



Potentially-modifiable Lifestyle Factors, Cognitive Reserve and Cognitive Function in Later Life

Clare, Linda; Wu, Yu-Tzu; Teale, Julia; MacLeod, Catherine; Matthews, Fiona; Brayne, Carol; Woods, Robert; CFAS-Wales study team

PLoS Medicine

DOI:

[10.1371/journal.pmed.1002259](https://doi.org/10.1371/journal.pmed.1002259)

Published: 21/03/2017

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):

Clare, L., Wu, Y.-T., Teale, J., MacLeod, C., Matthews, F., Brayne, C., Woods, R., & CFAS-Wales study team (2017). Potentially-modifiable Lifestyle Factors, Cognitive Reserve and Cognitive Function in Later Life: a Cross-sectional Study. *PLoS Medicine*, 14(3), 1-14. Article e1002259. <https://doi.org/10.1371/journal.pmed.1002259>

Hawliau Cyffredinol / General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1 **Full Title: Potentially-modifiable Lifestyle Factors, Cognitive Reserve and Cognitive**

2 **Function in Later Life: a Cross-sectional Study**

3 **Short Title: Lifestyle Factors, Cognitive Reserve and Cognitive Function in Later Life**

4 Linda Clare^{1,2,3*}, Yu-Tzu Wu^{1,2}, Julia C. Teale^{1,2}, Catherine MacLeod⁴, Fiona Matthews^{5,6},

5 Carol Brayne⁷ and Bob Woods⁴ on behalf of the CFAS-Wales study team

6 1. Centre for Research in Ageing and Cognitive Health (REACH), School of
7 Psychology, University of Exeter, Exeter, UK

8 2. PenCLAHRC, Institute of Health Research, University of Exeter Medical School,
9 Exeter, UK

10 3. Centre for Research Excellence in Promoting Cognitive Health, Australian National
11 University, Canberra, Australia

12 4. Dementia Services Development Centre Wales, School of Healthcare Sciences,
13 Bangor University, Bangor, UK

14 5. Institute of Health and Society, Faculty of Medicine, Newcastle University,
15 Newcastle, UK

16 6. MRC Biostatistics Unit, Institute of Public Health, University of Cambridge,
17 Cambridge, UK

18 7. Institute of Public Health, University of Cambridge, Cambridge, UK

19

20 Corresponding author

21 * l.clare@exeter.ac.uk

22 **Abstract**

23 Background: Potentially-modifiable lifestyle factors may influence cognitive health in later
24 life and offer potential to reduce the risk of cognitive decline and dementia. The concept of
25 cognitive reserve has been proposed as a mechanism to explain individual differences in
26 rates of cognitive decline, but its potential role as a mediating pathway has seldom been
27 explored using data from large epidemiological studies. We explored the mediating effect of
28 cognitive reserve on the cross-sectional association between lifestyle factors and cognitive
29 function in later life using data from a population-based cohort of healthy older people.

30 Methods and Findings: We analysed data from 2315 cognitively-healthy participants aged
31 65 and over in the Cognitive Function and Ageing Study Wales (CFAS-Wales) cohort
32 collected in 2011 - 2013. Linear regression modelling was used to investigate the overall
33 associations between five lifestyle factors - cognitive and social activity, physical activity,
34 diet, alcohol consumption and smoking - and cognition, adjusting for demographic factors
35 and chronic conditions. Mediation analysis tested for indirect effects of the lifestyle factors
36 on cognition via cognitive reserve. After controlling for age, gender and presence of chronic
37 conditions, cognitive and social activity, physical activity, healthy diet and light-to-moderate
38 alcohol consumption were positively associated with cognitive function, together
39 accounting for 20% (95% CI: 17%, 23%) of variance in cognitive test scores. Cognitive
40 reserve was an important mediator of this association, with indirect effects via cognitive

41 reserve contributing 21% (95% CI: 15%, 27%) of the overall effect on cognition. The main
42 limitations of the study derive from the cross-sectional nature of the data and the challenges
43 of accurately measuring the latent construct of cognitive reserve.

44 Conclusions: Cross-sectional associations support the view that enhancing cognitive reserve
45 may benefit cognition, and maintenance of cognitive health may be supported by a healthy
46 and active lifestyle, in later life.

47

48 **Non-technical author summary**

49 **Why Was This Study Done?**

- 50 • Individual differences in lifestyle factors such as physical activity or diet may be
51 related to differences in mental fitness in later life.
- 52 • Differences in the extent to which mental fitness declines in later life are thought to
53 arise because some people's earlier experiences (for example, staying on for further
54 education, or playing a leadership role in a job) make their brains more resilient to
55 changes resulting from age or illness – they have higher 'cognitive reserve'.
- 56 • We wanted to find out whether the concept of cognitive reserve explains how lifestyle
57 influences mental fitness.

58 **What Did the Researchers Do and Find?**

- 59 • We used data from 2315 mentally fit participants aged over 65 years who took part in
60 the first wave of interviews for the Cognitive Function and Ageing Study Wales
61 (CFAS-Wales)
- 62 • Our statistical analyses examined whether a healthy lifestyle (a healthy diet, more
63 physical activity, more social and mentally-stimulating activity, moderate alcohol
64 consumption and refraining from smoking), adjusted to take account of age, gender
65 and whether people had long-term health conditions, were associated with
66 performance on a test of mental ability.
- 67 • Where we found an association, we then investigated whether this association was
68 explained by level of cognitive reserve.
- 69 • We found that people with a healthier lifestyle had better mental fitness, and this was
70 partly accounted for by their level of cognitive reserve.

71 **What Do These Findings Mean?**

- 72 • A healthy lifestyle is associated with better mental fitness in later life.
- 73 • This highlights the importance of policies and interventions that encourage older
74 people to make changes in their diet, exercise more, and engage in more
75 socially-oriented and mentally-stimulating activities.

- 76 • Earlier life experiences build cognitive reserve which helps to maintain mental fitness
77 in later life, so access to education and opportunities to develop skills in the workplace
78 are important in developing this resilience.
- 79 • The main limitation of this study is that we used data collected at only one time-point,
80 which means that we cannot draw any conclusions about causes or trajectories – we
81 can only say for sure that lifestyle and mental fitness are related.

82 **Potentially-modifiable Lifestyle Factors, Cognitive Reserve and Cognitive Function in**
83 **Later Life: a Cross-sectional Study**

84

85 **Introduction**

86 Cognitive health is a major factor in ensuring the quality of life of older people and
87 preserving independence. Cognitive health is ‘the development and preservation of the
88 multidimensional cognitive structure that allows [older people] to maintain social
89 connectedness, an ongoing sense of purpose, and the abilities to function independently, to
90 permit functional recovery from illness or injury, and to cope with residual functional
91 deficits’ [1]. The key components of cognitive health are mental abilities and acquired
92 skills, and the ability to apply these so as to engage in purposeful activity [2].

93

94 Loss of cognitive health is not an inevitable part of ageing. Some influences on cognitive
95 health, such as gender, genetic profile, history of chronic disease, early life experiences, and
96 the impact of socioeconomic adversity and limited educational opportunity [3,4] cannot be
97 directly modified. Nevertheless, cognitive plasticity - the capacity for enhancement of
98 function in response to altered inputs or environments - is retained to some degree even in
99 later life [5,6]. Furthermore, a systematic appraisal of evidence regarding risk and protective
100 factors for Alzheimer’s disease has yielded robust evidence for several

101 potentially-modifiable lifestyle factors associated with risk level: cognitive activity, social
102 engagement, physical activity, diet, alcohol consumption and smoking [7]. The contribution
103 of modifiable lifestyle factors to cognitive health means that there may be potential to
104 stabilise or improve declining trajectories of cognitive function. Targeting
105 potentially-modifiable lifestyle factors could have positive benefits for cognitive health in
106 later life and serve as a counterweight to elevated genetic risk [8].

107

108 In considering the potential for risk reduction, it is important to consider by what
109 mechanisms these lifestyle factors influence cognitive health. Few studies have explored the
110 potential mechanisms involved. Many of the factors identified as relevant to increasing
111 (smoking, high alcohol consumption) or reducing (healthy diet, physical exercise) risk of
112 dementia are equally relevant to other health conditions, particularly through their impact
113 on cardiovascular health [9]. Engagement in cognitive and social activity, however, appears
114 more directly linked to cognitive health.

115

116 The concept of cognitive reserve has been proposed to account for individual differences in
117 trajectories of cognitive health and rates of cognitive decline [10]. Cognitive reserve has
118 been defined as the ability of the brain to optimize or maximize performance through
119 differential recruitment of brain networks or use of alternative strategies [10]. Engagement

120 in mental activity, for example through undertaking education or working in occupations
121 that place complex demands, is a key determinant of level of cognitive reserve [11,12].
122 Cognitive reserve reflects the capacity to provide a buffer against the effects of
123 dementia-related brain pathology, so that a greater burden of pathology is needed before
124 signs of cognitive decline or symptoms of dementia become evident. It is possible that
125 lifestyle factors may exert their effects on risk by increasing the efficiency of neural
126 networks and hence enhancing cognitive reserve, resulting in greater resilience against the
127 effects of developing neuropathology [13,14]. Cognitive reserve is a latent construct that
128 cannot be directly measured, and assessment therefore relies on proxy indicators. Although
129 cognitive reserve is often indexed by a single proxy measure such as education or IQ,
130 recently emphasis has been placed on the need to combine multiple indicators [15].

131

132 This potential pathway via cognitive reserve may help to explain the association between
133 lifestyle factors and cognitive function, and thus inform the development of dementia
134 prevention or risk reduction strategies. An appropriate first step is to explore the
135 relationships between these constructs cross-sectionally to determine whether cognitive
136 reserve does indeed play a mediating role. Few empirical studies have investigated this
137 potential mediating pathway and, in particular, it has seldom been explored in large
138 epidemiological cohorts of older people. Furthermore, most studies have used a single

139 indicator of cognitive reserve, typically education; we could not find any previous studies to
140 date that have used a combined measure of cognitive reserve when examining the
141 relationship between lifestyle factors and cognition [15]. Identifying a mediating role for
142 cognitive reserve in the relationship between current lifestyle factors and cognition is
143 complex because it is likely that past lifestyle will also have influenced these relationships.
144 Therefore, care is needed in selecting appropriate indices to include in a proxy measure of
145 cognitive reserve. In this study, education and occupational complexity were incorporated in
146 a combined proxy measure.

147

148 In this cross-sectional analysis we aimed to explore the potential mediating effect of
149 cognitive reserve, indexed by a combination of educational level and occupational
150 complexity, on the association between lifestyle factors and cognitive function in later life,
151 using data from a large population-based cohort of healthy older people in Wales, United
152 Kingdom. We hypothesized that cognitive reserve would mediate the association between
153 potentially-modifiable lifestyle factors (cognitive activity, social engagement, physical
154 activity, diet, alcohol consumption and smoking) and cognitive function.

155

156 **Methods**

157 Study population

158 Ethical approval for data collection was granted by the North Wales Research Ethics
159 Committee (West). The Cognitive Function and Ageing Study Wales (CFAS-Wales) is a
160 longitudinal population-based study of people aged 65 and over in rural (Gwynedd and
161 Ynys Môn) and urban (Neath Port Talbot) areas of Wales that aims to investigate physical
162 and cognitive health in older age and examine the interactions between health, social
163 networks, activity and participation. Individuals aged 65 and over were randomly sampled
164 from general medical practice lists between 2011 and 2013, stratified by age to ensure equal
165 numbers in two age groups, 65-74 and 75+. The response rate, in terms of the proportion of
166 those eligible and contactable who participated, was 44%. A further 13% were unable to
167 participate due to ill-health. Those who provided written consent to join the study were
168 interviewed in their own homes by trained interviewers and could choose to have the
169 interview conducted through the medium of either English or Welsh. Participants were
170 followed up two years later. In this study we conducted cross-sectional analyses with data
171 from the first wave of interviews (data version 2.0).

172

173 While CFAS-Wales is linked to CFAS-II conducted in three sites in England, there are some
174 differences between the two studies in terms of measures used, and importantly for this
175 study, Wales has over the generations had a somewhat different education system from
176 England. The original CFAS included sites in both England and Wales, and the analysis

177 attempted to compensate for these differences, but given that this was already a
178 cross-sectional analysis it was considered preferable to ensure as homogeneous a population
179 as possible, and hence we restricted our analyses to CFAS-Wales data.

180

181 The baseline sample consisted of 3593 individuals. For the present analysis, it was
182 important to exclude people with cognitive impairment to avoid potential reverse causality.
183 We excluded anyone with a Mini-Mental State Examination [MMSE; 16] score ≤ 25 (N=908)
184 or an AGECAT (Copeland et al., 1986) classification of dementia (N=185). We also
185 excluded those with an AGECAT classification of depression (N=333), those living in
186 institutions (N=95), those without complete interview data (N=80) and those with missing
187 cognitive test scores (N=4). The sample for this study therefore included 2315 participants
188 from CFAS-Wales.

189

190 Measures

191 Cognitive function was measured by the CAMCOG, a brief neuropsychological battery
192 designed to assess a range of cognitive functions in the older population, with possible
193 scores ranging from 0 - 107 [17].

194

195 Cognitive reserve was measured by combining two proxy indicators: educational level

196 (years of full-time education) and occupational complexity. Main occupation was recoded
197 using social class and socioeconomic group systems and then re-classified into 15 groups
198 reflecting different levels of occupational complexity [18]. The weights for each component
199 were generated based on the interquartile range to ensure equal contributions to the
200 combined cognitive reserve score, resulting in the following formula:

201 $\text{Cognitive reserve score} = 1.7 \times (\text{years of education}) + 1 \times (\text{occupational complexity level}).$

202

203 Level of physical activity was determined by the reported frequency of engagement in 18
204 types of mild (light gardening, bowls, light housework, home repairs), moderate (gardening,
205 electric lawn mowing, cleaning the car, walking at a moderate pace, dancing, floor or
206 stretching exercises, heavy housework) and vigorous (jogging, swimming, cycling, aerobics
207 or gym, tennis, heavy gardening, manual lawn mowing) physical activity. A continuous
208 scale was generated using the frequency levels (0=once a year or less, 1=several times a
209 year, 2=several times a month, 3=several times a week, 4=every day or almost every day)
210 multiplied by the intensity ratio (mild: moderate: vigorous=1:2:3), which was based on the
211 metabolic equivalent of task (MET) ratio suggested in the literature [19].

212

213 Current and ex-smokers were identified using two questions: “Do you smoke?” and “Have
214 you ever smoked?”

215

216 Self-reported information on the frequency of alcohol consumption over the last 12 months
217 was used to classify participants into four groups: nearly abstinent (not at all in the last 12
218 months, once or twice a year); infrequent drinkers (once or twice a month, once every
219 couple of months); frequent light-to-moderate drinkers (once or twice a week, three or four
220 times a week); and regular light-to-moderate drinkers (five or six times a week, almost
221 every day).

222

223 To describe the overall dietary pattern, a total score for healthy diet was generated.

224 CFAS-Wales investigated the frequency of eating (never; seldom; once a week; 2-4 times a
225 week; 5-6 times a week; daily) and the number of servings per day of fresh fruit, green leafy
226 vegetables, other vegetables, fatty fish, other fish, wholemeal/brown bread and daily
227 servings of starch foods, dairy foods and sugary foods. This analysis focused on the
228 frequency of “Mediterranean-style” food intake including fresh fruit, green leafy vegetables,
229 other vegetables, fatty fish, other fish and wholemeal/brown bread. The frequency included
230 six levels: never, seldom, once a week, 2-4 times a week, 5-6 times a week, daily. Although
231 evidence has suggested that these are all beneficial components for dementia risk reduction,
232 the amounts and cut-offs selected considerably vary across studies ([20,21]). To describe
233 the overall dietary pattern, a total score for healthy diet was generated based on the six

234 levels of frequency. The range was between 2 (least frequent) and 30 (most frequent) and
235 the mean was 18.2 (std.: 4.4).

236

237 A summary score for cognitive and social activity was generated based on the frequency of
238 seven cognitive (listen to radio; read a newspaper; read a magazine; read a book; play
239 games such as cards or chess; do crosswords; do puzzles) and three social activities (“How
240 often do you see any of your (children or other) relatives to speak to?” “Do you attend
241 meetings or any community or social groups?” and “How often do you see any of your
242 neighbours to have a chat or do something with?”). We combined the scores for cognitive
243 and social activity as in many activities cognitive and social elements are closely
244 interlinked.

245

246 Covariates

247 Information about age, gender and presence of chronic conditions was obtained from the
248 interview. Five chronic conditions (hypertension, diabetes, stroke, heart attack, and head
249 injury) were considered to be confounding factors which might influence both lifestyle
250 factors and cognitive function [7,22,23].

251

252 Statistical analysis

253 The proportion of missing data was small (4%); instances of missing data are documented
254 in Table 1. Comparison of complete cases and those with missing data showed no
255 significant difference in cognitive function. A sensitivity analysis was conducted to
256 investigate the associations in multiple imputation datasets. Distributions were examined
257 prior to finalising the analysis plan.

258

259 Linear regression modelling was used to investigate the overall associations between each
260 lifestyle factor and cognitive function adjusting for demographic factors and chronic
261 conditions. Since the five lifestyle factors were likely to be correlated, a full model was
262 tested that included all lifestyle factors and covariates.

263

264 Mediation analysis was used to investigate the mechanisms underlying observed
265 relationships between exposures and outcomes and examine additional variables
266 hypothesised to be on the causal pathway [22, 23]. Based on the results for the overall
267 associations, the measure of smoking was re-categorised into two groups (current vs
268 ex-smokers/never) in the mediation analysis. The frequency of alcohol consumption was
269 treated as a continuous variable and the ‘trend’ (changes in cognitive function per increase
270 in frequency level) was tested in the mediation analysis. To investigate the potential
271 mediating effect of cognitive reserve on the association between lifestyle factors and
272 cognitive function, three pathways (*a*, *b*, *c*) were estimated using linear regression modelling
273 and adjusting for age, gender and chronic conditions (Fig 1) [24]. For each lifestyle factor,
274 direct and indirect effects were calculated using the STATA mediation analysis syntax
275 (`sgmediation`) with bootstrapping confidence intervals [25]. The percentage of indirect
276 pathways among the total effect was calculated to indicate the mediating effect of cognitive
277 reserve on the association between lifestyle factors and cognitive function. All the lifestyle
278 factors were included in one regression model to explore the overall indirect effect of
279 cognitive reserve. Adjusted R-squared was used to indicate the proportion of variance
280 explained by the independent variables. All measures were standardised to provide
281 comparable coefficients across different lifestyle factors.

282

283 **Fig 1. Mediating effect of cognitive reserve on the association between lifestyle factors**
284 **and cognitive function**

285

286 **Results**

287 Descriptive information for socio-demographic factors, cognitive function, chronic
288 conditions and lifestyle factors is shown in Table 1. Among the 2315 participants, the mean
289 age was 74 years (standard deviation (std.): 6.3) and 51% were women. The mean
290 CAMCOG score was 93.4 (std.: 5.4; median: 94; IQR: 7). The average score for cognitive
291 reserve was 28.6 (std.: 6.8) with a range between 9.7 and 62.0.

292 **Table 1. Distributions of socio-demographic factors, chronic conditions and lifestyle factors (N=2315)**

Categorical measures		N (%)	Continuous measures	Mean (std)	Range
Sex	Men	1132 (48.9)	Age (year)	73.5 (6.3)	(65,100)
	Women	1183 (51.1)	Years of education (missing=6) (year)	12.0 (2.8)	(1, 30)
Chronic conditions (missing=7)	Hypertension	1102 (47.7)	Occupational complexity (missing=63) (level)	8.1 (3.3)	(1, 14)
	Diabetes	384 (16.6)	Cognitive function – CAMCOG (score)	93.4 (5.4)	(63, 105)
	Stroke	124 (5.4)	Physical activity (missing=5) (composite score)	19.8 (14.0)	(0, 87)
	Heart attack	196 (8.5)		Diet (missing=4) (composite score)	18.2 (4.4)
	Head injury	217 (9.4)	Cognitive and social activity (missing=12) (composite score)	32.1 (6.2)	(10, 49)
Smoking (missing=9)	Never	981 (42.5)			
	Current smoker	1128 (48.9)			
	Ex-smoker	197 (8.5)			
Alcohol consumption (missing=10)	Nearly abstinent	606 (26.3)			
	Infrequent	418 (18.1)			
	Frequent	784 (34.0)			
	Regular	497 (21.6)			

293 Table 2 reports the overall association between cognitive function and the
294 potentially-modifiable lifestyle factors. Apart from smoking, all the lifestyle factors were
295 significantly associated with cognitive function after adjusting for age, sex and chronic
296 conditions. Current smoking had negative associations with cognitive function but the
297 differences did not achieve statistical significance. As shown under model 3 in Table 2,
298 people who reported higher levels of cognitive and social activity (0.20; 95% CI: 0.16, 0.24),
299 higher levels of physical activity (0.11; 95% CI: 0.07, 0.15), and healthier dietary patterns
300 (0.13; 95% CI: 0.09, 0.17) had higher CAMCOG scores. There was a dose-response
301 relationship between cognitive function and frequency of alcohol consumption, with regular
302 light-to-moderate drinkers having higher average CAMCOG scores (0.34; 95% CI: 0.23,
303 0.46) than abstainers. In the full model including all the lifestyle factors (Model 4),
304 significant associations with cognitive and social activity, physical activity, healthy diet and
305 regular light-to-moderate alcohol consumption remained apparent but the effect sizes
306 slightly reduced. The estimate of adjusted R-squared shows that including all the lifestyle
307 factors explained about 5% of the variation in cognitive function.

308

309

310 **Table 2. Associations between lifestyle factors and cognitive function**

	Model 1	Model 2	Model 3	Model 4
	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)
Physical activity	0.20 (0.16, 0.24)	0.12 (0.08, 0.16)	0.11 (0.07, 0.15)	0.06 (0.01, 0.10)
p-value*	<0.01	<0.01	<0.01	0.01
Smoking: Ex-smoker vs never	0.11 (0.02, 0.20)	0.05 (-0.04, 0.13)	0.05 (-0.03, 0.14)	0.02 (-0.06, 0.10)
Smoking: Current smoker vs never	0.09 (-0.06, 0.25)	-0.05 (-0.19, 0.10)	-0.03 (-0.18, 0.12)	0.05 (-0.09, 0.20)
p-value*	0.04	0.32	0.30	0.77
Alcohol: Infrequent vs nearly abstinent	0.29 (0.16, 0.41)	0.19 (0.07, 0.31)	0.17 (0.05, 0.29)	0.11 (-0.01, 0.22)
Alcohol: Frequent vs nearly abstinent	0.41 (0.30, 0.51)	0.27 (0.16, 0.36)	0.24 (0.13, 0.34)	0.16 (0.06, 0.27)
Alcohol: Regular vs nearly abstinent	0.47 (0.35, 0.58)	0.37 (0.26, 0.48)	0.34 (0.23, 0.46)	0.26 (0.15, 0.38)
p-value*	<0.01	<0.01	<0.01	<0.01
Diet	0.14 (0.10, 0.18)	0.14 (0.10, 0.17)	0.13 (0.09, 0.17)	0.08 (0.04, 0.12)
p-value*	<0.01	<0.01	<0.01	<0.01
Cognitive and social activity	0.20 (0.16, 0.24)	0.20 (0.16, 0.24)	0.20 (0.16, 0.24)	0.17 (0.13, 0.21)
p-value*	<0.01	<0.01	<0.01	<0.01

311

312 *the overall p-value for the given lifestyle factor. Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, hypertension, diabetes,

313 stroke, heart attack, head injury; Model 4: full model including all lifestyle factors, age, sex, hypertension, diabetes, stroke, heart attack, head injury

314 Table 3 reports estimates for the three paths a (association between lifestyle factors and
315 cognitive reserve), b (association between cognitive reserve and cognitive function), and c
316 (association between lifestyle factors and cognitive function), and the percentage of indirect
317 effect (a to b) among the overall associations. Dietary pattern had the strongest indirect
318 effect (0.05; 95% CI: 0.04, 0.06) compared to the other lifestyle factors; the indirect effect
319 identified ranged from 36% for diet to 15% for cognitive and social activity. Although
320 smoking showed a potential indirect effect (-0.05; 95% CI: -0.09, -0.02), the association
321 between smoking and cognitive function was not significant.

322 **Table 3. Mediation analysis of the effects of cognitive reserve on the association of lifestyle factors with cognitive function**

	Path a (Association between lifestyle factor and cognitive reserve)			Path b (Association between cognitive reserve and cognitive function)			Path c (Association between lifestyle factor and cognitive function)			Indirect effect (a to b)	% of indirect effect
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3		
	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)	Coeff. (95% CI)		
Physical activity	0.11 (0.07, 0.16)	0.11 (0.06, 0.15)	0.09 (0.05, 0.14)	0.25 (0.21, 0.29)	0.24 (0.20, 0.28)	0.24 (0.20, 0.28)	0.17 (0.13, 0.21)	0.09 (0.05, 0.13)	0.08 (0.04, 0.12)	0.02 (0.01, 0.03)	21%
Smoking (current vs never/ex-smokers)	-0.20 (-0.35, -0.05)	-0.22 (-0.37, -0.07)	-0.20 (-0.35, -0.06)	0.27 (0.23, 0.31)	0.25 (0.21, 0.29)	0.25 (0.21, 0.28)	0.08 (-0.06, 0.22)	-0.02 (-0.16, 0.11)	-0.01 (-0.15, 0.12)	-0.05 (-0.09, -0.02)	-
Alcohol (higher vs lower frequency)	0.14 (0.10, 0.17)	0.14 (0.10, 0.17)	0.13 (0.09, 0.17)	0.25 (0.21, 0.29)	0.23 (0.20, 0.27)	0.24 (0.20, 0.28)	0.13 (0.09, 0.16)	0.09 (0.05, 0.12)	0.08 (0.05, 0.12)	0.03 (0.02, 0.04)	26%
Diet	0.21 (0.17, 0.25)	0.21 (0.17, 0.26)	0.21 (0.16, 0.25)	0.25 (0.21, 0.29)	0.23 (0.19, 0.27)	0.23 (0.19, 0.27)	0.09 (0.05, 0.13)	0.09 (0.05, 0.13)	0.08 (0.05, 0.12)	0.05 (0.04, 0.06)	36%
Cognitive and social activity	0.13 (0.09, 0.17)	0.13 (0.09, 0.18)	0.13 (0.09, 0.17)	0.25 (0.21, 0.29)	0.23 (0.19, 0.27)	0.23 (0.19, 0.27)	0.17 (0.13, 0.21)	0.17 (0.13, 0.21)	0.17 (0.13, 0.21)	0.03 (0.02, 0.04)	15%

323 Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, hypertension, diabetes, stroke, heart attack, head injury

324

325 Four lifestyle factors - cognitive and social activity, physical activity, regular
326 light-to-moderate alcohol consumption and healthy diet - had both direct (0.31; 95% CI: 0.24,
327 0.45) and indirect (0.08; 95% CI: 0.07, 0.11) associations with cognitive function. The
328 proportion of the total (direct plus indirect) effect of the four lifestyle factors that was
329 mediated by cognitive reserve was 21% (0.08; 95% CI: 0.06, 0.10) (Fig 2A). This full model
330 explained 20% (adjusted R-square=0.21) of the variation in cognitive function across the
331 CFAS-Wales participants. Fig 2B and Fig 2C show the mediating effects of individual
332 cognitive reserve components (years of education and occupational complexity) on the
333 associations between cognitive reserve and lifestyle factors. Although the results were similar
334 to those for the combined cognitive reserve score, the effect sizes for the indirect pathways
335 were smaller in these models. The results of sensitivity analysis from the imputed datasets
336 were similar to the main analysis and therefore the impact of missing data was small.

337

338 **Fig 2. Associations between lifestyle factors, cognitive reserve and cognitive function**
339 **(adjusted for age, gender and chronic conditions)**

340

341 **Discussion**

342 This study investigated the potential mediating effect of cognitive reserve on the association
343 between cognitive function and potentially-modifiable lifestyle factors through cross-sectional
344 analysis of data from a population-based cohort of older people in Wales. The hypothesis that
345 cognitive reserve plays a mediating role was largely supported. Cognitive and social activity,

346 physical activity, regular light-to-moderate alcohol consumption, and healthy diet were all
347 positively associated with cognitive function, and together accounted for 20% of the variance
348 in cognitive test scores. Smoking, however, was not associated with cognitive function. The
349 results of the mediation analysis showed that cognitive reserve, indexed by education and
350 occupational complexity, was an important mediator of the association between the four
351 lifestyle factors and cognition, with indirect effects via cognitive reserve contributing 21% of
352 the overall effect.

353

354 This study confirms the relevance of potentially-modifiable lifestyle factors for cognition in
355 later life, and in line with other reports emphasizes the possibilities this affords for supporting
356 the maintenance of cognitive health [7,22,26]. Our results are consistent with previous
357 cross-sectional and longitudinal findings on cognitive and social activity. Cognitive activity
358 may reduce risk of dementia [27], while aspects of social engagement are associated with
359 better cognitive function in later life, and possibly with reduced risk of dementia [28].

360 Similarly, most observational studies of the effects of physical activity on cognition show an
361 association between higher levels of physical activity and lower rates of cognitive decline or
362 dementia [27,29]. Our measure of healthy diet included fruit, vegetable and fish intake.

363 Research on healthy diets emphasises the benefits of vegetable consumption and adherence to
364 a Mediterranean-style diet [30-32] as protective of cognitive health, although only oily fish

365 consumption was identified as significant in a systematic review of risk factors [7]. Our
366 findings on alcohol intake are similar to those of studies reporting that light-to-moderate
367 alcohol intake is associated with lower risk than abstaining [33-35], although recent research
368 suggests that while frequent drinking earlier in life is significantly associated with increased
369 risk compared to infrequent drinking, abstaining is not [36]. Smoking, although commonly
370 identified as a risk factor, was not significantly associated with cognitive function in the
371 present study after adjusting for possible confounds.

372

373 This study also provides evidence that contributes to explaining the mechanisms underlying
374 the association between these lifestyle factors and cognition, and supports the view that
375 cognitive reserve plays an important role in this relationship. Cognitive reserve increases
376 resilience against the effects of neuropathology and hence supports maintenance of function
377 in later life [11]. Cognitive reserve is not a static property, but rather is thought to evolve
378 throughout the lifecourse [12], and lifestyle choices may contribute to protecting older people
379 against cognitive decline and dementia by supporting the development, connectivity and
380 maintenance of brain networks.

381

382 The study has several limitations that must be borne in mind. These are cross-sectional data
383 and hence we cannot infer causal relationships. Longitudinal follow-up may provide

384 additional information, while comparison of those with high and low cognitive reserve would
385 indicate whether there are differences in lifestyle that distinguish the two groups, or
386 alternatively whether cognitive reserve counteracts the effects of a less active cognitive
387 lifestyle. Evaluating these relationships is particularly complex because lifestyle factors such
388 as past engagement in cognitive and social activity may have influenced and contributed to
389 current levels of cognitive reserve. Indeed, some approaches to assessing cognitive reserve
390 include evaluation not only of past but also of current engagement in such activities as part of
391 the proxy cognitive reserve measure [15]. Conceptually, therefore, cognitive lifestyle and
392 cognitive reserve become difficult to distinguish, and this creates challenges for
393 understanding the mechanisms underlying observed associations. We addressed this possible
394 circularity by using only educational level and occupational complexity, two aspects of past
395 experience likely to be relatively stable, in our combined measure of cognitive reserve. As a
396 latent construct, cognitive reserve is difficult to assess accurately, and while evidence suggests
397 that combined proxy measures are more appropriate than single indicators such as educational
398 level, there is as yet no consensus about an optimal approach to measurement. The two
399 indicators we used might be subject to reporting or recall bias or, in the case of occupation,
400 influenced by changing circumstances. Our proxy measure was, therefore, a relatively crude
401 measure. The implication of this is that our findings are likely if anything to underestimate the
402 relationship of cognitive reserve to cognitive function and the extent to which cognitive

403 reserve mediates the association between lifestyle and cognitive function. However, there is a
404 need for greater clarity and consensus about the contributors to and measurement of cognitive
405 reserve, and for enhanced study designs that can truly tease out the complexities of the
406 associations between lifestyle factors, cognitive reserve and cognition.

407

408 We excluded people with cognitive impairment to reduce the risk of reverse causality, but it is
409 important to remember that people in the very early stages of cognitive decline may withdraw
410 from social contacts and other types of activity, and may change dietary and other habits.

411 Therefore the potential effects of reverse causality cannot be completely ruled out.

412 Assessment of lifestyle factors was based on self-report during interview and could be subject
413 to bias. In relation to alcohol consumption, the absence of self-reports of heavy drinking or
414 concerns about alcohol in the CFAS-Wales sample in particular might raise questions about
415 possible bias, but it is important to note that only 3 participants (0.1%) were considered by the
416 interviewer to have a possible drink problem. Assessment of cognitive function was limited to
417 a global score and a more fine-grained neuropsychological assessment might reveal more
418 specific associations with particular aspects of cognitive function. There were some missing
419 data, but the extent of this was small and is unlikely to have influenced the findings. Despite
420 these limitations, the particular strength of the study is that it draws on data from a large
421 contemporary population-based cohort of older people in the United Kingdom.

422

423 Conclusions

424 The findings of this study are consistent with the hypothesis that significant associations
425 between four potentially-modifiable lifestyle factors – cognitive and social activity, physical
426 activity, healthy diet and regular light-to-moderate alcohol consumption – and cognition in
427 later life are mediated by level of cognitive reserve. As these findings are derived from
428 cross-sectional data, confirmation from longitudinal analyses will be required. However, these
429 findings provide support for the possibility that enhancing cognitive reserve throughout the
430 lifespan, and encouraging participation in cognitive, social and physical activity and a healthy
431 diet, may help maintain cognitive health in later life.

432

433 **Acknowledgements**

434 The CFAS-Wales Study group includes Principal Investigators R.T Woods, L.Clare, G.Windle,

435 V. Burholt, J. Philips, C. Brayne, C. McCracken, K. Bennett, and F. Matthews.

436 We are grateful to the NISCHR Clinical Research Centre for their assistance in tracing

437 participants and in interviewing and in collecting blood samples, and to general practices in

438 the study areas for their cooperation.

439 **References**

- 440 1. Hendrie HC, Albert MS, Butters MA, Gao S, Knopman DS, Launer LJ, et al. The NIH
441 cognitive and emotional health project: report of the critical evaluation study committee.
442 *Alzheimer's & Dementia*. 2006;2(1):12-32. doi: 10.1016/j.jalz.2005.11.004.
- 443 2. Centers for Disease Control and Prevention and the Alzheimer's Association. The
444 Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health.
445 2007. doi: 10.1037/e664002007-001.
- 446 3. Polidori MC, Nelles G, Pientka L. Prevention of dementia: focus on lifestyle.
447 *International journal of Alzheimer's disease*. 2010;2010. doi: 10.4061/2010/393579
- 448 4. Scazufca M, Almeida OP, Menezes PR. The role of literacy, occupation and income in
449 dementia prevention: the São Paulo Ageing & Health Study (SPAH). *International*
450 *Psychogeriatrics*. 2010;22(08):1209-15. doi: 10.1017/S1041610210001213.
- 451 5. Hertzog C, Kramer AF, Wilson RS, Lindenberger U. Enrichment effects on adult
452 cognitive development can the functional capacity of older adults be preserved and enhanced?
453 *Psychological science in the public interest*. 2008;9(1):1-65. doi:
454 10.1111/j.1539-6053.2009.01034.x.
- 455 6. Van Muijden J, Band GP, Hommel B. Online games training aging brains: limited
456 transfer to cognitive control functions. *Frontiers in human neuroscience*. 2012;6:141-54. doi:
457 10.3389/fnhum.2012.00221
- 458 7. Anstey KJ, Cherbuin N, Herath PM. Development of a new method for assessing global
459 risk of Alzheimer's disease for use in population health approaches to prevention. *Prevention*
460 *Science*. 2013;14(4):411-21. doi: 10.1007/s11121-012-0313-2
- 461 8. Rovio S, Kåreholt I, Helkala E-L, Viitanen M, Winblad B, Tuomilehto J, et al.
462 Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease.
463 *The Lancet Neurology*. 2005;4(11):705-11. doi: 10.1016/S1474-4422(05)70198-8
- 464 9. Blazer DG, Yaffe K, Liverman CT, Committee on the Public Health Dimensions of
465 Cognitive Aging, Board on Health Sciences Policy, Institute of Medicine. *Cognitive aging:
466 Progress in understanding and opportunities for action*. Washington, D.C.: National
467 Academies Press; 2015.
- 468 10. Stern Y. What is cognitive reserve? Theory and research application of the reserve
469 concept. *Journal of the International Neuropsychological Society*. 2002;8(03):448-60. doi:
470 10.1017/S1355617702813248.
- 471 11. Stern Y. The concept of cognitive reserve: a catalyst for research. *Journal of clinical and*
472 *experimental neuropsychology*. 2003;25(5):589-93. doi: 10.1076/jcen.25.5.589.14571.
- 473 12. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review.
474 *Psychological medicine*. 2006;36(04):441-54. doi: 10.1017/s0033291705006264.
- 475 13. Richards M, Deary IJ. A life course approach to cognitive reserve: a model for cognitive

476 aging and development? *Annals of neurology*. 2005;58(4):617-22. doi: 10.1002/ana.20637.

477 14. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nature Reviews*

478 *Neuroscience*. 2008;9(7):568-78. doi: 10.1038/nrn2421.

479 15. Opdebeeck C, Martyr A, Clare L. Cognitive reserve and cognitive function in healthy

480 older people: a meta-analysis. *Aging, Neuropsychology, and Cognition*. 2015;23(1):40-60. doi:

481 10.1080/13825585.2015.1041450.

482 16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for

483 grading the cognitive state of patients for the clinician. *Journal of psychiatric research*.

484 1975;12(3):189-98. doi:

485 10.1002/(SICI)1099-1166(199805)13:5<285::AID-GPS753>3.0.CO;2-V.

486 17. Huppert FA, Brayne C, Gill C, Paykel E, Beardsall L. CAMCOG—A concise

487 neuropsychological test to assist dementia diagnosis: Socio- demographic determinants in an

488 elderly population sample. *British Journal of Clinical Psychology*. 1995;34(4):529-41. doi:

489 10.1111/j.2044-8260.1995.tb01487.x.

490 18. Valenzuela MJ, Brayne C, Sachdev P, Wilcock G. Cognitive lifestyle and long-term risk

491 of dementia and survival after diagnosis in a multicenter population-based cohort. *American*

492 *journal of epidemiology*. 2011;173(9):1004-12. doi: 10.1093/aje/kwq476.

493 19. Aaron DJ, Dearwater SR, Anderson R, Olsen T, Kriska AM, Laporte RE. Physical

494 activity and the initiation of high-risk health behaviors in adolescents. *Medicine & Science in*

495 *Sports & Exercise*. 1995. doi: 10.1249/00005768-199512000-00010.

496 20. Barberger-Gateau P, Letenneur L, Deschamps V, Pérès K, Dartigues J-F, Renaud S. Fish,

497 meat, and risk of dementia: cohort study. *BMJ*. 2002;325(7370):932-3. doi:

498 10.1136/bmj.325.7370.932.

499 21. Albanese E, Dangour AD, Uauy R, Acosta D, Guerra M, Guerra SSG, et al. Dietary fish

500 and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research

501 Group population-based study. *The American Journal of Clinical Nutrition*.

502 2009;90(2):392-400. doi: 10.3945/ajcn.2009.27580.

503 22. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention

504 of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology*.

505 2014;13(8):788-94. doi: 10.1016/s1474-4422(14)70136-x.

506 23. Richard E, Van den Heuvel E, van Charante EPM, Achthoven L, Vermeulen M, Bindels

507 PJ, et al. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized

508 trial in progress. *Alzheimer Disease & Associated Disorders*. 2009;23(3):198-204. doi:

509 10.1097/wad.0b013e31819783a4.

510 24. Zhao X, Lynch JG, Chen Q. Reconsidering Baron and Kenny: Myths and truths about

511 mediation analysis. *Journal of consumer research*. 2010;37(2):197-206. doi: 10.1086/651257.

512 25. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in

513 simple mediation models. *Behavior research methods, instruments, & computers*.

514 2004;36(4):717-31. doi: 10.3758/bf03206553.

515 26. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities
516 in healthy life years in the 25 countries of the European Union in 2005: a cross-national
517 meta-regression analysis. *The Lancet*. 2009;372(9656):2124-31. doi:
518 10.1016/s0140-6736(08)61594-9.

519 27. Plassman BL, Williams JW, Burke JR, Holsinger T, Benjamin S. Systematic review:
520 factors associated with risk for and possible prevention of cognitive decline in later life.
521 *Annals of Internal Medicine*. 2010;153(3):182-93. doi:
522 10.7326/0003-4819-153-3-201008030-00258.

523 28. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in
524 late life might protect against dementia. *The Lancet Neurology*. 2004;3(6):343-53. doi:
525 10.1016/s1474-4422(04)00767-7.

526 29. Rolland Y, van Kan GA, Vellas B. Physical activity and Alzheimer's disease: from
527 prevention to therapeutic perspectives. *Journal of the American Medical Directors Association*.
528 2008;9(6):390-405. doi: 10.1016/j.jamda.2008.02.007.

529 30. Morris M, Evans D, Tangney C, Bienias J, Wilson R. Associations of vegetable and fruit
530 consumption with age-related cognitive change. *Neurology*. 2006;67(8):1370-6. doi:
531 10.1212/01.wnl.0000240224.38978.d8.

532 31. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease,
533 and vascular mediation. *Archives of neurology*. 2006;63(12):1709-17. doi:
534 10.1001/archneur.63.12.noc60109.

535 32. Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a
536 systematic review of cohort studies. *The journal of nutrition, health & aging*.
537 2012;16(7):626-30. doi: 10.1007/s12603-012-0097-x.

538 33. Letenneur L. Risk of dementia and alcohol and wine consumption: a review of recent
539 results. *Biological research*. 2004;37(2):189-93. doi: 10.4067/s0716-97602004000200003.

540 34. Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of
541 dementia. *Journal of the American Geriatrics Society*. 2004;52(4):540-6. doi:
542 10.1111/j.1532-5415.2004.52159.x.

543 35. Neafsey EJ, Collins MA. Moderate alcohol consumption and cognitive risk.
544 *Neuropsychiatric disease and treatment*. 2011;7:465. doi: 10.2147/ndt.s23159.

545 36. Langballe EM, Ask H, Holmen J, Stordal E, Saltvedt I, Selbæk G, et al. Alcohol
546 consumption and risk of dementia up to 27 years later in a large, population-based sample: the
547 HUNT study, Norway. *European journal of epidemiology*. 2015;30(9):1049-56. doi:
548 10.1007/s10654-015-0029-2.

549

550

551 **Supporting Information**

552 S1 STROBE Checklist

553