Title: Subjective memory impairment, instrumental activities of daily living and longitudinal effect on mortality among older adults in a population-based cohort study – The HUNT Study

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Abstract

Background: Subjective impairment in memory and instrumental activities in daily living (IADL) are associated with future cognitive decline and poorer mental health in older adults, but their association with mortality is uncertain. Our aim was to examine the associations between subjective memory and IADL impairments and all-cause mortality, as well as the mortality risk for reporting both memory and IADL impairments.

Methods: Data from the 70 years+ cohort in the third survey of a population-based study, the Nord-Trøndelag Health Study (HUNT3), were linked to the Norwegian Causes of Death Registry. A total of 5802 older adults had complete data from HUNT3 (70.8 % of the 70+ cohort). Mean follow-up time was 8.0 years, and 1870 respondents had died. Associations between subjective memory and ADL impairments with mortality were analyzed in Cox regression models adjusted for covariates with attained age as the time scale. Analyses were performed separately for two age groups, 70–79 and 80+ years, to fulfill the proportional hazards assumption.

Results: Subjective impairments in short-term memory and IADL were significantly associated with mortality both separately and combined. These associations were strongest in the 70–79 years old group, where reporting impairment on one short-term memory item increased the mortality risk by 51% (HR (95% CI) = 1.51 (1.20-1.91)). Long-term memory impairments were not associated with mortality in the adjusted models.

Conclusions: Subjective short-term memory impairments and IADL impairments are associated with increased mortality risk. Neither of these symptoms should be regarded as benign aspects of ageing, and concerns should be properly addressed**.**

Keywords: Memory, ADL, all-cause mortality, cohort study, older adults

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Introduction

During recent years, there has been an increasing research interest in persons with subjective cognitive decline and, in particular, those with subjective memory impairment (SMI). There are two main reasons for this interest. The first is the aim to identify persons who are likely to later develop dementia at a very early stage. The other reason is that SMI is also associated with poorer mental health and depression in older adults.[1] There is no established definition for SMI since it is not part of the diagnostic frameworks, and its prevalence varies between studies accordingly. However, the term SMI is often used to refer to a subjective awareness of memory loss, which is not necessarily confirmed in formal testing of cognitive function.[2] Further, there is also a wide variety of tools used to assess SMI throughout the different studies.[3] Although the prognostic value of SMI for subsequent dementia varies between studies, it is argued that these subtle changes may be the first indicator of subsequent mild cognitive impairment or dementia.[4, 5] There is a higher risk of progression from SMI to mild cognitive impairment in memory clinic settings than in population-based settings.[6] However, the presence of SMI is also linked to psychological factors such as depression, stress and personal traits;[7-9] demographic factors such as less education and being female;[10] somatic disease such as stroke and heart disease;[11] and increased risk for home injuries.[12] Although the presence of SMI has been associated with adverse health outcomes, studies of the association between SMI and mortality are few and inconclusive.[13-17] In a previous study from HUNT3, the authors found that the Metamemory questionnaire (MMQ) they used to assess SMI measured two independent components of memory: short-term memory (related to information that is in the mind at the moment or very recently) and long-term memory (related to older knowledge or events that took

place in the past).[18] They also identified the short-term component as being more closely associated with disease than the long-term component. Although memory function is often divided into short-term and long-term components, we have not found any studies examining the association between these components and mortality in persons with SMI.

Activities of daily living (ADL) are traditionally categorized as either basic ADL (BADL) or the more complex instrumental ADL (IADL).[19] BADL covers activities such as eating, dressing, using the toilet, taking a shower and being mobile. IADL are activities such as cooking, doing laundry, shopping, paying bills, taking medications and using public transport. In studies of older adults, the focus has been on BADL since impairments in these activities are related to a need for health services. However, increasing focus has been given to IADL since these activities are often affected earlier, for example, during the development of cognitive impairment.[20] Further, impairment in ADL is a diagnostic criterion for a diagnosis of dementia in the ICD-10 framework.[21] The presence of impairment in ADL is also related to mortality in older persons in several studies.[22-25] Thus, older persons who report both SMI and difficulties with IADL may be an at-risk group for subsequent cognitive impairment and dementia as well as future functional decline and mortality.

Although SMI occurs frequently in the older population, few patients share their concerns about memory if the general practitioner does not actively ask them about their memory function.[26] This underreporting is also likely to happen in regard to emerging problems with IADL, such as paying bills, unless medical attention is needed. By using self-reported information from a large population-based cohort, linked with registry data on mortality over 10 years of follow-up, we have the possibility of shedding light on the associations between these symptoms and their prognostic role for mortality. The aim of this study was to identify the separate and combined prognostic values of SMI and impairments in IADL on all-cause mortality.

Methods

Study design, exposure variables and sample

In this prospective population-based cohort study, we used data from the 70-year-old and older cohort in the HUNT3 study (conducted from 2006–2008) linked with data from the Norwegian Cause of Death Registry. Participants were followed up until emigration, death or until January 4^{t}, 2017, whichever came first. The study population was determined based on responses on the MMQ, IADL and covariates.

Subjective memory impairment (SMI): The Metamemory questionnaire (MMQ) in HUNT3 has nine items about memory impairments. Based on factor analyses, these items loaded onto two independent factors that were interpreted as short-term (4 items) and long-term (5 items) memory impairments.[18] The short-term items focused on current or recently apprehended information, while the long-term items were related to previously acquired factual knowledge. Each item has a three-scaled response category: Never/Sometimes/Often or No problem/Yes, some/Yes, large. To focus on the persons with more-pronounced subjective memory concerns, we dichotomized each item so that we scored those with **"**Often**"**/**"**Yes, large**"** into one group (score 1) and the "Never"/"Sometimes" and "No problem"/"Yes, some" in the other group (score 0). We then totaled the scores 0–5 for long-term memory impairment and 0–4 for the short-term impairment.

Instrumental activities of daily living (IADL): The HUNT3 questionnaire comprises questions about nine different activities, providing a score from 0 (no problems) to 9. Each question is phrased as "Are you able to . . . without help?" The nine activities are as follows: preparing hot food, doing light housework, doing heavier housework, washing clothes, paying bills, taking medicine, moving outside the house, going shopping and taking a bus.

Covariates: We included a set of covariates from the HUNT3 at baseline known to be associated with the main exposure variables and mortality. Self-reported smoking status was grouped into non-

smokers, previous smokers, and current smokers. Body mass index (BMI) (kg/m^2) was categorized as <20 kg/m^2, 20–24.99 kg/m^2, 25–29.99 kg/m^2, ≥30 kg/m^2. Self-reported physical activity was dichotomized into activity at least 30 minutes/day or less. Anxiety and depressive symptoms were registered using the Hospital Anxiety and Depression Scale (HADS).[27] Information on comorbidity was based on self-reporting where participants were asked if they had been diagnosed with any diseases during the past year. We used a dichotomized comorbidity score (a score of 1 for the presence of one or more of the following: cardiovascular disease, respiratory disease, cancer, or diabetes).

Among 8191 respondents ages 70–100 years in HUNT3, we followed those with valid values for long-term (5 items) and short-term (4 items) memory, for IADL (9 items) and for covariates (Figure 1). Those with missing values for 3–5 items for the long-term memory battery (n=1330) and 3–4 missing values from the short-term memory battery (n=1441) were excluded, as well as those with 5–9 missing items for the IADL battery (n=1350). This left 6947 respondents with valid values for long-term memory, 6751 for short-term memory and 6842 for IADL. Additionally, 805 respondents were excluded because of missing data on covariates. To provide information regarding potential dose-response results, long-term memory impairments were grouped as 0, 1, 2 and 3–5; short-term memory impairments were grouped as 0, 1, 2–4 and IADL were grouped as 0, 1, 2, 3+. We also constructed a combined variable of IADL and short-term memory impairments with three categories grouped as “no impairments on either scale (none)”, “impairments on one of the scales (either)”, or “impairments on both scales (both)”. These groupings were performed to get sufficient sample sizes in each category and to achieve proportional hazards for the Cox regression.

Ethics

The Norwegian Data Inspectorate and the Regional Committee for Medical Research (REC) permitted HUNT3, and all participants in HUNT3 gave written informed consent. The present study is approved

by the REC (reference number 2016/829), by the Data Access Committee at HUNT Research Centre and by the Norwegian Institute of Public Health (reference number P16/12485).

Statistics

The association between subjective impairments in memory and in IADL with mortality was analyzed in Cox regression with attained age as the time scale. We used participants with complete data for these analyses. Analyses were performed separately for two age groups, 70–79 years and 80+ years, to fulfill the proportional hazards assumption (PH). PH were investigated using Schoenfeld residuals and graphical inspection, and there were no violations of the PH assumption. Stata 14 was used for the analyses.

Survival curves were estimated by fitting separate Cox regression models for each group, adjusting for covariates.

Results

The total sample at baseline was 8191, and 2389 were excluded due to missing data, leaving 5802 for analyses (Figure 1). The excluded sample was not missing at random as they were significantly older than the study population (78.4 vs 76.9 years); a significantly smaller percentage were men (41% vs 46%); they had significantly higher mortality (HR=1.25, p<0.001); they included significantly more current smokers (12.7% vs 10.6%); and they had significantly more comorbidity (56.1% vs 53.7%).

For the study sample (N=5802), age at entry was 70–96 years (mean 76.9, median 76.0); see Table 1. The maximum age at exit time was 103 years (mean 85.2, median 84.4). The mean follow-up time in our sample was 8.0 years and the maximum was 10.3 years, up to January 4, 2017.

Table 2 shows the hazard ratios for all-cause mortality for subjective impairments in short-term memory, long-term memory, and IADL and for having combined short-term memory and IADL impairments. Reporting difficulties with only one of the four items on the short-term memory questionnaire increased the mortality risk by 51% in the youngest group of 70–79-year-olds. The mortality risk increased to 62% if the respondent reported difficulties with 2–4 items. In the oldest group, subjective short-term memory impairments were associated with increased mortality in the simple model but not after adjusting for other factors.

In both age groups, reporting difficulties with 3–5 items on the long-term memory questionnaire was associated with mortality; however, these associations were no longer significant after adjusting for other factors in either of the two age groups.

IADL was strongly associated with mortality in both age groups (Table 2). In the youngest group, having difficulties with 1 item increased the risk for mortality by 49%, while having difficulties with 3 or more items increased the risk by 129% compared to those without IADL problems. Corresponding numbers for mortality risk in the oldest group were 29% (1 item) to 95% (3 or more items).

In the combined analyses, we observed an increased risk of mortality of 163% in persons 70–79 years old who reported difficulties in both short-term memory and IADL (Table 2). In the oldest group, those without any impairments had significantly less risk of mortality than those with impairments in either short-term memory or IADL, or in both domains (see also Figure 2).

Discussion

In this study, we sought to analyze the separate and combined associations between SMI, IADL and mortality in a population-based cohort of older adults. We found that subjective impairments in short-term memory and IADL were significantly associated with mortality both separately and combined. These associations were strongest in the youngest group of 70–79-year-olds.

The existing literature on the relationship between subjective cognitive impairment and mortality provides conflicting results. Our findings are in line with the results from the LEILA75+ Study, where they observed increased risk for mortality in persons with subjective cognitive impairment in a general population sample ages 75+ years.[17] In the French GAZEL study, researchers did not observe an increased risk of mortality from memory impairments but rather from self-reported difficulties in mental calculation.[16] While the participants of the LEILA75+ study were older than those in our study, the Gazel study focused on a middle-aged population. Thus, taken together, these three studies have identified the importance of subjective cognitive impairment across a relatively wide age span. By contrast, studies recruiting participants from general practitioners' offices have not observed the same association between SMI and mortality.[14, 15] The Danish study had only a 4-year follow-up and a population of 65 years old and older, which is a possible explanation for the lack of association.[15] The other study had a 7.5-year follow-up and included older (75 years+) participants; however, this study focused on incident cases of subjective cognitive decline, which may also explain the lack of association.[14] To further complicate the picture, Lee et al. found that, among older men, having trouble remembering had a protective effect on mortality.[13] In our study, we differentiated between questions related to long-term and short-term SMI, and our findings indicate that having concern for short-term memory is more strongly associated with mortality than concern for long-term memory. In our youngest group, mortality increased by 51% among those having impairments on only one of the four short-term items. The differentiation between short-term and long-term SMI can be a possible explanation for the stronger association between SMI and mortality in our study compared to studies that defined memory impairments as present based on a general question about memory decline.[13, 14] Although we have studied the associations between SMI and mortality, it is important to remember that such impairments are also related to other negative health issues such as lower quality of life, depression and poor health perception in older adults.[28, 29]

While impairment in recalling recent events is a hallmark of dementia, the first functional decline related to dementia is impairment in IADL. Impairment in IADL is likely associated with a broader spectrum of conditions than SMI and has been related consistently to increased risk of mortality in previous studies.[22-25] Our results corroborate these earlier findings, and we extend the previous findings by observing an increasing risk of mortality with a higher number of IADL impairments. Subjective memory impairments and impairments in IADL are associated in community-dwelling older adults.[29, 30] In our model, where we looked at the combined risk of reporting impairments in both short-term memory and IADL, the highest risk of mortality was observed in those who reported impairments in both functions. Our findings are strengthened by being significant even in models where we adjust for demographic factors, lifestyle factors, comorbidities, and symptoms of anxiety and depression. Impairments in memory function and IADL can be early indicators of subsequent dementia, and given the reduced life span of persons with mild cognitive impairment and dementia,[31] this may be a possible cause for the increased mortality risk in our sample. However, studies with information about cause of death are needed to examine this matter further.

Limitations of this study include the lack of objective assessments of memory and IADL at baseline, which could have provided a more extensive characterization of the concern reported by the respondents. Further, in the HUNT3 study, the main reasons for non-participation in the 70+ cohort were “too ill to attend” and “not having time to participate”, and non-participants also had higher mortality and higher prevalence of chronic diseases.[32] Therefore, our findings should be generalized to a healthier segment of the general population. In addition, low participation rates in the oldest age groups limit the generalizability of our findings to these groups. The participant rate in HUNT3 for the 70+ cohort overall was 54.6%; for the age span 70–79 years, it was 66.8%, for 80–89 years 41.6%, and for participants 90 years and older, it was 17.2%.[33] Further, we do not have information about education, which is a potential confounder to the association between cognition and mortality, nor do we have information about cause of death. Our interest in examining the combined association of

SMI and IADL impairments is related to the trajectory from the first subtle symptoms to development of dementia and subsequent death. However, although persons with SMI are twice as likely to develop further cognitive decline than persons without such impairments, we are still aware that a large proportion of persons with SMI never progresses to develop dementia.[5] In addition, despite having a mean follow-up time of 8 years in this study, this time span could still be too short to capture the entire trajectory.

CONCLUSION

In this study, we found that subjective impairments in short-term memory and in IADL were significantly associated with mortality, both separately and combined. These associations were strongest in the youngest group of 70–79-year-olds. This underlines that neither of these symptoms should be regarded as benign aspects of ageing. Hence, the clinical implication of this study is to increase the acknowledgement of and focus on subtle subjective memory impairments and IADL among otherwise healthy older people as well.

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Table 1. Baseline characteristics of the study sample.

	Total sample n=5802	70-79 years n=4274	80+ years n=1528
Gender			
Female (%)	3114 (54)	2239 (52)	875 (57)
Male (%)	2688 (46)	2035 (48)	653 (43)
Dead	1870	962	908
Person years (PY)	46915	36285	10630
Mortality rate per 1000 PY	39.8	26.5	85.4
Age, mean (SD)	76.9 (5.0)	74.5 (2.8)	83.8 (3.1)
Smoking, n (%)			
Never smoked	2601 (45)	1814 (42)	787 (52)
Previous smoker	2584 (45)	1955 (46)	629 (41)
Current smoker	617 (11)	505 (12)	112 (7)
Physical activity, n (%)			
< 30 minutes/day	1661 (29)	1142 (27)	519 (34)
≥ 30 minutes/day	4141 (71)	3132 (73)	1009 (66)
BMI (kg/m2)			
<20	127 (2)	85 (2)	42 (3)
20-24.99	1464 (25)	1006 (24)	458 (30)
25-29.99	2776 (48)	2058 (48)	718 (47)
≥30	1435 (25)	1125 (26)	310 (20)
HADS, mean (SD)	7.8 (5.1)	7.8 (5.1)	8.0 (5.2)
Comorbidity, n (%)			
No	2687 (46)	2071 (48)	616 (40)
Yes	3115 (54)	2203 (52)	912 (60)

Table 2. Impairments in memory and/or IADL and all-cause mortality hazard ratios (HR), N=5802, #deaths=1870. Estimated in Cox regression.

	70-79 years, n=4274 / 962 deaths				80+ years, n=1528 / 908 deaths		
Risk factors	N/#dead	HR (95% CI) Age and gender adjusted model.	HR (95% CI) Fully adjusted model.		N/#dead	HR (95% CI) Age and gender adjusted model	HR (95% CI) Fully adjusted model
Long-term memory impairments							
0	3057/647	1.00	1.00		985/544	1.00	1.00
1	632/142	0.99 (0.82, 1.18)	0.93 (0.77, 1.11)		254/168	1.14 (0.96, 1.36)	1.12 (0.94, 1.34)
2	341/91	1.11 (0.89, 1.39)	1.02 (0.81, 1.27)		146/94	1.15 (0.92, 1.43)	1.06 (0.85, 1.33)
3-5	244/82	1.45 (1.15, 1.82)	1.23 (0.97, 1.56)		143/102	1.48 (1.20, 1.83)	1.23 (0.99, 1.53)
Short-term memory impairments							
0	4011/858	1.00	1.00		1369/799	1.00	1.00
1	207/79	1.68 (1.34, 2.12)	1.51 (1.20, 1.91)		96/61	1.13 (0.87, 1.47)	1.04 (0.80, 1.35)
2-4	56/25	1.93 (1.30, 2.88)	1.62 (1.08, 2.43)		63/48	1.39 (1.04, 1.86)	1.19 (0.88, 1.60)
IADL impairments							
0	3546/679	1.00	1.00		913/457	1.00	1.00
1	392/131	1.66 (1.37, 2.00)	1.49 (1.23, 1.80)		277/185	1.40 (1.18, 1.66)	1.29 (1.09, 1.54)
2	167/68	1.95 (1.51, 2.50)	1.74 (1.35, 2.26)		169/123	1.47 (1.20, 1.79)	1.33 (1.09, 1.64)
3+	169/84	2.71 (2.16, 3.40)	2.29 (1.80, 2.90)		169/143	2.31 (1.92, 2.80)	1.95 (1.60, 2.39)
Combination of impairments in IADL and short-term memory							

None	3380/631	1.00	1.00		860/426	1.00	1.00
Either	797/275	1.73 (1.50, 2.00)	1.54 (1.33, 1.79)		562/404	1.57 (1.36, 1.80)	1.43 (1.24, 1.65)
Both	97/56	3.15 (2.40, 4.15)	2.63 (1.98, 3.49)		106/78	1.72 (1.35, 2.19)	1.40 (1.09, 1.81)

Fully adjusted model: adjusted for age, gender, smoking, physical activity, BMI, comorbidity and mental health (HADS)

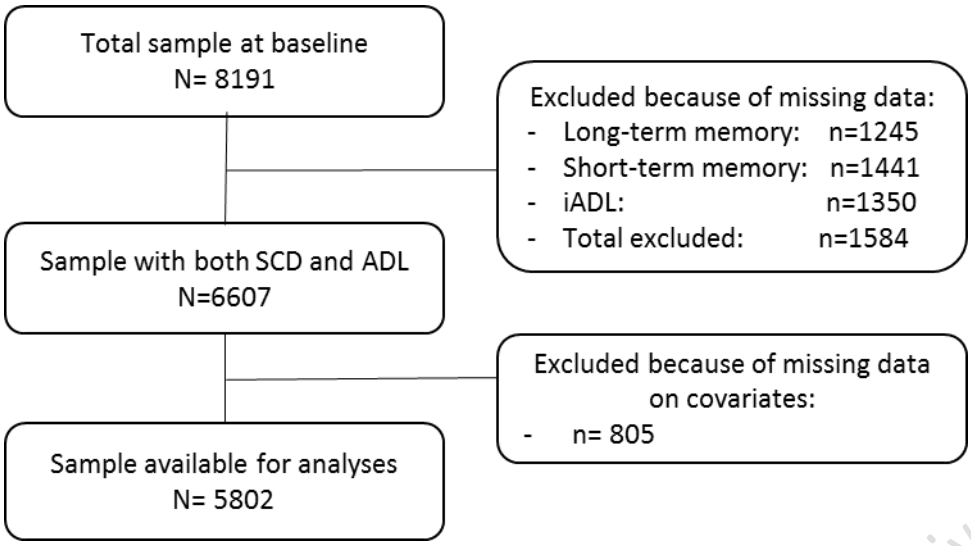

Figure 1. Sample attrition and sample.

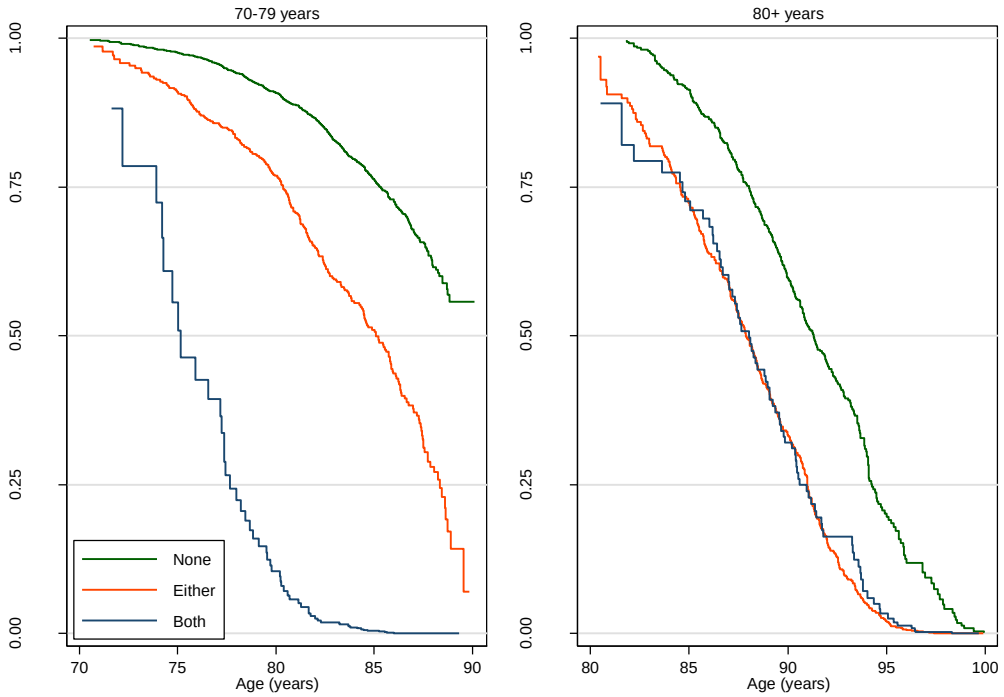

Figure 2. Survivor function for the combination of impairments in IADL- and short-term memory (none impairments, impairments on either, impairments on both), adjusted for age, gender and covariates. For figure at left for age 70-79 years, age was centered at age 70 years, and for the figure at right, for 80+ years, age was centered at 80 years. Genders were equally weighted, smoking was centered at never smokers, physical activity were equally weighted, BMI was centered at 25 kg/m^2, comorbidity was equally weighted, and HADS were centered at mean value 8.0. N=5802.