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Challenges and recommendations for the health-economic evaluation of primary prevention programmes for dementia

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Abstract
Objective: We aimed to review health-economic evaluations of (hypothetical) intervention programmes for the primary prevention of dementia, and highlight challenges and provide recommendations for future research to estimate its cost-effectiveness.

Methods: We searched the databases PubMed, MODEM, CEA and NHS for publications on the cost-consequence, -effectiveness, -utility or -benefit analysis of (hypothetical) interventions to reduce the risk of developing dementia for persons without dementia, and described the study characteristics.

Results: Three publications described the evaluation of a hypothetical risk reduction due to physical activity or a multidomain intervention programme. Two studies reported a reduction of care costs. One study yielded two scenarios of increased care costs and one scenario of reduced care costs. Only one study reported the impact in QALY terms, and found a QALY gain.

Conclusion: A few studies have evaluated a hypothetical multidomain prevention intervention, and reported that primary dementia prevention is potentially cost-saving or cost-effective. Various challenges remain to evaluate the health-economic impact of prevention interventions, including extrapolation of short-term trial effects, care costs in the dementia-free and life years gained, and accurate representation of usual care. We recommend extensive sensitivity analyses to examine the impact of assumptions regarding these aspects on the outcomes of cost-effectiveness studies.

Introduction

With a global prevalence of 47 million (Prince, Guerchet, & Prina, 2015) and a corresponding economic impact of US$818 billion (Prince et al., 2015) dementia constitutes a substantial burden on societies worldwide. The World Health Organization (WHO) has stated that dementia is a global health priority (WHO, 2012), as was emphasized during the first ministerial conference organized by the WHO in 2015 in Geneva (WHO, 2015). Limited national care budgets force governments to make choices on how to spend their resources. Cost-effectiveness studies assess the balance of additional costs and additional health gains when comparing two health interventions. Such evidence can help select those interventions considered ready for reimbursement in order to maximize a society’s health gain. In other words, reimbursing an intervention that is not cost-effective means losing the opportunity to spend these resources on another intervention that is cost-effective and achieve its correlated health gain. In addition, health-economic evidence could be useful for trial design, as was shown, for example, in estimating the impact of advanced diagnostic tests on trial subject selection to improve a trial’s efficiency (Van Rossum, Vos, Handels, & Visser, 2010). Health-economic evidence could also be used to identify which parts of evidence cause decision uncertainty (e.g. the impact of dementia-related mortality has been identified as a likely factor causing decision uncertainty (Gustavsson et al., 2017)). Health-economic evidence reflecting on the potential of an intervention under development can be used to anticipate further development or support governments in making decisions regarding potentially new medical interventions.

Basically, two approaches are being researched for preventing the onset of dementia. These include several drugs under development to modify Alzheimer’s disease (AD) by targeting amyloid, and multidomain interventions targeting modifiable risk factors by means of lifestyle and cardiovascular disease management (Winblad et al., 2016). The latter has been evaluated by various trials (Ngandu et al., 2015; Richard et al., 2016; van Charante et al., 2016; Vellas et al., 2014) on the primary prevention of dementia before the dementia-related symptoms occur. They include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study, which found that people aged 60–77 who were at risk for dementia, with normal or slightly diminished cognition, and received a multidomain intervention (consisting of diet, exercise, cognitive training and vascular risk monitoring), showed an 0.20 improvement in the Z-score of a neuropsychological test battery after two years, which was more than the control group (Ngandu et al., 2015). The Prevention of Dementia by Intensive Vascular care (preDIVA) study reported no significant difference in dementia incidence between a nurse-led, multidomain cardiovascular intervention and usual care among people aged 70–78 recruited from general practices, after six years follow-up (van Charante et al., 2016).
The long-term cost-effectiveness of these prevention interventions is unknown, so decision-makers are uncertain about the budget allocation to reimburse them. Prevention interventions are potentially cost-effective, as has been shown, for example, by simulating the health-economic impact of a plausible dementia risk reduction of 10% (Zhang, Kivipelto, Solomon, & Wimo, 2011). Their simulation predicted a reduced dementia incidence corresponding to the risk reduction using evidence from longitudinal cohorts on the correlation between risk factors (such as hypertension, physical inactivity, diabetes and obesity) and dementia incidence (Deckers et al., 2015; Kivipelto et al., 2006).

We aimed to review publications on health-economic evaluations of (hypothetical) intervention programmes for the primary prevention of dementia in persons at risk for dementia, and highlight challenges and provide recommendations for future research to estimate the cost-effectiveness of primary prevention of dementia. The results could support researchers in building the evidence base to aid decision-makers in their decision regarding the reimbursement of dementia prevention interventions.

**Methods**

A literature search was performed to identify studies reporting economic outcomes of existing or hypothetical dementia prevention programmes, published from the year 2000 up to 18 April 2017 and written in English. PubMed was searched using the following search string: ‘(dementia OR Alzheimer) AND (prevention) AND (cost-effectiveness OR cost-effective OR “costs and cost analysis”[MeSH Terms])’. The Modelling Outcome and Cost Impacts of Interventions for Dementia (MODEM) toolkit evidence database (MODEM, 2017) was searched using the term ‘cost-effectiveness’ OR ‘cost-utility’ OR ‘cost-benefit’ OR ‘cost-consequence’ and limited to intervention type ‘Risk Factor Modification.’ Tufts Medical Centre’s Cost-effectiveness Analysis Registry (CEA, 2017) was searched using the search string ‘(dementia OR Alzheimer) AND prevention.’ The Centre for Reviews and Dissemination database (CRD, 2017) was searched for ‘dementia’ and ‘prevention.’ Furthermore, references and citations were reviewed including the 2014 Alzheimer Disease International report on dementia and risk reduction. RH reviewed the titles, abstracts and full texts, and applied the following eligibility criteria for including studies for evaluation: (1) population under study does not have dementia at the start of the (real or hypothetical) intervention, (2) the (real or hypothetical) intervention aims to reduce the risk of developing dementia, (3) the study was a cost-consequence, cost-effectiveness, cost-utility or cost-benefit analysis.

The aim of the present study was not to systematically assess the quality of the studies, so we focused on describing the study characteristics, using a selection of items from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al., 2013). Topics for the discussion were restricted to those that probably have a large impact on the results of a cost-effectiveness study (i.e. are main sources of uncertainty).

**Results**

The database searches retrieved 334 records, including 10 duplicates. Three studies reported on economic outcomes of a (real or hypothetical) dementia prevention programme in a population of persons not having dementia, and met the eligibility criteria. Screening the references and citations of these three studies and the Alzheimer Disease International report 2014 report yielded no additional studies that met the eligibility criteria. Table 1 provides an overview of their characteristics. van Baal, Hoogendoorn, and Fischer (2016) evaluated the impact of physical exercise by people aged 40 in reducing the risk of developing dementia. They used a Markov model to simulate the effect of physical exercise in various subpopulations ranging from inactive to various levels of activity. The model consisted of three states: no dementia, dementia and death, stratified by age, gender and physical activity level. Their simulation estimated the care costs related to dementia and to other diseases during the life years gained. They found that the dementia-related savings achieved by promoting physical activity would offset the spending on care for other diseases during the life years gained in a population of people who were completely inactive. In a population of people who were low-active or somewhat active, the dementia-related savings did not offset the spending on other diseases.

The study by Lin, Yang, Fillit, Cohen, and Neumann (2014) anticipated the economic consequences of addressing modifiable risk factors. They used a set of regression equations to estimate annual care costs. This set included a cohort-based dynamic aging process simulation, which was used to predict body weight, prevalence of chronic diseases, development of functional disability, longevity and health care expenditures. The predictions served as input for an equation to estimate the probability of developing dementia and the related care costs. They evaluated the effect of a 10% reduction in the prevalence of diabetes, hypertension, and cardiovascular diseases, and a reduction of body mass index (BMI). This hypothetical effect size was chosen to correspond to the effect size of an existing diabetes prevention programme. The results indicated that reducing these risk factors would reduce dementia incidence and increase life expectancy. They estimated that this result corresponded to a reduction of dementia-related costs.

Zhang, Kivipelto, Solomon and Wimo (2011) evaluated the potential cost-effectiveness of a hypothetical health promotion programme combined with pharmacological treatment of cardiovascular risk factors. They used a Markov model consisting of three states: no dementia, dementia and death. The model simulated a situation of the currently observed 20-year risk of 4.2% for developing dementia, compared with a hypothetical programme reducing this risk to 1%. This hypothetical 3.2% reduction was chosen to evaluate whether large health trends in dementia would impact on health-economic outcomes. Their simulation yielded estimated cost savings and a gain in the number of quality-adjusted life years (QALY).

**Strengths and weaknesses**

Van Baal et al. and Zhang et al. included care costs due to other diseases during the time gained in which persons did not have dementia (i.e. dementia-free years), and van Baal et al. and Lin et al. also included the costs during the life years gained. Although the model by Lin et al. estimated costs due to other diseases, they explicitly omitted these costs by isolating the dementia-related costs, as this was the aim of their study. Zhang et al. assumed identical life expectancy in people with and without dementia, based on studies reporting.
Table 1. Characteristics of studies simulating the health-economic effects of a hypothetical dementia risk reduction intervention, derived from their base case analysis.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Baseline characteristics of studies</th>
<th>Simulating the possible consequences of addressing modifiable risk factors for dementia</th>
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<td>Target population</td>
<td>Aged 40-60, female</td>
<td>Healthcare sector</td>
<td>General population aged 60 with Medicare</td>
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no association between treatment and mortality in (pharmaco-logical) intervention studies of dementia. They did, how-ever, explore dementia-related mortality in a sensitivity analysis.

Plausible costs of the intervention programme were only examined by Zhang et al. The other studies implicitly assumed zero costs, which is highly unlikely.

Informal care was only examined by Zhang et al. These costs comprise 40% of the total costs (Wimo et al., 2014; Wimo, Jonsson, Bond, Prince, & Winblad, 2013) and might have influenced the health-economic results in terms of sav-ings gained by reducing the dementia risk.

Only the study by Zhang et al. included QALYs and esti-mated the relation between incremental costs and incremen-tal QALYs as a result of reducing the hypothetical risk. Only the results of this study can be used to evaluate whether the potential QALY gain from prevention programmes is worth the costs of such programmes. For example, the various situa-tions examined by van Baal et al. resulted in higher costs, which does not necessarily reflect a negative outcome, how-ever, as the potential QALYs gained by increased life expec-tancy might be worth the costs.

Discussion
This review retrieved three studies evaluating the impact of a hypothetical programme to reduce the risk of developing dementia on care costs and QALYs, using a health-economic simulation model. All three evaluated a hypothetical risk reduction resulting from physical activity or a multidomain intervention programme targeting weight, diabetes, hyper-tension and cardiovascular diseases, and consisting of lifestyle and drug treatment interventions. Two studies reported a reduction of care costs. One study yielded two scenarios involving increased care costs and one scenario involving reduced care costs. Only one study reported the impact on the number of QALYs and showed a QALY gain. The simula-tion frameworks of all three studies contained useful elements that, in combination with additional evidence, could serve as a basis for a cost-effectiveness studies.

Challenges and recommendations
Various challenges can be identified and recommendations can be made for evaluating the cost-effectiveness of current multidomain primary prevention programmes such as those addressed by the FINGER (Ngandu et al., 2015), PreDIVA (van Charante et al., 2016), Multidomain Alzheimer Preventive Trial (MAPT) (Vellas et al., 2014) and Healthy Ageing Through Internet Counselling in the Elderly (HATICE) (Richard et al., 2016) projects.

Long-term effects
A major challenge is that of estimating the lifetime costs and the quality-of-life impact of the relatively short-term (2–6 years) prevention intervention trials in people aged 60 and older. Merely relying on observations of care use and quality of life during the trial period would fail to account for any potential lifetime benefits resulting from the reduced demen-tia incidence after the trial period. We therefore recommend using a simulation approach similar to those used in the studies retrieved by this review to predict the lifetime health-econo-mic effects. This would entail using the effectiveness observed in prevention intervention studies on lifestyle and cardiovascular risk factors and translating them into a risk esti-mate for progression to dementia, for both the intervention situation and the usual care situation. This could be done by using one of the available risk scoring point systems, or their underlying risk prediction model, from the studies reviewed by Imtiaz, Tolppanen, Kivipelto, and Soininen (2014). This method of simulating the link between short-term modifiable risk factors and the lifetime incidence of dementia might, however, be subject to bias. Although statistical techniques in survival analysis can identify the contribution of a single risk factor, the often non-randomized designs in which such fac-tors have been estimated may be biased due to potential con-founding by non-observed factors (Prince, Albanese, Guerchet, & Prina, 2014). A health-economic simulation model implicitly relies on the assumption that a risk factor is fully causal regarding the onset of dementia, which may not or only partly be true. This could result in overestimating the benefits related to the risk factor. Furthermore, extrapolation to lifetime effects is heavily dependent on assumption around the persistence of the effect.

We recommend updating the cost-effectiveness analyses as longer-term results (5–7 years) of primary prevention trials will become available or when studies have estimated adjust-ment factors for the potential overestimation of causality in modifiable risk factors.

Risk factors
Another issue related to simulating the link between short-term modifiable risk factors and the lifetime incidence of dementia is that not all available modifiable risk factors may have been included as outcome measures in the current pre-vention trials and, conversely, not all outcome measures may have been tested as risk factors in longitudinal studies. As a result, part of the modifiable risk effects might not be included, leading to an underestimated health benefits. An example of the first is a positive result on a composite score for a battery of neuropsychological tests, as was reported by the FINGER study (Ngandu et al., 2015). Only a few risk prediction models have reported on cognition as a risk factor for developing dementia, although only in terms of general cog-nition as reflected by the Mini-Mental State Examination (MMSE) (Imtiaz et al., 2014). The change in MMSE correspon-ding to a change in a neuropsychological test battery score could be estimated using mapping methods. Nevertheless, improved cognition, and possibly other outcomes, might have a direct effect on care costs and quality of life. Evidence on aspects like the link between cognition and costs (Fowler et al., 2012; Leibson et al., 2015) is scarce.

We also recommend carefully matching the risk score to the age group under evaluation, as in midlife, other risk fac-tors (high blood pressure, cholesterol, BMI) have been reported to be most important than in later life (cardiovascu-lar and cerebrovascular conditions) (Imtiaz et al., 2014).

Indirect effects
Another challenge regards estimating indirect health-econo-mic effects of prevention interventions. These include the care costs and quality of life due to other diseases during the dementia-free years and the life years gained by the preven-tion intervention. They can be relatively easily incorporated by using age-dependent costs and quality-of-life estimates from general population samples, as was done in the studies
retrieved by this review. The challenge particularly concerns estimating the impact of a prevention intervention on mortality as well as the impact on the disease progression rate during dementia. Like the previous challenge, evidence is limited and estimates of cost-effectiveness rely on assumptions. In the plausible scenario of slower progression, the number of years with dementia increases, resulting in higher dementia-related costs. However, this scenario implies a higher average age at which persons enter the care-intensive stages of moderate and severe dementia. Since mortality rates increase with age, the time spent in these care-intensive stages will then be shorter. Various theoretical scenarios for the balance between costs and savings in relation to a reduced rate of disease progression and mortality have been discussed (Gustavsson et al., 2017).

A related challenge regards estimating the impact of the risk factors that are reduced by the prevention intervention on the incidence of other diseases, and its related costs savings and health benefits (e.g. cardiovascular and cerebrovascular disorders), also referred to as ‘unintended benefits’. Lin et al. (2014) estimated these costs using a dynamic aging process model (Yang, Zhang, Lin, Cleverenger, & Athery, 2012), and this issue will be addressed by a model currently under development (Comas-Herrera et al., 2017). As an alternative to the dynamic aging model, a Markov structure could make the costs in the ‘no dementia’ state depend on the modifiable risk factors, to reflect the health-economic effect of reducing the incidence of other diseases. This, however, could be difficult, as it requires data on late-life costs and quality of life related to mid-life risk factor status.

**Representation of usual care**
Accurate representation of usual care also poses a challenge. In the control arm of the FINGER and preDIVA studies, participants received health advice within a regular follow-up structure. This might have triggered a Hawthorne effect (participants being aware of their risk and anticipating it, for example, by being more physically active, while they would probably not have done so if they had not enrolled in the study (Davis, Bryan, Marra, Hsiung, & Liu-Ambrose, 2015)). It is likely that in usual care, part of the population would not be aware of their risk, nor seek medical advice and hence have a higher risk of dementia than the control group after the follow-up period in the current prevention intervention trials. For population-based interventions, we therefore recommend using the baseline risk score to represent usual care. For populations approached in clinical settings, the usual care (control) arm of a trial most likely does represent usual care, and we therefore recommend using the risk score for the control situation at follow-up.

**Optimized target population**
Another challenge is to optimize the target population for prevention interventions. A simulation can be performed using effectiveness data from subsamples, for example, of persons with a high risk, who have a larger window of opportunity to gain benefits, as their average response to the intervention is likely to be higher. In pharmaco-economic terms, identifying a subgroup with a high treatment response results in lower costs due to overtreatment, leading to a better cost-effectiveness ratio (Handels et al., 2015; Sköldunger, Johnell, Winblad, & Wimo, 2013). However, this comes with the disadvantage of undertreating part of the population who would have been able to benefit. Perhaps, various demographic and other characteristics can be identified that predict a better response to the prevention intervention, such as adherence. Similarly, the simulation approach could be used to identify the critical age window to which the resources required for the intervention can be limited. We recommend exploring cost-effectiveness ratios of subgroups within the trial samples.

**Intervention costs**
Estimating costs might be challenging as well. Typical resource use related to prevention interventions includes risk profile diagnostics by a general practitioner or related staff, (lab) tests, individual or group diet sessions, physical training, cognitive training and pharmacological treatment of risk factors (cardiovascular, diabetes, etc.). These might not be fully covered by current resource use measurement instruments developed for dementia (Wimo et al., 2013) and pre-clinical AD (Sano et al., 2006) and might require additional questions.

**Discounting**
The final challenge is discounting, due to the large time window of prevention effects as showed in the sensitivity analysis by van Baal et al. (2016). Discounting is the principle of valuing down future costs and benefits because there are opportunity costs involved in spending money now and people have a desire to receive benefits now rather than in the future. Compared to short-term savings (e.g. after 1 year) caused by an investment in a particular health intervention, an identical investment in a prevention programme (e.g. with identical savings but after 20 years) loses the opportunity to reinvest this short-term saving (and the opportunity to gain health using this short-term saving). Therefore, saving €100 after 20 years at the commonly applied discount rate for costs of 4% would be valued as a €46 saving. The reasoning behind discounting health is the desire to enjoy benefits now while ignoring future harms (e.g. smoking). Therefore, a gain of 1 QALY after 20 years at the commonly applied discount rate for QALYs of 1.5% would be valued at 0.74. We follow the recommendation by various national guidelines in European countries to discount both costs and effects and evaluate the effect of a range of plausible discount rates on the cost-effectiveness results.

**Recommendation**
In general, we recommend making plausible assumptions and evaluating them in a sensitivity analysis. The resulting uncertainty in health-economic outcomes can indicate what assumptions have the largest impact on the health-economic outcomes and requires more evidence to achieve estimates with increased precision in order to improve decision-making on reimbursement.

**Limitations**
The hypothetical nature of the studies retrieved by this review limited the systematic evaluation of their quality and the lessons we could draw from them. This is why we have focused on discussing the challenges and deriving recommendations based on a narrative review of the literature on health-economic evaluation of dementia prevention. We did not elaborate on various challenges regarding the health economics of dementia in general (Wimo et al., 2014; Winblad et al., 2016), such as the inclusion and valuation of informal care.
(Koopmanschap, van Exel, van den Berg, & Brouwer, 2008) and the problem of proxy- or self-rating quality of life (Jönnson et al., 2006).

Our search covered a limited number of databases and used limited variants of the terms for health-economic evaluations and prevention interventions. A systematic search in other databases as well as grey literature, and using other variants of the search terms, could have resulted in more potential studies of interest.

**Conclusion**

A few studies have evaluated hypothetical multidomain interventions to prevent dementia and reported that primary dementia prevention is potentially cost-saving or cost-effective. Various challenges remain in evaluating the health-economic impact of prevention interventions as currently studied, including extrapolation of the short-term trial effects, care costs during the dementia-free and life years gained, and accurate representation of usual care. We recommend extensive sensitivity analyses to examine the impact of assumptions regarding these aspects on the outcomes of cost-effectiveness studies.

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**ORCID**

Ron Handels http://orcid.org/0000-0002-8663-0630

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