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

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

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24 and on behalf of the Cretan Primary Health Care Ageing Network *

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37 **Abstract**

38 **Objectives**

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

44 **Design**

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

46 **Setting**

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

49 **Participants**

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

51 **Primary and secondary outcome measures**

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

55 **Results**

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

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3 62 primary or no formal education (AOR = 2.86; 95% CI 2.22-3.57), reporting one or
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5 63 more sleep complaints (AOR 1.41; 95% CI 1.11-1.79), dyslipidemia (AOR = 0.80;
6
7 64 95% CI 0.65-0.99) and history of depression (AOR = 1.83; 95% CI 1.37-2.45) were
8
9 65 associated with low MMSE scores. Region of residence accounted for 14.8% of the
10
11 66 total variability of low MMSE scores controlling for all other factors (p<0.001)
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15 67 **Conclusions**

16
17 68 This study identified a relatively high prevalence of low-MMSE scores amongst
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19 69 persons attending PHC practices in a southern European community setting and
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21 70 several risk factors associated with cognitive decline.
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5 88**Strengths and limitations of this study**6
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- This is the first study assessing the burden of cognitive impairment in a primary care setting in Greece, where there is a data paucity.

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- The sample size was relatively large (3,140 individuals) covering both rural and urban areas.

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- MMSE tool has a high sensitivity yet a low specificity as a dementia screening tool.

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95 **Introduction**

96 With the gradual increase in population longevity, chronic conditions have
97 become more prevalent, with cognitive disorders being amongst the most common
98 [1]. In the elderly, measurable decline in cognitive abilities, including memory, ranges
99 from age-related changes in cognitive functioning to mild cognitive impairment
100 (MCI) and dementia [2 3]. Lacking a disease-modifying drug treatment, early
101 detection and management of risk factors remains a key strategy in the reduction of
102 disease burden [4].

103 According to Alzheimer Europe it is estimated that the total population
104 prevalence of dementia in Greece is 1.77%, slightly exceeding the EU-28 average of
105 1.55% [5]. A more recent population study estimated the prevalence of dementia in
106 those aged 65 years or older at 5%, with 75% of the cases being attributed to
107 Alzheimer's disease [6]. Little is known about the burden and epidemiology of
108 cognitive impairment in primary care settings in Greece. Financial crisis since 2010
109 and its impact on population health and on the burden to health care services is well
110 documented [7-9]. In order to address these challenges, health care reforms were
111 implemented with a focus on primary care, disease prevention and health promotion
112 by establishing several new urban primary care units throughout the country [10].

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

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3 120 PHC setting in Greece and be endorsed in continuing medical education activities and
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5 121 health care planning. Specific objectives were the following:

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8 122 - To report the frequency of elders with low scores on a widely adopted screening
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10 123 instrument for dementia (Mini Mental Status Examination) among those served by
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12 124 primary care centers in Prefecture of Heraklion Crete, Greece.
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14 125 - To assess systematic geographic variability in the expected burden associated with
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16 126 cognitive impairment.
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18 127 - To identify key modifiable clinical and lifestyle, as well as demographic, variables
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20 128 associated with cognitive impairment.
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26 130 **Methods**

27 131 *Setting*

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30 132 A cross-sectional study was conducted between March 2013 and May 2014 in
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32 133 well-defined PHC settings in the prefecture of Heraklion on the island of Crete,
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34 134 Greece. Eligible units were staffed by GPs who were members of a previously
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36 135 established PHC research network coordinated by the Clinic of Social and Family
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38 136 Medicine, Faculty of Medicine, University of Crete. Fourteen PHC units from a total
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40 137 of 22 eligible units participated in the study: Eleven public PHC practices (two
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42 138 organized health centers and nine satellite practices) located in rural and semi-urban
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44 139 areas, serving a total population of 100,800 residents; and three urban PHC units (one
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46 140 public and two private) in the city of Heraklion, serving a total population of 174,000
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48 141 residents.
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54 142 55 143 *Population and inclusion criteria*

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3 144 Eligible participants were persons aged 60 years or older, who were
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5 145 consecutive visitors in the participating PHC units, for any reason other than urgent
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7 146 care. Acutely ill patients or those requiring urgent referral to a secondary health care
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9 147 center were excluded. Established diagnosis of dementia or MCI was not an exclusion
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11 148 factor.
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17 150 *Measurements*

19 151 A structured and pre-tested questionnaire was used to collect information from
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21 152 patients and caregivers on the following variables: socio-demographics (age, gender,
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23 153 place of residency, marital status, number of children, number of housemates,
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25 154 current/former employment status, number of rooms in the house, living situation,
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27 155 level and years of formal education received), health and lifestyle habits (smoking and
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29 156 alcohol consumption, number of days/week patient walked and total time of walking),
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31 157 self-reported night sleep duration (in hours) and presence of insomnia symptoms
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33 158 (difficulty falling asleep [DFA] or maintaining sleep [DMS], and early morning
34
35 159 awakening [EMA]) [11], and presence of chronic non-communicable, neurological or
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37 160 psychiatric illnesses and prescribed medication. Chronic conditions were self-reported
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39 161 by patients, or reported by their caregivers and cross-validated by their GPs against
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41 162 the patient's electronic health record. Participants were also administered the Greek
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43 163 version of the MMSE [12] to assess general cognitive ability and the Barthel index of
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45 164 Activities of Daily Living (ADL) [13 14] was completed as part of the interview with
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47 165 the participant or caregiver. Finally, anthropometric measurements were measures by
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49 166 the interviewer (weight, height, waist circumference).
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58 168 *Definitions*

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3 169 The Greek version of MMSE has been validated and cut-off scores of 23/24
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5 170 were found to have high specificity, sensitivity and positive predictive value [15] for
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7 171 detecting severe cognitive impairment or dementia in accordance with the original
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9 172 validation study of the English version [12]. In view, however, of the very high
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11 173 percentage of persons who had attained ≤ 6 years of formal education in the present,
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13 174 largely rural, sample (81.7%), we used education-adjusted MMSE cutoffs of $\leq 24/30$
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15 175 (for those with > 6 years of formal education) and $\leq 23/30$ (for those with ≤ 6 years) to
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17 176 classify participants in the low MMSE group [16]. A Barthel index score of 90/90 was
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19 177 used to indicate complete independence in activities of daily living [14]. Prolonged
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21 178 sleep was defined as reporting ≥ 9 hours of sleep in a given day [17 18]. Obese were
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23 179 considered participants with a BMI ≥ 30 kgs/m².
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31 181 *Data collection*

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33 182 All interviews were performed during PHC working hours by specially trained
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35 183 GPs and nurses. Data were initially recorded on paper and then transferred to the
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37 184 Clinic of Social and Family Medicine at the University of Crete where consistency
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39 185 checks and data entry and storage was performed.
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45 187 *Sample size estimation*

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47 188 The objective of the overall multi-disciplinary study was to enroll a minimum
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49 189 of 250 persons meeting formal DSM IV criteria for dementia. Assuming a 8% (95%
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51 190 Confidence Interval [CI] from 7.1% to 9.0%) prevalence of any type of dementia [19]
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53 191 among PHC visitors over 60 years of age a minimum sample size of 3,200
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55 192 participants was estimated.
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3 194 *Statistical analysis*
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5 195 Demographic and other characteristics were summarized using descriptive
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8 196 statistics. Between-gender univariate comparisons were made using Pearson's chi-
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10 197 square test of independence (for categorical variables) and independent samples t-test
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12 198 (for continuous variables).
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14 199 Two-level logistic regression models were used to assess possible associations
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16 200 between selected participant characteristics and low MMSE scores. Participants were
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18 201 classified according to their administrative district of residence in each of the 25
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20 202 administrative districts of the Heraklion region.
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23 203 Participant- (level-1) variables included in the model were: age (centered),
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25 204 gender (male, female), level of education (none, primary, secondary or greater),
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27 205 presence of obesity (yes, no), current smoker (yes/no), alcohol intake per month
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29 206 (measured in grams), reports at least one sleep complaint (yes/no), hypertension (yes,
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31 207 no), type-II diabetes (yes, no), dyslipidemia (yes, no), depression (yes, no) and
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33 208 traumatic brain injury (yes, no) .
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37 209 The following variables were used as district-level variables (defined as level-
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39 210 2) in the model: population density of each administrative region (measured as the
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41 211 number of inhabitants per Km²), travel time to the prefecture capital (measured in
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43 212 minutes), and distance to the prefecture capital (measured in kilometers). The above
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45 213 variables were selected on the basis of publicly available information.
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49 214 All participants with complete data on age, gender and MMSE scores were
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51 215 included in the analysis and any missing data were handled by pairwise deletion. The
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53 216 level of significance was set to 5%, IBM SPSS 21 and STATA 11 were used to
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55 217 conduct analyses and ArcMap 10.3.1 was used for geographical representation of the
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57 218 results.
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220 **Patient and public involvement**

221 There was no patient and public involvement

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223 **Results**224 *Participants*

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

232

233 *General description of the population*

234 Details regarding socio-demographic and other socio-economic characteristics
 235 of participants are presented in **Table 1**. The mean age of participants was 73.7 (SD =
 236 7.8) years, with most respondents being female (n=1,785, 56.8%). The majority
 237 (n=2,845, 90.6%) of individuals visited the selected PHC practices for prescription
 238 renewal.

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

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

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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

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240 Overall, 391 (12.5%) participants were current tobacco users and 1,368
 241 (43.7%) reported current alcohol consumption. Smoking and alcohol consumption
 242 were more frequent among men, as shown in **Table 2**. Average Body Mass Index
 243 (BMI) was higher among females than males [30.7 kg/m² (SD = 5.4) vs. 28.8 kg/m²

244 (SD = 4.1), respectively; $p < 0.0001$]. Nearly half of the participants ($n = 1,285$; 49.4%)
 245 reported walking for at least 10 minutes daily and averaging 6.3 (SD = 1.8) hours of
 246 sleep per night. Sleep-related problems were reported by 2,056 (67.1%) participants
 247 and were more frequently reported in females than males ($p < 0.0001$ across
 248 symptoms). Of the 3,140 participants, 2,594 (82.7%) were found to be fully
 249 independent in activities of daily living as measured by the Barthel index.
 250

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/m²), 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

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(%)ⁱ

5 6 7	Early awakening, n (%)^j	1,093 (35.1%)	733 (41.3%)	361 (26.9%)	<0.0001
8 9	At least one sleep complaint	2,056 (67.1%)	1,279 (73.0%)	777 (46.8%)	<0.0001
10 11 12 13	Fully independent in activities of daily living, n (%)^k	2,594 (82.7%)	1,427 (80.1%)	1,167 (86.3%)	<0.0001

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^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, ^k 21 missing values, ^l 7 missing values, ^m 24 missing values, ⁿ 5 missing values (Barthel index).

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252 The most frequently reported chronic conditions (see **Table 3**) were

253 hypertension (n=2,140; 68.2%), dyslipidemia (n=1,427; 45.4%), type-II diabetes

254 (n=786; 25.0%), and benign prostate hyperplasia (n=335; 24.8% in males).

255 Significant gender differences in the frequency of several chronic conditions were

256 noted.

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

	Overall	Females	Males	P-value
n (%)	(n=3,140)	(n=1,785)	(n=1,355)	
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

257

258 *The burden of cognitive impairment (according to MMSE scores)*

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

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Enter Figure 1 about here

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269 *Associations between MMSE scores and selected modifiable risk factors*

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

272 modifiable factors, the odds of having a low MMSE score increased with age
273 (Adjusted Odds Ratio [AOR] 1.11; 95% CI: 1.09 to 1.13; $p < 0.0001$) and with low
274 levels (none or primary) of education in both genders (AOR 3.03; 95% CI: 2.32 to
275 4.00 in females, AOR 2.56; 95% CI: 1.67 to 3.77 in males; $p < 0.0001$ for both).

276 Regarding modifiable risk factors, reporting at least one sleep complaint
277 increased the odds of having low MMSE score in females (AOR 1.69; 95% CI: 1.25
278 to 2.28; $p = 0.0001$; but not in males ($p = 0.483$). The presence of hypertension or type-
279 II diabetes were not associated with low MMSE scores, while dyslipidemia reduced
280 the odds of having low MMSE scores in females (AOR 0.70; 95% CI: 0.55 to 0.91;
281 $p = 0.008$). Depression increased the odds of having low MMSE scores in both genders
282 (AOR 1.71; 95% CI: 1.23 to 2.39; $p = 0.001$ in females; AOR 2.31; 95% CI: 1.31 to
283 4.07; $p = 0.004$ in males), while traumatic brain injury increased the odds of having
284 low MMSE scores in males only (AOR 3.77; 95% CI: 1.50 to 9.51; $p = 0.005$).

286 *Between-district variance in the predicted MMSE scores*

287 Results from the null two-level, random intercept logistic regression analysis
288 indicated significant between-district variance in the predicted MMSE scores (
289 $\sigma_u^2 = 0.34$, $\sigma_e^2 = 3.29$, VPC = 9.37%; $X^2 = 114.05$; $p < 0.0001$). For the full model the
290 between-district variance in the predicted MMSE scores remained significant (
291 $\sigma_u^2 = 0.58$, $\sigma_e^2 = 3.29$, VPC = 14.77%; $X^2 = 96.17$; $p < 0.0001$ and Median Odds Ratio
292 [MOR] = $e^{0.95\sigma_u} = 2.05$). No significant associations between the level-2 variables in
293 the model (population density, travel time to prefecture capital and distance to
294 prefecture capital) and the odds of having a low MMSE score were identified (**Table**
295 **4**). The predicted probabilities for low MMSE scores by district are geographically
296 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; p=0.034)	0.70 (0.55 to 0.91; p=0.006)	1.06 (0.71 to 1.58; p=0.743)

	p=0.042)	p=0.008)	p=0.761)
Depression (yes)	1.83 (1.37 to 2.45;	1.71 (1.23 to 2.39;	2.31 (1.31 to 4.07;
	p<0.0001)	p=0.001)	p=0.004)
Traumatic brain injury (yes)	1.43 (0.80 to 2.57;	0.82 (0.39 to 1.72;	3.77 (1.50 to 9.51;
	p=0.221)	p=0.604)	p=0.005)
Level-2 variables			
Population density (No citizens/km ²)	2.03 (0.39 to 10.71;	2.50 (0.38 to 16.24;	1.70 (0.28 to 10.14;
	p=0.400)	p=0.335)	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;	1.06 (0.96 to 1.18;
		p=0.159)	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;	0.93 (0.84 to 1.04;
		p=0.204)	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; $\chi^2=96.17$, 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; $\chi^2=71.954$, 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; $\chi^2=12.36$, p=0.0002

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Enter Supplementary Figure 2 about here

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300 Discussion

301 *Main findings*

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

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3 307 variability in probable cognitive impairment was also identified. Furthermore, certain
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5 308 modifiable risk factors related to low MMSE scores were identified some of which
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8 309 were common to both genders and some gender-specific. These factors included
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10 310 lifestyle habits, such as alcohol consumption, sleep disturbances, and specific chronic
11
12 311 illnesses such as depression and dyslipidemia, which are frequently treated in the
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14 312 context of PHC consultation.
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19 314 *Discussion in the light of the literature*

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21 315 Despite the older age of male compared to female participants, the burden of
22
23 316 probable cognitive impairment was almost double among females. This finding is
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25 317 consistent with other studies, which have also found the incidence and prevalence of
26
27 318 dementia to be greater in females compared to males [20 21]. Indeed there is growing
28
29 319 evidence that multiple cognitive abilities are more adversely affected by AD in
30
31 320 women than in men [20]. In addition to lower MMSE scores, morbidity was greater in
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33 321 females compared to males, with most chronic conditions being more frequently
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35 322 reported by females.
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40 323 In regard to the selected modifiable life-style risk factors and co-morbidities,
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42 324 the present results indicate that their impact on probable cognitive impairment varies
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44 325 by gender, a fact that is also previously reported in the literature (24, 25). In the
45
46 326 gender-specific analysis, self-reported sleep problems emerged as a significant
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48 327 correlate of low MMSE performance. In a recent French study the reported number of
49
50 328 sleep complaints as well as the difficulty maintaining sleep were associated cognitive
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52 329 decline according to MMSE scores [22]. Similar patterns were identified in the
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54 330 KORA study where cognitive decline was more pronounced in individuals with DMS
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56 331 [11]. The MrOS Sleep study, found waking after sleep onset and the number of long-
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3 332 wake episodes to be associated with a 1.4 to 1.5-fold increase in odds of clinically
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5 333 significant cognitive decline [17]. A more detailed analysis regarding specific
6
7 334 insomnia-type symptoms and cognitive impairment from the present study population
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9 335 have been already published [23].

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12 336 Results of this study indicated a positive relationship between presence of
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14 337 dyslipidemia and higher MMSE scores in females. This finding could add to the
15
16 338 debate regarding the potential protective role of the long-term use of statins, but the
17
18 339 cross-sectional nature of this work does not allow us to draw safe conclusions.[4 24-
19
20 340 26]. Our results did not indicate significant associations between type-II diabetes or
21
22 341 hypertension and cognitive impairment in contrast with several previous reports [4
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24 342 27]. On the other hand, a negative association between probable cognitive impairment
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26 343 and depression was identified in both genders and between probable cognitive
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28 344 impairment and traumatic brain injury in males. Similar findings have also been
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30 345 reported in the literature [28-31].

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33 346 Finally, our models indicated significant between-region variation in the
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35 347 predictive probability of having a low MMSE score a finding which seems to be
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37 348 consistent with conclusions from a systematic review and meta-analysis highlighting
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39 349 geographical variations in dementia rates in affluent countries at a variety of
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41 350 geographical scales [32]. Geographic variations within the island of Crete have also
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43 351 been reported for lung cancer incidence rates [33]. The geographic variation within
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45 352 the broader rural area of participant residence may form the basis for future
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47 353 explorations of genetic and environmental factors that could be involved in cognitive
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49 354 decline and aging [34].

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55 356 *Strengths and limitations*

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3 357 To our knowledge, this is the first study assessing the burden of probable
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5 358 cognitive impairment in a primary care setting in Greece. Furthermore, the study
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7 359 sample size is relatively large and although it did not employ a door-to-door approach
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9 360 or a randomly selected sample, the use of consecutive patients can provide a relatively
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11 361 accurate description of the characteristics of PHC visitors within a well-defined area.
12
13 362 In our study the MMSE was used for the detection of probable cognitive impairment.
14
15 363 The MMSE is characterized by high sensitivity and relatively low specificity as a
16
17 364 dementia screening tool (44), so to establish a clinical diagnosis in-depth
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19 365 neuropsychological examinations are needed. To this end, the reported rates of
20
21 366 probable cognitive impairment should be considered with caution.
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26 367 Although specific associations between MMSE scores and specific chronic
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28 368 conditions were identified, the cross-sectional nature of the study does not support
29
30 369 causal links between specific types of chronic conditions and cognitive impairment.
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32 370 Additionally, it should be noted that the majority participants visited the selected PHC
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34 371 for prescription renewal, most likely because they suffered from a chronic condition.
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36 372 In this manner, our population may not include healthy older adults, as well as
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38 373 persons suffering from debilitating conditions that are typically treated in acute care
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40 374 settings and would not typically visit PHC units in Greece.
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47 376 *Implications for practice and research*

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49 377 The findings of this cross-sectional study reveal a significant burden of
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51 378 probable cognitive impairment in a primary care setting. Given the progressive nature
52
53 379 of cognitive impairment in older persons, the results of this study emphasize the need
54
55 380 for improved screening in PHC. PHC practitioners may require additional training in
56
57 381 terms of the need, screening procedures, and management practices related to
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3 382 cognitive impairment and associated comorbidities. Moreover, specific conditions
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5 383 such as sleep disorders and depression could be used as an alarm sign so to investigate
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8 384 cognitive impairment.
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10 385 In Greece a recent health care reform with a focus on prevention has just been
11
12 386 applied with the establishment of local PHC units in urban centres. In the context of
13
14 387 the new national plan for dementia (2015-2020) that has just been prepared by the
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16 388 Ministry of Health, screening for cognitive impairment could be included among the
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18 389 tasks of the family physicians who serve these new PHC units.
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391 **Conclusions**

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

403 **AD** - Alzheimer's Disease

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3 404 **BMI** - Body Mass Index
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5 405 **BPH**: Benign Prostate Hyperplasia
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7 406 **CHD**: Coronary heart disease
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9 407 **CI** - Confidence Interval
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11 408 **COPD**: Chronic Obstructive Pulmonary Disease
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13 409 **CVD** – Cardio Vascular Disease
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15 410 **DFA** - Difficulty Falling Asleep
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17 411 **DMS** - Difficulty Maintaining Sleep
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19 412 **EMA** - Early Morning Awakening
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21 413 **EU** - European Union
22
23 414 **GERD**: Gastroesophageal Reflux Disease
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25 415 **GP** - General Practitioner
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27 416 **KM²** – Square Kilometer
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29 417 **MCI** - Mild Cognitive Impairment
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31 418 **MMSE** - Mini Mental State Examination
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33 419 **MOR** - Median Odds Ration
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35 420 **OR** - Odds Ratio
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37 421 **PHC** - Primary Health Care
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39 422 **SD** - Standard Deviation
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41 423 **VPC** - Variance Partition Coefficient
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27 440 **Contributor's statement**

28
29 441 AB: performed data entry, statistical analysis and drafted the first version of the
30
31 442 manuscript, CT, DB, CL and AV: conceived the idea of the project, IT: contributed to
32
33 443 drafting and revision of the manuscript, SP: supervised the data analysis and
34
35 444 contributed to drafting and revision of the manuscript, IZ: contributed to the project
36
37 445 coordination and drafting a revision of the manuscript, GD: was the PHC study-team
38
39 446 coordinator and contributed to drafting the manuscript, ES, PP, KM, EI, CT, MB, SP
40
41 447 and DB: contributed to drafting the manuscript and reviewed the manuscript, JM:
42
43 448 provided statistical advice on study design and analysis and reviewed the manuscript,
44
45 449 PS: contributed to drafting and revision of the manuscript, AV: was the PI of the
46
47 450 project and contributed to drafting and revision of the manuscript, CL: contributed to
48
49 451 drafting and revision of the manuscript and was supervisor and coordinator of the
50
51 452 PHC team. All authors have reviewed manuscript prior to submission.
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2324 461 **Competing interests**
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2627 462 The authors declare no competing interests
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31 463
3233 464 **Ethics approval and consent to participate**
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35

36 465 The study was approved by the Bioethics Committee of the University Hospital of
37 Heraklion (protocol number: 13541, 20.11.2010). All eligible persons or their
38 466 caregivers were informed both verbally and through a patient/caregiver information
39 467 sheet about the study by their GP and provided written consent if they agreed to
40 468 participate. For patients unable to provide it, informed consent was provided by their
41 469 caregivers.
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51 471 **Patient consent to publish**
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54 472 Not required
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58 473 **Availability of data and materials**
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3 474 Data and materials for this study are available from the authors upon reasonable
4
5 475 request. Due to restrictions stated in our ethical approvals data are not available on
6
7
8 476 public data repositories.
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12
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For peer review only

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3 **616 Figure legends**
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6 **617 Figure 1.** Rates of probable cognitive impairment according to MMSE scores by
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8 **618** gender and age group
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11 **619 Supplementary Figure 1.** Flowchart of the study
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14 **620 Supplementary Figure 2.** Map of the adjusted predictive probabilities of participants
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16 having a low MMSE score according to administrative region within the Heraklion
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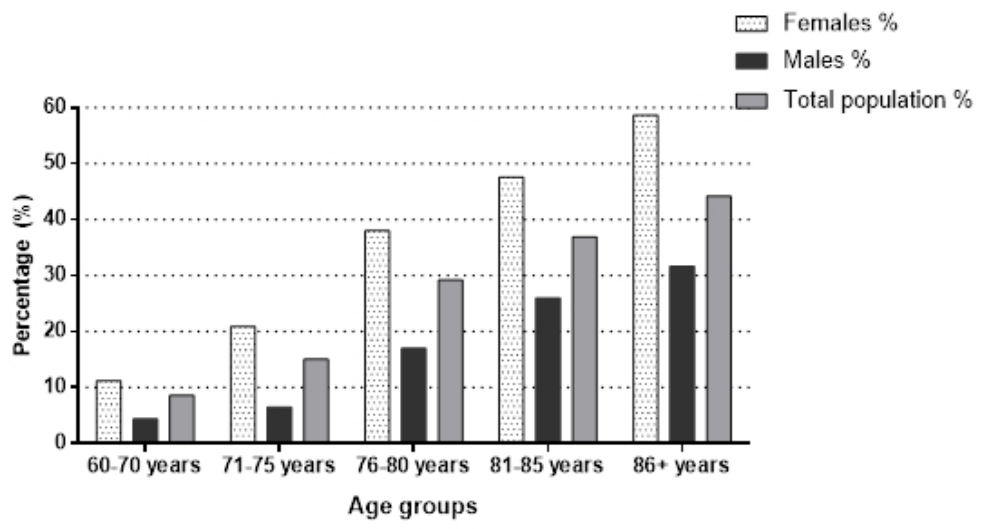
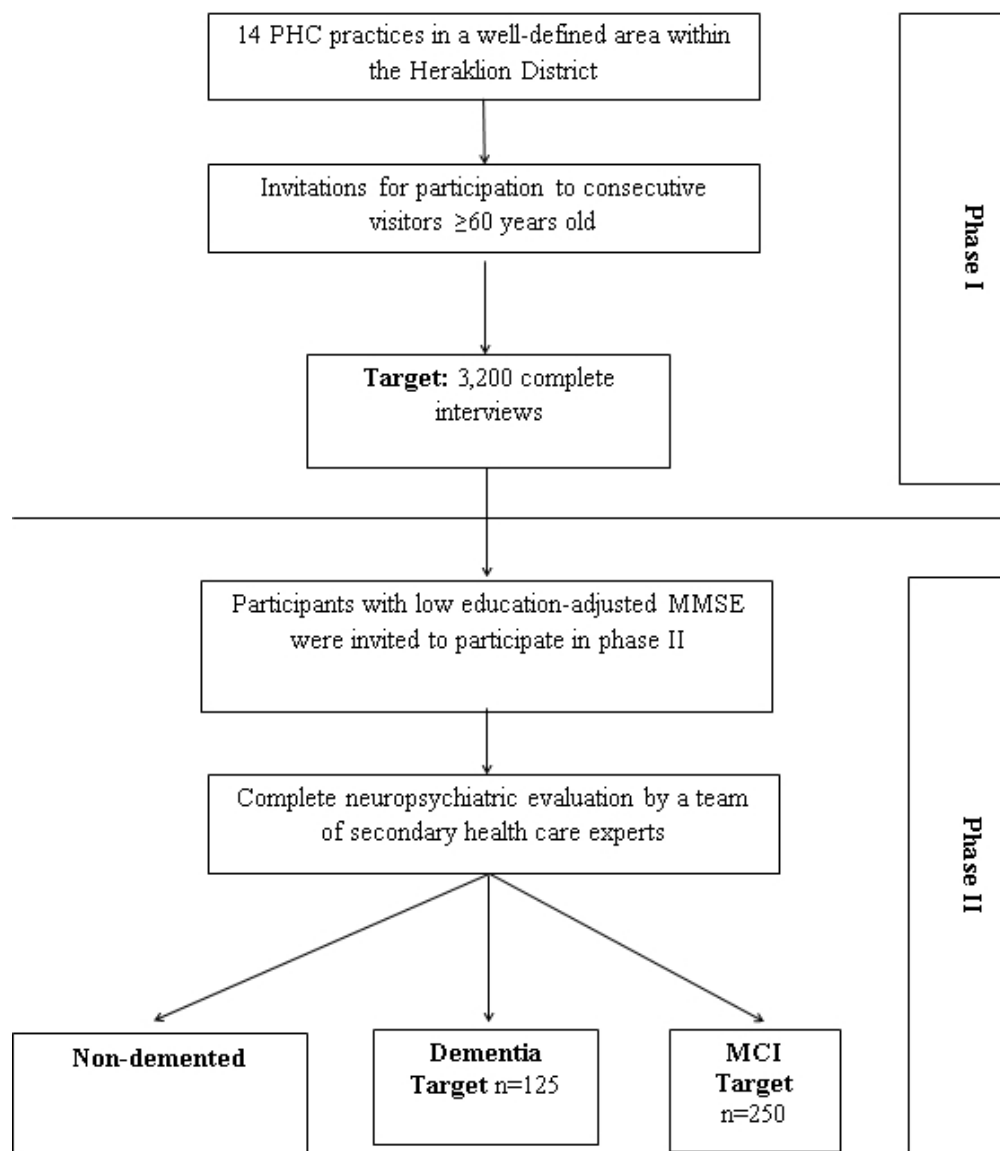
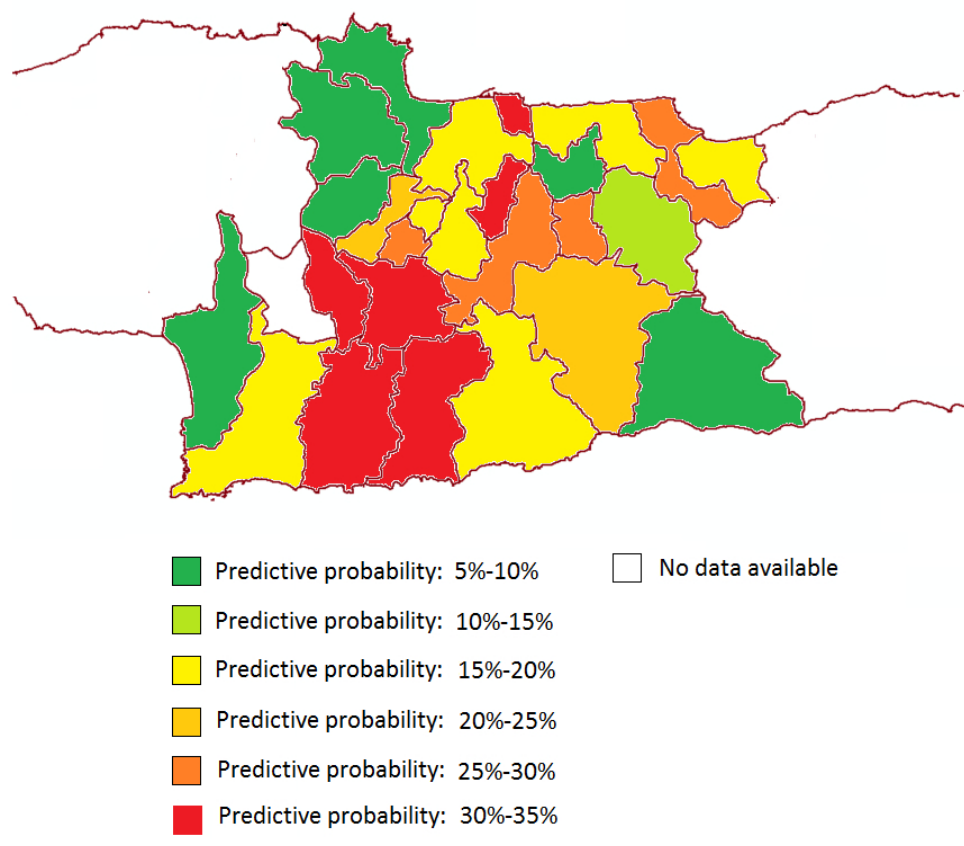


Figure 1. Proportion of participants with probable cognitive impairment according to MMSE scores by gender and age group



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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 included ^{16,17}	
		(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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Keywords:	Dementia < NEUROLOGY, EPIDEMIOLOGY, PRIMARY CARE

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32 **Abstract**

33 **Objectives**

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

39 **Design**

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

41 **Setting**

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

44 **Participants**

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

46 **Primary and secondary outcome measures**

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

50 **Results**

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

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3 57 education (AOR = 2.87; 95% CI 2.26-3.65), alcohol intake (AOR = 1.19; 95% CI
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5 58 1.03-1.37), reporting one or more sleep complaints (AOR 1.63; 95% CI 1.14-2.32),
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7 59 dyslipidemia (AOR = 0.80; 95% CI 0.65-0.98) and history of depression (AOR =
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9 60 1.90; 95% CI 1.43-2.52) were associated with low MMSE scores.
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62 **Conclusions**

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17 63 This study identified a relatively high prevalence of low-MMSE scores amongst
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19 64 persons attending PHC practices in a southern European community setting and
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21 65 associations with several known risk factors.
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99**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.

101 **Introduction**

102 With the gradual increase in population longevity, chronic conditions have
103 become more prevalent, with cognitive disorders being amongst the most common (1,
104 2). In the elderly, measurable decline in cognitive abilities, including memory, can be
105 caused by several reversible and non-reversible conditions, while mild cognitive
106 impairment (MCI) and dementia represent the most common conditions (3, 4).
107 Lacking a disease-modifying drug treatment, early detection and management of risk
108 factors remains a key strategy in the reduction of the rate of MCI and dementia (5, 6).
109 Several modifiable risk-factors for cognitive impairment as well as for the onset and
110 progression of MCI and dementia in particular, have been identified in the literature.
111 Some appear to be gender-specific, yet they have not been studied extensively (5, 7-
112 13).

113 According to Alzheimer Europe it is estimated that the total population
114 prevalence of dementia in Greece is 1.77%, slightly exceeding the EU-28 average of
115 1.55% (14). A more recent population study estimated the prevalence of dementia in
116 those aged 65 years or older at 5%, with 75% of the cases being attributed to
117 Alzheimer's disease (15). In regards to MCI, the estimated prevalence in population-
118 based studies ranges from 10 to 20% in persons older than 65 years of age (4, 16, 17).
119 Little is known about the extent and epidemiology of cognitive impairment in primary
120 health care settings in Greece, where the impact of the Greek financial crisis since
121 2010 on population health and the burden to health care services is well documented
122 (18-20). In order to address this challenge, health care reforms were implemented
123 with a focus on primary care, disease prevention and health promotion by establishing
124 several new urban primary care units throughout the country (21).

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3 125 In this context, a multi-disciplinary research network was established at the
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5 126 Faculty of Medicine, University of Crete, Greece including researchers and
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7 127 practitioners from various medical disciplines (Thales MNSAD-Multidisciplinary
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9 128 Network for the Study of Alzheimer's disease) to study the magnitude of this health
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11 129 problem and discuss the care challenges for the health care services (22). The present
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13 130 report utilizes baseline data from the Primary Health Care (PHC) team with the aim to
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15 131 inform health care providers and policy makers regarding the extent of cognitive
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17 132 impairment in the primary health care population, and associations with demographic
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19 133 and clinical risk factors, as judged by the Mini-Mental-State-Examination (MMSE).

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22 134 Specific objectives were the following:

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25 135 - To report the extent of elders with low scores on a widely adopted screening
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27 136 instrument for dementia (MMSE) among those served by primary care centers in
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29 137 Prefecture of Heraklion Crete, Greece.
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31 138 To identify key modifiable clinical, lifestyle, and demographic variables
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33 139 associated with cognitive impairment and report on probable between-gender
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35 140 variations.
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41 42 142 **Methods**

43 44 143 *Setting*

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47 144 A cross-sectional study was conducted between March 2013 and May 2014 in
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49 145 well-defined PHC settings in the prefecture of Heraklion on the island of Crete,
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51 146 Greece. Eligible units were staffed by GPs who were members of a previously
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53 147 established PHC research network coordinated by the Clinic of Social and Family
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55 148 Medicine, Faculty of Medicine, University of Crete. Fourteen PHC units (12 public
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57 149 and two private) from a total of 22 public units in the district of Heraklion participated
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3 150 in the study: Eleven public PHC practices (two organized health centers and nine
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5 151 satellite practices) were located in rural and semi-urban areas, serving a total
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7 152 population of 100,800 residents; and three urban PHC units (one public and two
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9 153 private) in the city of Heraklion, serving a total population of 174,000 residents
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11 154 (Supplementary Table 1).
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17 156 *Population and inclusion criteria*

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19 157 Eligible participants were persons aged 60 years or older, who were
20
21 158 consecutive visitors in the participating PHC units, for any reason other than urgent
22
23 159 care. Acutely ill patients or those requiring urgent referral to a secondary health care
24
25 160 center were excluded. Established diagnosis of dementia or MCI was not an exclusion
26
27 161 factor. Eligible participants were invited by the trained GPs to participate in the study.
28
29 162 All interviews were conducted by trained nurses. Participants' companions were
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31 163 asked to provide information in cases where participants had difficulty providing
32
33 164 adequate information. Participant responses on clinically-relevant questions were later
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35 165 verified by their GP. Further description of our population is reported elsewhere (22).
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42 167 *Measurements*

43
44 168 A structured and pre-tested questionnaire was used to collect information from
45
46 169 patients and caregivers on the following variables: socio-demographics (age, gender,
47
48 170 place of residency, marital status, number of children, number of housemates,
49
50 171 current/former employment status, number of rooms in the house, living situation,
51
52 172 level and years of formal education received), health and lifestyle habits (smoking and
53
54 173 alcohol consumption, number of days/week patient walked and total time of walking),
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56 174 self-reported night sleep duration (in hours) and presence of insomnia symptoms
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3 175 (difficulty falling asleep [DFA] or maintaining sleep [DMS], and early morning
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5 176 awakening [EMA]) (23), and presence of chronic non-communicable, neurological or
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7
8 177 psychiatric illnesses and prescribed medication. Chronic conditions were self-reported
9
10 178 by patients, or reported by their caregivers and cross-validated by their GPs against
11
12 179 the patient's electronic health record. Participants were also administered the Greek
13
14 180 version of the MMSE (24) to assess general cognitive ability and the Barthel index of
15
16 181 Activities of Daily Living (ADL) (25, 26) was completed as part of the interview with
17
18 182 the participant or caregiver. Finally, anthropometric measurements were measures by
19
20 183 the interviewer (weight, height, waist circumference).
21
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24
25

26 185 *Definitions*

27
28 186 The Greek version of MMSE has been validated and cut-off scores of 23/24
29
30 187 were found to have high specificity, sensitivity and positive predictive value (27) for
31
32 188 detecting dementia in accordance with the original validation study of the English
33
34 189 version (24). In view, however, of the very high percentage of persons who had
35
36 190 attained ≤ 6 years of formal education in the present, largely rural, sample (81.7%), we
37
38 191 used education-adjusted MMSE cutoffs of $\leq 24/30$ (for those with >6 years of formal
39
40 192 education) and $\leq 23/30$ (for those with ≤ 6 years) to classify participants in the low
41
42 193 MMSE group (28). A Barthel index score of 90/90 was used to indicate complete
43
44 194 independence in activities of daily living (26). Prolonged sleep was defined as
45
46 195 reporting ≥ 9 hours of sleep in a given day (29, 30). Obese were considered
47
48 196 participants with a BMI ≥ 30 kg/m².
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54 197

56 198 *Data collection*

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2
3 199 All interviews were performed during PHC working hours by specially trained
4
5 200 GPs and nurses. Data were initially recorded on paper and then transferred to the
6
7 201 Clinic of Social and Family Medicine at the University of Crete where consistency
8
9 202 checks and data entry and storage was performed.
10
11
12

13 203

14 204 *Sample size estimation*

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16
17 205 The objective of the overall multi-disciplinary study (Thales MNSAD-
18
19 206 Multidisciplinary Network for the Study of Alzheimer's disease) (22) was to enroll a
20
21 207 minimum of 250 persons meeting formal DSM IV criteria for dementia. Assuming a
22
23 208 8% (95% Confidence Interval [CI] from 7.1% to 9.0%) prevalence of any type of
24
25 209 dementia (31) among PHC visitors over 60 years of age a minimum sample size of
26
27 210 3,200 participants was estimated.
28
29

30 211

31 212 *Statistical analysis*

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33
34 213 Demographic and other characteristics were summarized using descriptive
35
36 214 statistics. Between-gender univariate comparisons were made using Pearson's chi-
37
38 215 square test of independence (for categorical variables) and independent samples t-test
39
40 216 (for continuous variables). The variability of estimated cognitive impairment was
41
42 217 calculated using robust standard errors clustering by PHC unit (32).
43
44

45
46
47 218 Logistic regression models were used to assess unadjusted associations
48
49 219 between participant characteristics and probable cognitive impairment (low MMSE
50
51 220 scores). The patient characteristics were: age (centered), gender (male, female), level
52
53 221 of education (none, primary, secondary or greater), presence of obesity (yes, no),
54
55 222 current smoker (yes/no), alcohol intake per month (measured in grams), reports at
56
57 223 least one sleep complaint (yes/no), hypertension (yes, no), type-II diabetes (yes, no),
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1
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3 224 dyslipidemia (yes, no), depression (yes, no) and traumatic brain injury (yes, no).
4
5 225 Multilevel logistic regression models were also performed in order to obtain odds
6
7
8 226 ratios adjusted for probable risk factors (that had been pre-selected based on the
9
10 227 literature) (5). The multilevel models included 12 predictor variables in addition to
11
12 228 PHC unit-specific random effects. The variance inflation factor (VIF) was computed
13
14 229 in order to assess potential multicollinearity. The operation of the participating PHC
15
16 230 units (public vs private) was used as a level-2 variable.

17
18
19 231 All participants with complete data on age, gender and MMSE scores were
20
21 232 included in the analysis and any further missing data were handled by pairwise
22
23 233 deletion. The level of significance was set to 5%, IBM SPSS 21 and STATA 11 were
24
25 234 used to conduct the analyses.
26
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235

236 **Patient and public involvement**

237 There was no patient and public involvement

238

239 **Results**

240 *Participants*

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

248

249 *General description of the population*

250 Details regarding socio-demographic and other socio-economic characteristics
 251 of participants are presented in **Table 1**. The mean age of participants was 73.7 (SD =
 252 7.8) years, with most respondents being female (n=1,785, 56.8%). The majority
 253 (n=2,845, 90.6%) of individuals visited the selected PHC practices for prescription
 254 renewal.

255

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

256

257 Overall, 391 (12.5%) participants were current tobacco users and 1,368
 258 (43.7%) reported current alcohol consumption. Smoking and alcohol consumption
 259 were more frequent among men, as shown in **Table 2**. Average Body Mass Index
 260 (BMI) was higher among females than males [30.7 kg/m² (SD = 5.4) vs. 28.8 kg/m²
 261 (SD = 4.1), respectively; p<0.0001]. Nearly half of the participants (n=1,285; 49.4%)
 262 reported walking for at least 10 minutes daily and averaging 6.3 (SD = 1.8) hours of
 263 sleep per night. Sleep-related problems were reported by 2,056 (67.1%) participants
 264 and were more frequently reported in females than males (p<0.0001 across
 265 symptoms). Of the 3,140 participants, 2,594 (82.7%) were found to be fully
 266 independent in activities of daily living as measured by the Barthel index.

267

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

	Overall	Females	Males	P-value
	(n=3,140)	(n=1,785)	(n=1,355)	
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/m²), 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, ^k 21 missing values, ^l 7 missing values, ^m 24 missing values, ⁿ 5 missing values (Barthel index).

268

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

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277

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

	Overall	Females	Males	P-value
n (%)	(n=3,140)	(n=1,785)	(n=1,355)	
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 Ulcerⁱ	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

279 *The extent of cognitive impairment (according to MMSE scores)*

280 The average MMSE score was 26.0 (SD = 3.8) and was significantly higher in
281 males than females (26.7 vs. 25.4; 95% CI for the difference: 1.00 to 1.54; $p < 0.0001$).
282 Low MMSE scores ($\leq 23/24$, depending on education) were detected in 631 (20.2%,
283 95% CI 13.6% to 27.4%) participants, 459 (25.9%, 95% CI 17.6% to 33.9%) females
284 and 172 (12.8%, 95% CI 8.4% to 18.1%) males; $p < 0.0001$). As can be seen in Figure
285 1, the proportion of females with low MMSE scores appeared consistently higher than
286 that of males across all age groups. The frequency of low MMSE scores was 8.6%
287 (95% CI 5.4% to 11.5%) in participants aged 60-70 years (11.2%, 95% CI 7.7% to
288 14.5% in females vs. 4.4% 95% CI 1.7% to 7.0% in males; $p < 0.00001$) and 44.2%
289 (95% CI 27.5% to 60.9%) in those aged 86 years or older (58.7% 95% CI from 30.7%
290 to 86.6% in females vs. 31.7% 95% CI 22.2% to 41.0% in males; $p < 0.00001$).

291

292 **Enter Figure 1 about here**

293

294 *Associations between MMSE scores and selected fixed and modifiable risk factors*

295 There were several significant associations between fixed and modifiable risk
296 factors and the odds of having low MMSE scores (**Table 4 & Supplementary Table**
297 **2**). In regards to non-modifiable factors, the odds of having a low MMSE score
298 increased with age (Adjusted Odds Ratio [AOR] 1.11; 95% CI: 1.09 to 1.13;
299 $p < 0.0001$) and with low levels (none or primary) of education in both genders (AOR
300 3.03; 95% CI: 2.32 to 4.00 in females, AOR 2.56; 95% CI: 1.67 to 3.77 in males;
301 $p < 0.0001$ for both).

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

304 adjusted analyses (AOR 1.54; 95% CI: 1.12 to 2.09; p=0.007; but not in males when
 305 adjusting for the other factors (p=0.715). The presence of type-II diabetes was not
 306 associated with low MMSE scores, neither overall nor in males and females
 307 separately (see Table 4 and Supplemental Table 2). The presence of hypertension was
 308 also not associated with low MMSE scores in either males or females, after adjusting
 309 for the other factors, while dyslipidemia was associated with a lower odds of having
 310 low MMSE scores in females but not males, both in unadjusted and adjusted analyses
 311 (AOR 0.70; 95% CI: 0.55 to 0.92; p=0.010). Monthly alcohol intake (in Kg) was
 312 associated with increased odds of low MMSE scores only in males (AOR 1.25; 95%
 313 CI from 1.01 to 1.45; p=0.014). Depression increased the odds of having low MMSE
 314 scores in both genders (AOR 1.74; 95% CI: 1.24 to 2.42; p=0.001 in females; AOR
 315 2.61; 95% CI: 1.41 to 4.55; p<0.0001 in males). Traumatic brain injury increased the
 316 adjusted odds of having low MMSE scores in males only (AOR 3.60; 95% CI: 1.41 to
 317 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; p<0.0001)	3.18 (2.36 to 4.29; p<0.0001)	2.45 (1.62 to 3.71; p<0.0001)

(≤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

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321 Discussion

322 Main findings

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3 323 The present report documents a significant extent of cognitive impairment, as
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5 324 indicated by low MMSE scores, among persons older than 60 years visiting
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7 325 community-based primary care settings in a Southern European island. Specifically,
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9 326 as many as one in five persons across genders (and twice as many women than men)
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11 327 were identified as having probable cognitive impairment. Furthermore, certain
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13 328 modifiable risk factors were associated with low MMSE scores, some of which were
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15 329 common to both genders and some gender-specific. These factors included lifestyle
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17 330 habits, such as alcohol consumption, sleep disturbances, and specific chronic illnesses
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19 331 such as depression and dyslipidemia, which are frequently treated in the context of
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21 332 PHC consultation.
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334 *Discussion in the light of the literature*

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31 335 Despite the older average age of male compared to female participants, the
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33 336 proportion of those with a low MMSE score (which indicates presence of probable
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35 337 MCI and/or dementia) was almost double among females. This finding is consistent
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37 338 with other studies, which have also reported lower average MMSE scores in females
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39 339 compared to males (13, 33, 34). In addition to lower MMSE scores, morbidity was
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41 340 greater in females attending PHC units compared to males, with a higher number of
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43 341 chronic conditions more frequently reported by females.
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47 342 In regards to the selected modifiable life-style risk factors and co-morbidities,
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49 343 the present results indicate that their impact on probable cognitive impairment varies
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51 344 by gender, a fact that is also previously reported in the literature (24, 25). In the
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53 345 gender-specific analysis, self-reported sleep problems emerged as a significant
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55 346 correlate of low MMSE performance in women. In a recent French study the reported
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57 347 number of sleep complaints as well as the difficulty maintaining sleep were associated
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3 348 cognitive decline according to MMSE scores (35). Similar patterns were identified in
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5 349 the KORA study where cognitive decline was more pronounced in individuals with
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8 350 DMS (23). The MrOS Sleep study, found waking after sleep onset and the number of
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10 351 long-wake episodes to be associated with a 1.4- to 1.5-fold increase in odds of
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12 352 clinically significant cognitive decline (29). A more detailed analysis regarding
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14 353 specific insomnia-type symptoms and cognitive impairment in the present study
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17 354 population has been reported elsewhere and has indicated a strong gender effect (36).
18
19 355 As regards alcohol consumption our study reported similar results with another study
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21 356 that indicated that excessive alcohol consumption in men (≥ 36 g/d) was associated
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23 357 with faster cognitive decline compared with light to moderate alcohol consumption
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26 358 (37).

27
28 359 This present study indicated a positive association between presence of
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30 360 dyslipidemia and higher MMSE scores in females but a lack of association in men.
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32 361 This finding deserves some explanation and it may reflect a favorable impact of long-
33
34 362 term use of statins. Recent studies have indicated that statins could decrease the risk
35
36 363 of dementia, Alzheimer's disease, and improve cognitive impairment in some cases,
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38 364 yet the reduction in disease risk can vary across statin molecules, sex, and
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40 365 race/ethnicity (38, 39). In our sample the majority of participants diagnosed with
41
42 366 dyslipidemia (~70%) were being treated with statins so it is hard to disentangle the
43
44 367 relative impact of dyslipidemia of statin use. (5, 40-42). Furthermore, the cross-
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46 368 sectional nature of this work does not allow us to draw causal conclusions. Our results
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48 369 did not indicate statistically significant associations between obesity, type-II diabetes
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50 370 or hypertension and cognitive impairment, based on the multivariable analysis, in
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52 371 contrast with several previous reports (5, 43). This picture could reflect other factors
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54 372 with a potential effect in the participants that they have not assessed in this study such
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3 373 as a traditional life-style or adherence to Mediterranean diet (44). On the other hand, a
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5 374 positive association between depression and probable cognitive impairment was
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7 375 identified in both genders and between history of traumatic brain injury and probable
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9 376 cognitive impairment in males. Similar findings have also been reported in the
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11 377 literature (45-48).
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17 379 *Strengths and limitations*

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19 380 To our knowledge, this is the first study assessing the extent of probable
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21 381 cognitive impairment in a primary health care setting in Greece. Furthermore, the
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23 382 study sample size is relatively large and although it did not employ a door-to-door
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25 383 approach or a randomly selected population sample (selection of the PHC facilities
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27 384 having been based on their being staffed by members of a PHC research network), the
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29 385 use of consecutive patients can provide a relatively accurate description of the
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31 386 characteristics of PHC visitors within a well-defined area. As most public PHC units
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33 387 were located in rural and semi-urban areas, generalization may be limited. In addition,
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35 388 information from the data may have been lost due to the dichotomization of the
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37 389 MMSE scores prior to model fitting. In our study the MMSE was used, however, for
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39 390 the detection of probable cognitive impairment. At the cut-off point that we used, the
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41 391 MMSE is characterized by high sensitivity and relatively low specificity as a
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43 392 screening tool for dementia: poor performance on cognitive tools such as MMSE
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45 393 could be due to other factors (46, 49). Thus, a comprehensive neuropsychological
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47 394 evaluation is necessary in order to establish clinical diagnosis. However, analysis of
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49 395 data from sub-group of the present sample defined by the corresponding DSM-IV
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51 396 criteria 303 of 344 (88%) participants with MMSE scores <24 were diagnosed as
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53 397 having either MCI or dementia (22). In addition to the above, in our study, we have
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3 398 excluded from recruitment patients visiting PHC facilities for an emergency, thus we
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5 399 have excluded delirium or other acute causes that may have an effect on cognition. As
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7
8 400 the cut-offs used in our study have previously been validated for detecting severe
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10 401 MCI or dementia (27), we are somewhat confident that cognitive impairment as
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12 402 judged by education-adjusted low MMSE in our population corresponds roughly to
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15 403 severe CI or dementia.

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17 404 Although associations between MMSE scores and specific chronic conditions
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19 405 and characteristics were identified, the cross-sectional nature of the study does not
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21 406 support causal links. Additionally, it should be noted that the majority of participants
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24 407 visited the selected PHC for prescription renewal, most likely because they suffered
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26 408 from a chronic condition. In this manner, our population may not include healthy
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28 409 older adults, as well as persons suffering from debilitating conditions that are
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30 410 typically treated in acute care settings and would not typically visit PHC units in
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32 411 Greece. Finally, it should be noted that our study was powered to estimate the
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34 412 prevalence of cognitive impairment and not for the associations observed using the
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36 413 multivariable regression models.

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41 415 *Implications for practice and research*

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44 416 The findings of this cross-sectional study reveal a significant extent of
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46 417 probable cognitive impairment in a primary care setting. Given the progressive nature
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48 418 of cognitive impairment in older persons, the results of this study emphasize the need
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50 419 for improved screening in PHC. PHC practitioners may require additional training in
51
52 420 terms of the need, screening procedures, and management practices related to
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54 421 cognitive impairment and associated comorbidities. In this respect, we have already
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56 422 reported that as many as 60% of patients with dementia have not received a diagnosis
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3 423 before seeing a specialist (22). Moreover, specific conditions such as depression could
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5 424 be used as an alarm signal to investigate cognitive impairment.
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8 425 In Greece a recent health care reform with a focus on prevention has just been
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10 426 applied with the establishment of local PHC units in urban centres. In the context of
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12 427 the new national plan for dementia that has been prepared by the Ministry of Health,
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14 428 screening for cognitive impairment could be included among the tasks of the family
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16 429 physicians who serve these new PHC units.
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23 431 **Conclusions**

24 432 This cross-sectional PHC-based study provides new information on the
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26 433 prevalence of probable cognitive impairment in a mainly rural Southern European
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28 434 primary care population aged 60 years and older. Our findings suggest that cognitive
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30 435 impairment is a challenge for the primary health care services in a country currently
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32 436 undergoing reform in the governance and role of primary care services.
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3 445 **List of abbreviations**
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6 446 **AD** - Alzheimer's Disease
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8 447 **BMI** - Body Mass Index
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11 448 **BPH**: Benign Prostate Hyperplasia
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13 449 **CHD**: Coronary heart disease
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15 450 **CI** - Confidence Interval
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18 451 **COPD**: Chronic Obstructive Pulmonary Disease
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20 452 **CVD** – Cardio Vascular Disease
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22 453 **DFA** - Difficulty Falling Asleep
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24 454 **DMS** - Difficulty Maintaining Sleep
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26 455 **EMA** - Early Morning Awakening
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29 456 **EU** - European Union
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31 457 **GERD**: Gastroesophageal Reflux Disease
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34 458 **GP** - General Practitioner
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36 459 **KM²** – Square Kilometer
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38 460 **MCI** - Mild Cognitive Impairment
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40 461 **MMSE** - Mini Mental State Examination
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42 462 **MOR** - Median Odds Ration
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44 463 **OR** - Odds Ratio
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46 464 **PHC** - Primary Health Care
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48 465 **SD** - Standard Deviation
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50 466 **VPC** - Variance Partition Coefficient
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33 483 **Note**
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42 487 **Contributor's statement**
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44

45 488 AB: performed data entry, statistical analysis and drafted the first version of the
46
47 489 manuscript, CT, DB, CL and AV: conceived the idea of the project, IT: contributed to
48
49 490 drafting and revision of the manuscript, SP: supervised the data analysis and
50
51 491 contributed to drafting and revision of the manuscript, IZ: contributed to the project
52
53 492 coordination and drafting a revision of the manuscript, GD: was the PHC study-team
54
55 493 coordinator and contributed to drafting the manuscript, ES, PP, KM, EI, CT, MB, SP
56
57 494 and DB: contributed to drafting the manuscript and reviewed the manuscript, JM:
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1
2
3 495 contributed to drafting and revision of the manuscript and advised on data analysis,
4
5 496 PS: contributed to drafting and revision of the manuscript, AV: was the PI of the
6
7 497 project and contributed to drafting and revision of the manuscript, CL: contributed to
8
9 498 drafting and revision of the manuscript and was supervisor and coordinator of the
10
11 499 PHC team. All authors have reviewed manuscript prior to submission.
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33 507

35 508 **Competing interests**

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37 509 The authors declare no competing interests
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44 511 **Ethics approval and consent to participate**

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46
47 512 The study was approved by the Bioethics Committee of the University Hospital of
48
49 513 Heraklion (protocol number: 13541, 20.11.2010). All eligible persons or their
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51 514 caregivers were informed both verbally and through a patient/caregiver information
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53 515 sheet about the study by their GP and provided written consent if they agreed to
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55 516 participate. For patients unable to provide it, informed consent was provided by their
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57 517 caregivers.
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3 518 **Patient consent to publish**
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6 519 Not required
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9 520 **Availability of data and materials**
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12 521 Data and materials for this study are available from the authors upon reasonable
13
14 522 request. Due to restrictions stated in our ethical approvals data are not available on
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16 523 public data repositories.
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46
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52
53 539 private primary care practitioner Dr. Eleni Klouva.
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687 **Figure legends**

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

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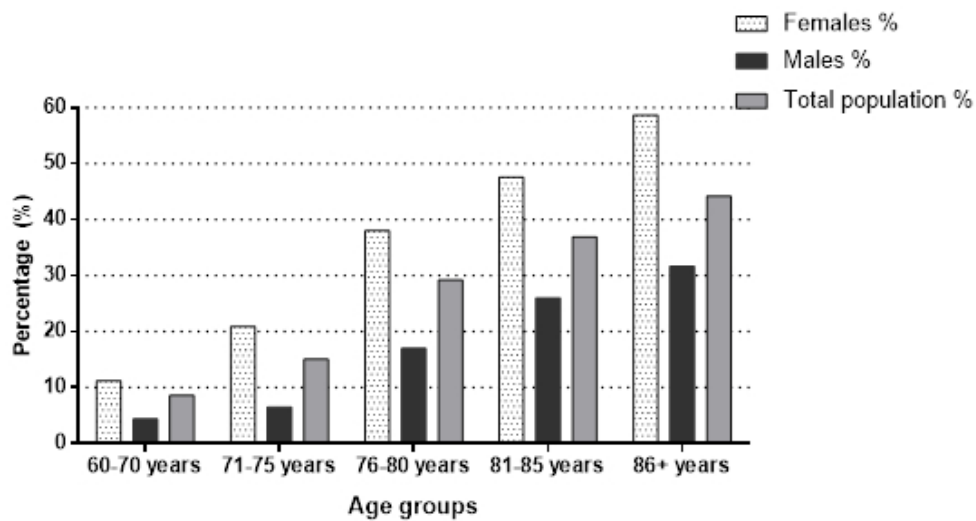


Figure 1. Proportion of participants with probable cognitive impairment according to MMSE scores by gender and age group

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)

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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 included ^{16,17}	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.