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Cognitive impairment from a Primary Health Care perspective: Reporting the burden and care challenges from a cross-sectional study in the island of Crete, Greece

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Abstract

Objectives

Cognitive impairment is known to have a significant impact on the quality of life of individuals and their caregivers, yet it is often underdiagnosed. The objective of this study is to assess the burden of cognitive impairment among elders visiting primary health [PHC] care practice settings, to explore associated risk factors and discuss current care challenges for PHC providers.

Design

A cross-sectional study was conducted between March 2013 and May 2014.

Setting

Fourteen PHC units located in both rural and urban areas of the Heraklion district in Crete, Greece.

Participants

Consecutive visitors aged at least 60 years attending selected PHC practices.

Primary and secondary outcome measures

The Mini Mental State Examination [MMSE] was used to indicate cognitive status. Other measurements included socio-demographic factors, comorbidities and lifestyle factors.

Results

A total of 3,140 PHC patients met inclusion criteria (43.2% male; mean age 73.7±7.8 years). The average MMSE score was 26.0±3.8; 26.7±3.5 in male and 25.4±3.9 in female participants ($p<0.0001$). Low MMSE scores (≤23/24, adjusted for education level) were detected in 20.2% of participants; 25.9% for females vs. 12.8% for males; $p<0.0001$. Female gender (Adjusted Odds Ratio [AOR] = 2.70; 95% Confidence Interval [CI] 2.12-3.45), age (AOR = 1.11; 95% CI 1.09-1.13), having received only

primary or no formal education (AOR = 2.86; 95% CI 2.22-3.57), reporting one or more sleep complaints (AOR 1.41; 95% CI 1.11-1.79), dyslipidemia (AOR = 0.80; 95% CI 0.65-0.99) and history of depression (AOR = 1.83; 95% CI 1.37-2.45) were associated with low MMSE scores. Region of residence accounted for 14.8% of the total variability of low MMSE scores controlling for all other factors ($p<0.001$)

Conclusions

This study identified a relatively high prevalence of low-MMSE scores amongst persons attending PHC practices in a southern European community setting and several risk factors associated with cognitive decline.

Strengths and limitations of this study

- This is the first study assessing the burden of cognitive impairment in a primary care setting in Greece, where there is a data paucity.
- The sample size was relatively large (3,140 individuals) covering both rural and urban areas.
- MMSE tool has a high sensitivity yet a low specificity as a dementia screening tool.

Introduction

With the gradual increase in population longevity, chronic conditions have become more prevalent, with cognitive disorders being amongst the most common [1]. In the elderly, measurable decline in cognitive abilities, including memory, ranges from age-related changes in cognitive functioning to mild cognitive impairment (MCI) and dementia [2 3]. Lacking a disease-modifying drug treatment, early detection and management of risk factors remains a key strategy in the reduction of disease burden [4].

According to Alzheimer Europe it is estimated that the total population prevalence of dementia in Greece is 1.77%, slightly exceeding the EU-28 average of 1.55% [5]. A more recent population study estimated the prevalence of dementia in those aged 65 years or older at 5%, with 75% of the cases being attributed to Alzheimer's disease [6]. Little is known about the burden and epidemiology of cognitive impairment in primary care settings in Greece. Financial crisis since 2010 and its impact on population health and on the burden to health care services is well documented [7-9]. In order to address these challenges, health care reforms were implemented with a focus on primary care, disease prevention and health promotion by establishing several new urban primary care units throughout the country [10].

In this context, a multi-disciplinary research network was established to study cognitive disorders at the Faculty of Medicine, University of Crete, Greece comprising scientists and practitioners from various medical disciplines (Thales MNSAD-Multidisciplinary Network for the Study of Alzheimer's disease; see **Supplementary Figure 1)**. The present report utilizes baseline data from the Primary Health Care (PHC) team with the aim to inform health care providers and policy makers regarding the burden associated with cognitive impairment in a community

PHC setting in Greece and be endorsed in continuing medical education activities and health care planning. Specific objectives were the following:

- To report the frequency of elders with low scores on a widely adopted screening instrument for dementia (Mini Mental Status Examination) among those served by primary care centers in Prefecture of Heraklion Crete, Greece.
- To assess systematic geographic variability in the expected burden associated with cognitive impairment.
- To identify key modifiable clinical and lifestyle, as well as demographic, variables associated with cognitive impairment.

Methods

Setting

A cross-sectional study was conducted between March 2013 and May 2014 in well-defined PHC settings in the prefecture of Heraklion on the island of Crete, Greece. Eligible units were staffed by GPs who were members of a previously established PHC research network coordinated by the Clinic of Social and Family Medicine, Faculty of Medicine, University of Crete. Fourteen PHC units from a total of 22 eligible units participated in the study: Eleven public PHC practices (two organized health centers and nine satellite practices) located in rural and semi-urban areas, serving a total population of 100,800 residents; and three urban PHC units (one public and two private) in the city of Heraklion, serving a total population of 174,000 residents.

Population and inclusion criteria

Eligible participants were persons aged 60 years or older, who were consecutive visitors in the participating PHC units, for any reason other than urgent care. Acutely ill patients or those requiring urgent referral to a secondary health care center were excluded. Established diagnosis of dementia or MCI was not an exclusion factor.

Measurements

A structured and pre-tested questionnaire was used to collect information from patients and caregivers on the following variables: socio-demographics (age, gender, place of residency, marital status, number of children, number of housemates, current/former employment status, number of rooms in the house, living situation, level and years of formal education received), health and lifestyle habits (smoking and alcohol consumption, number of days/week patient walked and total time of walking), self-reported night sleep duration (in hours) and presence of insomnia symptoms (difficulty falling asleep [DFA] or maintaining sleep [DMS], and early morning awakening [EMA]) [11], and presence of chronic non-communicable, neurological or psychiatric illnesses and prescribed medication. Chronic conditions were self-reported by patients, or reported by their caregivers and cross-validated by their GPs against the patient's electronic health record. Participants were also administered the Greek version of the MMSE [12] to assess general cognitive ability and the Barthel index of Activities of Daily Living (ADL) [13 14] was completed as part of the interview with the participant or caregiver. Finally, anthropometric measurements were measures by the interviewer (weight, height, waist circumference).

Definitions

The Greek version of MMSE has been validated and cut-off scores of 23/24 were found to have high specificity, sensitivity and positive predictive value [15] for detecting severe cognitive impairment or dementia in accordance with the original validation study of the English version [12]. In view, however, of the very high percentage of persons who had attained ≤6 years of formal education in the present, largely rural, sample (81.7%), we used education-adjusted MMSE cutoffs of ≤24/30 (for those with >6 years of formal education) and ≤23/30 (for those with ≤6 years) to classify participants in the low MMSE group [16]. A Barthel index score of 90/90 was used to indicate complete independence in activities of daily living [14]. Prolonged sleep was defined as reporting ≥9 hours of sleep in a given day [17 18]. Obese were considered participants with a BMI ≥ 30 kgs/m^2.

Data collection

All interviews were performed during PHC working hours by specially trained GPs and nurses. Data were initially recorded on paper and then transferred to the Clinic of Social and Family Medicine at the University of Crete where consistency checks and data entry and storage was performed.

Sample size estimation

The objective of the overall multi-disciplinary study was to enroll a minimum of 250 persons meeting formal DSM IV criteria for dementia. Assuming a 8% (95% Confidence Interval [CI] from 7.1% to 9.0%) prevalence of any type of dementia [19] among PHC visitors over 60 years of age a minimum sample size of 3,200 participants was estimated.

Statistical analysis

Demographic and other characteristics were summarized using descriptive statistics. Between-gender univariate comparisons were made using Pearson's chi-square test of independence (for categorical variables) and independent samples t-test (for continuous variables).

Two-level logistic regression models were used to assess possible associations between selected participant characteristics and low MMSE scores. Participants were classified according to their administrative district of residence in each of the 25 administrative districts of the Heraklion region.

Participant- (level-1) variables included in the model were: age (centered), gender (male, female), level of education (none, primary, secondary or greater), presence of obesity (yes, no), current smoker (yes/no), alcohol intake per month (measured in grams), reports at least one sleep complaint (yes/no), hypertension (yes, no), type-II diabetes (yes, no), dyslipidemia (yes, no), depression (yes, no) and traumatic brain injury (yes, no) .

The following variables were used as district-level variables (defined as level-2) in the model: population density of each administrative region (measured as the number of inhabitants per Km^2), travel time to the prefecture capital (measured in minutes), and distance to the prefecture capital (measured in kilometers). The above variables were selected on the basis of publicly available information.

All participants with complete data on age, gender and MMSE scores were included in the analysis and any missing data were handled by pairwise deletion. The level of significance was set to 5%, IBM SPSS 21 and STATA 11 were used to conduct analyses and ArcMap 10.3.1 was used for geographical representation of the results.

Patient and public involvement

There was no patient and public involvement

Results

Participants

A total of 3,471 individuals were invited to participate of whom 271 (7.8%) declined participation. The main reasons for non-participation were lack of time for the interview (80%) and unwillingness to participate in research (20%). In the majority of the 3,200 conducted interviews (n=2,698, 84.0%) a caregiver/companion was present. Upon checking for duplicate entries and data consistency, 60 entries were removed from the database resulting in a total of 3,140 entries included in the analysis.

General description of the population

Details regarding socio-demographic and other socio-economic characteristics of participants are presented in **Table 1**. The mean age of participants was 73.7 (SD = 7.8) years, with most respondents being female (n=1,785, 56.8%). The majority (n=2,845, 90.6%) of individuals visited the selected PHC practices for prescription renewal.

Table 1. Socio-demographic characteristics of participants and between-gender comparisons

	Overall (n=3,140)	**Females** (n=1,785)	**Males** (n=1,355)	**P-value**
Age, mean years (SD)	73.7 (7.8)	73.1 (7.6)	74.5 (7.9)	<0.0001
Marital status, n (%)[a]				<0.0001

Single-divorced	151 (4.8%)	86 (4.8%)	65 (4.8%)	
Married	2,217 (70.8%)	1,067 (59.9%)	1,150 (85.1%)	
Widowed	764 (24.4%)	627 (35.2%)	137 (10.1%)	
Level of education, n (%)[b]				<0.0001
None	251 (8.0%)	183 (10.3%)	68 (5.0%)	
Primary	2,304 (73.7%)	1,348 (76.0%)	956 (70.7%)	
Secondary or greater	570 (18.2%)	242 (13.6%)	328 (24.3%)	
Number of children, n (%)[c]				0.001
None	204 (6.5%)	140 (7.9%)	64 (4.7%)	
One or two	1,454 (46.6%)	792 (44.6%)	662 (49.1%)	
≥3	1,465 (46.9%)	843 (47.5%)	622 (46.2%)	
Living situation, n (%)[d]				<0.0001
Lives alone	694 (22.3%)	553 (31.2%)	141 (10.5%)	
One housemate	1,924 (61.9%)	973 (55.0%)	951 (71.0%)	
≥2 housemates	491 (15.8%)	244 (13.8%)	247 (18.5%)	
Number of rooms in home, n (%)[e]				<0.0001
One or two	652 (25.0%)	411 (28.1%)	241 (21.0%)	
≥3 rooms	1,958 (75.0%)	1,050 (71.9%)	908 (79.0%)	

[a] 8 missing values, [b] 12 missing values, [c] 14 missing values, [d] 28 missing values, [e] 0 missing values

Overall, 391 (12.5%) participants were current tobacco users and 1,368 (43.7%) reported current alcohol consumption. Smoking and alcohol consumption were more frequent among men, as shown in **Table 2**. Average Body Mass Index (BMI) was higher among females than males [30.7 kg/m^2 (SD = 5.4) vs. 28.8 kg/m^2

(SD = 4.1), respectively; p<0.0001]. Nearly half of the participants (n=1,285; 49.4%) reported walking for at least 10 minutes daily and averaging 6.3 (SD = 1.8) hours of sleep per night. Sleep-related problems were reported by 2,056 (67.1%) participants and were more frequently reported in females than males (p<0.0001 across symptoms). Of the 3,140 participants, 2,594 (82.7%) were found to be fully independent in activities of daily living as measured by the Barthel index.

Table 2. Health habits, anthropometric characteristics and reported sleep problems of participants and between-gender comparisons

	Overall (n=3,140)	**Females** (n=1,785)	**Males** (n=1,355)	**P-value**
Smoking, n (%)				
Current smoker[a]	391 (12.5%)	130 (7.3%)	261 (19.3%)	<0.0001
Ever smoker[b]	1,164 (37.3%)	221 (12.4%)	943 (70.0%)	<0.0001
Alcohol consumption, n (%)				
Current consumer[c]	1,368 (43.7%)	447 (25.1%)	921 (68.2%)	<0.0001
Ever consumer[d]	1,634 (52.3%)	547 (30.7%)	1,087 (80.6%)	<0.0001
Social alcohol consumer, n (%)[e]	832 (26.6%)	248 (13.6%)	585 (44.2%)	<0.0001
Daily alcohol consumer, n (%)[f]	840 (26.8%)	170 (9.4%)	670 (50.6%)	<0.0001
BMI (Kg/m^2), mean (SD)	29.9 (5.0)	30.7 (5.4)	28.8 (4.1)	<0.0001
Walks daily for >10 min, n (%)[g]	1,285 (49.4%)	590 (40.6%)	695 (60.5%)	<0.0001
Hours of sleep/night, mean (SD)	6.3 (1.8)	6.0 (1.8)	6.6 (1.8)	<0.0001
Prolonged sleep (≥9 hrs)	226 (7.3%)	100 (5.6%)	126 (9.7%)	<0.0001
Difficulty falling asleep, n (%)[h]	1,371 (44.0%)	944 (53.1%)	427 (31.8%)	<0.0001
Difficulty maintaining sleep, n	1,700 (54.3%)	1,060 (59.5%)	640 (47.3%)	<0.0001

(%)[i]				
Early awakening, n (%)[j]	1,093 (35.1%)	733 (41.3%)	361 (26.9%)	<0.0001
At least one sleep complaint	2,056 (67.1%)	1,279 (73.0%)	777 (46.8%)	<0.0001
Fully independent in activities of daily living, n (%)[k]	2,594 (82.7%)	1,427 (80.1%)	1,167 (86.3%)	<0.0001

[a] 9 missing values, [b] 12 missing values, [c] 8 missing values, [d] 13 missing values, [e] 13 missing values, [f] 3 missing values, [g] 539 missing values, [h] 18 missing values, [I] 4 missing values, [j] 43 missing values, [h] 21 missing values, [I] 7 missing values, [j]24 missing values, [k] 5 missing values (Barthel index).

The most frequently reported chronic conditions (see **Table 3**) were hypertension (n=2,140; 68.2%), dyslipidemia (n=1,427; 45.4%), type-II diabetes (n=786; 25.0%), and benign prostate hyperplasia (n=335; 24.8% in males). Significant gender differences in the frequency of several chronic conditions were noted.

Table 3. Frequency of most common chronic conditions for the entire population and by gender

n (%)	**Overall** (n=3,140)	**Females** (n=1,785)	**Males** (n=1,355)	**P-value**
Anemia[a]	175 (5.6%)	109 (6.1%)	66 (4.9%)	0.133
Anxiety [b]	128 (4.1%)	86 (4.8%)	42 (3.1%)	0.016
Arrhythmia[a]	284 (9.0%)	169 (9.5%)	115 (8.5%)	0.340
Arthritis [c]	348 (11.1%)	262 (14.7%)	86 (6.3%)	<0.0001
BPH[d]		-	335 (24.8%)	-
CHD[e]	522 (16.6%)	214 (12.0%)	308 (22.7%)	<0.0001
COPD [b]	294 (9.4%)	105 (5.9%)	189 (14.0%)	<0.0001
Depression[f]	387 (12.3%)	279 (15.6%)	108 (8.0%)	<0.0001
Dyslipidemia [b]	1,427 (45.4%)	883 (49.5%)	544 (40.1%)	<0.0001

GERD [b]	557 (17.7%)	334 (18.7%)	223 (16.5%)	0.100
Glaucoma [b]	196 (6.2%)	96 (5.4%)	100 (7.4%)	0.022
Hypertension [b]	2,140 (68.2%)	1,251 (70.1%)	889 (65.6%)	0.007
Hyperuricemia [b]	258 (8.2%)	93 (5.2%)	165 (12.2%)	<0.0001
Hypothyroidism[g]	291 (9.3%)	249 (13.9%)	42 (3.1%)	<0.0001
Type-II diabetes [b]	786 (25.0%)	444 (24.9%)	342 (25.2%)	0.819
Osteoporosis [h]	609 (19.4%)	583 (32.7%)	26 (1.9%)	<0.0001
Peptic Ulcer[i]	216 (6.9%)	135 (7.6%)	81 (6.0%)	0.083
Vertigo [b]	317 (10.1%)	218 (12.2%)	99 (7.3%)	<0.0001

[a,e,g] 1 missing values, [b] no missing values, [c,f] 2 missing values, [d] 3 missing values, [h,i] 4 missing values,
Abbreviations; GERD: gastroesophageal reflux disease; CHD: Coronary heart disease; BPH: Benign Prostate Hyperplasia; COPD: Chronic Obstructive Pulmonary Disease

The burden of cognitive impairment (according to MMSE scores)

The average MMSE score was 26.0 (SD = 3.8) and was significantly higher in males than females (26.7 vs. 25.4; 95% CI for the difference: 1.00 to 1.54; p<0.0001). Low MMSE scores (≤23/24, depending on education) were detected in 631 (20.2%) participants (459 (25.9%) females and 172 (12.8%) males; p<0.0001). The frequency of low MMSE scores was 8.6% in participants aged 60-70 years (11.2% in females vs. 4.4% in males; p<0.00001) and 44.2% in those aged 86 years or older (58.7% in females vs. 31.7% in males; p<0.00001; see **Figure 1**).

Enter Figure 1 about here

Associations between MMSE scores and selected modifiable risk factors

There were several significant associations between fixed and modifiable risk factors and the odds of having low MMSE scores (**Table 4)**. In regards to non-

modifiable factors, the odds of having a low MMSE score increased with age (Adjusted Odds Ratio [AOR] 1.11; 95% CI: 1.09 to 1.13; p<0.0001) and with low levels (none or primary) of education in both genders (AOR 3.03; 95% CI: 2.32 to 4.00 in females, AOR 2.56; 95% CI: 1.67 to 3.77 in males; p<0.0001 for both).

Regarding modifiable risk factors, reporting at least one sleep complaint increased the odds of having low MMSE score in females (AOR 1.69; 95% CI: 1.25 to 2.28; p=0.0001; but not in males (p=0.483). The presence of hypertension or type-II diabetes were not associated with low MMSE scores, while dyslipidemia reduced the odds of having low MMSE scores in females (AOR 0.70; 95% CI: 0.55 to 0.91; p=0.008). Depression increased the odds of having low MMSE scores in both genders (AOR 1.71; 95% CI: 1.23 to 2.39; p=0.001 in females; AOR 2.31; 95% CI: 1.31 to 4.07; p=0.004 in males), while traumatic brain injury increased the odds of having low MMSE scores in males only (AOR 3.77; 95% CI: 1.50 to 9.51; p=0.005).

Between-district variance in the predicted MMSE scores

Results from the null two-level, random intercept logistic regression analysis indicated significant between-district variance in the predicted MMSE scores ($\sigma_u^2 = 0.34$, $\sigma_e^2 = 3.29$, VPC = 9.37%; X^2 = 114.05; p<0.0001). For the full model the between-district variance in the predicted MMSE scores remained significant ($\sigma_u^2 = 0.58$, $\sigma_e^2 = 3.29$, VPC = 14.77%; X^2 = 96.17; p<0.0001 and Median Odds Ratio [MOR]= $e^{0.95\sigma_u}$ =2.05). No significant associations between the level-2 variables in the model (population density, travel time to prefecture capital and distance to prefecture capital) and the odds of having a low MMSE score were identified (**Table 4**). The predicted probabilities for low MMSE scores by district are geographically represented within the Heraklion prefecture in **Supplementary Figure 2**.

Table 4. Adjusted odds of probable cognitive impairment according to MMSE scores and their association with the selected level-1 and level-2 variables in the total sample and by gender

	Overall[+]	**Females**[*]	**Males**[†]
Independent variables	**AOR (95% CI; p-value)**	**AOR (95% CI; p-value)**	**OR (95% CI; p-value)**
Level-1 variables			
Gender (male)	2.70 (2.12 to 3.45; p<0.0001)	-	-
Age (centered)	1.11 (1.09 to 1.13; p<0.0001)	1.11 (1.09 to 1.14; p<0.0001)	1.11 (1.08 to 1.14; p<0.0001)
Level of education (≤primary)	2.86 (2.22 to 3.57; p<0.0001)	3.03 (2.32 to 4.00; p<0.0001)	2.56 (1.69 to 3,77; p<0.0001)
Obese (yes)	0.94 (0.76 to 1.16; p=0.560)	0.91 (0.71 to 1.17; p=0.460)	1.06 (0.72 to 1.56; p=0.779)
Current smoker (yes)	0.80 (0.55 to 1.18; p=0.266)	0.80 (0.45 to 1.41; p=0.447)	0.86 (0.50 to 1.46; p=0.571)
Kgs of monthly alcohol intake	1.17 (0.999 to 1.355; p=0.058)	0.99 (0.99 to 1.00; p=0.843)	1. 21 (1.015 to 1.42; p=0.036)
At least one sleep complaint (yes)	1.41 (1.11 to 1.79; p=0.005)	1.69 (1.25 to 2.28; p=0.001)	1.15 (0.78 to 1.74; p=0.483)
Hypertension (yes)	0.94 (0.74 to 1.19; p=0.614)	0.88 (0.66 to 1.19; p=0.433)	0.98 (0.65 to 1.47; p=0.931)
Type-II diabetes (yes)	0.89 (0.70 to 1.13; p=0.344)	0.92 (0.69 to 1.23; p=0.576)	0.81 (0.52 to 1.27; p=0.360)
Dyslipidemia (yes)	0.80 (0.65 to 0.99;	0.70 (0.55 to 0.91;	1.06 (0.71 to 1.58;

	p=0.042)	p=0.008)	p=0.761)
Depression (yes)	1.83 (1.37 to 2.45; p<0.0001)	1.71 (1.23 to 2.39; p=0.001)	2.31 (1.31 to 4.07; p=0.004)
Traumatic brain injury (yes)	1.43 (0.80 to 2.57; p=0.221)	0.82 (0.39 to 1.72; p=0.604)	3.77 (1.50 to 9.51; p=0.005)
Level-2 variables			
Population density (No citizens/km^2)	2.03 (0.39 to 10.71; p=0.400)	2.50 (0.38 to 16.24; p=0.335)	1.70 (0.28 to 10.14; p=0.561)
Travel time to prefecture capital (minutes)	1.07 (0.98 to 1.17; p=0.106)	1.07 (0.97 to 1.18; p=0.159)	1.06 (0.96 to 1.18; p=0.259)
Distance to prefecture capital (Kms)	0.93 (0.85 to 1.02; p=0.126)	0.94 (0.84 to 1.04; p=0.204)	0.93 (0.84 to 1.04; p=0.226)

AOR: Adjusted Odds Ratio; 95% CI: 95% Confidence Interval.
[+] Wald Chi-square=385.75, p<0.0001; for 24 level-2 groups and n=3008 observations. Level 2: estimate=0.5884; SE (0.119); 95% CI: 0.40 to 0.87; X^2=96.17, p<0.0001
[*] Wald Chi-square=245.85, p<0.0001; for 24 level-2 groups = 24 and n=1752 observations. Level 2: estimate=0.6383; SE (0.134); 95% CI: 0.422 to 0.963; X^2=71.954, p<0.0001
[†] Wald Chi-square=108.75, p<0.0001; for 24 level-2 groups and n=1256 observations. Level 2: estimate=0.5302; SE (0.167); 95% CI: 0.286 to 0.98; X^2=12.36, p=0.0002

Enter Supplementary Figure 2 about here

Discussion

Main findings

The present report documents a significant burden of cognitive impairment, as indicated by low MMSE scores, among persons older than 60 years visiting community-based primary care settings in a Southern European island. Specifically, as many as one in five persons across genders (and twice as many among women than among men) are at risk for probable cognitive impairment. Systematic between-region

variability in probable cognitive impairment was also identified. Furthermore, certain modifiable risk factors related to low MMSE scores were identified some of which were common to both genders and some gender-specific. These factors included lifestyle habits, such as alcohol consumption, sleep disturbances, and specific chronic illnesses such as depression and dyslipidemia, which are frequently treated in the context of PHC consultation.

Discussion in the light of the literature

Despite the older age of male compared to female participants, the burden of probable cognitive impairment was almost double among females. This finding is consistent with other studies, which have also found the incidence and prevalence of dementia to be greater in females compared to males [20 21]. Indeed there is growing evidence that multiple cognitive abilities are more adversely affected by AD in women than in men [20]. In addition to lower MMSE scores, morbidity was greater in females compared to males, with most chronic conditions being more frequently reported by females.

In regard to the selected modifiable life-style risk factors and co-morbidities, the present results indicate that their impact on probable cognitive impairment varies by gender, a fact that is also previously reported in the literature (24, 25). In the gender-specific analysis, self-reported sleep problems emerged as a significant correlate of low MMSE performance. In a recent French study the reported number of sleep complaints as well as the difficulty maintaining sleep were associated cognitive decline according to MMSE scores [22]. Similar patterns were identified in the KORA study where cognitive decline was more pronounced in individuals with DMS [11]. The MrOS Sleep study, found waking after sleep onset and the number of long-

wake episodes to be associated with a 1.4 to 1.5-fold increase in odds of clinically significant cognitive decline [17]. A more detailed analysis regarding specific insomnia-type symptoms and cognitive impairment from the present study population have been already published [23].

Results of this study indicated a positive relationship between presence of dyslipidemia and higher MMSE scores in females. This finding could add to the debate regarding the potential protective role of the long-term use of statins, but the cross-sectional nature of this work does not allow us to draw safe conclusions.[4 24-26]. Our results did not indicate significant associations between type-II diabetes or hypertension and cognitive impairment in contrast with several previous reports [4 27]. On the other hand, a negative association between probable cognitive impairment and depression was identified in both genders and between probable cognitive impairment and traumatic brain injury in males. Similar findings have also been reported in the literature [28-31].

Finally, our models indicated significant between-region variation in the predictive probability of having a low MMSE score a finding which seems to be consistent with conclusions from a systematic review and meta-analysis highlighting geographical variations in dementia rates in affluent countries at a variety of geographical scales [32]. Geographic variations within the island of Crete have also been reported for lung cancer incidence rates [33]. The geographic variation within the broader rural area of participant residence may form the basis for future explorations of genetic and environmental factors that could be involved in cognitive decline and aging [34].

Strengths and limitations

To our knowledge, this is the first study assessing the burden of probable cognitive impairment in a primary care setting in Greece. Furthermore, the study sample size is relatively large and although it did not employ a door-to-door approach or a randomly selected sample, the use of consecutive patients can provide a relatively accurate description of the characteristics of PHC visitors within a well-defined area. In our study the MMSE was used for the detection of probable cognitive impairment. The MMSE is characterized by high sensitivity and relatively low specificity as a dementia screening tool (44), so to establish a clinical diagnosis in-depth neuropsychological examinations are needed. To this end, the reported rates of probable cognitive impairment should be considered with caution.

Although specific associations between MMSE scores and specific chronic conditions were identified, the cross-sectional nature of the study does not support causal links between specific types of chronic conditions and cognitive impairment. Additionally, it should be noted that the majority participants visited the selected PHC for prescription renewal, most likely because they suffered from a chronic condition. In this manner, our population may not include healthy older adults, as well as persons suffering from debilitating conditions that are typically treated in acute care settings and would not typically visit PHC units in Greece.

Implications for practice and research

The findings of this cross-sectional study reveal a significant burden of probable cognitive impairment in a primary care setting. Given the progressive nature of cognitive impairment in older persons, the results of this study emphasize the need for improved screening in PHC. PHC practitioners may require additional training in terms of the need, screening procedures, and management practices related to

cognitive impairment and associated comorbidities. Moreover, specific conditions such as sleep disorders and depression could be used as an alarm sign so to investigate cognitive impairment.

In Greece a recent health care reform with a focus on prevention has just been applied with the establishment of local PHC units in urban centres. In the context of the new national plan for dementia (2015-2020) that has just been prepared by the Ministry of Health, screening for cognitive impairment could be included among the tasks of the family physicians who serve these new PHC units.

Conclusions

This cross-sectional PHC-based study provides new information on the prevalence of probable cognitive impairment in a rural Southern European primary care population aged 60 years and older. Our findings suggest that cognitive impairment deserves further attention in primary care in a country that is currently undergoing reform in the governance and role of a primary care services.

List of abbreviations

AD - Alzheimer's Disease

BMI - Body Mass Index

BPH: Benign Prostate Hyperplasia

CHD: Coronary heart disease

CI - Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CVD – Cardio Vascular Disease

DFA - Difficulty Falling Asleep

DMS - Difficulty Maintaining Sleep

EMA - Early Morning Awakening

EU - European Union

GERD: Gastroesophageal Reflux Disease

GP - General Practitioner

KM² – Square Kilometer

MCI - Mild Cognitive Impairment

MMSE - Mini Mental State Examination

MOR - Median Odds Ration

OR - Odds Ratio

PHC - Primary Health Care

SD - Standard Deviation

VPC - Variance Partition Coefficient

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Contributor's statement

AB: performed data entry, statistical analysis and drafted the first version of the manuscript, CT, DB, CL and AV: conceived the idea of the project, IT: contributed to drafting and revision of the manuscript, SP: supervised the data analysis and contributed to drafting and revision of the manuscript, IZ: contributed to the project coordination and drafting a revision of the manuscript, GD: was the PHC study-team coordinator and contributed to drafting the manuscript, ES, PP, KM, EI, CT, MB, SP and DB: contributed to drafting the manuscript and reviewed the manuscript, JM: provided statistical advice on study design and analysis and reviewed the manuscript, PS: contributed to drafting and revision of the manuscript, AV: was the PI of the project and contributed to drafting and revision of the manuscript, CL: contributed to drafting and revision of the manuscript and was supervisor and coordinator of the PHC team. All authors have reviewed manuscript prior to submission.

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Competing interests

The authors declare no competing interests

Ethics approval and consent to participate

The study was approved by the Bioethics Committee of the University Hospital of Heraklion (protocol number: 13541, 20.11.2010). All eligible persons or their caregivers were informed both verbally and through a patient/caregiver information sheet about the study by their GP and provided written consent if they agreed to participate. For patients unable to provide it, informed consent was provided by their caregivers.

Patient consent to publish

Not required

Availability of data and materials

Data and materials for this study are available from the authors upon reasonable request. Due to restrictions stated in our ethical approvals data are not available on public data repositories.

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Figure legends

Figure 1. Rates of probable cognitive impairment according to MMSE scores by gender and age group

Supplementary Figure 1. Flowchart of the study

Supplementary Figure 2. Map of the adjusted predictive probabilities of participants having a low MMSE score according to administrative region within the Heraklion prefecture

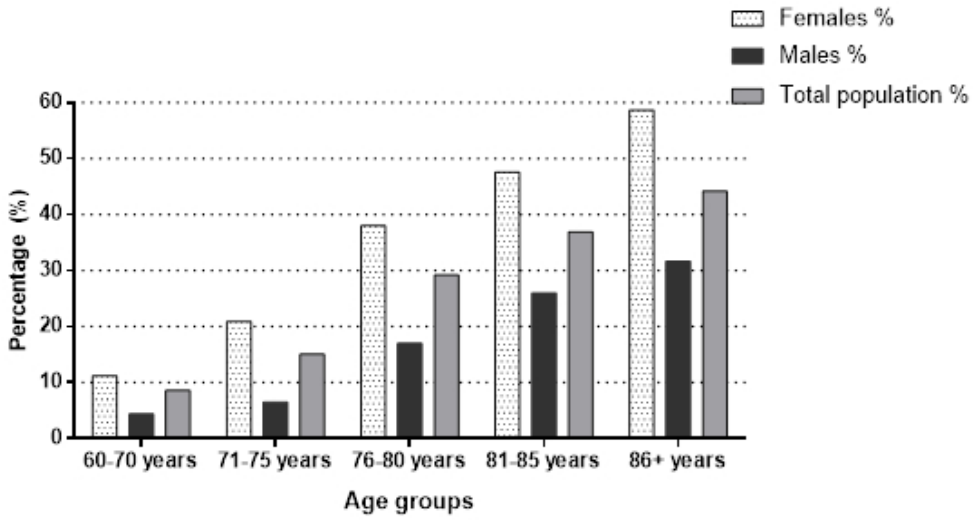
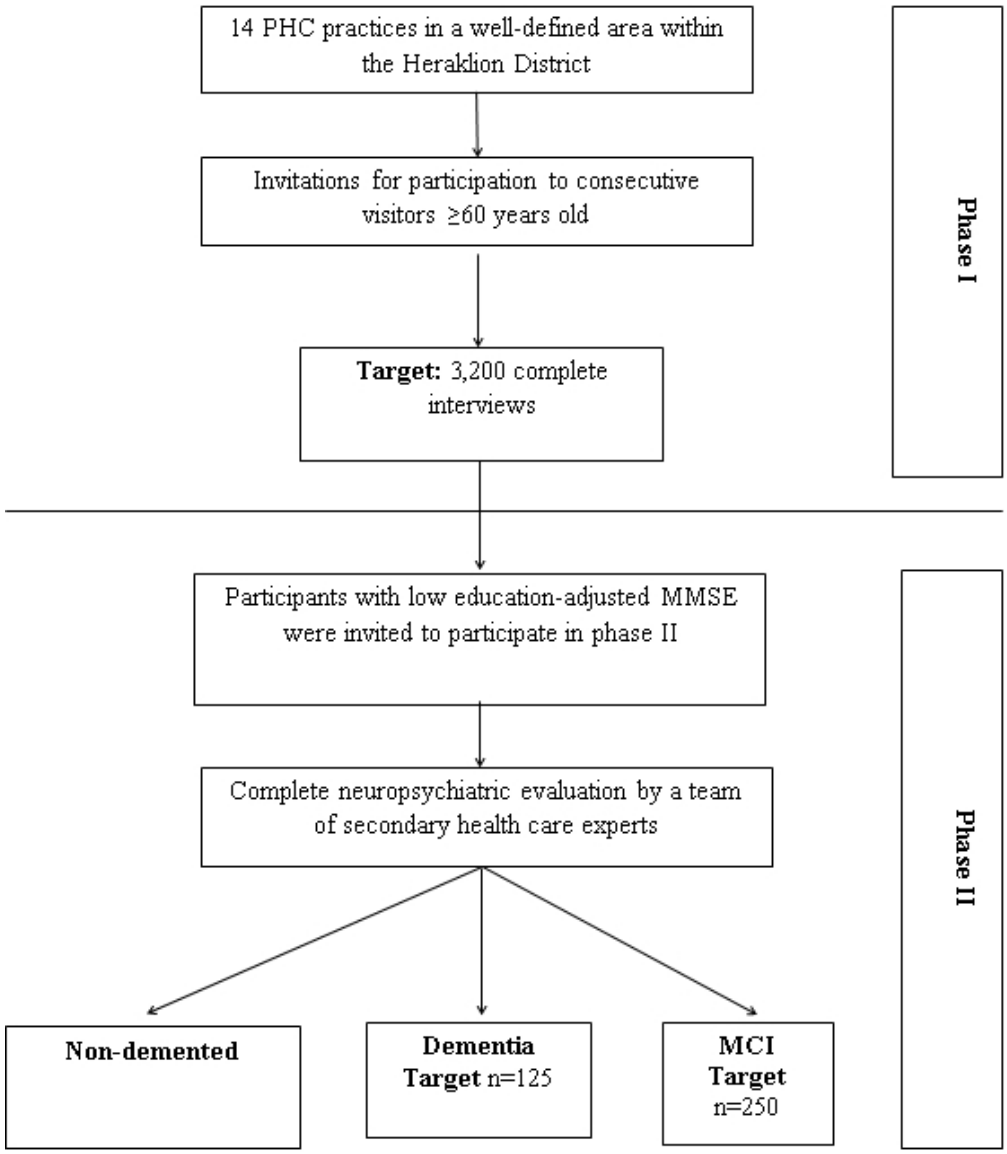
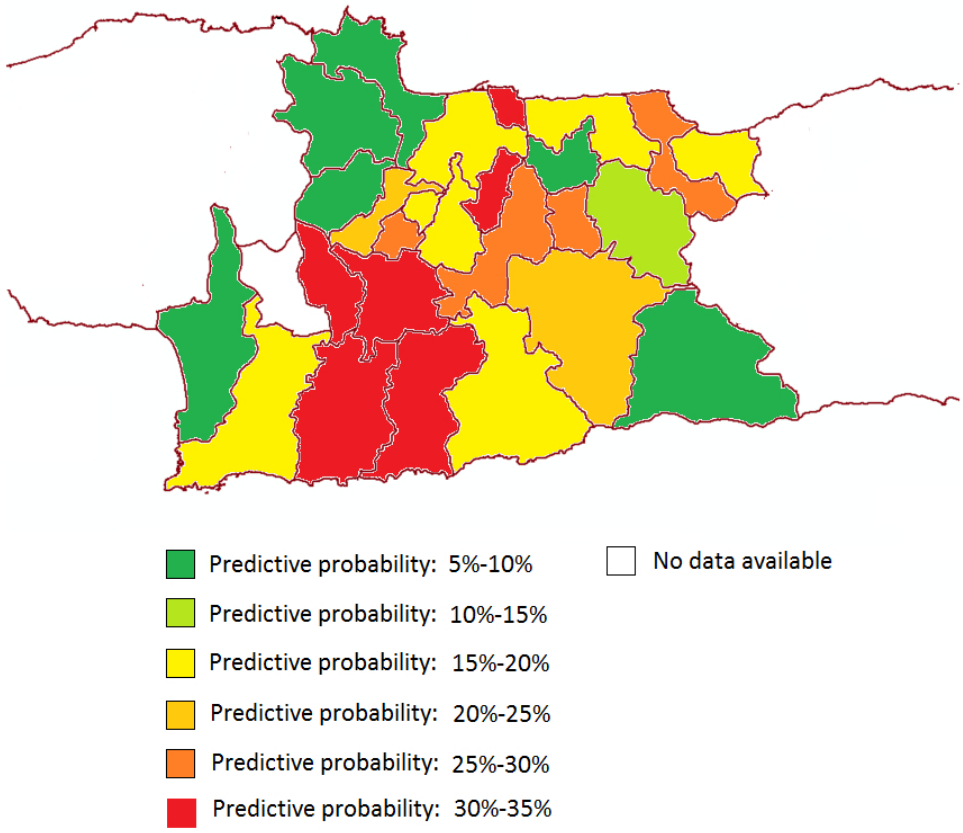


Figure 1. Proportion of participants with probable cognitive impairment according to MMSE scores by gender and age group





STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6,7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	10,11
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10,11
		(*b*) Describe any methods used to examine subgroups and interactions	10,11
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10,11
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Sup figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	In each Table
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	16,17

		which confounders were adjusted for and why they were included16,17	
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Sup. Figure 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21,22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21,22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24,25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cognitive impairment in a primary health care population: a cross-sectional study on the island of Crete, Greece

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Geriatric medicine, Epidemiology, Neurology, Mental health
Keywords:	Dementia < NEUROLOGY, EPIDEMIOLOGY, PRIMARY CARE

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Cognitive impairment in a primary health care population: a cross-sectional study on the island of Crete, Greece

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and on behalf of the Cretan Primary Health Care Ageing Network

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Abstract

Objectives

Cognitive impairment is known to have a significant impact on the quality of life of individuals and their caregivers, yet it is often underdiagnosed. The objective of this study is to assess the extent of cognitive impairment among elders visiting primary health [PHC] care practice settings, to explore associated risk factors and discuss current care challenges for PHC providers.

Design

A cross-sectional study was conducted between March 2013 and May 2014.

Setting

Fourteen PHC units located in rural and urban areas of the Heraklion district in Crete, Greece.

Participants

Consecutive visitors aged at least 60 years attending selected PHC practices.

Primary and secondary outcome measures

The Mini Mental State Examination [MMSE] was used to indicate cognitive status. Associations of low MMSE scores (≤23/24, adjusted for education level) with twelve socio-demographic factors, comorbidities and lifestyle factors were assessed.

Results

A total of 3,140 PHC patients met inclusion criteria (43.2% male; mean age 73.7±7.8 years). The average MMSE score was 26.0±3.8; 26.7±3.5 in male and 25.4±3.9 in female participants ($p<0.0001$). Low MMSE scores were detected in 20.2% of participants; 25.9% for females vs. 12.8% for males; $p<0.0001$. Female gender (Adjusted Odds Ratio [AOR] = 2.72; 95% Confidence Interval [CI] 2.31-3.47), age (AOR = 1.11; 95% CI 1.10-1.13), having received only primary or no formal

education (AOR = 2.87; 95% CI 2.26-3.65), alcohol intake (AOR = 1.19; 95% CI 1.03-1.37), reporting one or more sleep complaints (AOR 1.63; 95% CI 1.14-2.32), dyslipidemia (AOR = 0.80; 95% CI 0.65-0.98) and history of depression (AOR = 1.90; 95% CI 1.43-2.52) were associated with low MMSE scores.

Conclusions

This study identified a relatively high prevalence of low-MMSE scores amongst persons attending PHC practices in a southern European community setting and associations with several known risk factors.

Article summary

Strengths and limitations of this study

1. This is the first study assessing the burden of cognitive impairment in a primary care setting in Greece.
2. The sample size was relatively large (3,140 individuals) and recruited from both rural and urban areas.
3. Poor performance on cognitive tasks such as MMSE could be due factors other than cognitive decline. Comprehensive neuropsychological evaluation is necessary in order to establish clinical diagnosis.
4. Since the majority of participants visited the selected PHC for prescription renewal, the study population may include fewer healthy older adults than those living in the community.

Introduction

With the gradual increase in population longevity, chronic conditions have become more prevalent, with cognitive disorders being amongst the most common (1, 2). In the elderly, measurable decline in cognitive abilities, including memory, can be caused by several reversible and non-reversible conditions, while mild cognitive impairment (MCI) and dementia represent the most common conditions (3, 4). Lacking a disease-modifying drug treatment, early detection and management of risk factors remains a key strategy in the reduction of the rate of MCI and dementia (5, 6). Several modifiable risk-factors for cognitive impairment as well as for the onset and progression of MCI and dementia in particular, have been identified in the literature. Some appear to be gender-specific, yet they have not been studied extensively (5, 7-13).

According to Alzheimer Europe it is estimated that the total population prevalence of dementia in Greece is 1.77%, slightly exceeding the EU-28 average of 1.55% (14). A more recent population study estimated the prevalence of dementia in those aged 65 years or older at 5%, with 75% of the cases being attributed to Alzheimer's disease (15). In regards to MCI, the estimated prevalence in population-based studies ranges from 10 to 20% in persons older than 65 years of age (4, 16, 17). Little is known about the extent and epidemiology of cognitive impairment in primary health care settings in Greece, where the impact of the Greek financial crisis since 2010 on population health and the burden to health care services is well documented (18-20). In order to address this challenge, health care reforms were implemented with a focus on primary care, disease prevention and health promotion by establishing several new urban primary care units throughout the country (21).

In this context, a multi-disciplinary research network was established at the Faculty of Medicine, University of Crete, Greece including researchers and practitioners from various medical disciplines (Thales MNSAD-Multidisciplinary Network for the Study of Alzheimer's disease) to study the magnitude of this health problem and discuss the care challenges for the health care services (22). The present report utilizes baseline data from the Primary Health Care (PHC) team with the aim to inform health care providers and policy makers regarding the extent of cognitive impairment in the primary health care population, and associations with demographic and clinical risk factors, as judged by the Mini-Mental-State-Examination (MMSE). Specific objectives were the following:

- To report the extent of elders with low scores on a widely adopted screening instrument for dementia (MMSE) among those served by primary care centers in Prefecture of Heraklion Crete, Greece.

  To identify key modifiable clinical, lifestyle, and demographic variables associated with cognitive impairment and report on probable between-gender variations.

Methods

Setting

A cross-sectional study was conducted between March 2013 and May 2014 in well-defined PHC settings in the prefecture of Heraklion on the island of Crete, Greece. Eligible units were staffed by GPs who were members of a previously established PHC research network coordinated by the Clinic of Social and Family Medicine, Faculty of Medicine, University of Crete. Fourteen PHC units (12 public and two private) from a total of 22 public units in the district of Heraklion participated

in the study: Eleven public PHC practices (two organized health centers and nine satellite practices) were located in rural and semi-urban areas, serving a total population of 100,800 residents; and three urban PHC units (one public and two private) in the city of Heraklion, serving a total population of 174,000 residents (Supplementary Table 1).

Population and inclusion criteria

Eligible participants were persons aged 60 years or older, who were consecutive visitors in the participating PHC units, for any reason other than urgent care. Acutely ill patients or those requiring urgent referral to a secondary health care center were excluded. Established diagnosis of dementia or MCI was not an exclusion factor. Eligible participants were invited by the trained GPs to participate in the study. All interviews were conducted by trained nurses. Participants' companions were asked to provide information in cases where participants had difficulty providing adequate information. Participant responses on clinically-relevant questions were later verified by their GP. Further description of our population is reported elsewhere (22).

Measurements

A structured and pre-tested questionnaire was used to collect information from patients and caregivers on the following variables: socio-demographics (age, gender, place of residency, marital status, number of children, number of housemates, current/former employment status, number of rooms in the house, living situation, level and years of formal education received), health and lifestyle habits (smoking and alcohol consumption, number of days/week patient walked and total time of walking), self-reported night sleep duration (in hours) and presence of insomnia symptoms

(difficulty falling asleep [DFA] or maintaining sleep [DMS], and early morning awakening [EMA]) (23), and presence of chronic non-communicable, neurological or psychiatric illnesses and prescribed medication. Chronic conditions were self-reported by patients, or reported by their caregivers and cross-validated by their GPs against the patient's electronic health record. Participants were also administered the Greek version of the MMSE (24) to assess general cognitive ability and the Barthel index of Activities of Daily Living (ADL) (25, 26) was completed as part of the interview with the participant or caregiver. Finally, anthropometric measurements were measures by the interviewer (weight, height, waist circumference).

Definitions

The Greek version of MMSE has been validated and cut-off scores of 23/24 were found to have high specificity, sensitivity and positive predictive value (27) for detecting dementia in accordance with the original validation study of the English version (24). In view, however, of the very high percentage of persons who had attained ≤6 years of formal education in the present, largely rural, sample (81.7%), we used education-adjusted MMSE cutoffs of ≤24/30 (for those with >6 years of formal education) and ≤23/30 (for those with ≤6 years) to classify participants in the low MMSE group (28). A Barthel index score of 90/90 was used to indicate complete independence in activities of daily living (26). Prolonged sleep was defined as reporting ≥9 hours of sleep in a given day (29, 30). Obese were considered participants with a BMI ≥ 30 kg/m^2.

Data collection

All interviews were performed during PHC working hours by specially trained GPs and nurses. Data were initially recorded on paper and then transferred to the Clinic of Social and Family Medicine at the University of Crete where consistency checks and data entry and storage was performed.

Sample size estimation

The objective of the overall multi-disciplinary study (Thales MNSAD-Multidisciplinary Network for the Study of Alzheimer's disease) (22) was to enroll a minimum of 250 persons meeting formal DSM IV criteria for dementia. Assuming a 8% (95% Confidence Interval [CI] from 7.1% to 9.0%) prevalence of any type of dementia (31) among PHC visitors over 60 years of age a minimum sample size of 3,200 participants was estimated.

Statistical analysis

Demographic and other characteristics were summarized using descriptive statistics. Between-gender univariate comparisons were made using Pearson's chi-square test of independence (for categorical variables) and independent samples t-test (for continuous variables). The variability of estimated cognitive impairment was calculated using robust standard errors clustering by PHC unit (32).

Logistic regression models were used to assess unadjusted associations between participant characteristics and probable cognitive impairment (low MMSE scores). The patient characteristics were: age (centered), gender (male, female), level of education (none, primary, secondary or greater), presence of obesity (yes, no), current smoker (yes/no), alcohol intake per month (measured in grams), reports at least one sleep complaint (yes/no), hypertension (yes, no), type-II diabetes (yes, no),

dyslipidemia (yes, no), depression (yes, no) and traumatic brain injury (yes, no). Multilevel logistic regression models were also performed in order to obtain odds ratios adjusted for probable risk factors (that had been pre-selected based on the literature) (5). The multilevel models included 12 predictor variables in addition to PHC unit-specific random effects. The variance inflation factor (VIF) was computed in order to assess potential multicollinearity. The operation of the participating PHC units (public vs private) was used as a level-2 variable.

All participants with complete data on age, gender and MMSE scores were included in the analysis and any further missing data were handled by pairwise deletion. The level of significance was set to 5%, IBM SPSS 21 and STATA 11 were used to conduct the analyses.

Patient and public involvement

There was no patient and public involvement

Results

Participants

A total of 3,471 individuals were invited to participate of whom 271 (7.8%) declined participation. The main reasons for non-participation were lack of time for the interview (80%) and unwillingness to participate in research (20%). In the majority of the 3,200 conducted interviews (n=2,698, 84.0%) a caregiver/companion was present. Upon checking for duplicate entries and data consistency, 60 entries were removed from the database resulting in a total of 3,140 entries included in the analysis.

General description of the population

Details regarding socio-demographic and other socio-economic characteristics of participants are presented in **Table 1**. The mean age of participants was 73.7 (SD = 7.8) years, with most respondents being female (n=1,785, 56.8%). The majority (n=2,845, 90.6%) of individuals visited the selected PHC practices for prescription renewal.

Table 1. Socio-demographic characteristics of participants and between-gender comparisons

	Overall (n=3,140)	**Females** (n=1,785)	**Males** (n=1,355)	**P-value**
Age, mean years (SD)	73.7 (7.8)	73.1 (7.6)	74.5 (7.9)	<0.0001
Marital status, n (%)[a]				<0.0001
Single-divorced	151 (4.8%)	86 (4.8%)	65 (4.8%)	
Married	2,217 (70.8%)	1,067 (59.9%)	1,150 (85.1%)	
Widowed	764 (24.4%)	627 (35.2%)	137 (10.1%)	
Level of education, n (%)[b]				<0.0001
None	251 (8.0%)	183 (10.3%)	68 (5.0%)	
Primary	2,304 (73.7%)	1,348 (76.0%)	956 (70.7%)	
Secondary or greater	570 (18.2%)	242 (13.6%)	328 (24.3%)	
Number of children, n (%)[c]				0.001
None	204 (6.5%)	140 (7.9%)	64 (4.7%)	
One or two	1,454 (46.6%)	792 (44.6%)	662 (49.1%)	
≥3	1,465 (46.9%)	843 (47.5%)	622 (46.2%)	
Living situation, n (%)[d]				<0.0001

Lives alone	694 (22.3%)	553 (31.2%)	141 (10.5%)	
One housemate	1,924 (61.9%)	973 (55.0%)	951 (71.0%)	
≥2 housemates	491 (15.8%)	244 (13.8%)	247 (18.5%)	
Number of rooms in home, n (%)[e]				<0.0001
One or two	652 (25.0%)	411 (28.1%)	241 (21.0%)	
≥3 rooms	1,958 (75.0%)	1,050 (71.9%)	908 (79.0%)	

[a] 8 missing values, [b] 12 missing values, [c] 14 missing values, [d] 28 missing values, [e] 0 missing values

Overall, 391 (12.5%) participants were current tobacco users and 1,368 (43.7%) reported current alcohol consumption. Smoking and alcohol consumption were more frequent among men, as shown in **Table 2**. Average Body Mass Index (BMI) was higher among females than males [30.7 kg/m^2 (SD = 5.4) vs. 28.8 kg/m^2 (SD = 4.1), respectively; p<0.0001]. Nearly half of the participants (n=1,285; 49.4%) reported walking for at least 10 minutes daily and averaging 6.3 (SD = 1.8) hours of sleep per night. Sleep-related problems were reported by 2,056 (67.1%) participants and were more frequently reported in females than males (p<0.0001 across symptoms). Of the 3,140 participants, 2,594 (82.7%) were found to be fully independent in activities of daily living as measured by the Barthel index.

Table 2. Health habits, anthropometric characteristics and reported sleep problems of participants and between-gender comparisons

	Overall (n=3,140)	**Females** (n=1,785)	**Males** (n=1,355)	**P-value**
Current smoker n (%)[a]	391 (12.5%)	130 (7.3%)	261 (19.3%)	<0.0001
Ever smoker n (%)[b]	1,164 (37.3%)	221 (12.4%)	943 (70.0%)	<0.0001

Current alcohol consumer n (%)[c]	1,368 (43.7%)	447 (25.1%)	921 (68.2%)	<0.0001
Ever alcohol consumer n (%)[d]	1,634 (52.3%)	547 (30.7%)	1,087 (80.6%)	<0.0001
Social alcohol consumer, n (%)[e]	832 (26.6%)	248 (13.6%)	585 (44.2%)	<0.0001
Daily alcohol consumer, n (%)[f]	840 (26.8%)	170 (9.4%)	670 (50.6%)	<0.0001
BMI (Kg/m^2), mean (SD)	29.9 (5.0)	30.7 (5.4)	28.8 (4.1)	<0.0001
Walks daily for >10 min, n (%)[g]	1,285 (49.4%)	590 (40.6%)	695 (60.5%)	<0.0001
Hours of sleep/night, mean (SD)	6.3 (1.8)	6.0 (1.8)	6.6 (1.8)	<0.0001
Prolonged sleep (≥9 hrs)	226 (7.3%)	100 (5.6%)	126 (9.7%)	<0.0001
Difficulty falling asleep, n (%)[h]	1,371 (44.0%)	944 (53.1%)	427 (31.8%)	<0.0001
Difficulty maintaining sleep, n (%)[i]	1,700 (54.3%)	1,060 (59.5%)	640 (47.3%)	<0.0001
Early awakening, n (%)[j]	1,093 (35.1%)	733 (41.3%)	361 (26.9%)	<0.0001
At least one sleep complaint	2,056 (67.1%)	1,279 (73.0%)	777 (46.8%)	<0.0001
Fully independent in activities of daily living, n (%)[k]	2,594 (82.7%)	1,427 (80.1%)	1,167 (86.3%)	<0.0001

[a] 9 missing values, [b] 12 missing values, [c] 8 missing values, [d] 13 missing values, [e] 13 missing values, [f] 3 missing values, [g] 539 missing values, [h] 18 missing values, [I] 4 missing values, [j] 43 missing values, [h] 21 missing values, [I] 7 missing values, [j]24 missing values, [k] 5 missing values (Barthel index).

The most frequently reported chronic conditions (see **Table 3**) were hypertension (n=2,140; 68.2%), dyslipidemia (n=1,427; 45.4%), type-II diabetes (n=786; 25.0%), and benign prostate hyperplasia (n=335; 24.8% in males). Significant gender differences in the frequency of several chronic conditions were noted.

Table 3. Frequency of most common chronic conditions for the entire population and by gender

n (%)	Overall (n=3,140)	Females (n=1,785)	Males (n=1,355)	P-value
Anemia[a]	175 (5.6%)	109 (6.1%)	66 (4.9%)	0.133
Anxiety [b]	128 (4.1%)	86 (4.8%)	42 (3.1%)	0.016
Arrhythmia[a]	284 (9.0%)	169 (9.5%)	115 (8.5%)	0.340
Arthritis [c]	348 (11.1%)	262 (14.7%)	86 (6.3%)	<0.0001
BPH[d]		-	335 (24.8%)	-
CHD[e]	522 (16.6%)	214 (12.0%)	308 (22.7%)	<0.0001
COPD [b]	294 (9.4%)	105 (5.9%)	189 (14.0%)	<0.0001
Depression[f]	387 (12.3%)	279 (15.6%)	108 (8.0%)	<0.0001
Dyslipidemia [b]	1,427 (45.4%)	883 (49.5%)	544 (40.1%)	<0.0001
GERD [b]	557 (17.7%)	334 (18.7%)	223 (16.5%)	0.100
Glaucoma [b]	196 (6.2%)	96 (5.4%)	100 (7.4%)	0.022
Hypertension [b]	2,140 (68.2%)	1,251 (70.1%)	889 (65.6%)	0.007
Hyperuricemia [b]	258 (8.2%)	93 (5.2%)	165 (12.2%)	<0.0001
Hypothyroidism[g]	291 (9.3%)	249 (13.9%)	42 (3.1%)	<0.0001
Type-II diabetes [b]	786 (25.0%)	444 (24.9%)	342 (25.2%)	0.819
Osteoporosis [h]	609 (19.4%)	583 (32.7%)	26 (1.9%)	<0.0001
Peptic Ulcer[i]	216 (6.9%)	135 (7.6%)	81 (6.0%)	0.083
Vertigo [b]	317 (10.1%)	218 (12.2%)	99 (7.3%)	<0.0001

[a,,e,g] 1 missing values, [b] no missing values, [c,f] 2 missing values, [d] 3 missing values, [h,i] 4 missing values

Abbreviations; GERD: gastroesophageal reflux disease; CHD: Coronary heart disease; BPH: Benign Prostate Hyperplasia; COPD: Chronic Obstructive Pulmonary Disease

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The extent of cognitive impairment (according to MMSE scores)

The average MMSE score was 26.0 (SD = 3.8) and was significantly higher in males than females (26.7 vs. 25.4; 95% CI for the difference: 1.00 to 1.54; p<0.0001). Low MMSE scores (≤23/24, depending on education) were detected in 631 (20.2%, 95% CI 13.6% to 27.4%) participants, 459 (25.9%, 95 % CI 17.6% to 33.9%) females and 172 (12.8%, 95% CI 8.4% to 18.1%) males; p<0.0001). As can be seen in Figure 1, the proportion of females with low MMSE scores appeared consistently higher than that of males across all age groups. The frequency of low MMSE scores was 8.6% (95% CI 5.4% to 11.5%) in participants aged 60-70 years (11.2%, 95% CI 7.7% to 14.5% in females vs. 4.4% 95% CI 1.7% to 7.0% in males; p<0.00001) and 44.2% (95% CI 27.5% to 60.9%) in those aged 86 years or older (58.7% 95% CI from 30.7% to 86.6% in females vs. 31.7% 95% CI 22.2% to 41.0% in males; p<0.00001).

Enter Figure 1 about here

Associations between MMSE scores and selected fixed and modifiable risk factors

There were several significant associations between fixed and modifiable risk factors and the odds of having low MMSE scores (**Table 4 & Supplementary Table 2)**. In regards to non-modifiable factors, the odds of having a low MMSE score increased with age (Adjusted Odds Ratio [AOR] 1.11; 95% CI: 1.09 to 1.13; p<0.0001) and with low levels (none or primary) of education in both genders (AOR 3.03; 95% CI: 2.32 to 4.00 in females, AOR 2.56; 95% CI: 1.67 to 3.77 in males; p<0.0001 for both).

Regarding modifiable risk factors, reporting at least one sleep complaint increased the odds of having a low MMSE score in females both in unadjusted and

adjusted analyses (AOR 1.54; 95% CI: 1.12 to 2.09; p=0.007; but not in males when adjusting for the other factors (p=0.715). The presence of type-II diabetes was not associated with low MMSE scores, neither overall nor in males and females separately (see Table 4 and Supplemental Table 2). The presence of hypertension was also not associated with low MMSE scores in either males or females, after adjusting for the other factors l, while dyslipidemia was associated with a lower odds of having low MMSE scores in females but not males, both in unadjusted and adjusted analyses (AOR 0.70; 95% CI: 0.55 to 0.92; p=0.010). Monthly alcohol intake (in Kg) was associated with increased odds of low MMSE scores only in males (AOR 1.25; 95% CI from 1.01 to 1.45; p=0.014). Depression increased the odds of having low MMSE scores in both genders (AOR 1.74; 95% CI: 1.24 to 2.42; p=0.001 in females; AOR 2.61; 95% CI: 1.41 to 4.55; p<0.0001 in males). Traumatic brain injury increased the adjusted odds of having low MMSE scores in males only (AOR 3.60; 95% CI: 1.41 to 9.16; p=0.007).

Table 4. Odds of probable cognitive impairment according to MMSE scores and associations with the selected demographic and clinical variables in the total sample and by gender

	Overall[+]	**Females**[*]	**Males**[†]
Independent variables	**OR (95% CI; p-value)**	**OR (95% CI; p-value)**	**OR (95% CI; p-value)**
Gender (female)	2.72 (2.31 to 3.47; p<0.0001)	-	-
Age (centered)[X]	1.11 (1.10 to 1.13; p<0.0001)	1.12 (1.10 to 1.14; p<0.0001)	1.18 (1.09 to 1.15; p<0.0001)
Level of education	2.87 (2.26 to 3.65;	3.18 (2.36 to 4.29;	2.45 (1.62 to 3,71;

(≤primary)	p<0.0001)	p<0.0001)	p<0.0001)
Obese (yes)	0.92 (0.74 to 1.14; p=0.447)	0.89 (0.96 to 1.15; p=0.387)	1.02 (0.70 to 1.51; p=0.903)
Current smoker (yes)	0.77 (0.53 to 1.13; p=0.188)	0.66 (0.37 to 1.18; p=0.164)	0,94 (0.56 to 1.58; p=0.825)
Monthly alcohol intake (Kg)	1.19 (1.03 to 1.365; p=0.024)	0.99 (0.99 to 1.06; p=0.937)	1. 25 (1.010 to 1.45; p=0.014)
At least one sleep complaint (yes)	1.63 (1.15 to 2.32; p=0.006)	1.54 (1.12 to 2.09; p=0.007)	1.08 (0.71 to 1,64; p=0.715)
Hypertension (yes)	0.92 (0.73 to 1.61; p=0.475)	0.89 (0.67 to 1.20; p=0.482)	0.94 (0.63 to 1.41; p=0.777)
Type-II diabetes (yes)	0.92 (0.73 to 1.18; p=0.548)	0.93 (0.69 to 1.25; p=0.645)	0.91 (0.58 to 1.40; p=0.656)
Dyslipidemia (yes)	0.80 (0.65 to 0.98; p=0.038)	0.70 (0.55 to 0.92; p=0.010)	1.01 (0.68 to 1.49; p=0.986)
Depression (yes)	1.90 (1.43 to 2.52; p<0.0001)	1.74 (1.24 to 2.42; p=0.001)	2.61 (1.50 to 4.55; p<0.0001)
Traumatic brain injury (yes)	1.45 (0.80 to 2.65; p=0.218)	0.83 (0.37 to 1.71; p=0.569)	3.60 (1.41 to 9,16; p=0.007)
PHC unit operation (public vs private)	0.59 (0.29 to 2.66; p=0.489)	0.60 (0.11 to 3.39; p=0.564)	0.57 (0.19 to 1.68; p=0.311)

AOR: Adjusted Odds Ratio; 95% CI: 95% Confidence Interval.[X] AOR for the unit increase above the mean
Mean VIF = 1.09. All variables had VIF scores <1.5

Discussion

Main findings

The present report documents a significant extent of cognitive impairment, as indicated by low MMSE scores, among persons older than 60 years visiting community-based primary care settings in a Southern European island. Specifically, as many as one in five persons across genders (and twice as many women than men) were identified as having probable cognitive impairment. Furthermore, certain modifiable risk factors were associated with low MMSE scores, some of which were common to both genders and some gender-specific. These factors included lifestyle habits, such as alcohol consumption, sleep disturbances, and specific chronic illnesses such as depression and dyslipidemia, which are frequently treated in the context of PHC consultation.

Discussion in the light of the literature

Despite the older average age of male compared to female participants, the proportion of those with a low MMSE score (which indicates presence of probable MCI and/or dementia) was almost double among females. This finding is consistent with other studies, which have also reported lower average MMSE scores in females compared to males (13, 33, 34). In addition to lower MMSE scores, morbidity was greater in females attending PHC units compared to males, with a higher number of chronic conditions more frequently reported by females.

In regards to the selected modifiable life-style risk factors and co-morbidities, the present results indicate that their impact on probable cognitive impairment varies by gender, a fact that is also previously reported in the literature (24, 25). In the gender-specific analysis, self-reported sleep problems emerged as a significant correlate of low MMSE performance in women. In a recent French study the reported number of sleep complaints as well as the difficulty maintaining sleep were associated

cognitive decline according to MMSE scores (35). Similar patterns were identified in the KORA study where cognitive decline was more pronounced in individuals with DMS (23). The MrOS Sleep study, found waking after sleep onset and the number of long-wake episodes to be associated with a 1.4- to 1.5-fold increase in odds of clinically significant cognitive decline (29). A more detailed analysis regarding specific insomnia-type symptoms and cognitive impairment in the present study population has been reported elsewhere and has indicated a strong gender effect (36). As regards alcohol consumption our study reported similar results with another study that indicated that excessive alcohol consumption in men (≥36 g/d) was associated with faster cognitive decline compared with light to moderate alcohol consumption (37).

This present study indicated a positive association between presence of dyslipidemia and higher MMSE scores in females but a lack of association in men. This finding deserves some explanation and it may reflect a favorable impact of long-term use of statins. Recent studies have indicated that statins could decrease the risk of dementia, Alzheimer's disease, and improve cognitive impairment in some cases, yet the reduction in disease risk can vary across statin molecules, sex, and race/ethnicity (38, 39). In our sample the majority of participants diagnosed with dyslipidemia (~70%) were being treated with statins so it is hard to disentangle the relative impact of dyslipidemia of statin use. (5, 40-42). Furthermore, the cross-sectional nature of this work does not allow us to draw causal conclusions. Our results did not indicate statistically significant associations between obesity, type-II diabetes or hypertension and cognitive impairment, based on the multivariable analysis, in contrast with several previous reports (5, 43). This picture could reflect other factors with a potential effect in the participants that they have not assessed in this study such

as a traditional life-style or adherence to Mediterranean diet (44). On the other hand, a positive association between depression and probable cognitive impairment was identified in both genders and between history of traumatic brain injury and probable cognitive impairment in males. Similar findings have also been reported in the literature (45-48).

Strengths and limitations

To our knowledge, this is the first study assessing the extent of probable cognitive impairment in a primary health care setting in Greece. Furthermore, the study sample size is relatively large and although it did not employ a door-to-door approach or a randomly selected population sample (selection of the PHC facilities having been based on their being staffed by members of a PHC research network), the use of consecutive patients can provide a relatively accurate description of the characteristics of PHC visitors within a well-defined area. As most public PHC units were located in rural and semi-urban areas, generalization may be limited. In addition, information from the data may have been lost due to the dichotomization of the MMSE scores prior to model fitting. In our study the MMSE was used, however, for the detection of probable cognitive impairment. At the cut-off point that we used, the MMSE is characterized by high sensitivity and relatively low specificity as a screening tool for dementia: poor performance on cognitive tools such as MMSE could be due to other factors (46, 49). Thus, a comprehensive neuropsychological evaluation is necessary in order to establish clinical diagnosis. However, analysis of data from sub-group of the present sample defined by the corresponding DSM-IV criteria 303 of 344 (88%) participants with MMSE scores <24 were diagnosed as having either MCI or dementia (22). In addition to the above, in our study, we have

excluded from recruitment patients visiting PHC facilities for an emergency, thus we have excluded delirium or other acute causes that may have an effect on cognition. As the cut-offs used in our study have previously been validated for detecting severe MCI or dementia (27), we are somewhat confident that cognitive impairment as judged by education-adjusted low MMSE in our population corresponds roughly to severe CI or dementia.

Although associations between MMSE scores and specific chronic conditions and characteristics were identified, the cross-sectional nature of the study does not support causal links. Additionally, it should be noted that the majority of participants visited the selected PHC for prescription renewal, most likely because they suffered from a chronic condition. In this manner, our population may not include healthy older adults, as well as persons suffering from debilitating conditions that are typically treated in acute care settings and would not typically visit PHC units in Greece. Finally, it should be noted that our study was powered to estimate the prevalence of cognitive impairment and not for the associations observed using the multivariable regression models.

Implications for practice and research

The findings of this cross-sectional study reveal a significant extent of probable cognitive impairment in a primary care setting. Given the progressive nature of cognitive impairment in older persons, the results of this study emphasize the need for improved screening in PHC. PHC practitioners may require additional training in terms of the need, screening procedures, and management practices related to cognitive impairment and associated comorbidities. In this respect, we have already reported that as many as 60% of patients with dementia have not received a diagnosis

before seeing a specialist (22). Moreover, specific conditions such as depression could be used as an alarm signal to investigate cognitive impairment.

In Greece a recent health care reform with a focus on prevention has just been applied with the establishment of local PHC units in urban centres. In the context of the new national plan for dementia that has been prepared by the Ministry of Health, screening for cognitive impairment could be included among the tasks of the family physicians who serve these new PHC units.

Conclusions

This cross-sectional PHC-based study provides new information on the prevalence of probable cognitive impairment in a mainly rural Southern European primary care population aged 60 years and older. Our findings suggest that cognitive impairment is a challenge for the primary health care services in a country currently undergoing reform in the governance and role of primary care services.

List of abbreviations

AD - Alzheimer's Disease

BMI - Body Mass Index

BPH: Benign Prostate Hyperplasia

CHD: Coronary heart disease

CI - Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CVD – Cardio Vascular Disease

DFA - Difficulty Falling Asleep

DMS - Difficulty Maintaining Sleep

EMA - Early Morning Awakening

EU - European Union

GERD: Gastroesophageal Reflux Disease

GP - General Practitioner

KM² – Square Kilometer

MCI - Mild Cognitive Impairment

MMSE - Mini Mental State Examination

MOR - Median Odds Ration

OR - Odds Ratio

PHC - Primary Health Care

SD - Standard Deviation

VPC - Variance Partition Coefficient

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Contributor's statement

AB: performed data entry, statistical analysis and drafted the first version of the manuscript, CT, DB, CL and AV: conceived the idea of the project, IT: contributed to drafting and revision of the manuscript, SP: supervised the data analysis and contributed to drafting and revision of the manuscript, IZ: contributed to the project coordination and drafting a revision of the manuscript, GD: was the PHC study-team coordinator and contributed to drafting the manuscript, ES, PP, KM, EI, CT, MB, SP and DB: contributed to drafting the manuscript and reviewed the manuscript, JM:

contributed to drafting and revision of the manuscript and advised on data analysis, PS: contributed to drafting and revision of the manuscript, AV: was the PI of the project and contributed to drafting and revision of the manuscript, CL: contributed to drafting and revision of the manuscript and was supervisor and coordinator of the PHC team. All authors have reviewed manuscript prior to submission.

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Competing interests

The authors declare no competing interests

Ethics approval and consent to participate

The study was approved by the Bioethics Committee of the University Hospital of Heraklion (protocol number: 13541, 20.11.2010). All eligible persons or their caregivers were informed both verbally and through a patient/caregiver information sheet about the study by their GP and provided written consent if they agreed to participate. For patients unable to provide it, informed consent was provided by their caregivers.

Patient consent to publish

Not required

Availability of data and materials

Data and materials for this study are available from the authors upon reasonable request. Due to restrictions stated in our ethical approvals data are not available on public data repositories.

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Figure legends

Figure 1. Proportion of participants with probable cognitive impairment according to MMSE scores by gender and age group

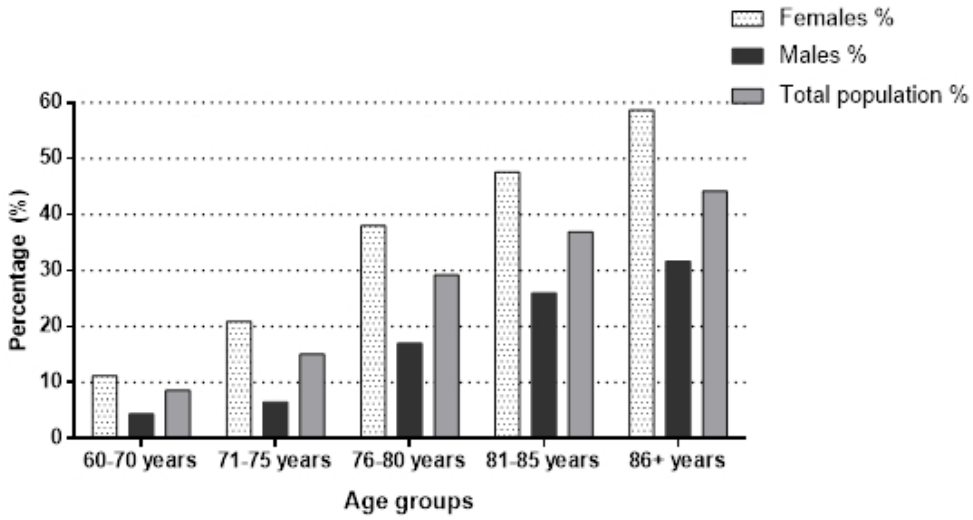

Figure 1. Proportion of participants with probable cognitive impairment according to MMSE scores by gender and age group

Supplementary Table 1. Number and percentage of participants per area (rural or urban) and by operation of PHC unit (public or private)

	Operation	N	%
Rural			
Three Health Centres and eight satellite clinics	Public	2,803	89.3
Urban			
Municipal PHC	Public	160	5.1
Two private practices	Private	177	5.6

Supplementary Table 2. Unadjusted odds of probable cognitive impairment according to MMSE scores and their associations with the selected demographic and clinical variables in the total sample and by gender.

	Overall[+]	**Females**[*]	**Males**[†]
Independent variables	**OR (95% CI; p-value)**	**OR (95% CI; p-value)**	**OR (95% CI; p-value)**
Gender (female)	2.26 (1.87 to 2.73; p<0.0001)	-	-
Age (centered)	1.10 (1.09 to 1.11; p<0.0001)	1.12 (1.10 to 1.14; p<0.0001)	1.16 (1.09 to 1.14; p<0.0001)
Level of education (≤primary)	3.89 (3.18 to 4.75; p<0.0001)	3.75 (2.91 to 4.77; p<0.0001)	3.47 (2.42 to 4.97; p<0.0001)
Obese (yes)	1.02 (0.85 to 1.21; p=0.851)	0.88 (0.71 to 1.09; p=0.254)	0.93 (0.66 to 1.31; p=0.694)
Current smoker (yes)	0.48 (0.35 to 0.66; p<0.0001)	0.41 (0.24 to 0.66; p<0.0001)	0.78 (0.51 to 1.1; p=0.258)
Monthly alcohol intake (Kg)	0.99 (0.99 to 1.07; p=0.236)	0.99 (0.99 to 1.03; p=0.154)	1. 17 (1.04 to 1.34; p=0.045)
At least one sleep complaint (yes)	1.97 (1.62 to 2.41; p<0.0001)	1.85 (1.44 to 2.36; p<0.0001)	1.71 (1.22 to 2.42; p=0.002)
Hypertension (yes)	1.32 (1.09 to 1.60; p=0.004)	1.33 (1.05 to 1.69; p=0.017)	1.18 (0.84 to 1.66; p=0.336)
Type-II diabetes (yes)	0.87 (0.71 to 1.06; p=0.184)	0.92 (0.72 to 1.18; p=0.526)	0.75 (0.51 to 1.11; p=0.158)

Dyslipidemia (yes)	0.74 (0.62 to 0.88; p=0.001)	0.65 (0.52 to 0.80; p<0.0001)	0.75 (0.54 to 1.05; p=0.104)
Depression (yes)	1.99 (1.58 to 2.52; p<0.0001)	1.53 (1.16 to 2.01; p=0.002)	2.90 (1.83 to 4.58; p<0.0001)
Traumatic brain injury (yes)	1.40 (0.86 to 2.29; p=0.165)	1.03 (0.55 to 1.92; p=0.909)	2.42 (1.11 to 5.29; p=0.026)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6,7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	10,11
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10,11
		(*b*) Describe any methods used to examine subgroups and interactions	10,11
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10,11
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Sup figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	In each Table
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	16-18 Supp.

		which confounders were adjusted for and why they were included16,17	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21,22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21,22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.