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Cognitive impairment, all-cause and cause-specific mortality among non-demented older adults

LAURA PERNA¹, HANS-WERNER WAHL², UTE MONS¹, KAI-UWE SAUM¹, BERND HOLLECZEK³, HERMANN BRENNER¹

¹German Cancer Research Center (DKFZ) - Division of Clinical Epidemiology and Aging Research, Im Neuenheimer Feld 581-69120 Heidelberg, Germany

²Department of Psychological Aging Research, Institute of Psychology, Heidelberg University, Hauptstrasse 47-51-69117 Heidelberg, Germany

³Saarland Cancer Registry, Präsident Baltz Straße 5-66119 Saarbrücken, Germany

Address correspondence to: L. Perna. Tel: (+49) 6221 421352; Fax: (+49) 6221 421302. Email: l.perna@dkfz-heidelberg.de

Abstract

Background: cognitive impairment is widespread among older adults even in the absence of dementia, but very little is known about the association between cognitive impairment not due or not yet converted to dementia and mortality. The association between cognitive impairment and mortality contributes to assessing cognitive impairment-related risk constellation in old age in the absence of manifest dementia.

Objective: to assess the impact of cognitive impairment on all-cause and cause-specific mortality among non-demented older adults and to explore the nature of the association between cognitive impairment and mortality.

Design: an observational cohort study (ESTHER study; 2000–present).

Setting: German state of Saarland.

Subjects: a subsample of 1,622 participants aged ≥ 70 with measurement of cognitive function through the Cognitive Telephone Screening Instrument (COGTEL) and exclusion of a possible dementia diagnosis at both COGTEL baseline (2005–08) and over the mortality follow-up (2005–13).

Results: during an average follow-up of 6.1 years, 231 participants (14.2%) died. Participants with low COGTEL total scores had ~60% increased mortality compared with participants with higher COGTEL total scores in Cox regression models adjusting for a wide range of possible confounders (hazard ratio = 1.62; confidence interval 1.13–2.33). Dose–response analyses with restricted cubic splines indicate a monotonic inverse relationship between cognitive function and mortality.

Conclusion: cognitive impairment in the absence of manifest dementia is an important independent predictor of mortality, especially among men. The administration of cognitive tests among older adults may provide relevant information for patient care and treatment decisions.

Sources of funding: financial sponsors played no role in the design, execution, analysis and interpretation of data.

Keywords: cognition, cognitive impairment, mortality, older people

Introduction

Dementia is a leading cause of death among older people [1–3], but very little is known about the association between cognitive impairment among non-demented older adults and mortality. Both psychological and epidemiological studies [4–7] showed that cognitive impairment at baseline is an important predictor of mortality, but since incidence of dementia increases exponentially with age [8] and people with mild cognitive impairment have a 3-fold greater risk of developing Alzheimer's disease (AD) over time [9], previous studies most likely included participants who had developed dementia over the long follow-up times.

Sachs and colleagues [4] specifically reported that dementia was the third leading cause of death among participants with moderate or severe baseline cognitive impairment. They found a positive association with total mortality over 13 years of follow-up, but no data on the association with non-dementia-related mortality were reported. Guehne and colleagues [5] observed that the mortality risk was increased if participants had developed dementia by the first follow-up. Johansson and Zarit [10] performed mortality analyses with assessment of cognitive status every 2 years over a 6-year period, but, despite the repeated measurements, given the advanced age of the participants in their study (84–90 years), they could not rule out that participants had developed dementia over the mortality follow-up. Also, a systematic review of the literature on cognitive impairment and mortality noted that the studies considered were likely to include mildly demented people [11].

As dementia is associated with mortality, the development of dementia over the follow-up might modify the association between cognition and mortality and limit the use and interpretation of mortality analyses focusing on baseline cognitive impairment. Investigating the association between cognitive impairment with mortality by excluding participants with a possible diagnosis of dementia developed over the mortality follow-up is of high relevance as it contributes to a comprehensive evaluation of the burden of cognitive impairment independently of dementia disease.

Other largely unexplored issues are causes of death among patients with cognitive impairment not due to dementia and the nature of the association between mortality

and cognitive impairment. Possible sex differences in the association between cognitive impairment and mortality among older adults have also been scarcely explored.

This study, based on a large population-based cohort of German elderly participants, aimed to assess the association between cognitive impairment not due or not yet progressed to dementia and all-cause and cause-specific mortality, and the nature of the association between mortality and cognitive impairment.

Methods

This study is based on data from a population-based longitudinal study conducted in the German state of Saarland to assess chances of prevention and early detection of various chronic diseases (ESTHER study). Details of the study design have been reported elsewhere [12]. See also Supplementary data, Appendix 1 available in *Age and Ageing* online. At the 5-year follow-up of the ESTHER study (May 2005–July 2008), a subsample ($N = 1,952$) of ESTHER participants aged ≥ 70 performed Version A of the Cognitive Telephone Screening Instrument (COGTEL), which allows a global assessment of cognitive function. In a validation study, examination of total scores provided evidence for the reliability and validity of COGTEL [13]. Previous analyses conducted with ESTHER data showed the plausibility of results obtained by COGTEL in large-scale epidemiological studies and in particular among older people in Germany; it also showed that COGTEL is not subject to ceiling effects [14].

Of the 1,952 participants, 255 were excluded because of invalid COGTEL results. Reasons for exclusion were, *inter alia*, hearing impairment, termination of tasks or interview, and cheating at COGTEL or getting help from others. To further exclude participants with a possible diagnosis of dementia over the follow-up, we used both death certificates and the criteria recommended by the National Institute on Aging and Alzheimer's Association workgroup [15], which hold that an important criterion differentiating dementia from mild cognitive impairment is the preservation of independence in performing functional tasks such as shopping alone, preparing meals, arranging to take public transportation. Following such recommendations, we excluded participants with baseline COGTEL total scores >1.0 standard deviation (SD) below

the sample mean [6, 16] and with additional impairment in functional activities either at COGTEL baseline in 2005–08 ($N = 21$) or at 8-year follow-up of the ESTHER study in 2008–10 ($N = 44$), or at 11-year follow-up in 2011–13 ($N = 9$). See Supplementary data, Appendix 2 available in *Age and Ageing* online. Furthermore, we excluded participants with dementia as cause of death in death certificates according to the International Classification of Diseases (ICD-10) code F01–F03 ($N = 1$). The resulting final study population was composed of 1,622 elderly individuals.

Complete mortality follow-up was available until 31 March 2013, with underlying causes of death available for 97.6% of the deaths until 31 December 2012. Information on vital status was obtained through inquiry at the residents' registration offices in Saarland, information relating to death certificates through public health departments.

The Kaplan–Meier method, including the log-rank test for statistical comparison, was used to compare survival curves among participants with COGTEL total score \geq sample mean (high), sample mean $- 1$ SD \leq COGTEL total score $<$ sample mean (medium), and COGTEL total score $<$ sample mean $- 1$ SD (low). Mean of the COGTEL total scores for the final sample of 1,622 participants was 27.7 (SD 8.4; range 2.8–51.1).

The association between cognitive impairment and mortality was furthermore assessed through Cox proportional hazards regression models. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). We selected co-variables to be included in Cox models on the basis of established statistical associations in previous studies both with the outcome variable (mortality) and exposure of interest (cognitive function). We restricted the choice of socio-economic indicators to attained education, because an association with mortality was more consistently found for this indicator than for other socio-economic indicators among older people [17]. To account for common chronic diseases at older age, which could confound the potential association between cognition and mortality both prevalence at baseline and incidence during follow-up of myocardial infarction, stroke, cancer and diabetes mellitus were included in Cox models. Information on disease was validated through medical records. We did not include depression, because it was self-reported and was not associated with COGTEL total scores in our sample. Lifestyle co-variables known to affect mortality and cognition, such as alcohol consumption per week (women: none, tolerable [1–70 g/week], harmful [>70 g/week]; men: none, tolerable [1–140 g/week], harmful [>140 g/week]) [18] and smoking habits (never/former versus current) were also included in fully adjusted Cox models. Body mass index (BMI) was categorised as follows: <25 kg/m² (normal), 25–29.9 kg/m² (overweight) and ≥ 30 kg/m² (obese) in descriptive statistics and used as continuous variable in survival analysis.

Restricted cubic splines [19] adjusted for the variables included in Cox regression Model 2 were employed to explore the nature of the association between cognitive impairment and mortality. Reference value was the sample mean of COGTEL

total scores. Predefined knots were 15.1 (1.5 SD below mean), 19.3 (1.0 SD below mean) and 36.1 (1.0 SD above mean).

All analyses were carried out using SAS[®] statistical software version 9.2 (SAS[®] Institute Inc., Cary, NC, USA). An alpha level of 0.05 was used for two-sided statistical significance testing.

Results

Of the 1,622 participants eligible for analysis, 966 (59.6%) were women and 656 (40.4%) were men (see Supplementary data, Appendix 3 available in *Age and Ageing* online). Mean age was 73.9 (SD 2.8) years and was similar among women (74.0 years; SD 2.8) and men (73.8 years; SD 2.7). In the whole sample, 16.5% ($N = 267$) had low, 33.6% ($N = 545$) medium and half (49.9%, $N = 810$) had high COGTEL total scores. Women and men had similar mean COGTEL total scores (27.6; SD 8.5 and 27.9; SD 8.3, respectively). COGTEL total scores were slightly positively skewed (0.05) with negative kurtosis (-0.43) probably as a result of excluding participants with indication of dementia and due to likely higher loss to follow-up of participants with cognitive impairment prior to COGTEL administration.

Over an average follow-up of 6.1 years, 14.2% ($N = 231$) of the participants died (Table 1). A significant larger proportion of participants with low COGTEL total scores than with high scores died during follow-up (21.0 versus 12.0%, respectively; χ^2 , $P = 0.0013$).

Kaplan–Meier curves showed that while survival probabilities among participants with high and medium COGTEL total scores followed similar patterns, especially at the beginning of the observation period, participants with low COGTEL total scores consistently showed the poorest survival over the observation period (see Supplementary data, Appendix 4 available in *Age and Ageing* online). The log-rank test, assessing homogeneity of survival curves for mortality among participants with low, medium and high COGTEL total scores, was significant with a P value of 0.0038.

Proportional hazards regression models adjusted for sex and age in the total sample (Table 2) showed that participants with low COGTEL total scores had $\sim 80\%$ increased mortality compared with participants with high COGTEL scores (HR = 1.77; CI 1.27–2.47). Additional adjustment for all other co-variables (years of education, alcohol consumption, health status, smoking status, BMI) only slightly reduced the strength of the association, which remained statistically significant (HR = 1.62; CI 1.13–2.33; $P = 0.0084$). The strongest predictor in the model was smoking, with current smokers having a 3-fold higher mortality compared with non-smokers or former smokers (HR = 2.99; CI 2.06–4.34). The presence of chronic diseases and age (per year) were also significantly associated with mortality with HRs of 1.86 (CI 1.41–2.46; $P \leq 0.0001$) and 1.07 per year of age (CI 1.01–1.12; $P = 0.0124$), respectively (data not shown). The analysis of the association stratified by sex revealed differing patterns, with a much stronger association between all-cause mortality

Table 1. Mortality characteristics and COGTEL total scores by cause-specific mortality (ESTHER cohort 2000–13)

	Total N (%)	COGTEL score mean (±SD)	Women N (%)	COGTEL score mean (±SD)	Men N (%)	COGTEL score mean (±SD)
Survival status ^a						
Alive	1,391 (85.8)	28.0 (8.4)	867 (89.7)	27.7 (8.5)	524 (79.9)	28.5 (8.2)
Deceased	231 (14.2)	25.8 (8.4)	99 (10.3)	26.3 (8.4)	132 (20.1)	25.4 (8.4)
Causes of death ^b						
Cancer	82 (38.7)	26.6 (8.7)	29 (31.5)	28.6 (9.0)	53 (43.8)	25.5 (8.5)
Cardiovascular diseases	74 (34.9)	25.5 (8.3)	35 (38.0)	25.6 (7.7)	39 (32.5)	25.4 (8.8)
Digestive system diseases	13 (6.1)	23.8 (7.7)	8 (8.7)	24.4 (8.7)	5 (4.2)	22.8 (6.8)
Urinary system diseases	11 (5.2)	21.0 (5.3)	5 (5.4)	21.4 (4.5)	6 (5.0)	20.6 (6.3)
Respiratory diseases	9 (4.2)	30.5 (5.4)	3 (3.3)	31.5 (4.8)	6 (5.0)	30.1 (6.1)
Others	23 (10.8)	25.3 (8.7)	12 (13.0)	24.2 (9.4)	11 (9.2)	26.4 (8.1)

^aAs of 31 March 2013, mean follow-up: 6.1 years.

^bCauses of death were available as of 31 December 2012 only. This explains the discrepancy ($N = 19$) between deaths due to all cause ($N = 231$) and deaths due to a specific cause ($N = 212$).

Table 2. Association of cognitive function with all-cause mortality overall and by gender (ESTHER cohort, 2000–13)

All causes of death	COGTEL total scores ^a	Number of events (%)	Mortality rate ^b	Model 1 ^c	Model 2 ^c
Total					
	Low ^d	56 (21.0)	18.7	1.77 (1.27–2.47)	1.62 (1.13–2.33)
	Medium ^e	78 (14.3)	12.6	1.14 (0.85–1.54)	1.05 (0.76–1.44)
	High ^f	97 (12.0)	10.6	Ref	Ref
Women					
	Low ^d	23 (13.6)	11.9	1.40 (0.85–2.33)	1.34 (0.77–2.31)
	Medium ^e	32 (10.0)	8.7	1.04 (0.66–1.64)	1.01 (0.63–1.64)
	High ^f	44 (9.2)	8.1	Ref	Ref
Men					
	Low ^d	33 (33.7)	31.0	2.14 (1.38–3.31)	1.90 (1.17–3.08)
	Medium ^e	46 (20.5)	18.3	1.23 (0.83–1.83)	0.99 (0.64–1.52)
	High ^f	53 (15.9)	14.2	Ref	Ref

^aSample mean = 27.7; standard deviation (SD) = 8.4.

^bPerson-years for all-cause mortality (up to 31 March 2013) by COGTEL total scores: Low = 2,999; Medium = 6,208; High = 9,134. Person-years for cause-specific mortality (up to 30 December 2012): Low = 2,947; Medium = 6,095; High = 8,963.

^cModel 1: adjusted for Age (continuous) and Sex (only total sample). Model 2: additionally adjusted for Years of school education (continuous); Alcohol consumption per week (abstainer, tolerable, harmful); Health status (presence of at least myocardial infarction, stroke, cancer or diabetes mellitus); Smoking status (never/former versus current); Body mass index (continuous).

^dCOGTEL total score < sample mean – 1 SD.

^eSample mean – 1 SD ≤ COGTEL total score < sample mean.

^fCOGTEL total scores ≥ sample mean.

and low COGTEL total scores among men (HR = 1.90; CI 1.17–3.08; $P = 0.009$) than among women (HR = 1.34; CI 0.77–2.31; $P = 0.30$) in the fully adjusted models. However, CIs of sex-specific estimates were overlapping widely, and an interaction test between sex and COGTEL total scores was not significant ($P = 0.22$ for low COGTEL scores and $P = 0.57$ for medium COGTEL scores).

The strongest associations were seen between low COGTEL total scores and deaths from cardiovascular diseases and between low COGTEL total scores and causes of death other than cardiovascular disease and cancer, but results were statistically significant in partially adjusted models only (Table 3). Interaction tests between low COGTEL total scores and chronic diseases were not significant.

Restricted cubic spline functions showing the dose–response association with 95% CI indicated a monotonic

inverse association between COGTEL scores and total mortality (see Supplementary data, Appendix 5 available in *Age and Ageing* online). Nevertheless, there seemed to be no further major improvement in survival among participants with COGTEL scores above the sample mean value.

Discussion

To our knowledge, this is the first study that investigates the association between cognitive impairment and mortality after excluding both participants with a possible dementia diagnosis developed over the mortality follow-up according to the concepts elaborated by the National Institute on Aging and Alzheimer's Association Workgroup [17] and participants with dementia as cause of death in death certificates. Our findings show that cognitive impairment in the absence of

Table 3. Association of cognitive function with cause-specific mortality (ESTHER cohort, 2000–13)

Causes of death	COGTEL total scores ^a	Number of events (%)	Mortality rate ^b	Model 1 ^c	Model 2 ^c
Cardiovascular disease	Low ^d	18 (6.7)	6.1	1.85 (1.02–3.33)	1.79 (0.91–3.5)
	Medium ^e	27 (5.0)	4.4	1.31 (0.77–2.21)	1.08 (0.60–1.95)
	High ^f	29 (3.6)	3.2	Ref	Ref
Cancer	Low ^d	19 (7.1)	6.4	1.54 (0.89–2.67)	1.38 (0.75–2.53)
	Medium ^e	23 (4.2)	3.8	0.83 (0.50–1.39)	0.70 (0.40–1.23)
	High ^f	40 (4.9)	4.5	Ref	Ref
Others	Low ^d	15 (5.6)	5.1	2.31 (1.17–4.56)	1.99 (0.93–4.22)
	Medium ^e	22 (4.0)	3.6	1.63 (0.88–3.02)	1.37 (0.71–2.66)
	High ^f	19 (2.3)	2.1	Ref	Ref

^aSample mean = 27.7; standard deviation (SD) = 8.4.

^bPerson-years for all-cause mortality (up to 31 March 2013) by COGTEL total scores: Low = 2,999; Medium = 6,208; High = 9,134. Person-years for cause-specific mortality (up to 30 December 2012): Low = 2,947; Medium = 6,095; High = 8,963.

^cModel 1: adjusted for Age (continuous) and Sex. Model 2: additionally adjusted for Years of school education (continuous); Alcohol consumption per week (abstainer, tolerable, harmful); Health status (presence of at least myocardial infarction, stroke, cancer or diabetes mellitus); Smoking status (never/former versus current); Body mass index (continuous).

^dCOGTEL total score < sample mean – 1 SD.

^eSample mean – 1 SD ≤ COGTEL total score < sample mean.

^fCOGTEL total scores ≥ sample mean.

manifest dementia is independently associated with increased mortality even during a relatively short follow-up of 6 years and after controlling for major risk factors known to have an impact on mortality. These findings provide important information relevant to the clinical characterisation of cognitive impairment and, additionally, to the assessment of health status among older people.

Also, this is the first analysis that explores the association of cognitive impairment with cause-specific mortality in Cox regression models. The main causes of death among people with low COGTEL total scores were cancer and cardiovascular diseases. The association of low COGTEL total scores with increased mortality appeared to be particularly strong for deaths from cardiovascular disease mortality and deaths from causes other than cardiovascular diseases and cancer, but evidence for cause-specific mortality is limited by the small number and heterogeneity of deaths.

While further analyses are necessary to fully explore the association with cause-specific mortality, our findings, also supported by the dose–response curve, tend to indicate that reduced cognitive function in the absence of manifest dementia represents rather a general decline in biological functions preceding death [20] than a specific disorder distinct from dementia. Cognitive impairment in the absence of dementia might thus be a highly predictive marker of health status among older people pointing to possible underlying physiopathological processes including yet undiagnosed pathologies known to have an impact on cognitive performance, such as cardiovascular diseases and diabetes mellitus, and incipient neurological diseases, such as preclinical AD. A support to the latter is given by the recent findings of Vos *et al.* [21] that found an association between Stage 3 of preclinical AD with early mortality, indicating that cognitive changes due to

underlying AD-related pathological processes might already have an impact on mortality before dementia becomes manifest.

Other possible explanations for the observed association are poor adherence to medications and treatment regimens due to cognitive deficits [22–24], potential side effects of medical treatments [25] and frailty, which is associated with both cognitive impairment [26] and mortality [27]. The impact of all such factors is difficult to be precisely measured and controlled for, but future studies should explore in detail these issues in order to understand the possible mechanisms responsible for the observed increased mortality among people with cognitive impairment in the absence of manifest dementia.

Nevertheless, the uncertainty about the mechanisms behind the association between cognitive function and mortality does not reduce the relevance of using cognitive performance as a biomarker for health status among older people, which, in addition to providing relevant health information, has also several advantages including availability, easiness and economy. Some tests for use as a brief assessment in primary care offices are, in fact, very short and only require a few minutes, a piece of paper and a pen to be performed.

Our findings seem to show differences in the mortality between men and women, with men with reduced cognitive performance seeming to show higher mortality than women (even though interaction by sex was not statistically significant). Although the comparison with other studies is difficult because of different neuropsychological testing, different statistical methods, different co-variables included in the models and different definition of cognitive impairment, this finding is in agreement with the study by Moritz *et al.* [28] who, among patients with AD, found shorter survival times in men than in women and the study by Perls *et al.* [29] who

found a significant association between reduced cognitive functioning with mortality only among men. There are, however, also studies that did not report sex-specific differences [30]. Further analyses are necessary to confirm possible different patterns of mortality among women and men with cognitive impairment.

An important limitation of this study is the potential of selection bias in favour of healthier individuals, which might contribute to explain the low percentage of participants with low COGTEL scores. Despite the possible under-representation of unhealthy individuals with low COGTEL scores and over-representation of healthier individuals, both mortality rate and chronic diseases were higher in the lowest COGTEL group, indicating that in the general population the observed associations might even be stronger than those reported here. Another limitation is the assessment of cognitive performance only at baseline and the paucity of information relating to the prognostic value of COGTEL scores for diagnosis of mild cognitive impairment and dementia, although preliminary results suggest that COGTEL, due to its statistical properties, might be very useful for detailed analyses of risk factors of cognitive decline [14].

Also, the retrospective exclusion of demented participants cannot definitively rule out the possibility of unrecognised dementia cases. This is because home visits were done in 2011–13 and mortality follow-up was performed in 2013. Given the older age of participants, it cannot be excluded that some participants with home visits in 2011 became subsequently demented. The additional dementia screening through death certificates also has its limitations, because dementia is notoriously under-diagnosed in death certificates. However, we think that the use of the recent criteria recommended by the National Institute on Aging and Alzheimer's Association workgroup and the general potential of selection bias in favour of healthier, non-demented individuals in population-based cohort studies make the occurrence of residual confounding by dementia rather unlikely.

Conclusions

This study suggests that cognitive impairment is an important marker of health status and a prognostic factor for mortality among older people, especially men, even in the absence of manifest dementia. These findings support the use of cognitive tests in clinical settings among non-demented older people.

Key points

- Cognitive impairment in the absence of dementia is an important marker of health status.
- Cognitive impairment among older people is a prognostic factor for mortality.
- There might be different patterns of mortality among men and women with cognitive impairment.

Conflicts of interest

None reported.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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