



Cognitively stimulating activities and risk of probable dementia or cognitive impairment in the English Longitudinal Study of Ageing

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ABSTRACT

Objectives: To examine the association between cognitive stimulating activities (CSA) in later life (internet/email use, employment, volunteering, evening classes, social club membership and newspaper reading) and risk of cognitive impairment or dementia using marginal structural models to account for time-varying confounding affected by prior exposure.

Methods: Data were used from the English Longitudinal Study of Ageing waves 1 (2002) to 7 (2014), a nationally representative sample of adults in England aged ≥ 50 . Self-reported participation in CSAs were measured as binary exposures from waves 2 (2004) to 6 (2012), with final sample sizes between $n = 3937$ and $n = 2530$ for different CSAs. Baseline exposure and covariates were used to create inverse probability of treatment and censoring weights (IPTCW). IPTCW repeated measures Poisson and linear regression were used to estimate each CSAs effect on risk of probable cognitive impairment or dementia at wave 7 (defined as a score of $\leq 11/27$ on a modified telephone interview for cognitive status (TICS-27)). Results were compared to standard regression adjustment.

Results: Internet use at any wave (Risk ratios between 0.62 and 0.69) and volunteering in waves 3 to 6 (RRs between 0.516 and 0.633) were associated with reduced risk of cognitive impairment in IPTCW models. Standard estimates were similar for both internet use and volunteering.

Newspaper reading (RR 95% Confidence interval 0.74–0.99) and social club membership (RR 95% CI 0.54–0.86) at wave 6 were significantly associated with risk of cognitive impairment in standard models, but not in the IPTCW models (RR 95% CI 0.82–1.11 and 0.60–1.08 respectively). Employment and evening classes were not associated with cognitive impairment in either model.

Conclusions: We found that volunteering and internet use were associated with reduced risk of cognitive impairment. Associations between newspaper reading or social club membership and cognitive impairment may be due to time-varying confounding affected by prior exposure.

1. Introduction

Dementia and cognitive impairment are now clearly established as a key global health problem (Livingston et al., 2017; Wittchen et al., 2011). Cognitively stimulating activities (CSA) have been suggested as an important potential preventative strategy against cognitive decline and dementia (Sajeed et al., 2016; Yates, Ziser, Spector, & Orrell, 2016). However, there has been ongoing debate regarding the association between CSA and cognitive function. CSA have been defined by the Global Council on Brain Health as 'mentally engaging activities or exercises that challenge a person's ability to think' (Global Council On Brain Health,

2017). This broad definition could include a wide range of activities such as those which are occupational or leisure, social or individual, targeted interventions or past-times and hobbies. Cognitive activity is the dementia prevention strategy most commonly identified by members of the adult population in industrialized Western countries (Friedman et al., 2015). Accordingly, it is common for older adults to report engaging in CSA with the intention of reducing their risk of dementia (Anderson, McCaul, & Langley, 2011; Hosking, Sargent-Cox, & Anstey, 2015).

It is therefore important to understand whether these activities are effective to inform public health interventions and the individual

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choices of older adults. However, conducting randomized controlled trials (RCTs) on the effect of CSA on cognitive function is very challenging due to the required length of follow-up, recruiting the necessary number of participants and cross-over effects from how participants spend their leisure time. As a result there are few RCTs in this area, and each uses its own specially designed intervention, not activities already available to community dwelling older adults (Kivipelto, Mangialasche, & Ngandu, 2018). This makes appropriate inferences from observational data particularly important.

Whilst most observational studies have found a positive association between CSA and cognition, some do not show protective effects (Aartsen, Smits, van Tilburg, Knipscheer, & Deeg, 2002, pp. P153–P162; Gow, Corley, Starr, & Deary, 2012; Mitchell et al., 2012). One reason may be that most studies have used composite measures including a wide range of CSA, such as reading, puzzles, participation in social organizations, cultural activities or formal education. It is possible that the protective effects seen for composites scores may not be due to overall activity levels, but specific activities included in some scores but not others. Another potential explanation for the discrepancy is reverse causation, that is to say it is better cognitive performance which predicts CSA (Gow et al., 2012). It has been estimated that the association between CSA and dementia could potentially be explained by reverse causation, but that it is not likely to be due to unobserved confounding (Sajeev et al., 2016).

If present, reverse causation could be time invariant, as in the case of childhood intelligence (Gow et al., 2012). However, there may also be time-varying confounding present (Robins, Hernan, & Brumback, 2000; VanderWeele, Hawkey, Thisted, & Cacioppo, 2011). Those with declining cognition are less likely to continue engagement in CSA (Aartsen et al., 2002, pp. P153–P162). So, if CSA improves cognition and cognition makes CSA exposure more likely, a longitudinal pattern of feedback between CSA and cognition is created. In this pattern, CSA and cognition at any one time have a causal relationship with CSA and cognition at future times. As common causes of future cognition and future CSA, past CSA and past cognition confound the association between future cognition and CSA. If you want to know the effect of both past and future CSA on future cognition using standard regression adjustment, you are now left with an uncomfortable choice. If you condition on past cognition then you stop it confounding the association between future CSA and future cognition, but you also block any effect of past CSA mediated via past cognition. If you don't condition on past cognition, then you allow the full effect of past CSA on future cognition but you leave past cognition confounding the association between future CSA and future cognition.

Marginal structural models (MSMs) were developed to address this type of time-varying confounding affected by prior exposure where standard regression methods cannot (Robins et al., 2000). MSMs estimated with inverse probability of treatment weights (IPTW) are a means of, under strict assumptions, making causal inferences from observational data (Robins et al., 2000). Even in the absence of complete adherence to those assumptions, they can still be seen as a progression on standard linear regression, by relaxing the assumption of no time varying confounding affected by prior exposure. Whilst gaining broad use across epidemiology in general, they have seen relatively limited application specifically in the field of cognitive ageing (Barnes et al., 2010; Marden, Tchetgen Tchetgen, Kawachi, & Glymour, 2017; Yao & Meng, 2015).

We sought to test whether the association between CSA and cognitive impairment of dementia was due to time-varying confounding affected by prior exposure, whilst also examining specific CSA rather than composite scores. We hypothesized that exposure to CSA will be associated with risk of dementia or impaired cognitive function using standard regression with covariate adjustment, but that this association will be attenuated or not observed in inverse probability of treatment weighted marginal structural models.

2. Materials and methods

2.1. Participants and Procedure

The English Longitudinal Study of Ageing has been described in detail elsewhere (Banks et al., 2016; Steptoe, Breeze, Banks, & Nazroo, 2013). The study sample was drawn from participants in Health Survey for England (HSE) years 1998, 1999 and 2001 who were born before March 1, 1952 and living in a private household or those in their households who were new partners. The initial sample was nationally representative of the age specific English population. Additional recruitment was undertaken in waves 3 and 4, but these participants were not included in the current analysis due to the inverse probability weighting used requiring a fully observed exposure history. Data was collected in biennial sweeps by interview in the participants homes. For this analysis data from waves 1 (2002) was used as baseline. Exposure to CSA used were from waves 2 to 6 (2004–2012) and the outcome from wave 7 (2014).

The size of the initial sample of core members at wave 1 was 11992, falling to 4062 by wave 7. Only data from participants present at all waves with full exposure and outcome data were utilized in the final analysis, resulting in final sample sizes between $n = 3937$ and $n = 2530$ being included in the final analysis for each CSA.

There was no formal process for the involvement of patients or public in the design and conduct of our analysis, but the ELSA database used has active participant involvement as part of its ongoing development process. Ethical approval for ELSA was granted by the South Central Berkshire Research Ethics Committee through an application to the National Research Ethics Service (Bridges, Hussey, & Blake, 2015). The current study was subject to the University of Manchester internal review process and no additional approval deemed necessary.

2.2. Outcome measure

The primary outcome was probable dementia or cognitive impairment at wave 7 diagnosed using questions from a modified telephone interview for cognitive status (TICS) (Crimmins, Kim, Langa, & Weir, 2011; Langa et al., 2017). For this a 27 point scale is generated using immediate and delayed 10 word free recall, backwards counting from 20 and serial 7 subtraction. The scoring system used has previously been validated in the Ageing, Demographics and Memory sub-study of the Health and Retirement Survey (Langa, Kabeto, & Weir, 2010). Scores of 0–6 are classified as dementia, 7–11 cognitive impairment no-dementia and 12–27 as normal (Tampubolon, Nazroo, & Pendleton, 2017). For this analysis we created a binary outcome of probable dementia or cognitive impairment (0–11) and non-impaired (12–27). As a secondary outcome we used the continuous TICS-27 score, where a higher score indicates better cognitive function.

2.3. CSA exposures

ELSA respondents report on a wide range of CSAs. We chose 6 CSAs from the range of activities reported by ELSA participants to represent variation in older adult's lifestyles and the type of cognitive challenge presented by the task (see Supplementary Information file for the reasons for choosing these 6 CSAs). We chose CSA where it is relatively clear how an intervention might be designed to alter an individual's exposure. This was an additional reason to avoid using a composite CSA score, because the intervention to increase one individual's CSA score could be completely different to another individual. This makes it unclear what effect is being estimated. The CSAs chosen were working, volunteering, regular newspaper reading, attending arts/music/evening classes (hereafter 'evening classes'), internet or email use and attending a social club. All of these activities have been previously found to have an association with cognitive function.

Being in work, often framed as later retirement, has been found in

some (though not all) studies to be related to less cognitive decline and slower decline once the individual does retire (Meng, Nexø, & Borg, 2017; Then et al., 2014). A positive association between volunteering and cognitive function was identified by Guiney and Machado in their review article (Guiney & Machado, 2018). They theorized that this may be because volunteering is a multi-domain exposure involving cognitive, social and physical activity. They also found that the better quality the study, the stronger the association seemed to become. Regular reading and attending evening classes are often included in measures of cognitive enrichment, which have largely been associated with better cognition (Sajeev et al., 2016; Yates et al., 2016; Zhu, Qiu, Zeng, & Li, 2017). Personal internet use has been identified as potentially preventing cognitive decline and mild cognitive impairment (Liapis & Harding, 2017). It has also previously been shown to be associated with lower dementia risk in ELSA using standard Cox regression (D'Orsi et al., 2017). Social activity has been linked to cognitive decline or dementia risk by some studies (Brown et al., 2012; Gleit et al., 2005; Marioni et al., 2015). Social clubs are only a small part of overall social activity. However, we used social club membership as an exposure because it can be used as an intervention to increase social activity amongst older adults (Hikichi, Kondo, Takeda, & Kawachi, 2017).

For working and volunteering participants were asked in the main ELSA interview 'Did you do any of these activities in the last month?'. Participants attending evening classes and social clubs were asked in a separate self-completion questionnaire 'Are you a member of any of these organizations, clubs or societies?'. 'I read a daily newspaper' and 'I use the internet and/or email' were response options for the question 'Which of these statements apply to you?' which was also in the self-completion questionnaire. Exposure at wave 1 was treated as a baseline variable and waves 2–6 were used to measure time-varying exposure (a maximum of 8 years exposure).

2.4. Covariates

Due to the large number of exposures, a wide range of potential covariates were considered that might plausibly confound the association between exposure and outcome. Across all exposures the time invariant covariates used were gender, centered date of birth, highest educational qualification achieved, 5-category social class, age of finishing formal education, income quintile, wealth quintile, ethnicity (white or non-white), and parental household structure, occupational classification and smoking. The time varying covariates were whether the participant was above retirement age, participation in other activities as described above, activities of daily living, caring, homemaking, self-rated health, self-rated hearing, self-rated eyesight, marital status, diagnosed chronic diseases including psychiatric illness, depression (score of modified center for epidemiological studies scale), number of cigarettes smoked per day (0, 1–10, 11–19 or 20), vigorous, moderate and light exercise and cognitive function. Verbal fluency (number of animals named in one minute) and episodic memory (sum score of immediate and delay recall of a 10-word list) were used as longitudinal measures of cognitive function.

2.5. Statistical analysis

To test for an association between each CSA and risk of cognitive impairment, whilst accounting for time variable confounding affected by prior exposure, we used inverse probability of treatment and censoring weighted (IPTCW) models. The statistical motivation for this is provided in the theory section below. In practice, a forward selection process was used to identify a unique set of covariates which predicted exposure to CSA at the next wave for each wave for each individual CSA. Covariates which were consistently associated with odds of CSA exposure across different waves were used to form a single model predicting CSA across all the ELSA waves. The odds of exposure to CSA were calculated using logistic regression for each time point and CSA

separately. Estimates from this model were used to calculate a non-stabilized IPTW for each person at each wave (Hernán & Robins, 2006; Robins et al., 2000). An interaction term between prior CSA exposure and episodic memory/verbal fluency were not included because IPTW MSMs are unable to estimate effect modification from a time varying covariate. Nevertheless, they are able to provide unbiased estimates of population average effect even if they are present (Newsome, Keogh, & Daniel, 2018). The IPTW were then stabilized (Fewell et al., 2004; Robins et al., 2000). Stabilized weights reduce the variance in the weights by replacing the numerator of 1 for the non-stabilized weights with the odds of exposure dependent on past exposure to CSA and baseline covariates only. With stabilized weights, the final estimation of the MSM for each of the 5 treatment occasions needs to be adjusted for the time-invariant confounders used in the numerator. The IPTW is the product of each wave specific exposure weight for waves 2–6.

As this method requires a full exposure history it uses a complete case analysis. In order to account for dropout between ELSA waves, the ELSA study provides longitudinal inverse probability of censoring weights (wave-IPCW) for core members and weights for non-response to the self-completion questionnaire (self-completion-IPCW) (Bridges et al., 2015; Fewell et al., 2004). Dropout was treated as monotone. The final inverse probability of treatment and censoring weights (IPTCW) were calculated as the product of IPTWs and either the wave-IPCW (working and volunteering) or both wave-IPCW and self-completion-IPCW (all other CSA). To estimate the MSM the IPTCW was applied to a Poisson regression with robust error variance (G. Zou, 2004; G. Y. Zou, 2009). Results were compared with the same modified Poisson regression using standard regression adjustment for cumulative covariate time-varying exposure and weighted only for non-response. For the secondary outcome of raw TICS-27 score the models were run in the same fashion (IPTCW vs regression adjustment) using a linear regression.

The data was analyzed using Stata version 13 and an example of the code for the full IPTCW for a single CSA are presented in appendix A (StataCorp, 2013). For the original references on which this was based we refer the reader to Fewell and colleagues for the Stata code for calculating IPTCW and to Bodnar and colleagues for the weighted repeated measures regression (with the straightforward amendment to a Poisson regression) (Bodnar, Davidian, Siega-Riz, & Tsiatis, 2004; Fewell et al., 2004).

3. Theory

The following section draw broadly from the works of Robins (Robins et al., 2000) for the initial development of MSMs, VanderWeele (VanderWeele et al., 2011) for his exposition of the approach and its application in older adult psychiatry, Daniel (Daniel, Cousens, De Stavola, Kenward, & Sterne, 2013) for detailed further exposition, Fewell (Fewell et al., 2004) for the implementation in Stata and Bodnar (Bodnar et al., 2004) for the informative application of a MSM of treatment over time with a single final outcome, as well as all their respective co-authors. We also utilize the work of Zou who has developed the use of a Poisson regression with robust error variance estimation to directly estimate relative risk, rather than the odds ratio more commonly obtained with logistic regression (G. Zou, 2004; G. Y. Zou, 2009). This method tends to provide a degree of additional efficiency, but the primary reason for its use is the more straightforward interpretation of the results.

One would ideally wish to draw causal inferences from these observational studies rather than commenting on associations whilst avoiding claims to possible causality. As described above, MSMs can be viewed as estimating the effect of a hypothetical interventions on the outcome and, under strict assumptions, tentative causal inferences about the effect of such an intervention can be drawn from observational data (Robins et al., 2000). The need to account for time varying confounding affected by prior treatment when making causal claims from observational data was one of the primary motivations for their

development and implementation using IPTW(Robins et al., 2000). Unlike time-invariant confounding, time varying confounding affected by past exposure cannot be adjusted for using standard regression even if measured adequately. For example, volunteering and employment in later life have been associated with improvements or better maintenance of cognitive function(Clouston & Denier, 2017a; Jenkinson et al., 2013; Kivipelto et al., 2018). But, better cognitive function is also associated with likelihood of remaining in employment and either continuing or starting volunteering(Clouston & Denier, 2017b; Shen, 2017). This creates a hypothetical causal model where participation in CSA improves cognition, which in turn increases the probability of continuing CSA participation. If CSA improves cognition and better cognition makes future participation more likely, then the treatment effect of earlier CSA will be blocked, or collider stratification bias will be introduced if one attempts using standard regression adjustment (see Fig. 1 for a generalized directed acyclic graph for our model) (Daniel et al., 2013).

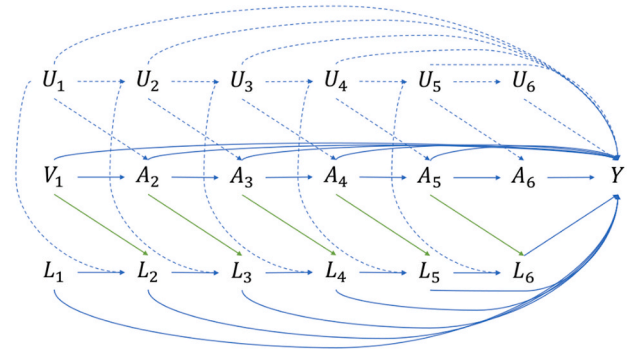
More formally, let a binary variable of CSA exposure be denoted A_1, A_2, \dots, A_t . Let L_1, L_2, \dots, L_t represent a vector of observed confounders at each time-point (including cognition at that time) and U_1, U_2, \dots, U_t be a vector of unmeasured confounders at each wave. Let C_1, C_2, \dots, C_t indicate whether an individual was censored at each measurement occasion (Daniel et al., 2013). Let Y be observed cognitive status at the end of follow-up. For illustration, L contains only one variable, cognitive function measured longitudinally. In our model, the association between CSA and covariates is always lagged though this need not always be the case. We will also not directly address censoring and unmeasured confounding, but will review the theory behind MSMs for readers new to the topic to illustrate why we have taken this approach to the analysis.

Starting from A_t in Fig. 1a let us assume CSA affects longitudinal cognitive function but cognitive function does not affect CSA exposure. From A_t we have the paths $A_t \rightarrow Y, A_t \rightarrow L_{t+1} \rightarrow Y, A_t \rightarrow A_{t+1} \rightarrow Y$ and several paths via the descendants of A_{t+1} . There is no path from any L_t to any A_{t+1} meaning L_t does not confound the association between any A and Y . This means that conditioning on L_t in the mistaken belief it is a confounder will block the path $A_t \rightarrow L_{t+1} \rightarrow Y$ and underestimate the total effect of A_t on Y . If the total effect is the quantity of interest, a naive analysis not adjusting for L_t will provide an unbiased estimate under this condition(Daniel et al., 2013).

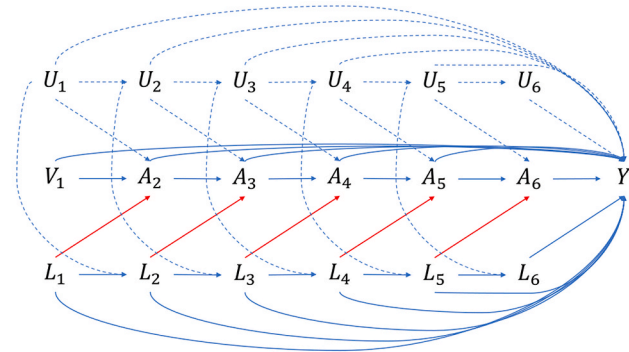
In the example in Fig. 1b the probability of CSA exposure is now affected by cognitive function but cognitive function is not affected by CSA. It can be seen that L_t is a confounder of the association between A_{t+1} and Y . Under these conditions those continuing CSA would become a progressively more cognitively elite group giving the appearance of CSA causing improvement in cognition. This should be possible to account for using standard regression analysis. However, difficulty may still arise if the direct effect of A_t not mediated by future treatment is of interest. This analysis would need to be conditioned on A_{t+1} which is a collider on the path $A_t \rightarrow A_{t+1} \leftarrow L_t \rightarrow Y$. So adjusting for A_{t+1} would inadvertently induce a conditional association between A_t and L_t and, therefore, between A_t and Y even if no true causal association exists (Daniel et al., 2013). As such the effect of A_t may be estimated incorrectly.

In Fig. 1c CSA affects cognition, which in turn affects the probability of future CSA, all of which affect cognitive status Y . This is time varying confounding which is affected by past treatment. We now wish to condition on L_{t+1} because it is a confounder of A_{t+2} and Y . However, doing so also blocks the indirect effect of A_t mediated via L_{t+1} and its descendants, meaning the estimate of the effect of A_t is likely to be biased. If both A_t and A_{t+1} have paths to L_{t+2} and Y then there is a backdoor path $A_{t+1} \rightarrow L_{t+2} \leftarrow A_t \rightarrow Y$. Conditioning on L_{t+2} may then introduce collider stratification bias for the association between A_{t+1} and Y . Lastly, if there is an unobserved confounder not of A_t and Y but L_{t+1} and Y then conditioning on L_{t+1} will also create collider stratification bias along the path $A_{t+1} \rightarrow L_{t+1} \leftarrow U_t \rightarrow Y$ (Daniel et al., 2013). So, if one wishes to estimate causal effects using a standard regression one must therefore assume that confounders are not affected by prior treatment. In the case of CSA

(a) indirect effects but no confounding.



(b) time dependent confounding.



(c) time dependent confounding affected by prior treatment.

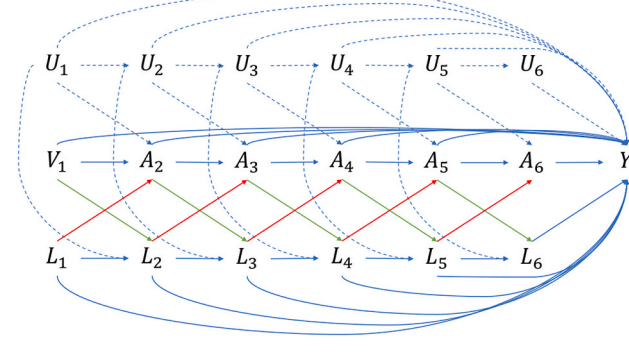


Fig. 1. Causal diagrams for the effect of CSA on probable dementia/cognitive impairment showing: (a) indirect effects but no confounding. (b) time dependent confounding. (c) time dependent confounding affected by prior treatment. Each line represents a hypothesized causal relationship, the color has been added to highlight the difference between models only. Y represents probable cognitive impairment or dementia at wave 7. $A_2, A_3 \dots A_t$ represents CSA exposure at each time point. V_1 represents CSA at baseline. $L_1, L_2 \dots L_t$ represent all observed potential confounders. $U_1, U_2 \dots U_t$ represent all unobserved potential confounders and the dashed lines unobserved potential causal relationships. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and cognitive function this is a very strong assumption to make.

Inverse probability of treatment weighting is an alternative means of estimation which avoids having to make this assumption. Before describing this further we will briefly describe the conventional notation as applied to our specific MSM(Robins et al., 2000). Let A_2, \dots, A_6 now represent observed CSA exposure at of the corresponding waves of ELSA. A_2 to A_6 can take the values of 0 for not exposed or 1 for exposed. The

confounding effect of L on A is lagged in our model. From this point forward we will be using V_1 to represent CSA exposure at wave 1. This is included as a baseline confounder rather than an exposure in order to account for unmeasured confounding at baseline mediated via baseline exposure by blocking the path $U_0 \rightarrow V_1 \rightarrow A_2 \rightarrow Y$. Let $\bar{A} = (A_2, \dots, A_6)$ and $\bar{L} = (L_1, \dots, L_5)$. Then let $\bar{a} = (a_2, \dots, a_6)$, denote all the possible combinations of exposure which the participants could have been exposed to. Let $Y_{\bar{A}}$ be the observed outcome for exposure history \bar{A} . There will be one exposure history for each individual where $Y_{\bar{A}} = Y_{\bar{a}}$ and others where $Y_{\bar{A}} \neq Y_{\bar{a}}$. These $Y_{\bar{a}}$, the expected outcome given an exposure history of \bar{a} , represent a counterfactual quantity, the outcome that would have been observed if a hypothetical intervention had set CSA exposure to any given a_2, \dots, a_6 .

Given that we are using Poisson regression where $E(Y_{\bar{a}}) = \lambda_{\bar{a}}$ and the use of a natural log link function the MSM takes the form:

$$\log(\lambda_{\bar{a}}) = \beta_0 + \beta_2 a_2 + \beta_3 a_3 + \beta_4 a_4 + \beta_5 a_5 + \beta_6 a_6 \quad (1)$$

It is not possible to directly estimate this MSM precisely because all \bar{a} are not observed. However, we are able to estimate

$$\log(\lambda_{\bar{a}} | \bar{A} = \bar{a}) = \beta'_0 + \beta'_2 a_2 + \beta'_3 a_3 + \beta'_4 a_4 + \beta'_5 a_5 + \beta'_6 a_6 \quad (2)$$

whereas model 1 describes the outcome under a hypothetical intervention to set the value of \bar{a} , model 2 describes the relative risk of those with an observed history of \bar{a} . Assuming that all confounders are observed in L_1 to L_5 then we are able to unbiasedly estimate β_0 with β'_0 , β_2 with β'_2 and so on (Bodnar et al., 2004; Robins et al., 2000) L_1 contains both a subset of time-invariant confounders and the first measurement of time-varying confounders. To this model we add a term for baseline

$$sw(t) = \prod_{i=2}^T pr(A_i | A_2, \dots, A_{(i-1)}, V_1, L_1) / pr(A_i | A_2, \dots, A_{(i-1)}, V_1, L_1, \dots, L_{(i-1)}) \quad (5)$$

confounders $\beta_7 L_1$ and baseline CSA exposures $\beta_1 v_1$. These are required for the stabilized weights inverse probability of treatment weights used

$$sw(t) = \prod_{i=2}^T pr(A_i = a_i | \bar{A}_{i-1} = \bar{a}_{i-1}, V_1 = v_1, L_1 = l_1) / pr(A_i = a_i | \bar{A}_{i-1} = \bar{a}_{i-1}, V_1 = v_1, \bar{L}_{i-1} = \bar{l}_{i-1}) \quad (6)$$

in the estimation of the model:

$$\log(\lambda_{\bar{a}} | \bar{A} = \bar{a}, \bar{L} = L_1) = \beta_0 + \beta_1 v_1 + \beta_2 a_2 + \beta_3 a_3 + \beta_4 a_4 + \beta_5 a_5 + \beta_6 a_6 + \beta_7 l_1 \quad (3)$$

There are a small number of different techniques for estimating MSMs in the presence of time varying confounding. Probably the most

$$logit pr(A_i = 1 | \bar{A}_{i-1} = \bar{a}_{i-1}, V_1 = v_1, \bar{L}_1 = \bar{l}_1) = \alpha_0 + \alpha_1 v_1 + \alpha_2 a_2 + \dots + \alpha_{i-1} a_{i-1} + \gamma_1 l_1 \quad (7)$$

commonly used of these is inverse probability of treatment and censoring weighting, which is the method we will employ. Instead of covariate adjustment in standard regression models but by weighting each individual by their probability of receiving their observed CSA exposure (hypothetical CSA treatment) estimated by their past CSA exposure and covariate history (Daniel et al., 2013; Robins et al., 2000; VanderWeele et al., 2011).

The basic principle is that each individual is given a weight w inversely proportional to their probability of having received the exposure history they actually received conditional upon their measured covariate history and history of exposure prior to time t (Hernán, Brumback, & Robins, 2002; Robins et al., 2000). This weight then effectively creates a 'pseudo-population' where there are a number of copies of individual i equal to the weight they are assigned and A_t is no longer confounded by L_{t-1} (Robins et al., 2000). The overall weight is the product of an individual's weight at each time point. This is given by:

$$w(t) = \prod_{i=2}^T 1 / pr(A_i | A_2, \dots, A_{(i-1)}, V_1, L_1, \dots, L_{(i-1)}) \quad (4)$$

As these weights tend to have very high variance and not to be normally distributed due to a few individuals having very extreme weights, they are then usually stabilized. To produce the stabilized weight sw the numerator of 1 is exchanged for the probability of the observed exposure conditional on past exposure history and, as in our case, a vector of baseline covariates can also be included. If stabilized weights are used $E(Y_{\bar{a}})$ is now estimated within levels of the baseline covariates and additional terms must be added to the MSM as seen in equation (3) above. The stabilized weights are then given by:

This may alternatively be annotated in counterfactual form as:

The weight at each time point is calculated for each measurement occasion t using a logistic regression model for the numerator and denominator.

The logistic regression models for the numerators were specified as:

Table 1
ELSA demographics showing the time-invariant covariates for participants used in the employment analysis compared to those excluded for incomplete data.

	Incomplete data -excluded	Complete data -included	P for a difference ^a
n	8055	3937	
Female (%)	4448 (55.2%)	2228 (56.6%)	0.156
Age at recruitment (S.D)	66.2 (11.5)	61.7 (7.9)	<0.001
Educational Attainment (%)	3862 (47.9%)	1156 (29.4%)	<0.001
No formal qualification			
High School	1563 (19.4%)	960 (24.4%)	
6th Form	457(5.7%)	291 (7.4%)	
Some higher education	735 (9.2%)	582 (14.8%)	
Degree or higher	757 (9.4%)	613 (15.6%)	
Foreign Qualification	681 (8.5%)	335 (8.5%)	
Non-white Ethnicity (%)	266 (3.4%)	62 (1.6%)	<0.001
TICS score		15.2 (S.D 5.2)	
Cognitive Status		3131 (79.5%)	
Non-impaired			
Cognitive Impairment		536 (14.6%)	
Dementia		270 (6.9%)	

^a Chi-squared test.

The logistic regression models for the denominators were specified as:

$$\text{logit } pr(A_t = 1 | \bar{A}_{t-1} = \bar{a}_{t-1}, V_t = v_t, \bar{L}_{t-1} = \bar{l}_{t-1}) = \alpha_0 + \alpha_1 v_1 + \alpha_2 a_2 + \dots + \alpha_{t-1} a_{t-1} + \gamma_1 l_1 + \dots + \gamma_{t-1} l_{t-1} \tag{8}$$

At this point it is worth noting that in order to draw a causal conclusion for observational data it must be assumed that U_1, U_2, \dots, U_t is either empty, which is the preferable situation, or at least that the degree of unmeasured confounding has inconsequential influence on effect size estimates. This is a very strong assumption to make when estimating the effect of social exposures over a long time period as in our analysis. We therefore take the view that, in comparison to standard regression, we

Table 2
Participation over time in cognitively stimulating activities by cognitive status.

Study Wave	Wave 1 (2002/3)		Wave 2 (2004/5)		Wave 3 (2006/7)		Wave 4 (2008/9)		Wave 5 (2010/11)		Wave 6 (2012/13)	
	TICS≥12	TICS≤11	TICS≥12	TICS≤11	TICS≥12	TICS≤11	TICS≥12	TICS≤11	TICS≥12	TICS≤11	TICS≥12	TICS≤11
Employment	1722 (53.9%)	226 (26.1%)	1479 (46.3%)	187 (21.6%)	1332 (41.7%)	153 (17.7%)	1102 (34.5%)	123 (14.2%)	860 (26.9%)	92 (10.6%)	628 (19.7%)	75 (8.7%)
Volunteering	572 (17.9%)	107 (12.4%)	621 (19.4%)	113 (13.0%)	648 (20.3%)	109 (12.6%)	641 (20.1%)	97 (11.2%)	664 (20.8%)	90 (10.4%)	675 (21.1%)	81 (9.3%)
Internet/Email	1417 (45.8%)	176 (21.8%)	1584 (53.0%)	195 (25.9%)	1665 (57.1%)	195 (25.9%)	1779 (60.5%)	197 (26.84)	1972 (65.2%)	214 (28.5%)	2060 (68.6%)	223 (33.0%)
Social Club	620 (20.3%)	185 (24.2%)	574 (19.8%)	162 (23.5%)	552 (19.3%)	159 (23.0%)	579 (20.2%)	142 (20.8%)	605 (20.4%)	134 (19.4%)	581 (19.7%)	115 (18.1%)
Newspaper	2092 (67.7%)	545 (67.5%)	1967 (65.8%)	479 (63.6%)	1951 (66.9%)	480 (63.8%)	1902 (64.7%)	436 (59.4%)	1919 (63.4%)	464 (61.9%)	1829 (60.4%)	408 (58.2%)
Evening Classes	591 (19.4%)	95 (12.4%)	516 (17.8%)	80 (11.6%)	482 (46.9%)	62 (9.0%)	441 (15.4%)	53 (7.8%)	472 (15.9%)	61 (8.8%)	490 (16.6%)	42 (6.6%)

are principally relaxing the assumption of no time-varying confounders being affected by prior exposure rather than making strong causal claims.

4. Results

The demographics of the sample with complete exposure data used for the analysis of employment (the biggest subsample by CSA) compared to those excluded due to incomplete data is shown in Table 1. The mean TICS-27 score was 15.2 (S.D 5.2). The proportion of participants classified as having probable cognitive impairment or dementia in wave 7 was 20.5% (n = 806). Missingness of each exposure at each time point is presented in appendix B and further detail can be found in the ELSA wave 7 study report (Littleford, Hussey, Begum, & Oskala, 2016). CSA exposure over time is presented in Table 2. As would be expected from the cohort and time period studied, employment reduced progressively and there was a strong trend towards increasing internet and email use. The prevalence of volunteering increased slightly over time, evening class attendance remain static and newspaper reading and social club membership fell.

The results for standard and IPTCW Poisson regression models are presented in Fig. 2 and in table format in appendix C.1 and the linear regression models in Fig. 3 and appendix C.2.

In the standard regression model internet/email use at any wave was associated with lower risk of cognitive impairment (all P < 0.001). The point estimates for the RR's were between 0.64 and 0.78. The IPTCW model results were very similar with all waves being significantly associated with lower risk and RR point estimates of between 0.62 and 0.69. Estimates of change in TICS-27 score were also statistically significant for all waves (all P < 0.001) in both standard and IPTCW models, with very similar estimates of effect size. In the standard model the point estimates were between 0.65 and 0.95 and in the IPTCW models between 0.86 and 0.93.

In the standard regression models, volunteering was significantly associated with reduced risk of cognitive impairment at waves 4, 5 and 6. In the standard regression models for continuous TICS-27 score, we see a similar pattern with an increase in score for waves 3, 4, 5 and 6 (Fig. 3). The estimated effect size became larger in later waves. After adjustment with IPTCW, volunteering was more strongly associated with reduced risk of cognitive impairment than estimated in the standard regression models in waves 3, 4, 5 and 6. The pattern differed to the standard models, in that the strength of the association was quite

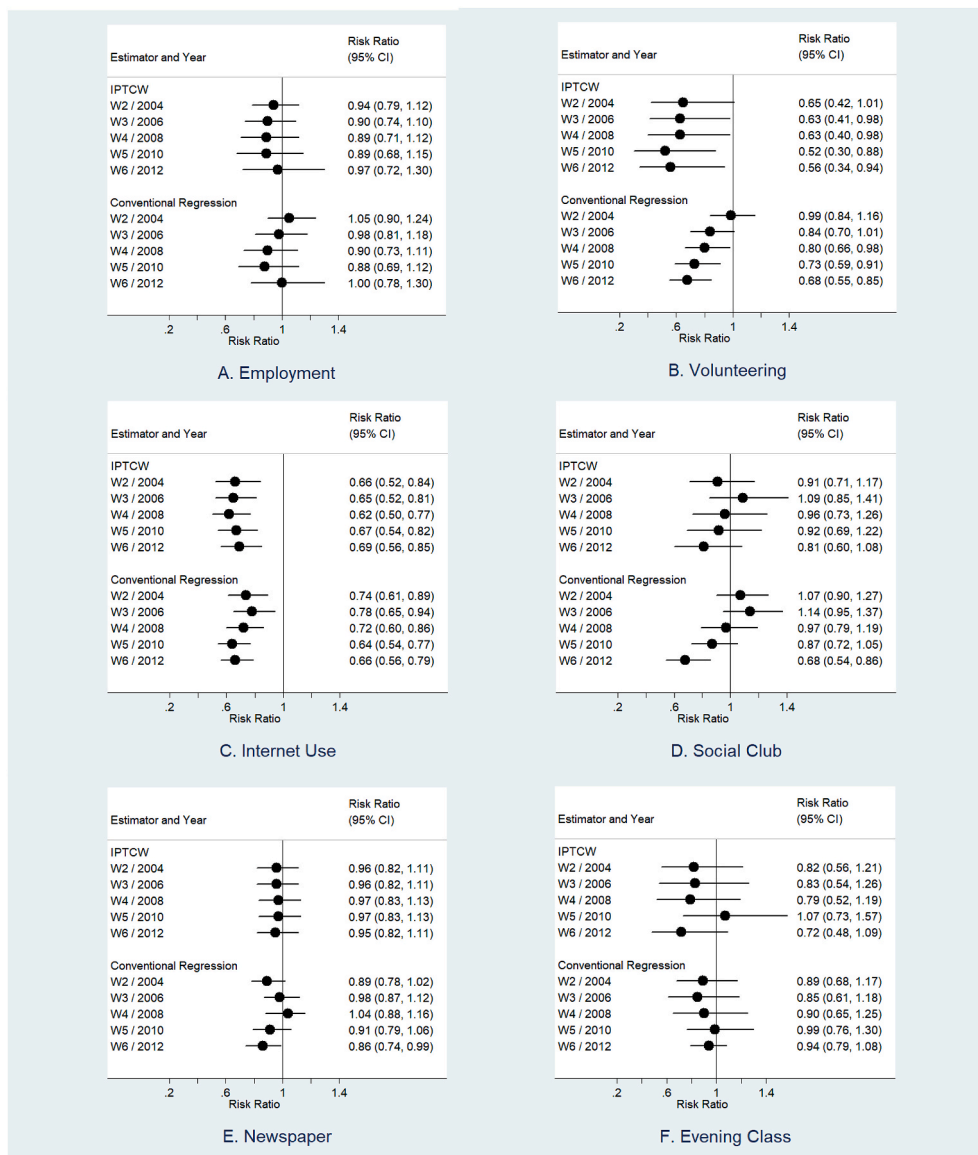


Fig. 2. IPTW vs standard regression models for CSA predicting risk of probable cognitive impairment in 2014 (wave 7).

consistent over time. Despite this strong association with lower risk of cognitive impairment, volunteering at any wave it was not significantly associated with TICS-27 (Fig. 3).

Belonging to a social club was significantly associated with reduced risk of cognitive impairment at wave 6 in the standard model (Fig. 2). Social club membership at wave 3 was associated with worse TICS-27 score, but at wave 6 with improved TICS-27 score. In the IPTCW models social club membership at any wave was not associated with either reduced risk of cognitive impairment or a change in TICS-27 score. In the standard regression model evening classes at any time were not associated with risk of cognitive impairment, but were associated with higher TICS-27 at wave 2 and 3. In the IPTCW models evening classes were not associated with either risk of cognitive impairment or TICS-27 score. Reading a daily newspaper was associated with reduced risk of cognitive impairment at wave 6, but not at any other time points in the standard model. In the IPTCW models, daily newspaper reading was not associated with reduced risk of cognitive impairment at any wave. In neither the standard nor the IPTCW models was newspaper reading associated with TICS-27 score. Employment was not associated with either risk of cognitive impairment or TICS-27 score in either the standard or IPTCW models. Working at baseline (wave 1)

was associated with lower risk of cognitive impairment (RR 0.656; 95% CI 0.529 to 0.813).

The primary analysis found a discrepancy between the results for cognitive impairment and TICS-27 for volunteering. It is possible that this may result from an effect of volunteering which is greater for people with greater cognitive impairment. A secondary analysis was conducted for the volunteering IPTCW restricted to only those participants bottom 50% of the TICS-27 distribution. In this subset of older adults with lower cognitive function volunteering now met the conventional significance threshold for an association at waves 2, 3, 4 and 6.

5. Discussion

We found that the association between volunteering or internet/email use and risk of cognitive impairment was not substantially different after taking into account time-varying confounding. This was contrary to our expectation. Employment, evening classes, newspaper reading and social clubs were not associated with improved cognitive function. Of these, the results for newspaper reading and social clubs were consistent with our hypothesis, in that significant associations using standard regression became non-significant using IPTCW. The

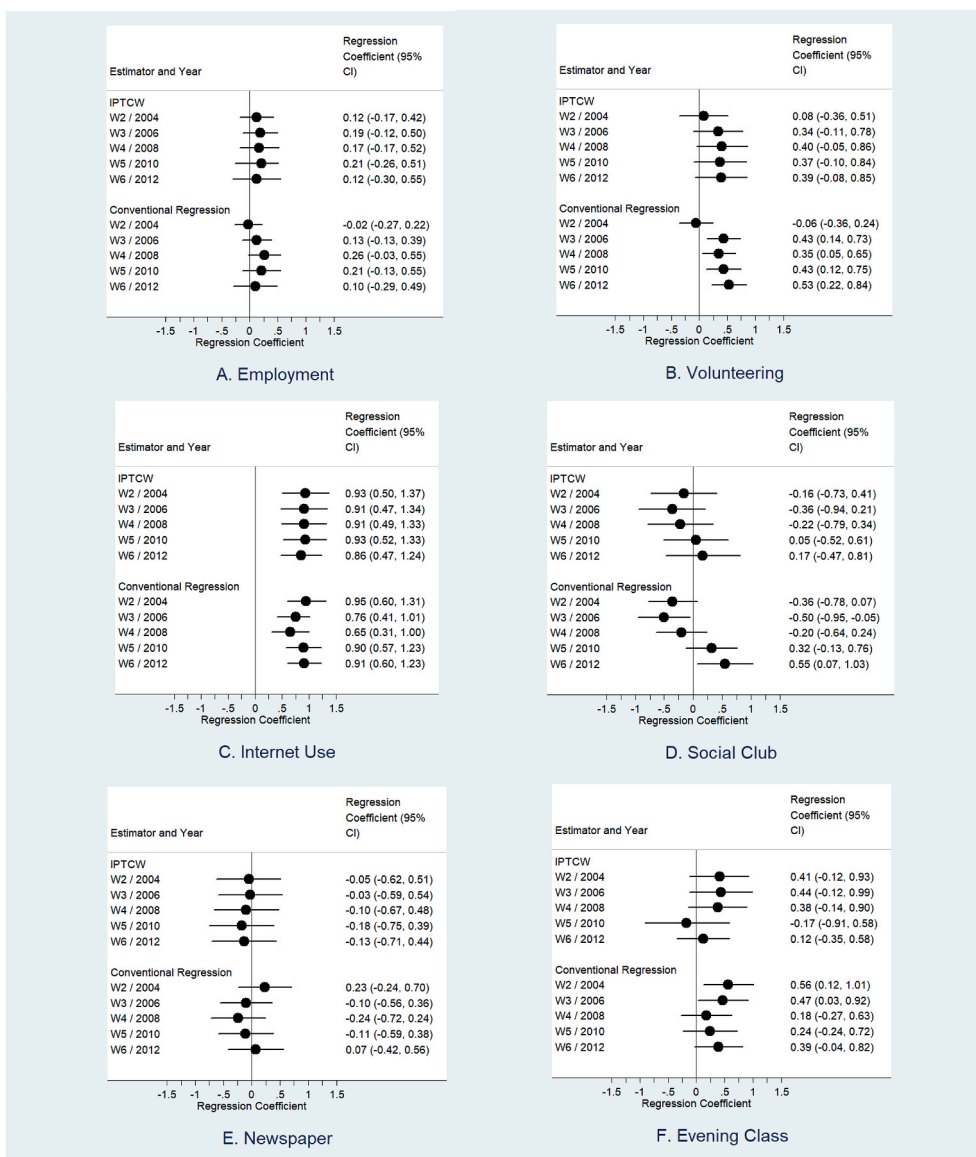


Fig. 3. IPTW vs standard regression models for CSA predicting TICS-27 score in 2014 (wave 7).

effect of volunteering and internet use appear to persist over a period of several years and, for volunteering, may be limited to those who have poorer cognitive function. In contrast with the approach taken in some prior research regarding cognitively enriched lifestyles, our analysis suggests the specific type of activity is likely to be important.[3,4].

The use of specific CSA rather than a measure of overall cognitive enrichment is both a limitation and a strength. The narrow definition of specific CSA leads to clearer inferences but loses the more holistic nature or potential cumulative effects seen with general measures of cognitive enrichment. The strengths of the ELSA dataset are that it is a large, nationally representative and rigorously conducted prospective cohort study with data on a wide range of potential confounders over a long follow-up period. However, the measures of CSA are self-reported, binary measures taken every 2 years. The long study duration provides good information on participation over time, but there is very little information on CSA ‘dose’ received. Our measures of CSA may be inadequate to detect effects which are present with higher levels of CSA engagement for some activities. Moreover, each CSA still captures a range of possible activities. Newspaper reading could mean passive reading of unchallenging materials. Alternatively, it could include walking to a shop to purchase the newspaper, completing puzzles and

reading complex prose. Likewise, we did not draw other distinctions such as between those in employment due to being unable to retire versus personal preference to remain in work. The use of a brief cognitive test as an outcome rather than physician diagnosed dementia or a more extensive cognitive battery is another limitation. The instrument used tends to under-diagnose cognitive impairment, but will correctly classify most non-impaired individuals(Crimmins et al., 2011). Under-detection of cognitive impairment would tend to bias results towards the null.

We used inverse probability of censoring weights to account for dropout, which is a standard approach to missingness at random that is readily integrated into IPTW(Fewell et al., 2004). This method does not account for participants missing not at random. The use of MSMs is the main development of the current study on previous research. They are particularly useful in cases such as CSA, where time-varying confounding is highly plausible, but there is always the potential for unobserved confounding. The use of baseline CSA at wave 1 to predict subsequent exposure should block a substantial proportion of the effect of confounders which are unobserved because of left censoring. However, there may be unobserved social stratification or social cognitive deficits which are inadvertently measured by one’s propensity to

volunteer or take up internet use. Moreover, a general tendency towards social participation endures through the life course which could lead to bias from life-long cognitive enrichment(Greenfield & Moorman, 2018). However, if this were the case it might be expected to affect other CSAs (particularly evening classes).

Our finding of an association between volunteering and better cognitive function agrees with the majority of longitudinal studies conducted to date(Guiney & Machado, 2018; Jenkinson et al., 2013; Proulx, Curl, & Ermer, 2018). Consistent with our findings, the effect seen in the Experience Corps studies seems to be more pronounced in those with poorer cognitive function(Carlson et al., 2009; Proulx et al., 2018). Volunteering may exert beneficial effects via combined increases in cognitive, social and physical activity leading to improved neurological and mental health which, in turn, improve cognitive functioning (Carlson et al., 2015; Guiney & Machado, 2018). Should these findings be robustly replicated, this would suggest that volunteering could be considered a potential public health intervention(Jenkinson et al., 2013). Whilst many older adults already volunteer a great amount of time, expansion of volunteering may have a role in preventing cognitive impairment or dementia and may motivate more older adults to volunteer(Carr, 2018). This finding may be generalizable across populations of older adults in the rest of the UK and other western industrialized nations with broadly comparable social conditions.

General internet use has been shown to be associated with improved cognitive function and reduced risk of dementia in several previous observational studies, including in previous analyses of ELSA(Almeida et al., 2012; D’Orsi et al., 2017; Liapis & Harding, 2017; Slegers, Van Boxtel, & Jolles, 2012; Xavier et al., 2013). This similarity is unsurprising given that the IPTCW estimates were similar to the standard regression estimates in our analysis. One mechanism through which internet use could lead to improved cognitive function is improved access to preventative and treatment health services(Clarke et al., 2017; Xavier et al., 2013). Other potential mechanisms for an association with personal computer use have had little investigation. Given the strong secular trend in personal computer use, it is possible that the exposure being measured is not computer use itself, but rather the acquisition and routine use of a new skill in later life. If this is the case, this finding is likely to be generalizable across similar populations of older adults but is unlikely to be generalizable to future cohorts.

We found that the association between cognitive impairment and social club membership was attenuated when IPTCW was used. Neuropsychiatric symptoms of neurodegenerative disorders have been shown to precede the onset of measurable cognitive impairment, and appear to confound the association between cognition, social circumstances and other mental health conditions(Cortés, Andrade, & Maccioni, 2018; Donovan et al., 2016; Sajeev et al., 2016; Singh-Manoux et al., 2017). It

seems likely the MSM accounted for this, whereas the linear regression did not. We used social club membership as this has a clear counterfactual quantity which is readily interpretable within the causal inference framework. However, this is a very limited measure of overall social activity. Future research may wish to use MSMs, or other related methods, to test whether a similar effect is seen for other measures of social activity or connectedness.

In conclusion, we found that out of several CSA examined, internet use and volunteering were associated with a lower risk of cognitive impairment using IPTCW. This analysis develops the existing literature by showing these associations are unlikely to be the result of time varying confounding affected by prior exposure. Further research may wish to consider the type, duration and intensity of CSA required to produce benefits in cognitive functioning and whether those benefits are realized by all older adults or are restricted to sub-populations, such as those with poorer cognition.

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Ethical statement

Ethical approval for the English Longitudinal Study of Ageing was granted by the South-Central Berkshire Research Ethics Committee through an application to the National Research Ethics Service. The current analysis was subject to the University of Manchester internal review process and no additional approval deemed necessary.

CRedit authorship contribution statement

Benjamin David Williams: Conceptualization, Funding acquisition, Data curation, Methodology, Formal analysis, Writing - original draft. **Neil Pendleton:** Conceptualization, Supervision, Writing - review & editing. **Tarani Chandola:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Declaration of competing interest

None.

Appendix D. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ssmph.2020.100656>.

Appendix A. Stata 13.0 Code for IPTCW – see separate file

Appendix B. Wave response rate and item non-response for all exposure variables

Table B.1 Wave response rate and item non-response for all exposure variables.

Non-response		Wave						Final numbers [‡]
		1	2	3	4	5	6	
Main survey	total n	11932	9249	7168	5971	5262	4711	
	Employment/ Volunteering	9 (0.1%)	0	1 (0.0%)	2 (0.0%)	2 (0.0%)	0 (0.0%)	3875 2487

(continued on next page)

(continued)

Non-response		Wave						Final numbers [†]
		1	2	3	4	5	6	
Questionnaire	Internet use/ Newspaper	1164 (9.7%)	1169 (12.6%)	1010 (14.1%)	807 (13.5%)	531 (10.1%)	555 (11.8%)	2401 2770
	Social Club/ Evening Classes	1577 (13.2%)	1597 (17.3%)	1264 (17.6%)	1021 (17.1%)	703 (13.4%)	665 (14.1%)	2460 2452

†The number of participants included in the final regression after accounting for all missing data at all time points required to estimate the IPTCW.

Appendix C. Results tables for IPTW vs standard regression models

Table C.1IPTW vs standard regression models for CSA predicting risk of probable cognitive impairment in 2014 (wave 7).

Year of Exposure	Employment		Volunteering		Internet Use		Social Club		Newspaper Reading		Evening Classes	
	RR (95% CI)	P > z	RR (95% CI)	P > z	RR (95% CI)	P > z	RR (95% CI)	P > z	RR (95% CI)	P > z	RR (95% CI)	P > z
IPTW												
W2/ 2004	0.94 (0.79–1.12)	0.466	0.65 (0.42–1.01)	0.055	0.66 (0.52–0.84)	0.001	0.91 (0.71–1.17)	0.46	0.96 (0.82–1.11)	0.575	0.82 (0.56–1.21)	0.315
W3/ 2006	0.90 (0.74–1.10)	0.298	0.63 (0.41–0.98)	0.042	0.65 (0.52–0.81)	0.001	1.09 (0.85–1.41)	0.481	0.96 (0.82–1.11)	0.554	0.83 (0.54–1.26)	0.376
W4/ 2008	0.89 (0.71–1.12)	0.322	0.63 (0.40–0.98)	0.039	0.62 (0.50–0.77)	0.001	< (0.73–1.26)	0.96 0.768	0.97 (0.83–1.13)	0.712	0.79 (0.52–1.19)	0.257
W5/ 2010	0.89 (0.68–1.15)	0.361	0.52 (0.30–0.88)	0.015	0.67 (0.54–0.82)	0.001	< (0.69–1.22)	0.564	0.97 (0.83–1.13)	0.694	1.07 (0.73–1.57)	0.736
W6/ 2012	0.97 (0.72–1.30)	0.816	0.56 (0.34–0.94)	0.026	0.69 (0.56–0.85)	0.001	< (0.60–1.08)	0.151	0.95 (0.82–1.11)	0.53	0.72 (0.48–1.09)	0.121
Standard												
W2/ 2004	1.05 (0.90–1.24)	0.523	0.99 (0.84–1.16)	0.877	0.74 (0.61–0.89)	0.001	1.07 (0.90–1.27)	0.458	0.89 (0.78–1.02)	0.1	0.89 (0.68–1.17)	0.411
W3/ 2006	0.98 (0.81–1.18)	0.843	0.84 (0.70–1.01)	0.061	0.78 (0.65–0.94)	0.009	1.14 (0.95–1.37)	0.162	0.98 (0.87–1.12)	0.81	0.85 (0.61–1.18)	0.337
W4/ 2008	0.90 (0.73–1.11)	0.327	0.80 (0.66–0.98)	0.029	0.72 (0.60–0.86)	0.001	< (0.79–1.19)	0.796	1.01 (0.88–1.16)	0.911	0.90 (0.65–1.25)	0.524
W5/ 2010	0.88 (0.69–1.12)	0.304	0.73 (0.59–0.91)	0.005	0.64 (0.54–0.77)	0.001	< (0.72–1.05)	0.147	0.91 (0.79–1.06)	0.222	0.99 (0.76–1.30)	0.96
W6/ 2012	1.00 (0.78–1.30)	0.978	0.68 (0.55–0.85)	0.001	0.66 (0.56–0.79)	0.001	< (0.54–0.86)	0.001	0.86 (0.74–0.99)	0.033	0.94 (0.79–1.08)	0.142

Table C.2IPTW vs standard regression models for CSA predicting TICS-27 score in 2014 (wave 7).

Year of Exposure	Employment		Volunteering		Internet Use		Social Club		Newspaper Reading		Evening Classes	
	beta (95% CI)	P > z	beta (95% CI)	P > z	beta (95% CI)	P > z	beta (95% CI)	P > z	beta (95% CI)	P > z	beta (95% CI)	P > z
IPTW												
W2/ 2004	0.12 (-0.17–0.42)	0.420	0.08 (-0.36–0.51)	0.732	0.93 (0.50–1.37)	< 0.001	-0.16 (-0.73–0.41)	0.581	-0.05 (-0.62–0.51)	0.851	0.41 (-0.12–0.93)	0.130
W3/ 2006	0.19 (-0.12–0.50)	0.232	0.34 (-0.11–0.78)	0.137	0.91 (0.47–1.34)	< 0.001	-0.36 (-0.94–0.21)	0.213	-0.03 (-0.59–0.54)	0.927	0.44 (-0.12–0.99)	0.127
W4/ 2008	0.17 (-0.17–0.52)	0.331	0.40 (-0.05–0.86)	0.082	0.91 (0.49–1.33)	< 0.001	-0.22 (-0.79–0.34)	0.434	-0.10 (-0.67–0.48)	0.742	0.38 (-0.14–0.90)	0.151
W5/ 2010	0.21 (-0.26–0.51)	0.536	0.37 (-0.10–0.84)	0.126	0.93 (0.52–1.33)	< 0.001	0.05 (-0.52–0.61)	0.877	-0.18 (-0.75–0.39)	0.532	-0.17 (-0.91–0.58)	0.661
W6/ 2012	0.12 (-0.30–0.55)	0.569	0.39 (-0.08–0.85)	0.103	0.86 (0.47–1.24)	< 0.001	0.17 (-0.47–0.81)	0.595	-0.13 (-0.71–0.44)	0.657	0.12 (-0.35–0.58)	0.631
Standard												
W2/ 2004	-0.02 (-0.27–0.22)	0.843	-0.06 (-0.36–0.24)	0.697	0.95 (0.60–1.31)	< 0.001	-0.36 (-0.78–0.07)	0.099	0.23 (-0.24–0.70)	0.331	0.56 (0.12–1.01)	0.014
W3/ 2006	0.13 (-0.13–0.39)	0.317	0.43 (0.14–0.73)	0.004	0.76 (0.41–1.01)	< 0.001	-0.50 (-0.95–0.05)	0.029	-0.10 (-0.56–0.36)	0.672	0.47 (0.03–0.92)	0.039
W4/ 2008	0.26 (-0.03–0.55)	0.082	0.35 (0.05–0.65)	0.023	0.65 (0.31–1.00)	< 0.001	-0.20 (-0.64–0.24)	0.373	-0.24 (-0.72–0.24)	0.321	0.18 (-0.27–0.63)	0.437
W5/ 2010	0.21 (-0.13–0.55)	0.224	0.43 (0.12–0.75)	0.007	0.90 (0.57–1.23)	< 0.001	0.32 (-0.13–0.76)	0.161	-0.11 (-0.59–0.38)	0.673	0.24 (-0.24–0.72)	0.333
W6/ 2012	0.10 (-0.29–0.49)	0.613	0.53 (0.22–0.84)	0.001	0.91 (0.60–1.23)	< 0.001	0.55 (0.07–1.03)	0.026	0.07 (-0.42–0.56)	0.782	0.39 (-0.04–0.82)	0.076

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