves a moderate level of effort relative to an individual's aerobic capacity (129). Although baseline activity, lifestyle PA and moderate-intensity PA are all very appropriate suggestions for many of the comorbidities associated with obesity (e.g. insulin resistance, chronic inflammation, impaired glucose homeostasis), none of these is particularly effective for preservation of skeletal muscle quantity or quality (i.e. strength/muscle mass).

Conversely, whereas lifestyle PA may contribute to maintenance or improvements in global health and enhanced quality of life, only certain types of exercise are known to have profound benefits for weakness and atrophy, and related outcomes. In particular, tailored exercise is necessary for targeting components of health-related physical fitness, which include cardiorespiratory fitness, muscular strength and endurance, body composition, flexibility and balance (130). Each of these components either indirectly mediates risk of chronic comorbidities, or is directly associated with reversal of muscle pathology itself. Table 1 offers the type of exercise needed to accommodate each of these health-related physical fitness outcomes, the mechanism(s) through which the adaptation occurs and the nature of this contribution to directly or indirectly influence health and/or function in CP.

This table is intended to represent a comprehensive framework for informing the development of lifestyle, PA and exercise prescriptive interventions for CP. Much work is still needed to identify appropriately tailored strategies for the spectrum of clinical needs specific to this population. Unfortunately, there has been very little focus on understanding the secondary mechanisms of muscle pathology or cardiometabolic risk in CP, independent of those exerted by the primary neurological insult. Thus, identifying appropriate preventive health strategies to reduce sedentary behaviour and increase PA/exercise participation is a vital step in preserving function, health and optimal quality of life for individuals with CP. Towards that end, we have recently shown that among previously sedentary, significantly motor-impaired adults with CP, recumbent stepping exercise can be completed at a sufficient level to stimulate a significant cardiorespiratory response without post-exercise pain (131). Although this is an important first step, future research is desperately needed to identify optimal interventions (e.g. comparative effectiveness and dose–response studies) for various levels of motor impairment. Until the time that such evidence exists, we caution that although the specific modalities recommended in Table 1 have documented safety and efficacy among obese, type 2 diabetic and elderly populations, future feasibility studies are needed in CP.

Conclusion

The extent of atrophy and weakness is widely variable among adults with CP, which, in combination with the neurological deficits, is likely attributable to the degree of sedentary behaviour and the peak in mass and strength attained earlier in life. These hallmark characteristics of CP place individuals at extremely high risk for cardiometabolic disease and early mortality, as well as premature sarcopoenia and functional deterioration. Thus, it may be hypothesized that the benefits of early intervention will translate to better preservation of long-term health and independence. Among the general population, studies have documented a disproportionate decline of strength and muscle mass, which suggests that these age-related phenomena are somewhat independent (132,133). Further, there is a robust association between strength deficit and diminished functional capacity (134,135), and although the rate of decline is largely an individual phenomenon, further decrement may be mitigated with early detection, and appropriate prescription of PA. Reducing the amount of pure sedentary behaviour may be the most appropriate first line of defence for many of the secondary comorbidities in CP. However, and in conjunction with the standard physical and occupational therapies prescribed for managing gait/mobility deficits, spasticity and range-of-motion in this population, participation in PA and progressive exercise is absolutely vital to prevent secondary muscle pathology and cardiometabolic comorbidity throughout adulthood.

Conflict of Interest Statement

No conflict of interest was declared.

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Table 1 Physical activity and exercise options for health-related fitness outcomes

Type of exercise	Health-related component of physical fitness	Example modality options	Mechanism(s) of adaptation	Influence on muscle pathology	Influence on related comorbidities
Moderate and vigorous PA: aerobic exercise	Cardiorespiratory fitness, body composition, muscular endurance, balance	Cycling, brisk walking, recumbent stepping, swimming and aqua aerobics, elliptical training	Central: (i) improved aerobic capacity (VO2 max) through increases in cardiac output and stroke volume and (ii) decreased heart rate at rest and during exercise. Peripheral: (1) increased capillarization of type I muscle fibres (arteriovenous oxygen difference); (ii) increased mitochondrial size, density and function (fatty acid oxidation); (iii) increased stores of metabolic energy (e.g. creatine phosphate, glycogen, triglycerides) and (iv) increased aerobic enzyme activity (e.g. myokinase).	Direct: significant improvement in muscle function (i.e. muscular endurance and fatigue resistance) Indirect: modest improvement in balance, and thus reduction of slip-and-fall risk.	Improvement in all risk factors for cardiometabolic diseases, i.e. body composition (reduced adiposity), decreased blood pressure, improved insulin sensitivity, improved cholesterol/triglyceride profile, reduction in chronic inflammation.
Progressive resistance exercise	Muscular strength and endurance, body composition, flexibility and balance	Selectorized machines, free-weights, pneumatic resistance equipment, body-weight movements (e.g. push-ups, squats), alternative resistive implements (e.g. medicine balls, elastic bands)	Morphological/architectural: (i) increases in single fibre physiological cross-sectional area and whole muscle hypertrophy and volume; (ii) increases in fascicle length (sarcomeres in series) and (iii) increases in pennation angle. Neuromuscular: (i) increased force production capacity and rate of force development through greater recruitment capacity of type II fibre and increased rate coding (motor-unit discharge frequency) and (ii) Improved neuromuscular efficiency through increased intra and intermuscular coordination, and decreased antagonist co-activation.	Direct: significant improvements in muscle size and function (i.e. hypertrophy, strength, power and endurance) Indirect: significant improvements in balance and flexibility. Modest improvements in cardiorespiratory fitness, particularly for previously sedentary adults with CP.	(i) Decreases risk of slip-and-fall accident; (ii) Improvement in glucose homeostasis and insulin sensitivity; (iii) Increases in bone-mineral density and tendon strength and (iv) Improvement in gross motor function.
Balance exercises	Balance	Lateral weight-shift exercises, unstable surface walking and isometric poses, single-leg stance exercises, tai chi	(i) Small increases in strength capacity of ankle, knee, hip and spinal stabilizer muscles and (ii) Improved proprioception and kinaesthetic awareness.	Minimal increases in strength capacity, particularly for previously sedentary adults with CP.	Decreased risk of slip-and-fall accidents.
Stretching/range-of-motion exercise	Flexibility, balance	Static stretching, passive stretching, dynamic range-of-motion exercise, tai chi, yoga, pilates, active-isolated stretching	(i) Decreased stiffness of musculotendinous unit; (ii) Decreased passive resistive force and (iii) Increased stretch tolerance.	Decreased resistance to passive stretch.	(i) Improvement in mobility and (ii) Decreased risk of slip-and-fall accidents.

CP, cerebral palsy; PA, physical activity.

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