Challenges moving forward with economic evaluations of exercise intervention strategies aimed at combating cognitive impairment and dementia*

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Cognitive decline among adults aged 65 years and older is a substantial public health problem in terms of incidence, health burden to the individual and care givers, as well as health care related costs.¹ With the world's ageing population increasing, the number of older adults with dementia is estimated to rise from 26.6 million in 2007 to 106.2 million in 2050.²

The economic burden of cognitive impairment and dementia cannot be ignored. In 2000, dementia was the third most costly health condition to care for in the United States, with annual costs estimated at \$100 billion (in 1997 US prices). Another study calculated that the mean annual costs for dementia care is at 28,000 per patient.³ The direct costs in the UK of Alzheimer's disease were estimated at £23 billion annually.⁴ Clearly, the cost of care for dementia is extremely high, and any strategies that delay the onset and or slow the progression of cognitive decline and dementia can have enormous societal return in terms of

*This commentary is a direct result of discussions from participants of the International Symposium on Exercise for Cognition and Everyday Living (EXCEL), May 27 to 29, 2010, Vancouver BC. Funding provided by Canadian Institutes of Health Research (Institute of Aging) to TLA

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Competing Interest: None to declare.

costs and consequences. To date, effective pharmacotherapy for cognitive decline remains a challenge.¹ Rather, recent evidence emphasizes the importance of behavioural strategies such as physical activity to promote cognitive function.^{5–10} Specifically, results from randomized controlled trials suggests that exercise has benefits for cognitive function among cognitively-normal older adults^{5–7} and among older adults with mild cognitive impairment^{8,9}. However, more research is needed to ascertain the direct effect of exercise on cognition among those with dementia – such as Alzheimer’s disease and vascular dementia. Nevertheless, as previously highlighted by Erickson and Kramer,¹⁰ physical activity provides clear benefits for cognition among seniors. These neuroscientists contend that “physical activity is an inexpensive treatment that could have substantial preventative and restorative properties for cognitive and brain function.”¹¹

However, to emphasize the value in terms of costs and consequences of physical activity interventions for promoting cognitive function among older adults – such that these research findings are meaningful to government and policy makers – health economic evaluations must be incorporated in future randomized controlled trials in this field.

To date, the importance of economic evaluation applied to the field of exercise and cognitive function has largely been overlooked. Yet, under our current state of limited health care resources, health care decisions should ideally be based on efficiency. Efficiency – the cornerstone of economic theory – is a ‘guiding principle’ for decision makers as they decide among competing alternatives against a background of health care resource scarcity.¹² Therefore, studies comparing new interventions that combat cognitive decline with existing treatments should include essential economic data in order to facilitate efficient medical decision-making.

We note that one may assume that because exercise interventions are generally more cost-effective than pharmacological treatment that all economic evaluations of effective exercise interventions are unnecessary. However, we highlight that to date, this is only an assumption and research studies are needed to validate this assumption. Furthermore, even if the effect size of targeted exercise training on cognitive function is smaller than pharmacological treatment, exercise as an intervention strategy may still provide good value for money because of its lower cost. Further, exercise is also likely to provide good value for money because of its established broad benefits – such as promoting cardiovascular health and optimal musculo-skeletal function.^{14,15}

In health care, cost-effectiveness analysis (CEA) has emerged as one of the favored techniques for economic evaluation. In CEA health outcomes are quantified in terms of health benefits (i.e., number of life years saved). “CEAs show the relationship between the net resources used (costs) and the net health benefits achieved (effects) for a specific intervention compared with a specific alternative strategy.”¹³ The primary outcome of a CEA is the incremental cost effectiveness ratio (ICER). By definition, an ICER is the difference in mean costs required by the intervention compared with an alternative (e.g. usual care or a ‘do nothing’ alternative) divided by the difference in mean health benefit gained from the intervention compared with an alternative.¹⁴ One major limitation of CEAs is that the units used to express the health benefits may limit comparability across disease

states if an outcome specific to the intervention or disease treatment is used.¹³ In an attempt to mitigate this problem, CEAs can be standardized by reporting health effects of interventions by life years gained. Although this approach sounds appealing, the endpoints of clinical trials are often shorter than what would be needed for the economic evaluation. However, not all interventions have an impact on mortality, so in some cases, the endpoint of the clinical trial may be appropriate. This limitation of the CEA led to the widely recommended approach that incorporates both quantity and quality of gains or losses – the Quality Adjusted Life Year (QALY) is an example of one such measure used in cost-utility analysis that incorporates both quality and quantity of life.¹³ The prominent difference between CEA and cost-utility analysis (CUA) is that in CEA, the incremental cost of a program is compared with the incremental effects of a program where the health effects are measured in naturalistic units (i.e., life years gained). In CUA, the health effects are measured in QALYs gained, a measure that includes QALYs gained.

Based on current evidence, we already know that cognitive impairment and dementia are costly to care for. However, to our knowledge there is only one published economic evaluation investigating a primary prevention strategy of resistance training on executive functions in community dwelling older adults.¹⁵ This could be due in part to the methodological challenges of conducting economic evaluations alongside trials of individuals with dementia or mild cognitive impairment.

As we consider the methodological challenges of conducting economic evaluations alongside trials among older adults where the primary outcome is cognitive function, we highlight three key items that warrant consideration.

1. The choice of outcome measure is of particular importance for CEAs of interventions aimed at promoting cognitive function. A key limiting factor for conducting CEAs in this area is the lack of tangible units to measure cognitive function. Often for CEAs, the mean change in a tangible unit is measured, such as the drop in mean systolic blood pressure, the mean number of falls prevented, or the mean number of asthma exacerbations avoided. These are all examples of tangible units that have clinically relevant meaning. The challenge with CEAs for cognitive function is that no clinically relevant tangible units have yet been defined. For example, what does a 2 second improvement on the Stroop test mean clinically? This gap in the literature highlights the need for large prospective population based studies that determine what change on measures of cognition translates into a minimally clinically important difference (MCID). To our knowledge, there has only been one economic evaluation of exercise as primary prevention for cognitive decline.¹⁵ In this study, falls were used as the 'effectiveness' outcome for the economic evaluation because falls are tangible units that are clinically significant consequences of cognitive decline among senior.¹⁹²⁰ Further, the costs of falls are more comprehensively documented in other studies compared with cognition-related costs.²⁰²¹ One notable limitation of using falls as a tangible units is that a decrease in the number of falls may be due to other factors aside from cognition that are affected by exercise, thus we suggest both adjusted and un-adjusted analyses be presented. One alternative

way of establishing tangible units in trials aimed at promoting cognitive function is to establish a set of patient-oriented goals that would make a difference to both the individual and the carers (i.e., better sleep, less wandering or fewer repetitive questions). The limitation of this approach is that these items will be more difficult to measure and quantify.

2. The validity of participant responses among those with objective cognitive decline is of great concern. Previous studies have demonstrated that individuals who suffer the most severe cognitive impairment tend to rate their health related quality of life (HRQL) as higher than those who are at the onset of cognitive decline.¹⁶ To our knowledge, there are no studies investigating the underlying reasons for these differences in HRQL. Rather, research has focused on the use of proxies (i.e., clinicians or caregivers) to assess older adults HRQL. Thus, careful consideration needs to be given to both the validity and the mode for the collection of outcomes. Further, carers are important not only as proxies but also as beneficiaries of any improvement the individual they are caring for gains from exercise. Thus, we recommend measurement of caregiver QALYs.
3. The use of falls as an outcome measure for economic evaluations highlights another important question to consider. First, is it appropriate to use falls as an outcome measure when the clinical trial was powered for cognitive function? Second, would it be more appropriate to consider QALYs for the economic evaluation? If so, should all trials be powered based on QALYs gained? Does the primary outcome measure of the clinical trial need to match the primary outcome measure of effectiveness for the economic evaluation?

Recommendations for studies addressing these concerns as we move forward

In conducting future economic evaluations of interventions aimed at combating cognitive decline and dementia, we have number of recommendations. We recommend that the MCIDs be determined for the primary outcomes of these trials (i.e., Stroop Colour/Word test, Trail Making A/B). MCIDs are defined as “the smallest difference in a score of a disease measure of interest that patients perceive as beneficial and that would mandate, in the absence of side effects, a change in the patient’s management.”¹⁷ Thus, MCIDs are an essential step if research tools are to be useful in a clinical context. The development of MCID for the Stroop Colour/Word test, Trail Making A/B will enable future economic evaluations to use cognitive outcomes while having immediate clinical and health policy relevance. Although determination of MCIDs could be expanded to include gold standard measures for function such as Independent Activities of Daily Living (IADL),^{24,25} we recommend that MCIDs first be determined for measures of executive functions using the Stroop Colour/Word or Trail Making A/B tests. To our knowledge, few studies have examined the MCID of global cognition using the Mini Mental State Examination (MMSE).^{26,27} On review paper ascertained that a sample of 53 individuals was required to ascertain the MCID of the MMSE among individuals with Alzheimer’s disease.¹⁸ Given that the

MCID outcomes will differ depending on the severity of cognitive decline, a sample of 53 individuals may be too small for population with mild cognitive impairment.

Until this is done, we propose alternatives that include at least one of the two relevant outcomes for economic evaluations of randomized controlled trials of exercise and cognitive function: 1) QALYs and 2) falls. Using QALYs as a measure of health benefit is advantageous because they are a universal measure that captures multiple health benefits.¹⁴ Approximately 60% of seniors with cognitive impairment fall annually; this is nearly twice that of peers without cognitive impairment.^{19,20} Further, recent evidence suggests that even mild reductions in cognitive abilities increase falls risk.^{19,21–24}

Conclusions

An important goal of clinical research is to inform policy decisions, whether they be through maintaining the status quo or through new investment or disinvestment.²⁵ To adequately address cognitive impairment and its associated health and economic burden, it is essential to engage policy makers by providing information about specific interventions and their value for money when delivered to a specific population.²⁵ Although there is increasing use of evidence-informed policy making based on efficacy and effectiveness data for exercise interventions that combat cognitive decline, there is still a substantial gap in the literature regarding the economic costs and benefits of such interventions. A solution to fill this gap is to include MCID of primary outcomes in future randomized controlled trials of exercise and cognitive function. The development of MCID for the Stroop Colour/Word test, Trail Making A/B, and other frequently used neuropsychological measures will greatly enhance future economic evaluations of studies with cognitive outcomes that are meaningful to clinicians and policy makers.

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