

# Cognitive impairment and cancer mortality: a biological or health care explanation?

Michail Katsoulis · Andeas Kyrozis · Antonia Trichopoulou ·  
Christina Bamia · Dimitrios Trichopoulos · Pagona Lagiou

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## Abstract

**Purpose** To examine whether the documented association of suboptimal cognitive function with total and cardiovascular (CVD) mortality also applies to cancer mortality and probe whether the explanation for this association is biomedical or health care related.

**Methods** In a subsample of 733 participants of the EPIC-Greece cohort from Athens and surrounding area, we assessed cognitive function at age 65 or older in the period 2004–2006, using the Mini-Mental State Examination (MMSE). Incidence of cancer, mortality from cancer and CVD, and overall mortality were ascertained through active follow-up for a median of 4 years after MMSE assessment using Cox proportional hazards models.

**Results** A total of 86 participants died during follow-up. A 2-point decrease in MMSE score was associated with increase in overall (hazard ratio (HR) 1.26, 95 % confidence interval (CI) 1.11–1.43), CVD (HR 1.26, 95 % CI 1.02–1.56), and cancer (HR 1.32, 95 % CI 1.02–1.70) mortality. In contrast, there was no noticeable difference in cancer incidence associated with a 2-point decrease in MMSE score (HR 1.07, 95 % CI 0.79–1.45).

**Conclusions** Cognitive function appears to be inversely associated not only with CVD and overall, but also with cancer mortality. Although for CVD mortality there is a biomedical explanation invoking vascular mechanisms, for cancer mortality we may need to focus on socially conditioned factors, such as compromised ability to identify early signs and suboptimal compliance to treatment. Our hypothesis-generating results need to be confirmed in larger studies, as the issue is of major importance, since cognitive decline is not uncommon among the elderly.

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M. Katsoulis (✉) · A. Kyrozis · A. Trichopoulou ·  
D. Trichopoulos  
Hellenic Health Foundation, 13 Kaisareias Street,  
115 27 Athens, Greece  
e-mail: mkatsoulis@hhf-greece.gr

A. Kyrozis  
1st Department of Neurology, Eginition Hospital, University of  
Athens Medical School, 74 Vas. Sofias Avenue, 11528 Athens,  
Greece

A. Trichopoulou · D. Trichopoulos · P. Lagiou  
Bureau of Epidemiologic Research, Academy of Athens, 23  
Alexandroupoleos Street, 115 27 Athens, Greece

C. Bamia · P. Lagiou  
Department of Hygiene, Epidemiology and Medical Statistics,  
University of Athens Medical School, 75 M. Asias Street,  
Goudi, 115 27 Athens, Greece

D. Trichopoulos · P. Lagiou  
Department of Epidemiology, Harvard School of Public Health,  
677 Huntington Avenue, Boston, MA 02115, USA

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## Introduction

Since 1990, several studies, using variable designs, have reported that low cognitive performance or decline in cognition is associated with increased mortality [1–6]. The association is consistent across studies, but the focus has been on cardiovascular diseases (CVD) [3, 4, 6–10]. Frailty [5], biological aging [11, 12], reduced efficiency of processing information [13], and underlying cardiovascular conditions [7] have been invoked as possible underlying mechanisms. Little work has been done on a possible relation between cognitive function and cancer mortality or

on comparing the association across causes of death, thus allowing additional insight into the possible underlying mechanisms.

In the present paper, we evaluated the association of cognitive performance with overall and cause-specific mortality in a subsample of the Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC-Greece). Our study population comprised men and women aged 65 years or older when cognition was evaluated (6–12 years after their enrollment in EPIC-Greece) and who were followed up afterwards for a median of 4 years.

## Subjects and methods

### Study subjects

The European Prospective Investigation into Cancer and nutrition (EPIC) is conducted in 10 European countries and investigates the relationships of diet and other lifestyle and environmental factors, as well as genetic factors, with the risk of cancer and other chronic diseases [14]. The Greek segment of EPIC, EPIC-Greece, is a cohort consisting of 28,572 volunteers, women and men, who were recruited from several regions of Greece between 1993 and 1999 (age at recruitment 20–86 years). Active follow-up started in January 1997 and has been repeated every 2–4 years [15, 16].

The present study was conducted in a sub-sample of the EPIC-Greece cohort [17]. Inclusion criteria included residence in the Attica region that surrounds and includes Athens and age at enrolment around 60 years or more. A total of 1,225 eligible subjects were identified. Beginning in March 2004, subjects were invited for assessment of cognitive function and emotional status. Of them, 165 refused to participate, 151 had died during follow-up, 25 had a new permanent residence outside Attica and another 68 could not be traced. Of the 816 volunteers who agreed to participate in the study, 3 with missing information on one or more of the studied variables and 80 without further information on their vital status after their cognitive assessment were excluded from the analysis. Thus, 733 participants were included in the final analyses.

The study was conducted in accordance with the Helsinki Declaration; all participants provided written informed consent before enrolment in the EPIC study and again before enrolment in the study of cognitive function. The study protocol was approved by the Bioethics Committee University of Athens Medical School.

### Lifestyle and anthropometry

Baseline socioeconomic, medical and lifestyle characteristics, notably age, years of schooling (as an indicator of

socio-economic status), and tobacco smoking were recorded with the help of trained interviewers. Diet was assessed through a validated interviewer-administered FFQ including approximately 150 foods and beverages commonly consumed in Greece [18–20].

The frequency and duration of participation in occupational and leisure-time physical activities were recorded in the questionnaire [21] and allowed the calculation of a metabolic equivalent index (MET value) to each activity [22] and eventually an overall MET  $\times$  hour sum, which indicates the amount of energy per kilogram of body weight expended during an average day by each participant. Body weight was measured to the nearest 100 g, and height was measured to the nearest 1 cm. Body mass index (BMI) was then calculated as the ratio of weight over the square of height (in kg/m<sup>2</sup>).

### Cognitive function assessment

Subjects were examined by a team of specially trained staff, comprising a nurse, a social worker and a physician, from May 2004 to October 2006 [17], 6.4–12.6 years after enrolment in the EPIC-Greece cohort (median 8.0 years); when the assessment of cognitive function was performed, the participants were 65 years or older. All participants were requested to complete the Mini-Mental State Examination (MMSE). MMSE is a quantitative indicator of cognitive function widely used clinically and epidemiologically, and has been consistently validated as a good indicator of a person's mental capacity for everyday activities, both internationally [23–26] and in Greece [27]. It consists of thirty questions that assess orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands, providing a score that places the individual on a scale of cognitive function from 0 (worst) to 30 (best) [28, 29]. In our analyses, MMSE score was considered in four categories [30]: (1) 25–30 (roughly equivalent to normal cognitive function), (2) 21–24 (mild cognitive impairment), (3) 10–20 (moderate cognitive impairment), and (4) <10 (severe cognitive impairment).

### Statistical analysis

Distributions by sociodemographic, lifestyle, medical, and anthropometric variables of study participants were examined by different categories of MMSE scores separately for men and women.

In the main analysis, to evaluate the association of cognitive impairment with mortality (overall and cause-specific), as well as cardiovascular disease (CVD) and cancer incidence, we applied Cox proportional hazards models, assuming as entry time the date of MMSE

measurement. In these models, we adjusted for age at MMSE assessment (continuously, in years), sex, BMI (continuously, in  $1 \text{ kg/m}^2$ ), height (continuously, in cm), marital status (cohabiting with partner vs alone), physical activity (continuously, in  $1 \text{ MET} \times \text{h}$  increments), education level (categorically,  $<6$ ,  $6\text{--}11$ ,  $12$  and  $>12$  years of schooling), smoking status (categorically, never/former/current smokers), alcohol intake (categorically, moderate consumption vs low/high consumption; moderate: if males

and females consumed  $\geq 10$ ,  $\leq 50$  and  $\geq 5$ ,  $\leq 25$  g/day, respectively, low/high: if males and females consumed  $<10$  or  $>50$  and  $<5$  or  $>25$  g/day respectively [15], hypertension at enrollment (yes/no), diabetes at MMSE (yes/no), cancer prevalent at MMSE and CVD events prevalent at MMSE (yes/no). In the cancer incidence analysis, we exclude the prevalent at MMSE cancer cases. For BMI, marital status, physical activity and alcohol intake, we used information collected at recruitment. Tests were considered

**Table 1** Distributions of the 733 study participants by sociodemographic, lifestyle, medical and anthropometric variables evaluated at enrollment or at MMSE<sup>a</sup>

MMSE score categories <sup>b</sup>	Men ( <i>n</i> = 265)			Women ( <i>n</i> = 468)		
	25–30	21–24	10–20	25–30	21–24	10–20
Number of participants	207 subj.	46 subj.	12 subj.	329 subj.	89 subj.	50 subj.
Age (in years) <sup>a</sup>	74.5 (4.5)	77.0 (5.3)	76.6 (7.0)	73.1 (4.1)	75.0 (4.1)	76.5 (5.1)
Height (in meters)	1.69 (0.06)	1.66 (0.06)	1.62 (0.06)	1.56 (0.06)	1.54 (0.06)	1.53 (0.06)
BMI (in $\text{kg/m}^2$ )	28.9 (4.1)	30.2 (4.2)	28.4 (3.3)	29.0 (4.6)	31.4 (5.2)	30.2 (5.1)
Physical activity (in METS)	32.1 (4.1)	30.0 (3.0)	30.0 (1.8)	34.4 (3.3)	32.7 (3.1)	32.6 (2.7)
Alcohol intake <sup>c</sup> [ <i>n</i> (%)]						
Low	120 (58)	28 (61)	7 (58)	264 (80)	79 (89)	42 (84)
Moderate	82 (40)	17 (37)	5 (42)	58 (18)	10 (11)	8 (16)
High	5 (2)	1 (2)	0 (0)	7 (2)	0 (0)	0 (0)
Education (years) [ <i>n</i> (%)]						
$\leq 6$	103 (50)	39 (85)	11 (92)	152 (46)	82 (92)	48 (96)
7–12	49 (24)	7 (15)	1 (8)	124 (38)	6 (7)	1 (2)
$>12$	55 (27)	0 (0)	0 (0)	53 (16)	1 (1)	1 (2)
Marital status [ <i>n</i> (%)]						
Married/live together	196 (95)	42 (91)	12 (100)	226 (69)	52 (58)	31 (62)
Alone/divorced/widowed	11 (5)	4 (9)	0 (0)	103 (31)	37 (42)	19 (38)
Smoking status [ <i>n</i> (%)]						
Never	61 (29)	13 (28)	3 (25)	230 (70)	73 (82)	41 (82)
Former	99 (48)	18 (39)	4 (33)	52 (16)	8 (9)	3 (6)
Current	47 (23)	15 (33)	5 (42)	47 (14)	8 (9)	6 (12)
Hypertension at baseline [ <i>n</i> (%)]						
No	58 (28)	9 (20)	2 (17)	146 (44)	17 (19)	12 (24)
Yes	149 (72)	37 (80)	10 (83)	183 (56)	72 (81)	38 (76)
Prevalent diabetes <sup>a</sup> [ <i>n</i> (%)]						
No	160 (77)	30 (65)	8 (67)	261 (79)	57 (64)	35 (70)
Yes	47 (23)	16 (35)	4 (33)	68 (21)	32 (36)	15 (30)
Prevalent CHD and stroke <sup>a</sup> [ <i>n</i> (%)]						
No	136 (66)	29 (63)	5 (42)	271 (82)	65 (73)	34 (68)
Yes	71 (34)	17 (37)	7 (58)	58 (18)	24 (27)	16 (32)
Prevalent cancer <sup>a</sup> [ <i>n</i> (%)]						
No	183 (88)	45 (98)	10 (83)	302 (92)	82 (92)	47 (94)
Yes	24 (12)	1 (2)	2 (17)	27 (8)	7 (8)	3 (6)

<sup>a</sup> Evaluated at cognitive assessment (2004–2006)

<sup>b</sup> None of the 733 participants had MMSE score below 10

<sup>c</sup> The categories for the alcohol consumption are defined as follows: low,  $<5$  g/day for women and  $<10$  g/day for men; moderate,  $\geq 5$  g/day and  $<25$  g/day for women and  $\geq 10$ ,  $<50$  g/day for men; high,  $>25$  g/day for women and  $>50$  g/day for men

statistically significant when  $p$  values were less than 5 % (two-tailed). All statistical analyses were conducted using the Stata Statistical Software, release 11 (Stata Corp. 2009, Stata Corp LP).

## Results

Table 1 presents the distributions of the characteristics of the participants by sex and different MMSE score categories. When comparing men with women, we see that men are generally more educated, had higher rates of smoking and hypertension at enrollment, whereas they also had higher prevalence at cognitive assessment of CHD and stroke. With respect to the MMSE score categories, we observe that, in both men and women, the participants with lower MMSE score were less educated, had higher prevalence of diabetes, CHD and stroke at cognitive assessment, as well as higher rates of hypertension at enrollment. Among men, 17 % (46 out of 265) were found to have mild cognitive impairment (MMSE: 21–24) and 5 % (12 out of 265) moderate cognitive impairment (MMSE: 10–20). The respective percentages for women were 19 and 11 %. No participant was found to have severe cognitive impairment (MMSE < 10). The small difference in cognitive function between men and women could be attributed to the difference in educational level.

Table 2 shows mortality ratios (hazard ratios, HR) overall, as well as from CVD and cancer, comparing subjects with mild and moderate cognitive impairment in relation to those with unaffected cognitive function. There

are statistically significant trend associations of the same magnitude for all studied outcomes. A 2-point decrease in MMSE was associated with 26 % increase in overall mortality (HR 1.26, 95 % confidence interval (95 % CI) 1.11–1.43) and in CVD mortality (HR 1.26, 95 % CI 1.02–1.56) and with a 32 % increase in cancer mortality (HR 1.32, 95 % CI 1.02–1.70). We repeated the analyses also in a subsample of 508 subjects for whom blood levels of total and HDL cholesterol were also available, controlling also for these variables and the results remained essentially unchanged (data not shown).

Excluding cancers prevalent at MMSE assessment, we also calculated HR for incident cancer overall (21 cases) in Table 3 and we found that a 2-point decrease in MMSE had a non-significant association with cancer incidence in the same direction with mortality, but so weak (HR 1.07, 95 % CI 0.79–1.45) that it could be considered that MMSE decline was essentially unrelated to cancer occurrence.

## Discussion

From a moderately sized cohort of 733 subjects aged 65 or more at cognitive function assessment and followed up a median of 4 years after this assessment, we found that lower cognitive function was associated with higher overall and CVD mortality, as well as higher mortality from cancer. We did not, however, find an association between cognitive function and cancer incidence.

An inverse association between cognitive function and mortality has been reported from several previous studies

**Table 2** Hazard ratios of mortality, overall and from cardiovascular diseases and cancer, by MMSE score category<sup>a</sup>

	MMSE score category	No. of events	Hazard ratio <sup>b</sup>	CI (HR)
Overall Mortality (# of events = 86)	25–30	50	Ref	Ref
	21–24	20	1.48	(0.83–2.63)
	10–20	16	3.65	(1.88–7.06)
	Per 2-point decrease in MMSE		1.26	(1.11–1.43)
Cardiovascular Mortality (# of events = 35)	25–30	21	Ref	Ref
	21–24	7	1.01	(0.40–2.50)
	10–20	7	3.29	(1.21–8.89)
	Per 2-point decrease in MMSE		1.26	(1.02–1.56)
Cancer Mortality (# of events = 17)	25–30	9	Ref	Ref
	21–24	5	2.13	(0.58–7.78)
	10–20	3	3.10	(0.60–16.01)
	Per 2-point decrease in MMSE		1.32	(1.02–1.70)

<sup>a</sup> Mini Mental State Examination. Score categories: 25–30 (roughly equivalent to normal cognitive function); 21–24 (mild cognitive impairment); 10–20 (moderate cognitive impairment); and < 10 (severe cognitive impairment)

<sup>b</sup> Adjusted for sex, age at MMSE; prevalent at MMSE cancer, coronary heart disease and stroke, or diabetes; as well as the following variables assessed at initial enrollment in the EPIC-Greece cohort: marital status, height, body mass index, physical activity, education level, smoking status, hypertension, alcohol intake

**Table 3** Hazard ratios of incident cancer by level of cognitive function

		No. of events	Hazard ratio <sup>a</sup>	CI (HR)
Incident cancer <sup>b</sup>	MMSE 25–30	14	Ref	Ref
No. of subjects = 669	MMSE 21–24	5	1.13	(0.37–3.40)
No. of events = 21	MMSE 10–20	2	1.42	(0.29–6.92)
	2-Point decrease in MMSE		1.07	(0.79–1.45)

<sup>a</sup> Adjusted for sex, age at MMSE; prevalent at MMSE cancer, coronary heart disease and stroke, or diabetes; as well as the following variables assessed at initial enrollment in the EPIC-Greece cohort: marital status, height, body mass index, physical activity, education level, smoking status, hypertension, alcohol intake

<sup>b</sup> We excluded prevalent cancer cases

[3–6]. Explicitly or implicitly, the focus has been on CVD [3, 4, 6–10] with vascular conditions [7] suspected as the culprit mechanisms underlying both cognitive decline and mortality. Our results suggest that the inverse association is also present with respect to mortality from cancer. Since systematic conditions, like the vascular ones suspected for CVD, are unlikely to operate for cancer at initial stages, our findings are more compatible with an alternative explanation, i.e., that cognitive decline is associated with a delay in symptom recognition, or poor treatment compliance—both factors affecting mortality rather than incidence of cancer. Our findings, if confirmed in larger studies, would highlight the need for special attention to prompt recognition of symptoms and better treatment compliance among those with suboptimal cognitive function.

The weakness of the present study springs from its moderate sample size, notwithstanding the statistical significant results. However, the findings help to formulate a hypothesis of social conditioning of the association between cognitive decline and survival, which should be more rigorously evaluated in larger prospective investigations. Notwithstanding this limitation, our study also has strengths, including a prospective cohort design, validated instruments, application of these instruments by specially trained health professionals and confirmed outcomes.

In conclusion, the results of our study indicate that the inverse association of cognitive function with cancer mortality is likely to be as strong as that with CVD mortality. Although for CVD mortality a biomedical explanation invoking systematic vascular problems appears plausible, no such explanation is apparent with respect to mortality from cancer. Therefore, for cancer mortality, we may need to focus on socially conditioned factors, which may well apply also to other chronic conditions, including CVD, that substantially contribute to total mortality. Thus, our hypothesis-generating findings, if confirmed in larger studies, would help delineate an important issue, given the non-negligible prevalence of suboptimal cognitive function in aging populations. The implications of our findings with respect to health care and equity could be considerable.

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