



**HAL**  
open science

# Comparison of the predictive accuracy of multiple definitions of cognitive impairment for incident dementia: a 20-year follow-up of the Whitehall II cohort study

Marcos Machado-Fragua, Aline Dugravot, Julien Dumurgier, Mika Kivimaki, Andrew Sommerlad, Benjamin Landré, Aurore Fayosse, Séverine Sabia, Archana Singh-Manoux

## ► To cite this version:

Marcos Machado-Fragua, Aline Dugravot, Julien Dumurgier, Mika Kivimaki, Andrew Sommerlad, et al.. Comparison of the predictive accuracy of multiple definitions of cognitive impairment for incident dementia: a 20-year follow-up of the Whitehall II cohort study. *The Lancet. Healthy longevity*, 2021, 2 (7), pp.e407-e416. 10.1016/S2666-7568(21)00117-3 . hal-03539133

**HAL Id: hal-03539133**

**<https://hal.science/hal-03539133>**

Submitted on 2 Aug 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

1 **Comparison of the predictive accuracy of multiple definitions of cognitive impairment for**  
2 **incident dementia: A 20-year follow-up of the Whitehall II cohort study**

3

4 Marcos D. Machado-Fragua\* PhD

5 Aline Dugravot MSc

6 Julien Dumurgier MD

7 Mika Kivimaki PhD Full Professor

8 Andrew Sommerlad PhD

9 Benjamin Landré PhD

10 Aurore Fayosse MSc

11 Séverine Sabia PhD

12 Archana Singh-Manoux PhD Full Professor

13

14 Université de Paris, Inserm U1153, Epidemiology of Ageing and Neurodegenerative diseases, Paris,  
15 France (MD Machado-Fragua PhD, A Dugravot MSc, J Dumurgier MD, B Landré PhD, A Fayosse  
16 MSc, S Sabia PhD, A Singh-Manoux PhD)

17 Department of Epidemiology and Public Health, University College London, UK (M Kivimaki PhD, S  
18 Sabia PhD, A Singh-Manoux PhD)

19 Cognitive Neurology Center, Saint Louis - Lariboisiere - Fernand Widal Hospital, AP-HP, Université  
20 de Paris, Paris, France (J Dumurgier MD)

21 Helsinki Institute of Life Sciences, University of Helsinki, Helsinki, Finland (M Kivimaki PhD)

22 Division of Psychiatry, University College London, London, UK (A Sommerlad PhD)

23 Camden and Islington NHS Foundation Trust, London, UK (A Sommerlad PhD)

24

25 \*Corresponding author & address

26 Université de Paris

27 Inserm U1153, Epidemiology of Ageing and Neurodegenerative diseases

28 10 Avenue de Verdun

29 75010 Paris, France

30 Tel: +33 (0) 157279045

31 Email: marcos.machado@inserm.fr

32

33 **Manuscript statistics:** 249 words in abstract, 3876 words in main text, 34 references, 4 tables, 1  
34 figure

35 **ABSTRACT**

36 **Background** Studies use cognitive assessment at one point in time to define cognitive impairment  
37 in order to examine conversion to dementia. Our objective was to examine the predictive accuracy  
38 and conversion rate of seven alternate definitions of cognitive impairment for dementia.

39 **Methods** 5687 participants from the Whitehall II study, mean age 65.5 (SD 5.8) years in 2007,  
40 were followed up for a mean 10.0 (SD 1.9) years for clinically-diagnosed dementia (N=270).

41 Algorithms based on poor cognitive performance (defined using age and sex thresholds, and  
42 subsequently education or occupation) and objective cognitive decline (using data from 1997-  
43 1999, 2002-2004, and 2007-2009) were used to generate seven alternate definitions of cognitive  
44 impairment. We compared predictive accuracy using Royston's  $R^2$ , Akaike's information criterion  
45 (AIC), sensitivity, specificity, and C-statistic.

46 **Findings** Cognitive impairment defined using both cognitive performance and decline had higher  
47 hazard ratios (between 5.08 to 5.48) for dementia than definitions based on cognitive  
48 performance alone (3.25 to 3.39). However, all definitions had poor predictive performance (C-  
49 statistic ranged from 0.59 to 0.63), primarily due to low sensitivity (21.6% to 48.4%). A predictive  
50 model containing age, sex and education without measures of cognitive impairment had better  
51 predictive performance (C-statistic 0.78, sensitivity 74.2%, specificity 72.2%) than all seven  
52 definitions of cognitive impairment (all  $p < .001$ ).

53 **Interpretation** These findings suggest that cognitive impairment in early old age is not useful for  
54 dementia prediction, even when it is defined using longitudinal data on cognitive decline and  
55 thresholds of poor cognitive performance defined by education or occupation.

56 **Funding** NIH, UK Medical Research Council

57 **Keywords:** cognitive impairment; cognitive decline; dementia; predictive accuracy; C-statistic;  
58 longitudinal study

## 59 INTRODUCTION

60 Late-onset dementias are complex diseases with a long preclinical phase with pathophysiological  
61 hallmarks appearing 15-20 years before clinical symptoms.<sup>1</sup> It has been estimated that even small  
62 delays in onset could substantially reduce the burden of ADRD and result in substantial savings to  
63 health care systems.<sup>2</sup> There are no established methods of early identification of individuals at risk  
64 of dementia. Alongside biological models of Alzheimer's disease there is considerable research on  
65 understanding changes in clinical trajectory, primarily cognitive function, leading to dementia. The  
66 intermediate stage between healthy ageing and dementia has been studied using concepts such  
67 as cognitive impairment,<sup>3</sup> to identify the intermediate, transitional phase between normal  
68 cognitive ageing and dementia onset.

69 The criteria for these diagnostic constructs typically include subjective complaint from the  
70 patient or an informant or loss of cognition from a previous state, measurable poor cognitive  
71 performance, and absence of dementia diagnosis.<sup>3-5</sup> The best definition of loss of cognition from a  
72 previous state remains unclear; most studies rely on clinical judgement but repeated cognitive  
73 testing is thought to be more informative.<sup>6,7</sup> Most studies on cognitive impairment (CI) show  
74 increased risk of dementia in these individuals.<sup>3,4,8,9</sup> Much research on CI has focused on  
75 conversion rates, reflecting the percentage of CI cases who transition to dementia, rather than  
76 assessments of the predictive accuracy of CI for dementia, which may be more meaningful for  
77 assessment of the risk of dementia and informative in clinical settings.

78 We therefore tested the hypothesis that inclusion of objective measures of cognitive  
79 decline using serial assessments of cognitive function in addition to a measure of poor cognitive  
80 performance at one time point improves prognostic performance of CI for dementia. Poor  
81 cognitive performance was defined using age and sex specific thresholds, and then also using  
82 education and occupational position at age 50 as sex and socioeconomic factors are known to

83 shape cognitive trajectories.<sup>10,11</sup> The predictive accuracy of these CI, definitions was examined and  
84 analyses repeated with mortality, the secondary outcome.

85

86

## 87 **METHODS**

### 88 ***Study population***

89 Data are from the ongoing Whitehall II cohort study which was established in 1985-1988 among  
90 10,308 British civil servants (6895 men and 3413 women) aged 35-55 years.<sup>12</sup> A cognitive test  
91 battery was introduced to the study in 1997-1999 and repeated in 2002-2004, 2007-2009, 2012-  
92 2013, and 2015-2016. In addition to data collection within the study, data over the follow-up were  
93 available using linkage to electronic health records of the UK National Health Service (NHS) for all  
94 but 10 of the 10,308 participants recruited to the study. Participants gave informed written  
95 consent at each contact and the latest ethical approval was from National Health Service (NHS)  
96 London Harrow Research Ethics Committee (reference number 85/0938).

97

### 98 **Measures**

#### 99 *Exposure: Cognitive impairment*

100 The cognitive test battery was composed of tests of memory (assessed using a 20-word free recall  
101 test in 2 minutes), language (measures of phonemic and semantic fluency where participants were  
102 asked to produce as many words as they would starting with “s” and then “animals” names, one  
103 minute was allowed for each test), executive function (timed (10 minutes) Alice Heim 4-I test  
104 (AH4-I),<sup>13</sup> a test which includes a set of 65 verbal and mathematical reasoning items of increasing  
105 difficulty), and the Mini Mental State Examination (MMSE).<sup>14</sup>

106 Poor cognitive performance in 2007-2009 was defined as MMSE <24<sup>15</sup> or cognitive test scores  
107 (memory, language, or executive function) below 1.5 SD<sup>16</sup> using the distribution of the cognitive  
108 test score within the study population using the following steps (syntax provided in appendix p 2).

- 109 ▪ standardize measures of memory, language, and executive function
- 110 ▪ regress each cognitive test score for every individual using age (at date of clinical assessment  
111 in 2007-2009) and sex
- 112 ▪ extract residuals (observed-predicted test score)
- 113 ▪ calculate the root-mean-squared error
- 114 ▪ standardize the residuals using the root-mean-squared error
- 115 ▪ apply the 1.5 SD threshold to the standardized residuals.

116 The procedure described above was repeated by first adding education (university or higher  
117 degree, higher secondary school, lower secondary school or less) and then occupation (three-level  
118 variable categorized as high, intermediate, and low using the British Civil Service grade of  
119 employment at age 50) to the regression model.

120 Cognitive decline was defined using slopes of change in cognitive test scores using data from 1997-  
121 1999, 2002-2004, and 2007-2009. Cognitive decline was defined being in the worst 10<sup>th</sup> percentile  
122 of the slope of change on at least one cognitive domain or below the 20<sup>th</sup> percentile on more than  
123 one domain.<sup>16</sup>

124 Seven definitions of CI were determined using the following criteria:

- 125 1. Age and sex-specific threshold for poor cognitive performance.
- 126 2. Cognitive decline.
- 127 3. Age and sex-specific threshold for poor cognitive performance and cognitive decline.
- 128 4. Age, sex and education-specific threshold for poor cognitive performance.
- 129 5. Age, sex and education-specific threshold for poor cognitive performance and cognitive  
130 decline.

- 131 6. Age, sex and occupation-specific threshold for poor cognitive performance.  
132 7. Age, sex and occupation-specific threshold for poor cognitive performance and cognitive  
133 decline.

134

135 *Primary outcome: Dementia*

136 Dementia ascertainment was undertaken using linkage to Hospital Episode Statistics (HES), the  
137 Mental Health Services Data Set (MHDS), and the mortality register using ICD-10 codes F00-F03,  
138 F05.1, G30, and G31. Record linkage was available until 31<sup>st</sup> of March 2019. HES contains clinical  
139 diagnoses from inpatient, outpatient, and emergency departments and has sensitivity and  
140 specificity of 78.0% and 92.0%, respectively.<sup>17</sup> MHDS contains dementia diagnoses from inpatient,  
141 outpatient and community mental health services, including memory services. The British national  
142 mortality register collects information about cause-specific mortality. Date of dementia was set at  
143 the first record of dementia diagnosis in any of these three databases.

144

145 *Secondary Outcome: Mortality*

146 The personal NHS identification number was used to identify participants who died during the  
147 follow-up. Mortality data were collected until 31<sup>st</sup> of September 2019 from the British national  
148 mortality register.

149

150

151 **Statistical analysis**

152 Participants' characteristics in 2007-2009 were examined as a function of concurrent CI status as  
153 well as dementia status at the end of follow-up. Differences in sociodemographic variables and CI  
154 status were assessed using  $\chi^2$  test and student's *t* test, as appropriate. Cohen's kappa coefficients  
155 were used to describe the agreement between the seven definitions of CI.



156

157 *Predictive accuracy of cognitive impairment for dementia*

158 We calculated dementia rate per 1000 person-years for each CI definition. Cox proportional  
159 hazard regression analysis were used to examine the association between CI and incidence of  
160 dementia for all 7 definitions. The start of follow-up was the date of the 2007-2009 clinical  
161 examination and participants were censored at date of record of dementia, death or 31<sup>st</sup> of March  
162 2019, whichever came first. We accounted for competing risk of death using cause-specific hazard  
163 models by censoring at date of death participants who died during follow-up.<sup>18</sup> The predictive  
164 accuracy of seven CI definitions were assessed using: a) Royston's modified R<sup>2</sup> for survival data<sup>19</sup>  
165 with confidence intervals using 2000 bootstrap replications in order to measure the overall  
166 performance; higher values indicate greater explained variation; b) Akaike information criterion  
167 (AIC), a measure of the relative goodness of fit of a statistical model, where lower values indicate  
168 better model fit. Differences of 10 or more in AIC were considered to be meaningful; c) sensitivity  
169 and specificity using survival models, as measures of classification accuracy; and d) Harrell's C-  
170 statistic for survival models with 95% confidence intervals for discrimination,<sup>20</sup> formally compared  
171 using a nonparametric approach using definition 1 (age and sex threshold for poor cognitive  
172 performance) as the reference. In these analyses, we also compared Harrell's C-statistics obtained  
173 for the seven CI definitions with that obtained using only age, sex, and education to predict  
174 dementia.

175 *Predictive accuracy of cognitive impairment for mortality*

176 The analyses described above were repeated using mortality as the outcome. The start of follow-  
177 up in these analyses was also the date of the 2007-2009 clinical examination and participants were  
178 censored at date of death or 31<sup>st</sup> of March 2019, whichever came first.

179

180

181 *Sensitivity Analyses*

182 We performed the following analyses to assess the robustness of our results.

- 183 1. Use of a 3-category variable (non-CI, only poor cognitive performance, poor cognitive  
184 performance and cognitive decline) to assess the importance of cognitive decline in CI when  
185 both poor cognitive performance and cognitive decline are included in the definition  
186 (definition 3, 5 and 7) using age, sex, and then education and occupation as described in the  
187 main analyses.
- 188 2. To address the impact of missing data we undertook analysis using inverse probability  
189 weighting to reflect the study population at baseline (1985). Of 9362 participants who were  
190 alive in 2007-2009 (start of follow-up in these analyses) and did not have a dementia diagnosis  
191 we first calculated the probability of being included in the present study using data from  
192 baseline on sociodemographic factors, health behaviours, cardiometabolic risk factors, and  
193 mental health and data on chronic conditions over the follow-up (1985 to 2019). The inverse of  
194 these probabilities was used to weight the analyses of the association between CI and  
195 dementia.
- 196 3. Alternate thresholds to define poor cognitive performance (1 SD and 1.96 SD instead of 1.5  
197 SD).
- 198 4. Analyses restricted to participants 65 years and older at CI assessment.
- 199 5. To examine reversion from CI to normal status between 1997-2009, we used a 3-category  
200 variable (non-CI, non-CI but previous poor cognition, and CI) to assess its association with the  
201 risk of dementia. Unstable CI was considered when a participant was classified as non-CI after  
202 being identified as cognitively impaired in any previous examination.
- 203 6. Adding age, sex, and education to CI definitions in predicting dementia. The optimal cut-off  
204 point for sensitivity and specificity was established by maximizing the Youden index (sensitivity  
205 + specificity – 1).<sup>21</sup>

206 All analyses were conducted with Stata version 15.0 (Stata Corp.). Two-sided  $p < 0.05$  was  
207 considered statistically significant in all analyses.

### 208 **Role of the funding source**

209 The funders had no role in the study design, data collection, data analysis, data interpretation, or  
210 writing of the report. All authors had access to all the data reported in the study and the  
211 corresponding author had final responsibility for the decision to submit for publication.

212

213

## 214 **RESULTS**

215 Of the 10,308 participants in the Whitehall II cohort study, 954 (9.3%) died and 2593  
216 (25.2%) were lost to follow-up between 1985 and 2007, before the assessment of CI (2007-2009).  
217 We also excluded 1064 (10.3%) participants with missing cognitive data and 10 (0.1%) prevalent  
218 cases of dementia at baseline, leading to analysis on 5687 participants (**Figure 1**). The average age  
219 of participants at CI assessment was 65.7 years, and 27% were women (**Table 1**). Compared with  
220 non-CI participants, those who were identified as having CI were older, had lower education and  
221 occupational attainment, and had lower cognitive scores and greater 10-year decline in all  
222 cognitive domains.

223 Over a median follow-up of 10.5 (IQR 10.1-10.9) years, a total of 270 (4.8%) participants  
224 were diagnosed with dementia and 649 (11.4%) died. Participants' characteristics in 2007-2009  
225 according to dementia status at the end of follow-up are shown in **Table 2**. Participants with  
226 dementia diagnosis were older, had lower educational level and occupational attainment, and  
227 they also had higher prevalence of CI.

228 The agreement between the seven definitions of CI (appendix p 3) showed that the  
229 definition based only on cognitive decline (definition 2) had poor agreement with definitions  
230 based only on cognitive performance (definitions 1, 4 and 6: kappa's 0.13, 0.14, and 0.15

231 respectively). Definitions based on cognitive performance alone (definition 1, 4, and 6) had  
232 considerable agreement with each other, kappa between 0.69 and 0.79. Similarly, definitions  
233 based on both cognitive performance and cognitive decline (definition 3, 5, and 7) agreed with  
234 each other, kappa between 0.78 and 0.86.

235 Dementia incidence rates, associations between CI and dementia, and predictive accuracy  
236 of the seven CI definitions are shown in **Table 3**. The rate of dementia per 1000 person-years was  
237 higher in CI than non-CI cases; these differences were larger when CI was defined using both  
238 cognitive performance and cognitive decline (19.8 vs. 3.9, 20.2 vs. 3.9, and 19.0 vs. 3.9 for  
239 definitions 3, 5 and 7, respectively) than when using only cognitive performance (11.6 vs. 3.7, 11.9  
240 vs. 3.6, and 11.6 vs. 3.6 for definitions 1, 4, and 6 respectively) or only cognitive decline (9.4 vs.  
241 3.2). This pattern of results was reflected in results from Cox regression, with the highest hazard  
242 ratio (HR) seen for definition 5 (age, sex, education threshold for poor cognitive performance AND  
243 cognitive decline: HR 5.48 (95% Confidence Interval 4.13, 7.26)) and lowest for definition 2 (only  
244 cognitive decline: HR 3.01 (95% Confidence Interval 2.37, 3.82)).

245 **Table 3** also shows definition 5 (age, sex, education threshold for poor cognitive  
246 performance and cognitive decline) to have the highest explained variance ( $R^2 = 0.214$ , 95%  
247 Confidence Interval 0.130, 0.311) and the best model fit (lowest AIC). The CI definitions including  
248 both poor cognitive performance and cognitive decline had the better goodness of fit in terms of  
249  $R^2$  and AIC ( $\Delta$  AIC  $> -10$  for definitions 3, 5 and 7 compared to definition 1). The C-statistic for  
250 definition 1 (age, sex threshold for cognitive performance) was modest (0.608, 95% Confidence  
251 Interval 0.580, 0.637) and p-values for difference in C-statistic using definition 1 as reference (all  
252  $p > 0.05$ ) suggest similar discrimination for all seven definitions of CI. Sensitivity of the definitions  
253 ranged from 21.6% to 48.4%, specificity from 75.1% to 94.9%, with definitions that included both  
254 cognitive performance and decline (definitions 3, 5, and 7) showing lower sensitivity but greater

255 specificity. A prediction model only with demographic variables (age, sex, and education) had a C-  
256 statistic of 0.783 (0.758, 0.809), better than all seven CI measures ( $p$ -values were  $<0.0001$ ).

257 Additional analyses (appendix p 4) showed systematically stronger associations with  
258 dementia when cognitive decline was included in the definition of CI ( $p$ -value  $<0.0001$  for  
259 comparison of hazard ratios). Inverse probability weighting to account for missing data yielded  
260 results (appendix p 5) similar to those reported in Table 3, with the highest HR for definition 5 (HR  
261 4.99 (95% Confidence Interval 3.69, 6.74)) and lowest for definition 2 (HR 2.70 (95% Confidence  
262 Interval 2.09, 3.48)). When thresholds of 1 SD rather than 1.5 SD were used (appendix p 6), the  
263 highest HR was found for definition 7 (HR 4.17 (95% Confidence Interval 3.24, 5.37)) and lowest  
264 for definition 4 (HR 2.63 (95% Confidence Interval 2.07, 3.34)). For the 1.96 SD threshold  
265 (appendix p 7), the highest HR was for definition 3 (HR 7.09 (95% Confidence Interval 5.07, 9.93))  
266 and lowest for definition 2 (HR 3.01 (95% Confidence Interval 2.37, 3.82)). Analysis restricted to  
267 participants 65 years and older ( $N=2837$ ) (appendix p 8) showed definition 5 to have the highest  
268 HR (HR 4.84 (95% Confidence Interval 3.58, 6.55)) and definition 2 the lowest (HR 2.75 (95%  
269 Confidence Interval 2.12, 3.56)). The risk of dementia in participants with unstable CI (reversion  
270 from CI to non-CI status) was similar to non-CI participants (appendix p 9).

271 Adding age, sex and education to CI measures considerably improved the predictive  
272 accuracy of all definitions (appendix p 10). For example, definition 1 (age, sex threshold for  
273 cognitive performance) had its C-statistic change from 0.608 (Table 3) to 0.807 (appendix p 10),  
274 with improvement in  $R^2$  from 0.155 to 0.643 and sensitivity from 32.9% to 77.2%. In these analyses  
275 all predictive models performed equally well irrespective of the definition of CI.

276 **Table 4** shows all seven definitions of CI to be associated with mortality, compared to non-  
277 CI persons, the HR for mortality using age and sex threshold of CI (definition 1) was 1.71 (95% CI  
278 1.42, 2.06). The  $R^2$  for mortality associated with all seven CI definitions were lower than those  
279 observed for dementia. CI defined using only cognitive decline (definition 2) had the best overall

280 fit ( $R^2$  and AIC) and the best discrimination (C-statistic 0.566, 95% Confidence Interval 0.547,  
281 0.585), significantly better than definition 1 ( $p=0.02$ ).

282

283

## 284 **DISCUSSION**

285 This prospective study has five key findings. First, CI defined using objective measure of 10-  
286 year cognitive along with poor cognitive performance was more strongly associated with dementia  
287 compared to definitions using only poor cognitive performance or only cognitive decline. Two, the  
288 discrimination and predictive accuracy of all CI definitions for dementia was modest, it was  
289 characterized by high specificity but modest sensitivity. Most studies on CI are based on older  
290 adults,<sup>22,23</sup> restricting our analyses to participants older than 65 years did not alter main findings.  
291 Three, using education or occupation specific thresholds for poor cognitive performance in  
292 addition to age and sex had a small impact in improving predictive performance of CI for  
293 dementia. Four, in general CI had a weaker association with mortality than with dementia. Five,  
294 demographic variables (age, sex, education) on their own were substantially better predictors of  
295 dementia than all seven CI definitions and thus adding these measures to the prediction model  
296 substantially improved prediction accuracy.

297 Much of the research on CI focusses on conversion rates to dementia. A 2009 meta-  
298 analyses reported cumulative conversion rate to be 22.7% (95% CI 14.2, 32.6) in community  
299 settings.<sup>22</sup> In our study, with assessment of cognitive decline over a 10-year span and a  
300 subsequent 10-year follow-up, the cumulative conversion ranged from 9% to 18% for the seven  
301 definitions of CI. Conversion to dementia may not be meaningful as an annual conversion rate of  
302 10% from MCI to dementia reported in a review<sup>23</sup> seems implausible because it implies that nearly  
303 two-third of the study population would convert to dementia after ten years.

304 Two recent studies used data from Alzheimer's Disease Neuroimaging Initiative study  
305 (ADNI), based only on persons with an MCI diagnosis, to examine conversion. One study found  
306 cognitive measures to be more robust predictors of conversion than cerebrospinal fluid (CSF)  
307 biomarkers,<sup>24</sup> and the second used over 750 predictors and found the best performing model to  
308 include demographic measures, cognitive/functional markers and morphometric MRI measures  
309 (83% sensitivity, 76% specificity, area under the curve (AUC) = 0.87).<sup>25</sup> As in our study, the role of  
310 demographic variables in prediction has also been noted in a recent study that examined  
311 conversion from normal cognition to MCI, with an AUC of 0.68; in this study adding 6 (APOE e4, 2  
312 cognitive tests, right hippocampus volume, right entorhinal cortex thickness, CSF p-tau) other  
313 measures improved the AUC to 0.85.<sup>26</sup> Taken together, these findings highlight the importance of  
314 demographic variables in dementia prediction, they also have the advantage of being widely  
315 available compared to CSF or imaging biomarkers.

316 An important element in the conceptualization of CI is loss of cognition from a previous  
317 state with recommendations that this shall be undertaken using serial measurement,<sup>4</sup> preferably  
318 with a minimum of 3 data points.<sup>7</sup> Cognitive testing at one point of time is less reliable and subject  
319 to random variation, particularly at older ages.<sup>6,7</sup> However, most studies do not use cognitive  
320 decline in the diagnosis of CI, either because the study period is short or repeat data on cognitive  
321 function are not available. One exception is a study on 618 adults aged 70-90 years with data on  
322 cognitive decline over 2 years and a 6-year follow-up that found objective cognitive decline not to  
323 improve the predictive accuracy for progression to dementia (AUC 0.52 to 0.62 compared to 0.59  
324 to 0.72 for measures of poor cognitive performance).<sup>27</sup> Another multi-cohort study on the  
325 progression from normal cognition to MCI also reported better performance with cognitive  
326 decline, specifically an improvement in specificity.<sup>28</sup> Our results also show that including both poor  
327 cognitive performance and cognitive decline (definitions 3, 5 and 7) increases specificity so these  
328 metrics should be used in contexts where it is important to avoid false positive cases.

329 Education and occupation have been studied extensively in the onset of CI and dementia,  
330 with a recent study showing education to delay the onset of CI but not the subsequent  
331 progression to dementia.<sup>29</sup> Likewise, our results suggest that using education specific thresholds  
332 for poor cognitive performance have a marginal effect in terms of improving prediction of  
333 dementia. Taken together, our results support the position that cognitive impairment is a poor  
334 predictor of dementia.<sup>22,27</sup> While CI definitions without demographic variables have high  
335 specificity, the low prevalence of dementia implies a large proportion of false positive test results,  
336 resulting in low positive predictive value for CI. A similar observation has been made for blood  
337 based biomarkers for Alzheimer's disease that have high negative predictive value but low positive  
338 predictive value.<sup>30</sup> Combining multiple predictors (such as biomarkers, imaging data, risk factors  
339 and cognitive markers) to define CI does improve prediction accuracy<sup>25,31,32</sup> but even in these  
340 studies the major predictive ability continues to be from demographic variables. Our results on CI  
341 reflects findings on multivariable prediction models for dementia where reviews of existing  
342 models have found their predictive accuracy to be poor.<sup>33</sup>

343 The primary strength of this study is use of a large scale, longitudinal study spanning over  
344 20 years that allows assessment of the usefulness of CI for dementia. Cognitive decline spanning  
345 ten years could be used to determine CI status, following recommendations in this domain.<sup>4,6,7</sup> As  
346 such data are unlikely to be available in clinical practice we also used measures of cognitive  
347 performance alone in CI definitions 1, 4, and 6. Other advantages were the use of an algorithm to  
348 guide diagnostic classification of CI, which reduces random variability and biases due to variability  
349 in clinical judgment. Finally, the use of predictive statistics in addition to conversion rates and  
350 hazard ratios to show strength of associations allows assessment of the utility of CI.

351 Notwithstanding, when interpreting our results, the limitations of the study must also be  
352 taken into account. The cognitive battery did not include all possible cognitive domains,  
353 particularly measures of visuospatial memory or delayed recall, or multiple cognitive tests in each



354 domain that may measure CI better. Ascertainment of dementia via linkage to electronic health  
355 records rather than clinical evaluation is likely to miss milder cases of dementia. However, this  
356 approach has the advantage of being able to include all participants in the analyses rather than  
357 just those who participate in-person in ascertainment of dementia. In the UK, HES records on  
358 dementia have been shown to have high specificity but modest sensitivity (78%) due to missing of  
359 milder cases of dementia,<sup>17</sup> we additionally used the mental health data to improve the sensitivity  
360 of dementia diagnosis. Previous studies using these data on dementia show expected associations  
361 with risk factors<sup>11</sup> suggesting that the quality of the dementia data is an unlikely explanation of the  
362 findings of the present study. Further, the presence of false negatives would affect all prediction  
363 models rather than only those using CI. The analysis on dementia is based on smaller numbers  
364 than that used for mortality and the confidence intervals accompanying the HR are wider but the  
365 number of events is large enough not to violate the guideline of 10-15 events per predictor. Small  
366 numbers did not allow examination of dementia-related mortality or dementia sub-types. Finally,  
367 Whitehall II study participants are likely to be healthier than the general population, though we  
368 have shown risk factor-outcome associations in the study to be similar to those of the general  
369 population.<sup>34</sup>

370 In conclusion, our study suggests that cognitive decline is necessary but not sufficient for  
371 later dementia. Adding an objective measure of cognitive decline over 10 years does not improve  
372 the predictive accuracy of CI, and is unlikely to be a cost-effective approach to identifying persons  
373 who would benefit from therapeutic strategies aimed at delaying or preventing dementia. Further  
374 research is needed to determine risk factors or biomarkers that are useful in early identification of  
375 persons at increased risk of dementia.

376 **ACKNOWLEDGEMENT**

377 We thank all of the participating civil service departments and their welfare, personnel, and  
378 establishment officers; the British Occupational Health and Safety Agency; the British Council of  
379 Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the  
380 Whitehall II study team. The Whitehall II Study team comprises research scientists, statisticians,  
381 study coordinators, nurses, data managers, administrative assistants and data entry staff, who  
382 make the study possible.

383 The Whitehall II study is supported by grants from the National Institute on Aging, NIH  
384 (R01AG056477, RF1AG062553); UK Medical Research Council (R024227, S011676); the British  
385 Heart Foundation (RG/16/11/32334). MK was supported by the UK Medical Research Council  
386 (R024227, S011676), Academy of Finland (311492), Helsinki Institute of Life Science, and  
387 NordForsk. AS is funded by the UCL / Wellcome Trust Institutional Strategic Support Fund  
388 (204841/Z/16/Z) and by the University College London Hospitals' (UCLH) National Institute for  
389 Health Research (NIHR) Biomedical Research Centre (BRC). SS is supported by the French National  
390 Research Agency (ANR-19-CE36-0004-01).

391

392 **AUTHOR CONTRIBUTIONS**

393 Conceptualization: AD, SS, ASM.

394 Methodology: MDM-F, AD, AF, SS, ASM.

395 Investigation: MDM-F, AD, JD, MK, AS, BL, AF, SS, ASM.

396 Validation: MDM-F, AD, SS, ASM.

397 Formal analysis: MDM-F, AD.

398 Access and verified the data: MDM-F, AD.

399 Data Curation: AD, AF.

400 Writing –original draft preparation: MDM-F, ASM.

401 Writing –review and editing: MDM-F, AD, JD, MK, AS, BL, AF, SS, ASM.

402 Visualization: MDM-F, AD, SS, ASM.

403 Supervision: AD, SS, ASM.

404 Funding acquisition: MK, ASM.

405

406 **COMPETING INTERESTS**

407 MK has received grants from the UK Medical Research Council (R024227, S011676), US National  
408 Institute on Aging (R01AG056477, RF1AG062553), Academy of Finland (311492), Helsinki Institute  
409 of Life Science, NordForsk, and The Wellcome Trust (221854/Z/20/Z). AS is funded by the UCL /  
410 Wellcome Trust Institutional Strategic Support Fund (204841/Z/16/Z; 200163/Z/15/Z), by the  
411 University College London Hospitals' (UCLH) National Institute for Health Research (NIHR)  
412 Biomedical Research Centre (BRC), and by the Alzheimer's society. ASM has received grants from  
413 the NIH (R01AG056477, RF1AG062553).

414

415 **DATA AVAILABILITY**

416 Whitehall II data cannot be shared publicly because of constraints dictated by the study's ethics approval  
417 and IRB restrictions. The Whitehall II data are available for sharing within the scientific community.

418 Researchers can apply for data access at [https://www.ucl.ac.uk/epidemiology-health-  
419 care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing](https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing).

420

## References

1. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013; **12**(2): 207-16.
2. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* 2016; **15**(5): 455-532.
3. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *Journal of internal medicine* 2014; **275**(3): 214-28.
4. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**(3): 270-9.
5. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine* 2004; **256**(3): 240-6.
6. Weir DR, Wallace RB, Langa KM, et al. Reducing case ascertainment costs in U.S. population studies of Alzheimer's disease, dementia, and cognitive impairment-Part 1. *Alzheimers Dement* 2011; **7**(1): 94-109.
7. Evans DA, Grodstein F, Loewenstein D, Kaye J, Weintraub S. Reducing case ascertainment costs in U.S. population studies of Alzheimer's disease, dementia, and cognitive impairment-Part 2. *Alzheimers Dement* 2011; **7**(1): 110-23.
8. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med* 2013; **29**(4): 753-72.
9. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; **56**(3): 303-8.
10. Bloomberg M, Dugravot A, Dumurgier J, et al. Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies. *Lancet Public Health* 2021; **6**(2): e106-e15.
11. Rusmaully J, Dugravot A, Moatti JP, et al. Contribution of cognitive performance and cognitive decline to associations between socioeconomic factors and dementia: A cohort study. *PLoS medicine* 2017; **14**(6): e1002334.
12. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991; **337**(8754): 1387-93.
13. Heim AW. AH 4 group test of general Intelligence. Windsor, UK: NFER-Nelson Publishing Company Ltd.; 1970.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**(3): 189-98.
15. Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A Comprehensive Review. *Journal of the American Geriatrics Society* 1992; **40**(9): 922-35.
16. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)* 2016; **2**: 1-11.
17. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008-2016. *Alzheimers Dement* 2018; **14**(7): 933-43.
18. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009; **170**(2): 244-56.
19. Royston P. Explained variation for survival models. *Stata Journal* 2006; **6**: 83-96.

20. Newson RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *The Stata Journal* 2010; **10**(3): 339-58.
21. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; **3**(1): 32-5.
22. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiat Scand* 2009; **119**(4): 252-65.
23. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. *Int Psychogeriatr* 2004; **16**(2): 129-40.
24. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE, Alzheimer's Disease Neuroimaging I. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Arch Gen Psychiat* 2011; **68**(9): 961-9.
25. Korolev IO, Symonds LL, Bozoki AC, Alzheimer's Disease Neuroimaging I. Predicting Progression from Mild Cognitive Impairment to Alzheimer's Dementia Using Clinical, MRI, and Plasma Biomarkers via Probabilistic Pattern Classification. *Plos One* 2016; **11**(2): e0138866.
26. Albert M, Zhu Y, Moghekar A, et al. Predicting progression from normal cognition to mild cognitive impairment for individuals at 5 years. *Brain* 2018; **141**(3): 877-87.
27. Brodaty H, Aerts L, Crawford JD, et al. Operationalizing the Diagnostic Criteria for Mild Cognitive Impairment: The Salience of Objective Measures in Predicting Incident Dementia. *Am J Geriatr Psychiatry* 2017; **25**(5): 485-97.
28. Gross AL, Hassenstab JJ, Johnson SC, et al. A classification algorithm for predicting progression from normal cognition to mild cognitive impairment across five cohorts: The preclinical AD consortium. *Alzheimers Dement (Amst)* 2017; **8**: 147-55.
29. Robitaille A, van den Hout A, Machado RJM, et al. Transitions across cognitive states and death among older adults in relation to education: A multistate survival model using data from six longitudinal studies. *Alzheimers Dement* 2018; **14**(4): 462-72.
30. O'Bryant SE. Blood Biomarkers for Use in Alzheimer Disease-Moving From "If" to "How?". *JAMA Neurol* 2019.
31. Steenland K, Zhao L, John SE, et al. A 'Framingham-like' Algorithm for Predicting 4-Year Risk of Progression to Amnesic Mild Cognitive Impairment or Alzheimer's Disease Using Multidomain Information. *J Alzheimers Dis* 2018; **63**(4): 1383-93.
32. Zhao A, Li Y, Yan Y, et al. Increased prediction value of biomarker combinations for the conversion of mild cognitive impairment to Alzheimer's dementia. *Transl Neurodegener* 2020; **9**(1): 30.
33. Stephan BC, Tang E, Muniz-Terrera G. Composite risk scores for predicting dementia. *Current opinion in psychiatry* 2016; **29**(2): 174-80.
34. Batty GD, Shipley M, Tabak A, et al. Generalizability of occupational cohort study findings. *Epidemiology* 2014; **25**(6): 932-3.

**Table 1. Characteristics of the participants as a function of Cognitive Impairment.**

	Total Population N=5687	Cognitive Impairment <sup>a</sup>						
		Definition 1 N=821	Definition 2 N=1485	Definition 3 N=338	Definition 4 N=837	Definition 5 N=347	Definition 6 N=826	Definition 7 N=354
Age, M (SD)	65.7 (5.9)	65.8 (5.9)	67.0 (6.0)	67.2 (6.0)	66.0 (6.0)	67.2 (6.1)	65.8 (6.1)	67.2 (6.1)
Women, %	27.3	32.2	30.6	33.4	30.2	31.1	29.2	30.8
Low education, %	41.7	59.3	43.7	56.5	41.5	43.2	48.4	48.3
Low occupation, %	10.7	30.2	12.8	29.0	27.0	24.8	14.4	15.8
<b>Cognitive scores in 2007/09</b>								
Memory (Range 0-20), M(SD)	6.21 (2.21)	4.32 (2.21)	5.51 (2.19)	3.86 (2.22)	4.38 (2.29)	3.98 (2.35)	4.48 (2.25)	4.05 (2.30)
Language (Range 0-35), M(SD)	15.34 (3.46)	11.64 (3.44)	14.56 (3.63)	11.56 (3.97)	11.78 (3.48)	11.63 (3.96)	12.03 (3.51)	11.83 (3.85)
Executive function (Range 0-65), M(SD)	43.92 (10.82)	30.38 (11.34)	41.31 (11.27)	31.05 (11.78)	31.35 (11.74)	32.14 (12.04)	33.06 (11.84)	33.30 (11.86)
MMSE <24, %	0.8	5.5	3.0	13.3	5.4	13.0	5.5	12.7
<b>Mean 10-y decline</b>								
Memory, M(SD)	- 0.32 (1.15)	- 0.56 (1.39)	- 1.05 (1.46)	- 1.23 (1.58)	- 0.56 (1.39)	- 1.22 (1.59)	- 0.62 (1.35)	- 1.27 (1.50)
Language, M(SD)	- 0.37 (0.79)	- 0.49 (1.01)	- 0.87 (1.02)	- 0.92 (1.27)	- 0.51 (1.01)	- 0.94 (1.26)	- 0.54 (1.02)	- 0.97 (1.25)
Executive function, M(SD)	- 0.27 (0.60)	- 0.45 (0.69)	- 0.60 (0.79)	- 0.78 (0.84)	- 0.45 (0.69)	- 0.75 (0.85)	- 0.48 (0.70)	- 0.79 (0.85)

<sup>a</sup>Cognitive Impairment defined as follows:

1. Age and sex threshold for poor cognitive performance.
2. Cognitive decline.
3. Age, sex threshold for poor cognitive performance AND cognitive decline.
4. Age, sex, education threshold for poor cognitive performance.
5. Age, sex, education threshold for poor cognitive performance AND cognitive decline.
6. Age, sex, occupation threshold for poor cognitive performance.
7. Age, sex, occupation threshold for poor cognitive performance AND cognitive decline.

**Table 2. Sample characteristics in 2007-2009 as a function of dementia status at the end of follow-up (31<sup>st</sup> March 2019).**

	Dementia <sup>a</sup>		p-value <sup>b</sup>
	No	Yes	
N, %	5417 (95.2)	270 (4.8)	
Age at baseline, M(SD)	65.5 (5.8)	71.4 (4.9)	<.0001
Women	1463 (27.0)	89 (33.0)	.03
Low education	2224 (41.1)	150 (55.6)	<.0001
Low occupation	552 (10.2)	57 (21.1)	<.0001
<b>Cognitive Impairment definitions</b>			
1. Age and sex threshold for poor cognitive performance	730 (13.5)	91 (33.7)	<.0001
2. Cognitive decline	1351 (24.9)	134 (49.6)	<.0001
3. Age, sex threshold for poor cognitive performance AND cognitive decline	278 (5.1)	60 (22.2)	<.0001
4. Age, sex, education threshold for poor cognitive performance	742 (13.7)	95 (35.2)	<.0001
5. Age, sex, education threshold for poor cognitive performance AND cognitive decline	284 (5.2)	63 (23.3)	<.0001
6. Age, sex, occupation threshold for poor cognitive performance	734 (13.6)	92 (34.1)	<.0001
7. Age, sex, occupation threshold for poor cognitive performance AND cognitive decline	293 (5.4)	61 (22.6)	<.0001

Data are n (%), unless otherwise specified.

<sup>a</sup>Data on dementia subtype was as follows: Alzheimer's disease (N=108), Vascular dementia (N=43), Parkinson's dementia (N=9), Mixed Alzheimer's & vascular dementia (N=14), Mixed Vascular and Parkinson's dementia (N=2), Mixed Alzheimer's and Parkinson's dementia (N=4), Other/Missing subtype (N=90).

<sup>b</sup>p values for differences in  $\chi^2$  test (categorical data) or student's t test (continuous).

**Table 3. Predictive performance of seven cognitive impairment definitions for dementia.**

	N cases /total	Rate of dementia/ 1000 person- years	Follow-up years M(SD)	HR (95% Confidence Interval)	R <sup>2</sup> (95% Confidence Interval)	AIC	Δ AIC	Sensitivity %	Specificity %	C-Statistic (95% Confidence Interval)	p- value <sup>a</sup>	p- value <sup>b</sup>
<b>COGNITIVE IMPAIRMENT DEFINITIONS</b>												
<b>1. Age and sex threshold for poor cognitive performance</b>												
Non-CI	179/4866	3.7	10.1 (1.7)	1 (Ref.)	0.155	4527.9	Ref.	32.9	86.6	0.608	Ref.	<.0001
CI	91/821	11.6	9.5 (2.4)	3.26 (2.53, 4.19)	(0.088, 0.238)					(0.580, 0.637)		
<b>2. Cognitive decline</b>												
Non-CI	136/4202	3.2	10.1 (1.7)	1 (Ref.)	0.169	4521.4	- 6.5	48.4	75.1	0.631	.23	<.0001
CI	134/1485	9.4	9.6 (2.3)	3.01 (2.37, 3.82)	(0.102, 0.248)					(0.601, 0.660)		
<b>3. Age, sex threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	210/5349	3.9	10.1 (1.8)	1 (Ref.)	0.200	4506.3	- 21.6	21.8	94.9	0.592	.09	<.0001
CI	60/338	19.8	9.0 (2.9)	5.30 (3.98, 7.07)	(0.117, 0.292)					(0.566, 0.617)		
<b>4. Age, sex, education threshold for poor cognitive performance</b>												
Non-CI	175/4850	3.6	10.1 (1.7)	1 (Ref.)	0.169	4521.0	- 6.9	34.3	86.4	0.612	.64	<.0001
CI	95/837	11.9	9.5 (2.5)	3.39 (2.64, 4.36)	(0.099, 0.257)					(0.583, 0.641)		
<b>5. Age, sex, education threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	207/5340	3.9	10.1 (1.8)	1 (Ref.)	0.214	4499.2	- 28.7	22.4	94.8	0.595	.25	<.0001
CI	63/347	20.2	9.0 (2.9)	5.48 (4.13, 7.26)	(0.130, 0.311)					(0.569, 0.621)		
<b>6. Age, sex, occupation threshold for poor cognitive performance</b>												
Non-CI	178/4861	3.6	10.1 (1.8)	1 (Ref.)	0.155	4527.7	- 0.2	32.5	86.5	0.608	.99	<.0001
CI	92/826	11.6	9.6 (2.4)	3.25 (2.52, 4.17)	(0.088, 0.234)					(0.579, 0.637)		
<b>7. Age, sex, occupation threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	209/5333	3.9	10.1 (1.8)	1 (Ref.)	0.194	4509.0	- 18.9	21.6	94.6	0.591	.15	<.0001
CI	61/354	19.0	9.0 (2.9)	5.08 (3.82, 6.76)	(0.115, 0.285)					(0.565, 0.616)		
<b>DEMOGRAPHIC MODEL</b>												
<b>Age, sex, &amp; education</b>	270/5687	NA	NA	NA	0.543 (0.465, 0.626)	4312.6	-215.3	74.2	72.2	0.783 (0.758, 0.809)	<.0001	Ref.

HR: Hazard Ratio, CI: Cognitive impairment, R<sup>2</sup>=Royston's R<sup>2</sup>, AIC: Akaike information criterion, C-Statistic=Harrell's C-index, M(SD)=Mean (Standard Deviation), NA: Not Applicable.

<sup>a</sup>p values for difference in C-statistic using definition 1 as reference.

<sup>b</sup>p values for difference in C-statistic using demographic model as reference.



**Table 4. Predictive performance of seven cognitive impairment definitions for mortality.**

	N cases /total	Rate of mortality/ 1000 person- years	Follow-up years M(SD)	HR (95% Confidence Interval)	R <sup>2</sup> (95% Confidence Interval)	AIC	Δ AIC	Sensitivity %	Specificity %	C-Statistic (95% Confidence Interval)	p- value <sup>a</sup>	p- value <sup>b</sup>
<b>COGNITIVE IMPAIRMENT DEFINITIONS</b>												
<b>1. Age and sex threshold for poor cognitive performance</b>												
Non-CI	508/4866	9.8	10.6 (1.8)	1 (Ref.)	0.027	11058.3	Ref.	22.1	86.5	0.540	Ref.	<.0001
CI	141/821	16.7	10.3 (2.2)	1.71 (1.42, 2.06)	(0.011, 0.050)					(0.524, 0.556)		
<b>2. Cognitive decline</b>												
Non-CI	400/4202	8.9	10.7 (1.7)	1 (Ref.)	0.050	11033.2	- 25.1	38.4	75.5	0.566	.02	<.0001
CI	249/1485	16.3	10.3 (2.1)	1.84 (1.57, 2.16)	(0.026, 0.080)					(0.547, 0.585)		
<b>3. Age, sex threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	572/5349	10.1	10.6 (1.8)	1 (Ref.)	0.036	11048.4	- 9.9	12.2	94.9	0.533	.21	<.0001
CI	77/338	22.9	9.9 (2.5)	2.31 (1.82, 2.93)	(0.015, 0.066)					(0.520, 0.545)		
<b>4. Age, sex, education threshold for poor cognitive performance</b>												
Non-CI	505/4850	9.8	10.6 (1.8)	1 (Ref.)	0.028	11057.4	- 0.9	22.7	86.3	0.542	.79	<.0001
CI	144/837	16.7	10.3 (2.2)	1.71 (1.43, 2.07)	(0.010, 0.052)					(0.526, 0.557)		
<b>5. Age, sex, education threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	569/5340	10.1	10.6 (1.8)	1 (Ref.)	0.038	11045.8	- 12.5	12.7	94.7	0.534	.36	<.0001
CI	80/347	23.2	10.0 (2.5)	2.35 (1.86, 2.96)	(0.016, 0.067)					(0.522, 0.547)		
<b>6. Age, sex, occupation threshold for poor cognitive performance</b>												
Non-CI	514/4861	10.0	10.6 (1.8)	1 (Ref.)	0.020	11065.7	7.4	21.0	86.3	0.534	.29	<.0001
CI	135/826	15.8	10.3 (2.2)	1.60 (1.32, 1.93)	(0.518, 0.549)					(0.518, 0.549)		
<b>7. Age, sex, occupation threshold for poor cognitive performance AND cognitive decline</b>												
Non-CI	569/5333	10.1	10.6 (1.8)	1 (Ref.)	0.037	11047.8	- 10.5	12.7	94.6	0.534	.35	<.0001
CI	80/354	22.7	10.0 (2.5)	2.29 (1.81, 2.90)	(0.016, 0.065)					(0.521, 0.546)		
<b>DEMOGRAPHIC MODEL</b>												
<b>Age, sex, &amp; education</b>	649/5687	NA	NA	NA	0.322 (0.267, 0.385)	10718.0	- 340.3	64.8	71.5	0.708 (0.688, 0.729)	<.0001	Ref.

HR: Hazard Ratio, CI: Cognitive impairment, R<sup>2</sup>=Royston's R<sup>2</sup>, AIC: Akaike information criterion, C-Statistic=Harrell's C-index, M(SD)=Mean (Standard Deviation), NA: Not Applicable.

<sup>a</sup>p values for difference in C-statistic using definition 1 as reference.

<sup>b</sup>p values for difference in C-statistic using demographic model as reference.