Association Between Cognition, Health Related Quality of Life, and Costs in a Population at Risk for Cognitive Decline

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Handling Associate Editor: Bernhard Michalowsky

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Abstract.

Background: The association between health-related quality of life (HRQoL) and care costs in people at risk for cognitive decline is not well understood. Studying this association could reveal the potential benefits of increasing HRQoL and reducing care costs by improving cognition.

Objective: In this exploratory data analysis we investigated the association between cognition, HRQoL utilities and costs in a well-functioning population at risk for cognitive decline.

Methods: An exploratory data analysis was conducted using longitudinal 2-year data from the FINGER study ($n = 1,120$). A change score analysis was applied using HRQoL utilities and total medical care costs as outcome. HRQoL utilities were derived from the Short Form Health Survey-36 (SF-36). Total care costs comprised visits to a general practitioner, medical specialist, nurse, and days at hospital. Analyses were adjusted for activities of daily living (ADL) and depressive symptoms.

Results: Although univariable analysis showed an association between cognition and HRQoL utilities, multivariable analysis showed no association between cognition, HRQoL utilities and total care costs. A one-unit increase in ADL limitations was associated with a -0.006 ($p < 0.001$) decrease in HRQoL utilities and a one-unit increase in depressive symptoms was associated with a -0.004 ($p < 0.001$) decrease in HRQoL utilities.

Conclusion: The level of cognition in people at-risk for cognitive decline does not seem to be associated with HRQoL utilities. Future research should examine the level at which cognitive decline starts to affect HRQoL and care costs. Ideally, this would be done by means of cross-validation in populations with various stages of cognitive functioning and decline.

Keywords: At-risk, care costs, cognition, cognitive decline, dementia, HRQoL utilities, sf-6d

INTRODUCTION

Dementia is one of the most frequent neuropsychiatric disorders of the elderly [1], and it is related to a considerable social and economic burden for the persons concerned, their families, and the society as a whole. Due to the progressive nature of the condition, people with dementia have an increasing need for care [1, 2], leading to substantial informal and formal care related costs. Additionally, dementia can affect health related quality of life (HRQoL) [3], and this may happen in earlier stages of cognitive decline [4]. There is an increasing interest to develop preventive or disease-modifying interventions/treatments for persons at increased risk of dementia or prodromal AD. Both HRQoL and care costs are considered important outcomes in burden of disease studies [5, 6], and these outcomes furthermore can be used to demonstrate the potential value of treatments [7, 8]. Whether such interventions might have benefits in cognition and whether that benefit would potentially result in improved HRQoL and reduced care costs already before the onset of dementia is not known.

HRQoL can be expressed using utilities, which are preference based values derived from the general population [5, 9, 10]. Utilities can be incorporated into health-economic decision models, useful for policy and decision making, and additionally be used to compare to other populations. Until now, there is lack of longitudinal evidence regarding the association between cognition and HRQoL utilities and care costs among people at risk of dementia. Evidence

of, mainly, cross-sectional studies show contradictory results. Three cross-sectional studies using utilities derived from the EuroQoL 5-D examined this relation in older people without dementia, and two of them found an association [11, 12] while one [13] did not. Although the latter did find an association between cognition and utility related to wellbeing measured by the ICECAP-O [13]. Other studies [14–17] which did not incorporate utilities, but instead looked at other HRQoL measures (Visual Analogue Scale or total scores) also showed contradictory results among older adults without dementia. The existing studies differ in, for example, setting and measurement instruments used, and evidence on this association remains inconclusive. However, studies that examined HRQoL in populations with varying degrees of cognitive impairment, ranging from no cognitive impairment to Alzheimer's disease dementia, suggest an important role of depressive symptoms and functioning in activities of daily living [4, 18, 19].

Besides HRQoL utilities, there is a knowledge gap in understanding the impact of cognition on care costs in people without dementia, but at risk for cognitive decline or dementia. Some studies that have compared care costs across the cognitive continuum found that direct medical and non-medical costs did not differ between people with normal cognition and people with mild cognitive impairment (MCI) [20, 21], although another study found a significant difference in direct medical care costs between people with normal cognition and people with MCI [7]. Furthermore, a difference in costs is found between people with

MCI and dementia [21]. Overall, care costs in people with dementia are known to be associated with the level of cognition and severity of dementia [22–24], even after adjusting for functioning in daily life [22].

In summary, there is limited evidence on the association between cognition and HRQoL utilities and care costs in people at risk for cognitive decline, and the majority of research is based on cross-sectional studies. With the increasing interest in developing disease modifying treatments or interventions for people at risk of cognitive decline or dementia it is important to investigate this association further. The aim of the current study is to examine the association between cognition and HRQoL utilities and care costs in old people at risk for cognitive decline over a 2-year time period.

MATERIAL AND METHODS

Design and setting

The study comprised an exploratory data analysis using data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). The FINGER study is a multicenter (six sites: Helsinki, Vantaa, Kuopio, Oulu, Seinäjoki, and Turku), randomized controlled trial performed in Finland [25]. The effects of a 2-year multidomain intervention aiming at reducing cognitive decline were examined in older people with an increased risk of cognitive decline.

Description of the FINGER study

Participants from the general population (age 60–77 at the start of the study) were recruited from participants of previous population-based national surveys. Screening criteria for the study inclusion comprised 1) a Cardiovascular Risk Factors, Aging and Dementia (CAIDE) [26] Dementia Risk Score of at least 6 points, 2) the mean level or slightly lower level of cognitive performance as would be expected for age, defined as meeting at least one of the following criteria: 1) Word List Learning task (10 words x3) ≤19 words, 2) Word List Recall ≤75%, or 3) Mini-Mental State Examination (MMSE) ≤26/30 points [27]. Exclusion criteria included previously diagnosed dementia, suspected dementia, or significant cognitive impairment, MMSE < 20, medical conditions affecting safe participation in interventions and participation in other ongoing intervention studies (further details on exclusion described elsewhere

[25, 28]). The participants were randomly allocated into either the intervention group receiving the multidomain intervention including dietary counselling, exercise training, cognitive training, and management of vascular risk factors [26] or the control group that received regular health advice. The coordinating ethics committee of the hospital district for Helsinki and Uusimaa region approved the FINGER study. Before enrollment in the study, participants gave their written informed consent [25].

Participants

The total FINGER sample comprised 1260 participants. For the present analysis, 97 had missing data of interest at follow up (see *Analysis*), and another 43 participants had missing data of interest at baseline and were therefore excluded. The final sample eligible for analysis comprised 1,120 participants. Of them, 72 (6%) did not have 12 months data and 106 (9%) did not have 24 months data available (data completely missing or a too large fraction missing on the variables of interest).

Outcome variables

HRQoL utility score

HRQoL was measured using the 36-item Short Form Health Survey (SF-36) instrument [29]. The preference based utility score, the SF-6D, is based on a selection of the SF-36 items [30, 31] comprising physical functioning, role limitations, social functioning, pain, mental health, and vitality [29]. In the absence of a Finnish value set, scorings on these six dimensions were transformed into utilities using general population values from the UK [10], with a maximum of '1' indicating perfect health.

Total medical care costs

Costs of care, i.e., direct costs were estimated from a medical viewpoint, including visits to/from a medical professional (GP or medical specialist or nurse) and days in hospital. Visits to a medical professional were inquired separately for public health centers, hospital outpatient and inpatient care, occupational health care, home visits or private sector doctor's visits. Care use was assessed by a questionnaire filled out by the participant. The recall period was 12 months. Total costs of medical care, which was used as one of the outcomes, were obtained by multiplying visits to care professionals and hospital days by their respective unit costs and summing these. Unit costs

were retrieved from a Finnish report from the Finnish National Institute for Health and Welfare [32] and converted to 2015 prices using price indexes retrieved from Eurostat (https://ec.europa.eu/eurostat), also see Supplementary Table 1. A log transformation was applied to reduce the skewness of care costs (12.84) and deal with extreme cost values (ln (cost -26.28)).

Independent variables

Cognition, ADL, and depressive symptoms

Cognition was reflected by a composite neuropsychological test battery (NTB) score [27], comprising the domains of executive functioning, memory, and processing speed. This composite score was based on results of 14 standard neuropsychological tests which were calculated as z-scores (standardized to the baseline mean and standard deviation (SD) and averaged to total scores [25, 27], with higher scores indicating better performance.

Activities of daily living (ADL) were assessed through 17 questions measuring both basic and instrumental ADLs as defined by Katz et al. [33] and Lawton and Brody [34], with each question having five answer options: i.e., being able to perform an activity *without any*, *with minor* or *with major* difficulties, *only when assisted*, or *not able to perform them* [33, 34]. Item scores, ranging from 1 to 5 were summed where higher scores indicated being more dependent in ADLs, ranging from 17 to 85. An ADL score 17 indicated no problems at any task. The total score was divided by the maximum possible score in case some items (less than 20%) were missing.

Depressive symptoms were measured with the Zung depression scale [35], ranging from 20 – 80 with higher scores indicating presence of more symptoms.

Change scores

Both outcome variables (HRQoL utilities and total costs), and the three independent variables (cognition, ADL, and depressive symptoms) were transformed into change scores. The change scores were generated by subtracting the assessment at baseline and 12-month follow-up, between 12- and 24-month follow-up, and for those not having 12-month data available also between the baseline and 24-month follow-up.

Statistical analysis

Two mixed models were fitted, one to change in HRQoL utilities, one to change in care costs.

The predictor was the change in cognition. Possible confounding factors change in ADL and change in depressive symptoms [4, 18] were added if p-value was lower than 0.1 in a univariable analysis with the outcome (change in HRQoL utilities, change in care costs). The model contained a random intercept at the participant level. The baseline status of HRQoL utilities or care costs was not included as a predictor in these models (Supplementary Material).

The mixed models were furthermore adjusted for group status (intervention/control), sex, baseline age, and years of education. Regression assumptions were tested by examining linearity, normality of residuals, homoscedasticity, and multicollinearity (Variance Inflation Factor < 10). All analyses were performed using Stata (StataCorp v.16.1).

Data were case wise deleted (i.e., all data from an observation) if > 50% of the SF-36 items were missing, and/or > 55% of the care use items were missing and/or > 50% was missing on cognitive measures. Otherwise, if data was missing, these were multiple imputed using a chained equation procedure, with predictive mean matching (PMM) for continuous variables, ordered logistic regression for ordinal variables, and logistic regression for dichotomous variables (StataCorp v.13). The ADL and ZUNG scale were imputed at the scale level (i.e., its sum score), whereas the care use categories and items of the SF-36 were imputed at the item level. In total, 20 datasets were created using multiple imputations. Diagnostics (e.g., frequencies, kernel density plots) were examined. for plausibility of imputed datasets before analyses were performed.

Post-hoc analysis

A *post-hoc* exploratory mediation analysis was performed to evaluate if the association between the change in cognition and HRQoL was mediated by change in ADL or depressive symptoms. The mediation analysis was based on the criteria suggested by Baron and Kenny [36], please see Supplementary Figure 1 for a visual representation. The following steps can be distinguished. First, a regression was performed between cognition (independent) and HRQoL utilities (dependent), or path c (Supplementary Figure 1A). Second, a regression was performed between ADL or depressive symptoms (dependent; mediating variables) and cognition as the independent variable, or path a (Supplementary Figure 1B). The third step comprised a regression using HRQoL utilities as the dependent variable and cognition, ADL

Table 1
Baseline characteristics of the (non-imputed) analytic sample (n = 1,120)

	Descriptive statistic Mean (SD)	Range (min to max)	Missing (%)
Sex, male	603 (54%)*	–	0%
Age	69 (4.6)	60 to 80	0%
Education, y	10 (3.4)	0 to 30	<0.1%
NTB total score (z-score)	0.02 (0.57)	–1.88 to 1.54	0%
MMSE	26.8 (2.02)	20 to 30	<1%
Adjusted ADL	18 (2.5)	17 to 46	<0.1%
ZUNG depression scale	33.8 (7.4)	20 to 63	2%
Outcomes			
Medical care costs (among users; non-transformed)	€1,084 (€2,285)	€30 to €31,836	–
Medical care costs (total sample, non-transformed)	€933 (€2,152)	0 to €31,836	13%
SF6D Utility	0.78 (0.12)	0.32 to 1.00	3%

Minimum and maximum possible score on the scales: SF6D utility 0.296 to 1 with higher score indicating better HRQoL utilities; ADL range 17 to 85 with higher score indicating more dependence; ZUNG depression scale range 20 to 80 with higher score indicating more depressive symptoms. *frequency (%).

Table 2
Results of the univariable regression of changes in cognition, ADL, and depressive symptoms on HRQoL and costs

	Increase in HRQoL utility score*		Increase in log costs*	
Variable	Coefficient (S.E.)	significance	Coefficient (S.E.)	significance
Change in cognition[†]	**0.015 (0.007)**	**0.033**	0.022 (0.118)	0.851
Change in ADL[†]	**–0.006 (0.001)**	**< 0.001**	–0.002 (0.016)	0.923
Change in depressive symptoms[†]	**–0.004 (0.0003)**	**< 0.001**	**0.015 (0.006)**	**0.014**

*results of mixed linear model using change scores. Log costs were used in calculations; [†]increase in ADL score and depressive symptoms indicates worse outcome and increase in cognition and HRQoL indicates better outcome.

and depressive symptoms as the independent variables, visualized as path c'.

RESULTS

Baseline characteristics are depicted in Table 1. Mean cognition at baseline was 0.020 (SD 0.57) measured with NTB total score, and 26.8 (SD 2.02) measured with MMSE. The mean of HRQoL utilities at baseline was 0.78 (SD 0.12; ranging between 0.32 and 1.00). Mean cost at baseline (preceding last 12 months) was €1,084 (SD €2,285) among those participants that used medical care. Participants with too many missing data (completely missing or too large fraction missing), who were therefore not included in the analyses (n = 140), had a lower mean score for cognition (both composite and MMSE score), and lower education than those who were included in present analysis.

Increase in HRQoL utilities was associated with an improvement in cognition ($p = 0.033$), reduction in ADL problems ($p < 0.001$) and decrease in depressive symptoms ($p < 0.001$) during 2 years in univariable analyses. Increase in depressive symptoms (p 0.014) was associated with an increase in costs in univariable analyses.

Table 3 shows the results of the multivariable model. After adjustments, reduction in ADL limitations (-0.006; $p < 0.001$) and depressive symptoms (-0.004; $p < 0.001$) were associated with increasing HRQoL utilities, while change in cognition was not associated with a change in HRQoL utilities (0.008; $p = 0.277$). In addition, a change in cognition was not significantly associated with a change in costs (0.054; $p = 651$). An increase in depressive symptoms, however, was associated with an increase in costs (0.015; $p = 0.014$).

Post hoc results

As cognition did show not to be significant anymore in multivariable analysis (after adjusting for ADL and depressive symptoms), a *post hoc* regression analysis was performed to explore (see Supplementary Table 4 and Supplementary Figure 1) if the association between change in cognition and HRQoL was mediated by change in ADL or depressive symptoms. Results showed that the indirect (mediating) effect of ADL was borderline significant (0.0020; $p = 0.052$). The indirect effect of depressive symptoms was significant (0.0049; $p = 0.011$), indicating that

Table 3
Results of the multivariable regression of changes in cognition, ADL, and depressive symptoms on HRQoL and costs

Variable	Increase in HRQoL utility score*		Increase in log costs*	
	Coefficient (S.E.)	significance	Coefficient (S.E.)	significance
Change in cognition[†]	0.008 (0.007)	0.277	0.054 (0.119)	0.651
Change in ADL[†]	**−0.006 (0.001)**	**< 0.001**	n/a[‡]	n/a
Change in depressive symptoms[†]	**−0.004 (0.0004)**	**< 0.001**	**0.015 (0.006)**	**0.014**
Age (baseline)	−0.0002 (0.0004)	0.589	0.002 (0.008)	0.749
Sex	0.004 (0.004)	0.304	−0.056 (0.069)	0.414
Education	−0.0001 (0.0006)	0.830	−0.0089 (0.0099)	0.369
Intervention allocation	−0.006 (0.004)	0.166	0.032 (0.069)	0.639

*results of mixed linear model using change scores. Log costs were used in calculations; [†]increase in ADL score and depressive symptoms indicates worse outcome and increase in cognition and HRQoL indicates better outcome. [‡]excluded because not significant in univariable analysis. Analyses were adjusted for age, sex, education and intervention allocation.

depressive symptoms may mediate the association between cognition and HRQoL.

DISCUSSION

This analysis was based on data from the Finger Study that has previously shown positive effects of a 2-year multidomain intervention on cognition [28], HRQoL [37], and ADL [38]. In this study we did not examine the effect of the intervention, but rather aimed at examining the longitudinal associations between cognition and HRQoL utilities and care costs to identify whether there is a potential health-economic gain in terms of HRQoL utilities and care costs for (non-)pharmacological interventions that aim at improving cognition. For this exploratory analysis we were not examining the role of the intervention on this relation. We found that, after adjustment, a change in cognition was not related with a change in HRQoL utilities or with a change in medical care costs in this population of fairly well-functioning older adults at increased risk of developing dementia.

Cognition and HRQoL utilities

One explanation for the non-significant association between the change in cognition and change in HRQoL utilities could be that, overall, the cognitive performance among all participants at baseline was relatively good as indicated by the mean baseline MMSE of 26.8 (SD 2.02). Therefore, possibly not enough people existed with a level of cognitive change that would interfere with ADL, HRQoL utilities, or costs. In a univariable analysis, improvement in cognition was associated with improvement in HRQoL utilities, but the association was diluted in multivariable analyses, indicating that cognition

did not directly impact HRQoL utilities, but instead possibly followed an indirect pathway via ADL. In line with that, one previous study [39] has shown that the executive functioning is related to performance in ADL among older people without dementia. ADL limitations in turn may lead to a reduction in HRQoL [11, 19]. In our *post hoc* analysis, the indirect effect via ADL limitations was only borderline significant.

A more methodological explanation relates to the domains underlying the utility score, comprising physical functioning, role limitation, social functioning, bodily pain, mental health, and vitality. These domains may be more strongly correlated with ADL than with cognition. Although the SF-36 is a validated instrument to measure HRQoL, it would be useful to examine other generic preference-based HRQoL instruments as well. These may include the EQ-5D [40], or the ICECAP-O which measures wellbeing in a broader sense [13]. Future comparisons could address the sensitivity of the instruments and consider possible similarities and differences that may exist between utilities derived from these utilities [41, 42].

Besides ADL, having more depressive symptoms was associated with a lower HRQoL. Depressive symptoms are common in people with cognitive impairment [4] and known to be related with HRQoL [4, 15, 16]. Although our *post-hoc* analysis was explorative in nature, its results suggested a presence of a potential mediating pathway between depressive symptoms and cognition on HRQoL and that this pathway needs to be examined further.

Cognition and costs

Up to a certain point, before significant problems appear, cognition may not affect HRQoL utilities or medical costs among older adults without dementia.

Also, cognition may have a limited effect on ADL. Although the study population in our study is different, our findings are in line with previous studies [20, 21] showing no significant difference in direct medical and non-medical costs between people with MCI compared with those without MCI. This indicates that costs occur with increasing dependency [43] which was not (yet) the case in the current sample where participants presented with a mean ADL score of 18 (on a scale from 17 to 85). This is further highlighted in other studies, where among people with MCI and dementia, care costs tended to increase with increasing dependency [44, 45].

Implications

The results of no (strong) association between cognition and HRQoL, and medical care costs suggests a low potential for interventions aimed at improving cognition on its own in persons at risk of developing dementia in the general population to impact health-economic outcomes. Nevertheless, a (non-)pharmacological intervention aimed at postponing dementia (and its related cognitive disability) is potentially beneficial [46, 47]. However, spill-over health-economic benefits, before dementia onset are possibly absent. We hypothesize the decrement in utilities due to low cognitive performance on its own to be low or absent, and thus the potential health-economic benefit (in terms of HRQoL utilities and costs) for preventing low cognitive performance is low. Notwithstanding, preventing low cognitive performance related to depressive symptoms and/or activities of daily living has the potential to improve health-economic outcomes, and reflects the potential of multi-domain interventions.

This study has several strengths including a well-defined study population, low drop-out rate, and comprehensive assessments of cognition, HRQoL, and ADL. Although the HRQoL of the participants in the FINGER study was found to be better compared with the general population [37], the population is well-representative of older people at increased risk of cognitive decline or dementia [27], but well-functioning in terms of cognition, ADL and HRQoL at baseline. Although our study cohort was a population-based sample, it should be noted that, in terms of generalizability, this cohort may differ from the general high risk population for example due to selection criteria but also possible differences in those who agree to participate in the trial and those who do not. One limitation of the current study is that only direct (medical) costs were included. However, it is doubtful whether cognition would have affected indirect costs such as informal care, since there were not much difficulties in ADL, and they were not strongly associated with cognition. Related to this limitation is the potential recall bias that could arise because of the reference period being 12 months, leading to a possible underreporting of health service use [48]. One further methodological consideration that should be mentioned concerns the value set used to calculate the utility score. At present, no Finnish value set exists and therefore we used the UK value set. Overall, differences between country specific value sets may exist [49], and therefore it is often recommended to use the country specific value set when examining treatment effects. However, we do not expect a large influence on our results due to this value set. One methodological consideration to keep in mind relates to the statistical model used to study the association between cognition and utilities and (transformed) care costs. In current explorative study, we evaluated this association by applying a mixed model using change scores. A variety of statistical models exist that could potentially be applied including two-part models, often applied to data with a large proportion of zero costs [50, 51]. Although their application in longitudinal studies suggests some challenges [52], findings from such models could be interesting to examine.

Conclusion

In a well-functioning population of older adults at increased risk of dementia, no strong association was found between cognition and HRQoL utilities, and no association was found between cognition and costs; after adjusting for ADL and depressive symptoms. ADL and depressive symptoms were associated with HRQoL. Based on this evidence, the potential of improving HRQoL utilities by improving cognition among at-risk older adults is likely limited. Future research in a population with a larger variety of cognitive performance, including people with mild cognitive impairment and dementia, is needed to understand at which level cognitive disability potentially affects HRQoL utilities and lead to (non)medical care costs.

ACKNOWLEDGMENTS

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5304r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-215304.

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