The Role of Physical Activity in the Prevention and Management of Alzheimer's Disease—Implications for Ontario

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EXECUTIVE SUMMARY

Statement of the Problem: Alzheimer's disease is an irreversible progressive neurodegenerative condition that is characterized by changes to brain structure and function that commonly results in a deterioration of cognition, memory, and physical function and mobility. In 2011, approximately 15% of older adults (65 y+) in Ontario were living with some form of cognitive impairment or dementia, an estimated 60%-70% of whom have Alzheimer's disease. Because of the substantial personal, caregiver, and economic burden of Alzheimer's disease, there is an urgent need to identify factors that may assist in the prevention and management of Alzheimer's disease to reduce the impact of projected increases in Alzheimer's disease. Given the challenges of pharmaceutical treatment for modifiable and non-modifiable risk factors for Alzheimer's disease, a focus on modifiable risk factors such as physical inactivity is warranted.

Approach: To better understand how physical activity can contribute to the prevention and management of Alzheimer's disease, 871 research articles were reviewed. After closer inspection and quality scoring, 24 randomized control trials and 21 prospective cohort studies examining physical activity and Alzheimer's disease were selected for further analysis.

Results: Within older adults with Alzheimer's disease, regular physical activity improved quality of life (QOL), activities of daily living (ADL), and decreased the occurrence of depression. In older adults without Alzheimer's disease, those who were very physically active were almost 40% less likely to develop Alzheimer's disease as those who were inactive. At the population level, it was observed that more than 1 in 7 cases of Alzheimer's disease could be prevented if everyone who is currently inactive were to become physically active at a level consistent with current activity recommendations. On this basis, potential cost-savings (~$88 to $970 million CDN per year) in healthcare for community-dwelling older adults with Alzheimer's disease are substantial.

Context: Physical activity has the potential to impact both the prevention and management of Alzheimer's disease in Ontario. Additional work is necessary to identify the optimal dose and mode of activity, as well as opportunities for community-based physical activity promotion in older adults.

OVERVIEW OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative condition that is characterized by changes to brain structure and function[1], the consequences of which can be measured in significant personal and societal costs[2]. It is not uncommon for the resulting emotional, neurocognitive, and physical changes to substantially reduce quality of life, increase reliance on others, and decrease functional mobility[2]. Subsequently, the prevalence of depression-like symptoms amongst individuals with AD is up to ten times that of the general population[3,4,5].

In 2011 approximately 747 000 (or 15% of) older Canadians (65 y+) were living with some form of cognitive impairment or dementia[6], an estimated 60%-70% of whom have Alzheimer's[2]. Comparable American statistics estimate that approximately 1 in 8 older adults have AD[7], with an annual cost of treatment approaching $600 billion USD[2]. If current trends continue, the cumulative 40-year cost of care for Americans with AD is expected to approach $20 trillion[8]. While the economic costs are somewhat lower in Canada[9], the psychosocial caregiver burden of Alzheimer's-related disease remains substantial[2]. In Ontario, the age-standardized death rate (per 100 000) older adults has remained relatively constant, and is higher amongst women than men (**Figure 1**)[10]. Given that older adults (65 y+) represent a growing proportion of the Ontario population[11,12,13], the early identification and management of Alzheimer's disease is a challenging, but necessary priority for public health.

Diagnosis and Treatment

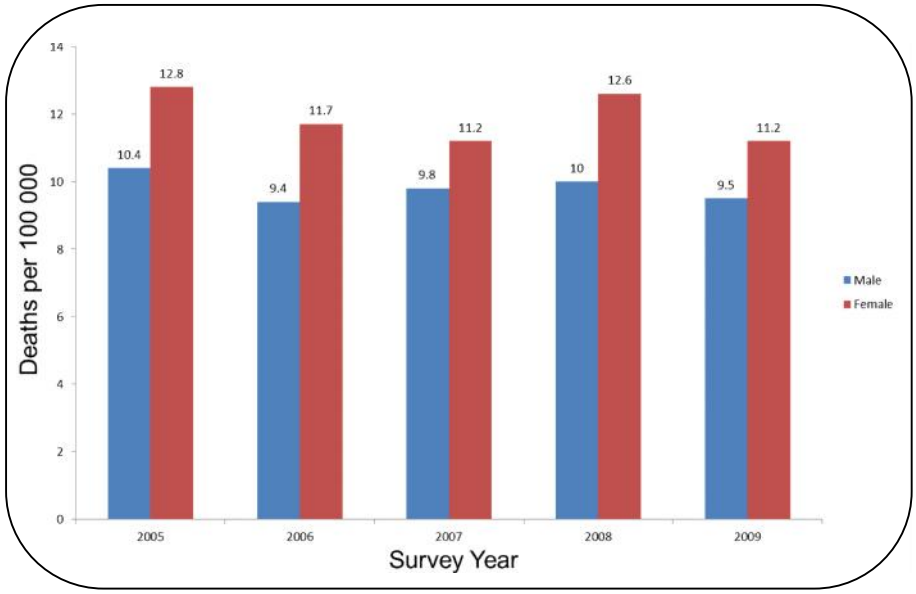

Figure 1: Age-Standardized Death Rates for Alzheimer's Disease in Ontario

According to the 2011 definition proposed by the National Institute on Aging[14], Alzheimer's disease is defined by three progressive and overlapping phases of impairment: i) Preclinical Alzheimer's disease; ii) Mild Cognitive Impairment (MCI) due to Alzheimer's disease; and iii) Dementia due to Alzheimer's disease. In early stages of the disease, many of these symptoms can be mistaken for general changes in behaviour, attention, and forgetfulness[1]. The complexity and gradual nature of these symptoms have also led some to classify this cluster of features as a 'syndrome', with varying lengths of each stage[15]. As a result, a definitive diagnosis of Alzheimer's disease is only obtained at autopsy through a detailed examination of brain tissue[16]. Nonetheless, within the clinical setting, it is believed that physician diagnosis can approach 90% accuracy[16]. Factors involved in the clinical investigation of Alzheimer's cases include a detailed medical history and physical examination to identify family history of dementia, changes in behaviour, mood, and motor performance, and to exclude alternative explanations[1]. In this way, physicians can monitor, treat and arrange supportive services over time. When taken together,

such an approach may be an effective strategy for the early identification of AD[1], which has been shown to contribute to prolonged independence and function[17].

Modifiable and Non-Modifiable Risk Factors

Established non-modifiable risk factors for Alzheimer's disease include advancing age (65 y+), first degree family history, mild cognitive impairment, presence of the apolipoprotein E-ε4 (APOE- ε 4) genetic variant, traumatic brain injury and head trauma[2,7,18]. Evidence also suggests that chronic disease risk factors (e.g. physical inactivity, diabetes, smoking, abdominal obesity, and high cholesterol[19,20]) may increase the risk of developing AD, and factors such as social engagement and low saturated fat / high vegetable diets may reduce the risk of developing AD[7].

Despite this, the management of AD remains challenging. Pharmacological treatment to date is limited to three classes of drugs, the most common of which include: acetylcholinesterase inhibitors for behavioural symptoms; N-methyl D-aspartate (NMDA) antagonists to treat cognitive decline and slow Alzheimer's progression; and antipsychotic medication (not recommended)[21]. Other complementary therapeutic approaches such as group-based social (e.g. art and music), cognitive, and emotion-oriented therapy (e.g. psychotherapy, validation, reminiscence, etc.) programs have been employed, with varying effectiveness[22,23].

PHYSICAL ACTIVITY AND ALZHEIMER'S DISEASE

Given the difficulties noted above, the need for effective population-based prevention and management are critical. While not yet definitive, accumulating animal and human research now suggests that regular physical activity (PA) is beneficial for the prevention and management of AD. Moderate-to-high levels of aerobic PA has also been shown to improve quality of life, maintain functional performance, and positively impact on mood and depression[24,25,26]. Although the exact mechanisms are not yet known, experimental research suggests that PA may promote the maintenance of grey matter brain volume, and slow the rate of cognitive decline[26]. In turn, regular physical activity has also been associated with increased cellular resistance to oxidative stress, and more efficient energy metabolism[27]. In animal models, adaptations in neural networks, cerebral blood flow, angiogenesis and brain perfusion has been shown to occur in as little as 3 to 4 weeks of treadmill running[28]. Cardiovascular health and fitness in turn has been related to better cognitive outcomes, lower age-related brain atrophy, plasticity, and improved cerebral blood flow[29].Higher levels of PA are also associated with prolonged survival in AD[30], and cardiorespiratory fitness has been shown to lower the risk of dementia-related deaths[31,32].

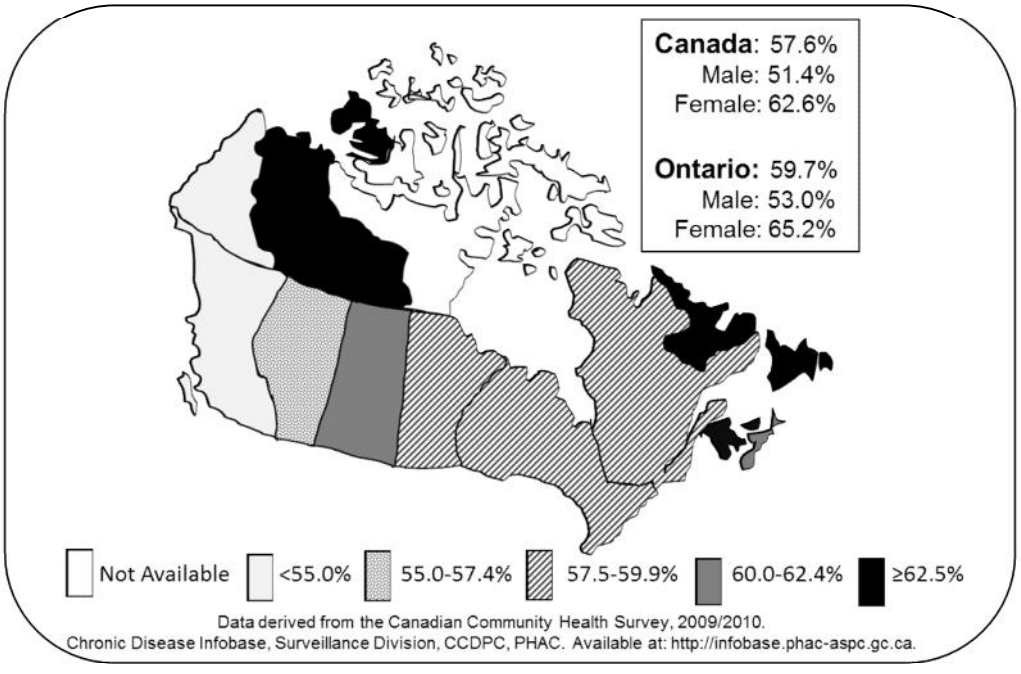

Figure 2: Regional Variation in Physical Inactivity in Canada (age 65 y+), 2009/2010.

Despite the apparent health benefits of PA, the majority of older Canadians (65y+) remain physically *in*active (<1.5 kcal/kg/day) (**Figure 2**) [34]. This level of energy expenditure can be thought of as only small amounts of activity (~15 minutes of walking) each day. Moreover, only modest changes in the prevalence of inactivity have occurred in *any* age group since 1994 (**Figure 3)** [34]. According to joint guidelines from the Canadian Society for Exercise Physiology and Public Health Agency of Canada[35], every Canadian adult is advised to accumulate 30 minutes of moderate-to-vigorous intensity PA (MVPA), on most if not all days of the week. In addition to a minimum of 150 minutes of MVPA per week, older adults are advised to engage in muscular endurance, flexibility, and balance training as a supplement to regular aerobic activities[35]. It is now understood that the recommended dose of 150 minutes of MVPA per week can be accumulated (with equal benefit) through either traditional exercise sessions, or multiple bouts of lifestyle-based activity (≥10 minutes in duration)[35,36,37]. However, on the basis of this recommendation, less than half of older adults in Ontario are physically active at a level consistent with current recommendations for health[38]. While not a focus of the overall recommendations, accumulating evidence now suggests that even small breaks in 'sitting time' (or sedentary behaviour) may also impact on intermediate health risk, and represents an area of ongoing research[39].

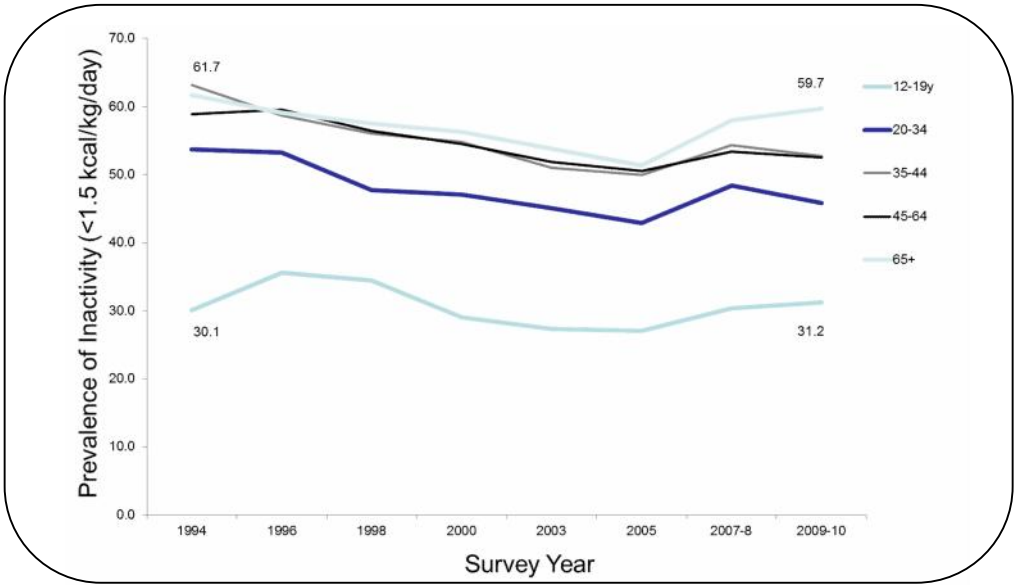

Figure 3: Temporal Trends in Physical Inactivity in Ontario, 1994-2009/2010

While the above guidelines are based on accumulated evidence of the relationship between PA and several chronic diseases, they are intended to be general guidelines for maintaining health, rather than specific guidelines for prevention or management of a particular condition. This means that depending on the disease, the 'optimal' dose, intensity, and mode of PA is likely to vary as a function of disease pathology, activity preference, and individual variation (e.g. baseline health, PA/fitness, heritability and genetics)[36,37,40].

OVERVIEW OF LITERATURE SYNTHESIS

PURPOSE

In a recent systematic review from the Alzheimer's Society Systematic Review group[41], evidence was found in support of a role of PA in the prevention of vascular dementia, whereas the Cochrane Collaboration found insufficient evidence for a role of PA in its *management*[42]. Given that one of the hallmark adaptations of regular PA is improved mood and overall well-being[24,25,26], the purpose of the

current literature synthesis is to update earlier work from the Cochrane Collaboration and others to examine the influence of PA on both the primary prevention and management of Alzheimer's in community and residential-dwelling older adults.

OBJECTIVES

Objective 1: To examine whether PA is beneficial for the management of AD

> **Study Eligibility:** All studies with random assignment and concealment, comparing a PA intervention to a control or other standard of care condition were considered for inclusion.

Objective 2: To quantify the protective effect of PA on the development of AD

> **Study Eligibility:** All prospective cohort studies of 'cognitively healthy' older adults (65 y+), with follow-up for incident Alzheimer's disease.

METHODOLOGY

Search and Selection Criteria

MEDLINE was searched on January 5th, 2013 for all publications (1966-) using the search terms "Alzheimer's AND ("physical activity" OR exercise OR sedentary OR "energy expenditure")". Of the total 871 abstracts identified, 595 were related to the management of AD, whereas 276 dealt with its primary prevention. This list was subsequently used to scan the Cochrane Library and recent published literature reviews for additional articles of interest. After screening of abstracts, 234 review, editorial, and case-report studies were immediately excluded. Out of the remaining articles (N=66 randomized controlled trials (RCT) and 571 cohort or other studies), 146 articles were identified as potentially eligible. All studies meeting inclusion criteria for Objective 1 were evaluated on the quality of their study design, using a 26-item (32 point) rating approach proposed by Downs and Black[43]. This checklist included subscales for 'reporting' (9 items), 'external validity' (3 items), 'bias' (7 items), 'confounding' (6 items), and 'power' (1 item). Consequently, data from 24 RCTs was abstracted for exploratory data analysis. These included primary and secondary study endpoints related to quality of life (N=3), mood / depression (N=6), cognition / memory (N=7), motor function / functional performance (N=11), activities of daily living (N=5), fall risk (N=2), neuropsychiatric disorders (N=2), and other measures. For objective 2, an additional 21 prospective cohort studies were identified for further analysis of the relationship between PA and incident (new onset) AD.

Description of Outcomes

Management of Alzheimer's Disease: Due to differences in measurement and study design[44], several of the above outcomes (including memory and cognition) were excluded from the present analysis. For the purpose of this report, the three most uniformly measured outcomes will be discussed: i) Depression; ii) Activities of Daily Living (ADL), and; iii) Quality of Life (QOL).

Primary Prevention: New onset Alzheimer's disease (all stages).

Statistical Approach

Meta-analysis techniques were used to combine results of different studies to provide a single overall measure of 1) whether or not PA is an effective treatment for different outcomes in patients with AD; and 2) whether or not there is evidence that PA can prevent the developing of AD later in life. This

approach weights each study estimate by its precision, so that larger studies, which are typically more precise, are given higher weight in the analysis. These general meta-analysis methods follow those provided by the Cochrane Collaboration[45].

Due to differences in study participants, prescribed physical activity regimens, group assignment, and measurement of the outcome variable of interest, a *random effects meta-analysis model* was used to examine the first objective on secondary treatment outcomes. Given that these study differences commonly lead to inconsistent results, random effect models typically provide a more conservative estimate in the effectiveness of PA. In contrast, the primary prevention studies in the second objective were significantly more consistent in their study methodology and results, allowing for the use of a *fixed effects meta-analysis model* for this objective. For additional details regarding the merits and limitations of the fixed vs. random effects meta-analysis models, see Fleiss[46]. A description of study heterogeneity was calculated by the I^2 statistic[47]. Where appropriate, all analyses in this report include 95 % confidence intervals (CI).

The Standardized Mean Difference (SMD)

In order to evaluate whether PA is an effective treatment for AD, the *standardized mean difference* was used to provide a uniform measure of treatment efficacy across studies. This approach is necessary as individual studies often measure the same outcome (e.g. depression) using a variety of different scales (e.g. Beck Depression Inventory, Center for Epidemiologic Studies-Depression Scale, etc.), which prohibits the simple pooling of study results (see reference 45, Section 9.4.5.1). In this manner the SMD can adjust for differences in study scales and allow a valid combination of similar outcomes across studies. For reference, a standardized mean difference of zero shows no difference between the PA and control groups in the treatment of AD symptomology.

Focus on Study Endpoints

Although all randomized trials in the first objective appropriately adjusted for baseline characteristics in the respective studies, use of the SMD as our effect measure prohibits adjustment for these baseline values, which typically leads to a reduction in the observed effectiveness of PA. For this reason, although a number of studies had higher levels of statistical significance, our analysis strategy is more conservative in practice. This approach, which focuses on study endpoints is consistent with meta-analysis guidelines published by the Cochrane Collaboration[45].

The Hazard Ratio (HR)

In order to determine whether PA is effective at reducing the risk of developing AD, the Hazard Ratio (HR) is used to quantify this objective (see reference 45, Section 9.2.6). In all statistical models, a HR of 1 corresponds to no difference in the risk of developing AD, while a HR < 1 indicates that this group has a lower risk (probability) of developing AD. Note that for mathematical reasons, we often consider the logarithm (log) of the HR, which corresponds to a value of 0 for no difference in risk between the PA and comparison group, while a log HR < 0, indicates that the group has a lower risk of developing AD.

Adjusted vs. Unadjusted Analyses

A randomized trial ensures that on average, both the treatment (PA) and control groups are roughly balanced on factors that may affect how well or how poorly the treatment works, such as age, gender, family history, etc. Unfortunately, cohort studies which follow-up individuals for a period of time to determine if they develop AD do not benefit from this 'group balance' property of randomized trials. For this reason, we included both unadjusted and adjusted meta-analyses for our secondary objective of

preventing AD with PA. These adjusted models include statistical adjustments for factors such as age, gender, socio-economic status, as well as other potential factors that may influence an individual's risk of developing AD, and are thus more reliable in their estimation of the prevention of AD through PA.

Population Health Metrics

Whereas the SMD and log HR provide estimates of the average effect of an activity intervention, the population attributable risk (PAR%) is a theoretical estimate of the impact of an intervention applied at a population level. A simplified version of the PAR% can be calculated using the prevalence of an exposure (P), and the relative risk (RR) estimate of the exposure-disease relationship, as follows: PAR%=[P(RR-1)]/[1+P(RR-1)][48]. In this case, the HR derived from the adjusted analysis of prospective cohort studies was used to represent the RR, while the exposure, the prevalence of inactivity in Ontario was drawn from age-specific analyses (65 y+) of the Canadian Community Health Survey 2009-10[49]. Because the PAR% is a theoretical representation of the proportion of a disease that can be attributed to a particular exposure, there are a number of assumptions with its use, most notably, that the risk factor under investigation (e.g. physical inactivity) is the only modifiable exposure for the disease[50]. While the PAR% is a valid measure of a potential intervention, PA is known to influence many other psychosocial and cardiovascular risk factors associated with Alzheimer's disease development. As such, a conservative approach was adopted in which the upper boundary of the 95% confidence interval was applied to describe this potential outcome.

RESULTS

Physical Activity as Treatment for Alzheimer's Disease

PA as Treatment for Depression in AD Patients

This objective relied on pooling together five studies[51,52,53,54,55], which measured depression in Alzheimer's patients before and after a PA intervention or a control condition. This analysis produced an overall SMD of 0.84 [0.03, 1.66] which suggests a significant reduction of depression through PA in AD patients **(Figure 4)**. Note that for this analysis, an I^2 = 90.2 % was obtained, which suggests extreme differences in study results. However, upon examining the results, the two smallest trials[51,53] showed an extremely high treatment effect, while the three larger studies showed a more moderate effect of PA; leading to extreme heterogeneity. Finally, Steinberg et al.[56] showed a statistically significant interaction between exercise and time, but could not isolate the effect of exercise in their analysis adjusting for differences in MMSE between the two groups and was therefore omitted.

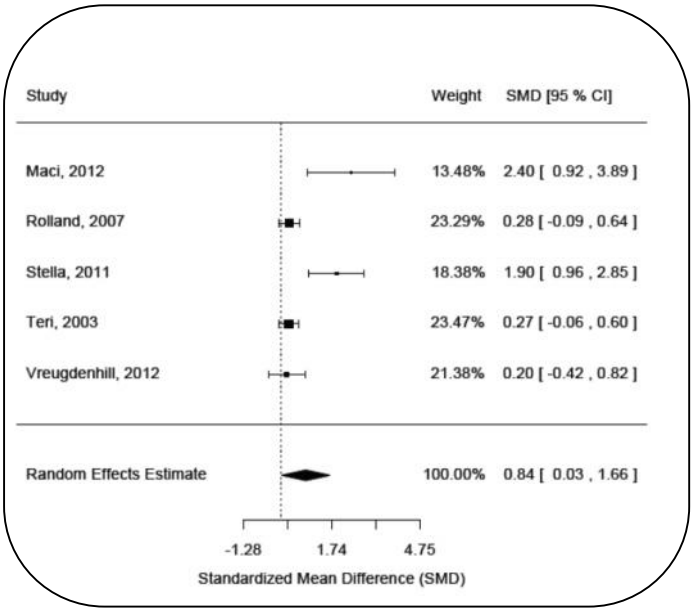

Figure 4: Effect of Physical Activity on Depression in Alzheimer's Patients

PA Improves Activities of Daily Living (ADL) Scores in AD Patients

Activities of daily living represent a range of personal care and function activities required for independent daily living (e.g. bathing, dressing, meal preparation, etc.). A meta-analysis of four studies[52,55,57,58] provided strong evidence that PA interventions improve ADL scores for Alzheimer's patients. This is demonstrated by an SMD of -0.65 [-1.29, -0.01], which suggests a moderate effect of PA on reducing ADL dependencies **(Figure 5)**. For reference, the studies were again heterogeneous as demonstrated by an I^2 value of 79.3 %. However, the majority of this variation can be attributed to the Venturelli et al.[58] study, which observed a very large effect of PA on the reduction of ADL scores. For consistency with other studies and to avoid repeated inclusion of the same control group, we included only the Physical Activity vs Control comparison in our analyses of Roach et al.[57]. Finally, an additional study[59] did not include final study values for ADL, but showed a significant interaction between exercise and control group and time, which supports our final conclusion.

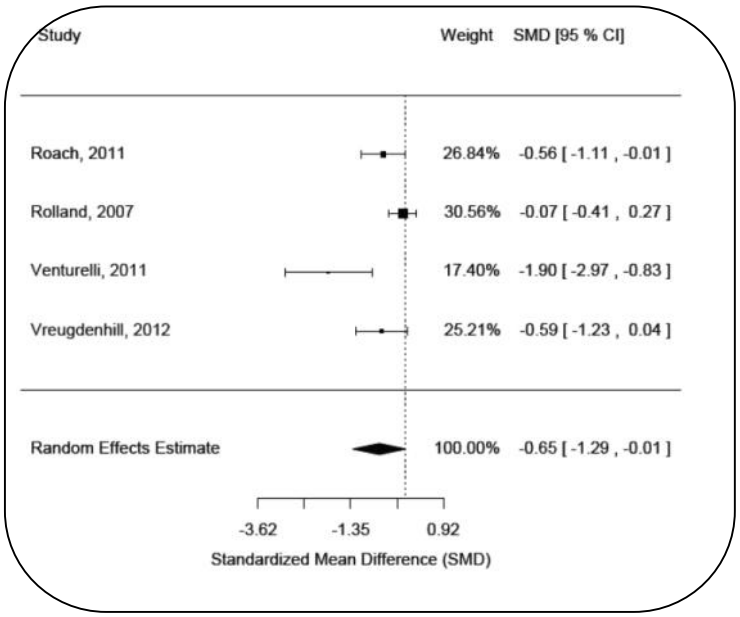

Figure 5: Effect of Physical Activity on Activities of Daily Living in Alzheimer's Patients

PA Improves Quality of Life (QOL) in AD Patients

A meta-analysis of two studies[51,54] provided evidence that PA improves QOL in Alzheimer's patients. This is demonstrated by a pooled SMD of -0.82 [-1.59, -0.06] in the random effects model **(Figure 6)**. In this analysis, moderate differences between the two studies were observed (I^2 = 46.0 %). Here again, this analysis should be interpreted with some caution as an additional study[56] demonstrated a negative (not statistically significant) impact of exercise on QOL in their results. However, due to differences in the method of analysis, it was not feasible to combine this result with the other two studies.

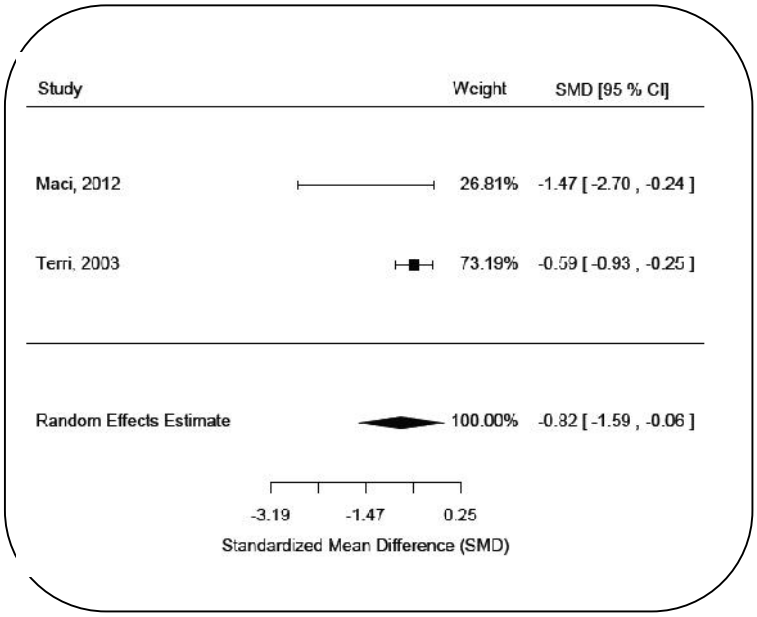

Figure 6: Effect of Physical Activity on Quality of Life in Alzheimer's Patients

Primary Prevention (Cohort Studies) of Alzheimer's Disease

Occupational Physical Activity and the Prevention of AD

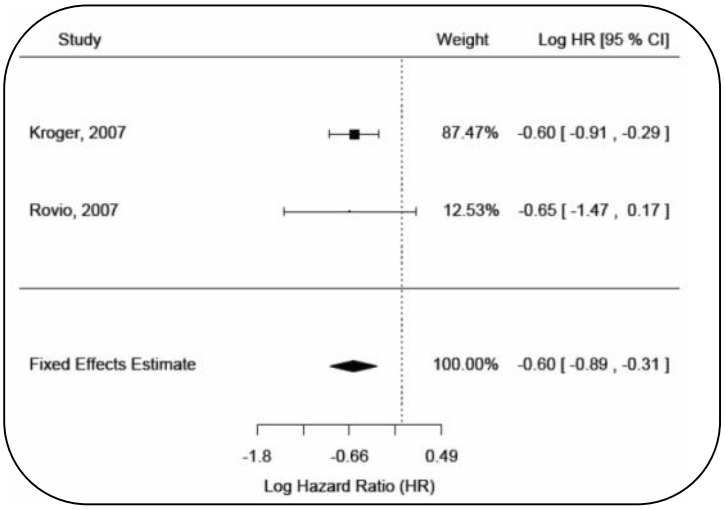

Figure 7: Relationship between Occupational Physical Activity and Incident Alzheimer's Disease

Two studies[60,61] were found which examine the risk of developing AD based on the amount of PA that is included in an individual's occupation. After pooling these results, a fixed effects meta-analysis estimate of the log HR of -0.60 [-0.89, -0.31] was obtained; suggesting an approximate 45.2 % reduction in the risk of developing AD for individuals with physically active occupations vs. those in inactive occupations. Note that this is an unadjusted model, as no statistical adjustments were provided in Kröger et al.[60]. Nonetheless, both studies were very consistent in their findings, as the I^2 statistic was estimated as 0 %.

Self-Reported Physical Activity and the Prevention of AD

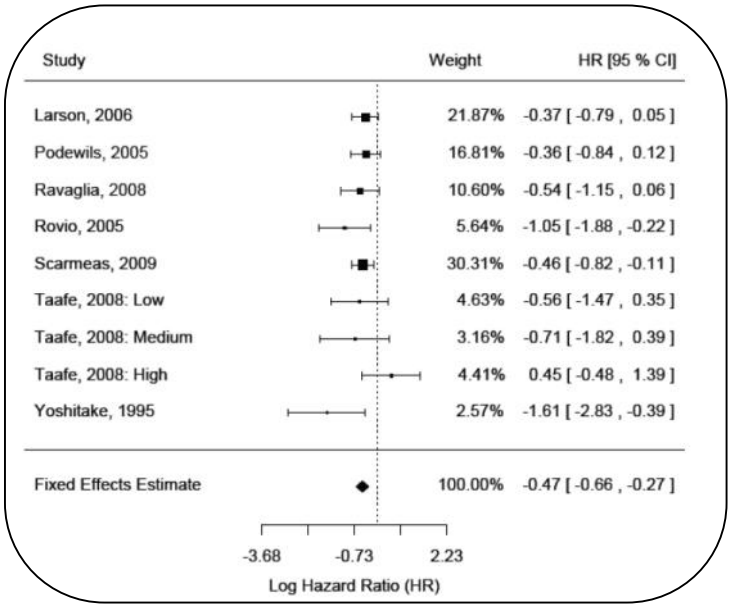

Figure 8: Relationship between Total Physical Activity and Incident Alzheimer's Disease

Among all of the analyses, perhaps the most significant finding was the consistently demonstrated protective effect of PA in the (primary) prevention of Alzheimer's. After examining the literature, a total of seven cohort studies[61,62,63,64,65,66,67] were identified which, when combined, produced a fixed effects meta-analytic estimate of the log HR of -0.58 [-0.76 , -0.40] **(Figure 7)**. This was replicated in our meta-analysis of adjusted effect measures, which found a log HR of -0.47 [-0.66 , -0.27]. This result corresponds to an approximate 38 % reduction in the risk of developing AD in individuals who are most physically active ("very active"), compared to individuals who are the least physically active in each study. Note that both analyses observed very small differences between studies as the I^2 statistic was estimated at 2.9 % and 0 % in the unadjusted (crude) and adjusted models, respectively.

As a follow-up analysis, an additional aim was to determine if there was a dose-response relationship between PA and the prevention of AD. For this analysis, three studies[63,65,66] were identified that examine the impact of varying levels of PA on the development of AD. For the purpose of this exploratory analysis, one study[63] was treated as three different studies due to their stratification by PA

category. After performing a simple meta-regression analysis, no statistically significant trend was observed. For this reason, there is insufficient evidence to suggest that lower levels of PA have the same, or different, beneficial effects as the highest levels of PA.

Potentially Preventable Cases of Alzheimer's: Population Attributable Risk%

When results of Objective 2 (comparing the HR of AD in the most active vs least active individuals) was combined with the prevalence of inactivity in Ontario (59.7%), the "generic" PAR% was 26.4%, whereas when the more "conservative" lower limit of the HR was applied, the PAR% for inactivity was 15.6% (**Table 1**). Using this conservative approach, this means that more than 1 in 7 cases of Alzheimer's in Ontario can be attributed to inactivity, and could be prevented through an accumulated energy expenditure of ~1600 kcal/week (**Figure 8**). Assuming a 1 in 20 rate of AD[68] amongst the 1.98 million older adults in Ontario[13], it can be calculated that at there were approximately 98 790 cases of AD in 2012. Applying the conservative PAR% (15.6%), 15 411 of these cases were potentially preventable through a complete elimination of physical inactivity (Scenario 1). However, if even 10% to 20% of previously inactive older adults were to become 'very active' (Scenarios 2 and 3), between 1 284 and 2 667 cases of AD could be prevented in Ontario alone.

Table 1. Theoretical Effect of a Reduction in Physical Inactivity on Potential Cases of Alzheimer's Disease and Subsequent Direct and Indirect Healthcare Costs

Theoretical Intervention	Inactivity (%)	Generic Approach		Conservative Approach	
		Potentially Avoidable Cases	Range of Cost-Savings (Millions per year)	Potentially Avoidable Cases	Range of Cost-Savings (Millions per year)
Scenerio 1: Entire inactive population becomes 'very active'					
Ontario	0%	26 081	$148-$1 641	15 411	$88-$970
Scenerio 2: 20% of inactive people become 'very active'					
Ontario	47.8%	4 051	$23-$255	2 667	$15-$168
Scenerio 3: 10% of inactive people become 'very active'					
Ontario	53.7%	1 977	$11-$124	1 284	$7-$81

Using cost-estimates from Hermann et al.[69], the annual direct (i.e. hospitalization, physician visits, and medication) and indirect (i.e. informal home care and loss of productivity) cost of treatment for community-dwelling AD patients in 2000 was between $4 406 (for 'very mild' early stage AD) and $48 752 (for 'severe or very severe' late stage AD). After adjusting for inflation, the potential cost of care for very mild and severe/very severe AD in 2012 ($CDN) was $5 688 and $62 934, respectively. Based on the conservative PAR%, if physical inactivity were eliminated from the population, the annual cost-savings in AD treatment in Ontario would be between $88 and $970 million CDN.

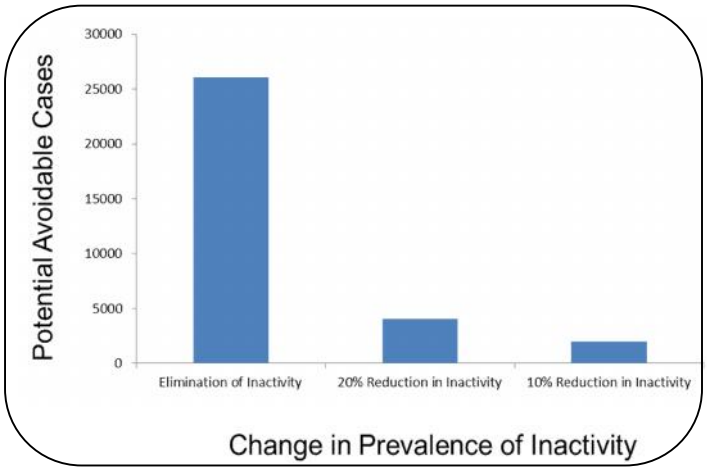

Figure 9: Number of Alzheimer's Cases that Could Theoretically be Avoided by Elimination of Physical Inactivity in Ontario (2012)

CONTEXT:

Limitations and Summary

Despite the many acknowledged differences in study design, population (e.g. age, sex, demographics, network supports, Alzheimer's disease stage, comorbidities, etc.), and analytical strategies employed, results of these analyses provide relatively consistent support for the finding of a protective effect of PA on the primary prevention and management of QOL, ADL, and depression in Alzheimer's patients. In accordance with findings from Paterson and Warburton[40], a qualitative assessment of these studies also suggests that the greatest opportunity for reducing new onset Alzheimer's disease amongst middle-aged adults is within the "very active" segment of the population. In the case of Objective 2, a "very active" level of PA is approximately equivalent to a total weekly energy expenditure of 1600 kcal. At an intensity of ~6kcal/min, an average 75 kg male could achieve this recommendation with five, thirty minute bouts of relatively modest walking activity each week[70]. However, it is likely that doing anything will provide benefit to other aspects of health, and that gradual increases in moderate levels of activity be undertaken to ensure high levels of adherence and lower likelihood of injury[71].

Areas for Future Research

- ***Focus on Defining Dose-Response Relationships:*** To date, the optimal dose and intensity of activity for the treatment and management of AD is not yet clear, and is an important area for future research. Although the potential influence of PA in the prevention of AD is impressive, one of the many challenges in translating PA research into practice stems from the uncertainty with which it is measured. An examination of studies included in Objective 2 suggests a clear need for more consistent measurement of PA, as several studies based their analyses on self-reported walking or work-related PA, whereas others include measures of total energy expenditure, usual exercise, or sport participation. As opposed to physical fitness, which is an attribute of PA, PA is a *behavior* that is not easy to quantify, and self-reported PA has been shown to be over-reported when compared to direct assessment of PA by accelerometry[72,73]. However, this is unlikely to influence the current analysis, as an underestimation in the level of PA would have only strengthened the relationship between PA and incident AD, by placing more "inactive" individuals into the active or very active groups.

- ***Focus on Longitudinal Study:*** Given that all of the cohort studies that were included in Objective 2 were limited to age 65 y and above, it remains to be seen whether there are differences in how PA impacts on Alzheimer's risk and cognitive function across the life course. Specifically, it is also not yet known how *changes in* PA interact with other modifiable and non-modifiable risk factors. Through longitudinal population-based cohorts such as the *Ontario Health Study* (https://www.ontariohealthstudy.ca/), new insight into the tracking of PA and the pre-clinical onset of Alzheimer's and related dementias may be possible.

- ***Focus on Primary Care:*** As one of the five key action points of the Alzheimer's Society of Ontario *10by20 Action Plan for Dementia*[74], a renewed focus on prevention of Alzheimer's through modifiable behaviours such as physical inactivity is needed, and well aligned with the proposed life-stage approach to PA promotion of *Active Canada 20/20* (http://www.activecanada2020.ca). Although there are many patient and physician barriers to PA assessment in clinical practice[75], initiatives such as the U.S. and Canadian *Exercise is Medicine* initiatives[76,77] have identified physician consultations as critical opportunities for the assessment, intervention, and promotion of PA.

ACKNOWLEDGEMENTS

The OBI would like to acknowledge Chris Ardern, Assistant Professor at York University and Michael Rotondi, Assistant Professor at York University for their significant contributions to the design, data collection, analysis, interpretation and writing of this study.

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