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Title: Bidirectional relations between cognitive function and oral health in ageing persons: a longitudinal cohort study

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Abstract

BACKGROUND: Evidence suggests a reciprocal relationship between cognitive function and oral health, but no study has demonstrated this inter-relationship in a longitudinal population.

OJBECTIVE: To investigate the bidirectional relationship between cognitive function and oral health in an ageing cohort.

DESIGN: Cohort study

SETTING: General community

SUBJECTS: Participants from the English Longitudinal Study of Ageing

METHODS: Oral health, measured by teeth status, self-reported oral health and oral health-related quality of life (OHRQoL), and cognitive function were collected at three time points in 2006/07, 2010/11, and 2014/15. Cross-lagged structural equation models were used to investigate the association between cognitive function and oral health, adjusted for potential confounding factors.

RESULTS: 5477 individuals (56.4% women) were included (mean age=63.1 years at 2006/07, 67.2 at 2010/11, and 70.4 at 2014/15, SD=8.9) in analyses. The average cognitive function score was 46.5(SD=12.3) at baseline and 41.2(SD=13.4) at follow-up. 3350 (61.2%) participants had natural teeth only and 622(11.2%) were edentulous. In the fully adjusted model, better cognition at baseline was associated with better oral health at follow-up (beta coefficient = 0.02, 95% CI:0.01-0.03); conversely better oral health at baseline predicted better cognition (beta coefficient = 0.12, 95% CI:0.06-0.18). Similar magnitude and direction of the reciprocal association was evident between cognition and OHRQoL.

CONCLUSIONS: This is the first longitudinal study to demonstrate the positive reciprocal association between cognitive function and oral health. The findings suggest the importance of maintaining both good cognitive function and oral health in old age.

Key words: Cognitive function, Oral health, Tooth loss, English Longitudinal Study of Ageing, bidirectional, cross-lagged, structural equation model

KEY MESSAGES

- This is the first longitudinal study to demonstrate the bidirectional association between cognitive function and oral health.
- There is a positive reciprocal relationship between oral health and cognitive function.
- The mutual benefit of maintaining both good cognitive function and oral health is not to be neglected in old age.

Introduction

Changes of cognitive function are associated with ageing, both normal and pathologic. [1] Oral health also deteriorates with ageing, resulting in increased need for preventive, restorative, and periodontal care. [2] Cognitive impairment is often linked with poor oral health in older adults.[3-5] A recent study has identified *Porphyromonas gingivalis,* an organism associated with chronic periodontitis, in the brain of Alzheimer's disease patients, and suggested that this microorganism may play a role both in periodontitis and Alzheimer's disease. [6] However, evidence for the longitudinal association between cognitive function (e.g. cognitive impairment, and Alzheimer's Disease and related Dementias) and oral health (e.g. chronic periodontitis) is mixed, with some studies showing associations and others not [3, 5], due to methodological deficiencies of the studies (small sample size, lack of representativeness of the population, short duration of study follow-up). Moreover, existing studies usually focused on unidirectional associations between cognitive function and oral health. [7] There is a need to disentangle the temporal nature of the association, for which a longitudinal cohort like the English Longitudinal Study of Ageing (ELSA) is a good source. [8]

Oral health can be assessed through clinical examination or self-reported questionnaires. Number of remaining teeth is a robust and objective measure of total tooth mortality as edentulousness was irreversible [9], self-reported oral health and self-rated oral health-related quality of life (OHRQoL) has been shown to be a valid and reliable tool to measure oral health. [10, 11] QHRQoL could be used to quantify the impact of oral health or diseases on an individual's daily functioning, well-being or overall quality of life, but less expensive and easier to collect. [11] Few studies had reported the association between OHRQoL and cognitive function, thus further investigation is necessary to quantify this association.

This study aimed to examine the bidirectional longitudinal relationships between cognitive function and oral health using the ELSA study with up to 10 years follow up.

Methods

Study design and participants

The study was reported in accordance with the STROBE guidelines. Study participants came from a cohort of noninstitutionalized persons age 50 and above residing in England, United Kingdom. The detailed description of ELSA is available elsewhere [8, 12]. For the present study, we included the participants who were interviewed at all three time points: 2006/07, 2010/11, and 2014/15. Data collected at 2006/07 was regarded as the baseline because this was the first wave containing information with both cognitive function and oral health assessment. Supplement Figure S1 shows the flow chart of the study participants. Ethical approval was granted by the London Multicentre Research Ethics Committee.

Exposure and outcome measures

Cognitive function was assessed using a battery of tests [12], and covered two domains associated with age-related cognitive decline at three time points in 2006/07, 2010/11 and 2014/15: a memory measure (range 0-20) calculated by summing immediate word recall (range 0-10) and delayed word recall (range 0-10); and an executive function measure using word fluency test (range 0-67) assessing how many different animals participants could name in one minute. A processing speed measure using Digit Symbol Substitution Test was not assessed in 2014/15 and therefore we excluded this measure when calculating general cognitive function (see below). All scores were normally distributed with no evidence of ceiling or floor effects, and therefore were summed to represent cognitive function (range 0-87) for baseline descriptive purpose.

Oral health was measured using teeth status (natural teeth only, teeth with denture, and edentulous), self-rated oral health (excellent, very good, good, fair, and poor), and OHRQoL measured by Oral Impact on Daily Performances (OIDP, no difficulty, or at least one of the problems in eating food, speaking clearly, smiling without embarrassment, emotional stability, and enjoying company of other people), during a face-to-face interview at each time point. The detailed interview questions on oral health were presented in Supplement Material S1.

Covariates

Analyses adjusted for the following set of variables as they may be associated with cognitive function and oral health:

Demographic variables: Age (50 and above, scale), gender (male or female), education qualification (Higher education degree or equivalent, some qualification, and no qualification), marital status (not married, married), total net wealth (lowest quintile, others),

Cardiovascular conditions: self-reported doctor diagnosed cardiovascular conditions (abnormal heart rhythm, angina, congestive heart failure, diabetes mellitus, heart attack, heart murmur, hypertension, and stroke),

Other systemic conditions including psychosocial variables: self-reported doctor diagnosed non-cardiovascular conditions (arthritis; asthma; cancer; chronic lung disease; osteoporosis; Parkinson’s disease; and emotional, nervous, and psychiatric problems), depression symptoms (≥4 symptoms on eight-item Centre of Epidemiological Studies Depression (CESD) scale) [13]

Lifestyle factors: weekly physical activity (None, mild, moderate, vigorous); alcohol consumption (daily or almost daily, others); smoking status (never smoker, ex-smoker, current smoker); body mass index (BMI, kg/m^2, categorized into underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9) and obese (≥30)),

Dental attendance: dental visit (regular, occasional, never),

Inflammatory Biomarkers: C-reactive protein level (mg/L, <1, 1-3, >3).

All covariates were measured at baseline in 2006/07, except dental visit which was obtained through linkage to health survey England, 1999 and 2001, and BMI and C-reactive protein level that were measured in 2004/2005.

Statistical analyses

Cognitive function scores at baseline were categorised into quintiles (1: 0-37, 2: 38-44, 3: 45-50, 4: 51-56, and 5: 57-86) to demonstrate relations with other variables. Higher cognitive scores or quintiles correspond to better cognitive function. Oral health was measured in three domains: teeth status, self-rated oral health, and OHRQoL. Continuous variables were presented as mean (SD) and categorical variables were reported as frequency (%).

Cross-lagged structural equation models were used to analyse the relationship between cognitive function and oral health at the three time points. The latent variable measuring cognitive function was termed 'general cognition', using the two observed cognitive variables— memory and executive function (entered independently into SEM). The latent variable measuring oral health was termed 'oral health', using the two observed variables relating to oral health—teeth status and self-reported oral health. Model 1 investigated the cross-lagged association between general cognition and oral health across three time points. Model 2 investigated the cross-lagged association between general cognition and OHRQoL. Cross-lagged effects were constrained to be equal for both models. Both models were also adjusted for baseline covariates. The plausibility of each model was assessed using the comparative fit index (CFI more than 0.9 would indicate good model fit) and root mean square estimate (RMSEA, less than 0.06 indicate good fit).[14] All models employed maximum likelihood estimation with robust standard errors, and accounted for between-participant difference.

Subgroup analysis was conducted for age groups 50-70 and >70 years to assess the impact of baseline age. Sensitivity analysis was performed for unconstraint model where cross-lagged effects were not constrained to be equal. Analyses were performed for the complete data only to assess the impact of missing data. Further sensitivity analysis was performed by excluding participants diagnosed with dementia. Mediation analysis investigated the effect of the inflammatory factor CRP on the association between cognitive function and oral health. The mediation effect of positive and negative social support from spouse, children, family and friends which are considered as modifiable risk factors, was also assessed.

Missing data in the covariate variables were imputed five times through multiple imputation by chained equations. Pooled modelling estimates and accompanying standard errors (SE) were generated according to Rubin's rules.[15]. Statistical analyses were performed in R version 3.4.1 (https://cran.r-project.org/) with various packages including SEM.

Results

Of 5477 participants included in the analyses, the average age was 63.1 years (SD 8.9 years) and 3087 (56.4%) were women. The average cognitive function score was

46.5(SD 12.3) and 3350 (61.2%) had natural teeth only, 1505 (27.5%) had teeth and a denture, and 622 (11.4%) were edentulous.

Baseline characteristics

Baseline characteristics of the study participants are summarized by the quintile of cognitive function score in table 1, and by oral health (table S1-3).

Better cognitive function (higher quintile) was associated with younger age (quintile 5, aged 59.55 (6.79) years vs quintile 1, aged 67.76 (9.72) years); higher proportion of participants having an educational degree (38.8% vs 7.2%); a lower proportion in the lowest quintile of total wealth (7.1% vs 21.1%); with less multimorbidity conditions; more physically active (87.2% vs 61.9%); and more regular dentist visits (77.9% vs 52.9%) (Table 1).

Similar patterns were found for oral health measured by teeth status (Table S1), self-rated oral health (Table S2), and OHRQoL (Table S3).

Relationship between cognitive function and Oral health

There was a strong association between cognitive function and oral health at baseline (Table1): a lower proportion of participants were edentulous in the highest cognitive function quintile compared with those in lowest cognitive quintile (4.5% vs 21.8%), fewer self-rated oral health as fair/poor (14.1% vs 20.7%), and fewer reported oral impacts on daily performances (OIDP 6.0% 10.3%).

Cross-lagged structural equation models were used to investigate the relation between general cognition and oral health, or OHRQoL. Both models fitted the data well (CFI = 0.95 and 0.97, RMSEA = 0.09 and 0.04, respectively). Figure 1 demonstrate the standardized estimates for both models, showing the factor loading for the measurement model and the coefficients for regression pathway model.

For model 1, general cognition was an important predictor of better oral health at later stage (beta = 0.02, 95% CI: 0.01-0.03), and vice versa (beta = 0.12, 95% CI: 0.06-0.18). The residuals were correlated between cognition and oral health at later two time points (p=0.004 and 0.013, respectively). For model 2, general cognition predicted better OHRQoL (beta = 0.02, 95% CI: 0.01-0.03), and vice versa (beta = 0.09, 95% CI: 0.01-0.17).

The pathway was stable when various modelling strategies were applied with different covariates to test the robustness the association (Table 2). The results for participants with complete data were similar to the main analysis (Table S4). Removing the equal constraint of the cross-lagged effects did not influence the bidirectional association between cognitive function and oral health (Table S5). Subgroup analyses for age groups 50-70 and >70 years showed consistent results to the main analysis (Table S6. Teeth status, when treated as single-item construct in the SEM, was a predictor of cognitive function. However, self-reported oral health became nonsignificant in predictions of cognitive function when treated separately (Figure S3). Excluding 23 (0.42%) participants with dementia did not affect the association. Cognitive function and oral health measures over the three time points at 2006/07, 2010/11, and 2014/15 was presented in Table S7.

Mediation analysis did not find an effect of inflammatory factor CRP on the association between cognitive function and oral health (Figure S2a). Similarly, social support did not mediate the relation between cognitive function and oral health (Figure S2b, c).

Discussion

In this 10-year longitudinal cohort study, we have demonstrated, for the first time, a positive reciprocal relationship between cognitive function and oral health in an ageing population using cross-lagged structural equation modelling. Better cognitive function at earlier stage predicted better oral health at later stage, and vice versa. This predictive association was robust despite adjustment for various demographic variables, comorbidities and/or health behaviours.

Our finding of the reciprocal relationship is consistent with previous unidirectional studies. Studies have shown evidence for the positive impact of cognitive function on better oral health , while other studies have demonstrated the negative impact of poor oral health on cognitive function [7, 16, 17]. A few longitudinal studies also reported negative findings of the association possibly due to small sample size and inadequate data collection.[7, 18] Several mechanisms could explain the link between oral health and cognitive function. Microorganisms, such as *Porphyromonas gingivalis*, could play a vital role in the disease pathway.[6] Combined with findings from murine models [19-21], it suggests that treating people with periodontitis and possibly reducing exposure to *Porphyromonas gingivalis* might reduce or delay the development of cognitive decline and prevent Alzheimer's disease in the long term. Another possible mechanism refers to the inflammatory pathway, where people with periodontitis or other oral disease are affected systemically by chronic oral inflammation. In this study we did not find any mediation effect from an inflammatory factor CRP, but people with regular dental visits showed better cognitive function at the later stages. This is consistent to the findings from a recent longitudinal study, which demonstrated that dental care service utilization was independently associated with cognitive decline among older adults in the U.S. [22] Diet and nutrition may also explain the association. Poor quality diet has been linked to cognitive decline in elderly people.[23] Older individuals with tooth loss, particularly edentulism, could suffer from impaired masticatory function and resultant poor nutritional status.[24, 25] However such mechanism could not be tested with the data available in ELSA. Additionally, people with poor cognitive function may lose the ability to self-care and fail to attend regular dental check-up, which in turn could contribute to poorer oral hygiene and lead to worse oral health and related quality of life.[26, 27] This study provides new knowledge on such interrelationship between cognitive function and oral health and related quality of life. The reciprocal benefit has important policy and clinical implications for designing interventions and providing care delivery programs that can integrate both dental and medical care to improve the overall health of the ageing population.

Our study has several strengths. Cross-lagged SEM has several advantages over more commonly used linear mixed model (LMM) approach for longitudinal data. SEM captures the simultaneous longitudinal bidirectional associations between cognitive function and oral health over time with less bias in the latent variables, and increases flexibility of modelling. [28] This study benefits from a large representative prospective longitudinal study cohort with a long period of follow-up as well. In addition, there were few missing data, especially with extensive assessment of cognitive function for a large-scale investigation.

That said, this study does have some limitations. First, there was no clinical assessment of oral health, and the available oral health measures were limited to teeth status, self-rated oral health, and OHRQoL. Second, a proportion of participants (44%) were lost at final follow-up from the 2006/07 baseline. However, their baseline cognitive function and oral health status were not different to the analytical sample in this study (data not shown). In addition, dental attendance was extracted from earlier data and was only available for half of the participants. Third, there might be unmeasured covariates that could impact or mediate the relationship between cognitive function and oral health, such as diet [29], oral hygiene behaviour (e.g. daily tooth brushing), or other systemic inflammatory biomarkers (e.g. interleukin-6) [30]. However, ELSA does not have such data to explore these potential confounding and mediating effects.

Conclusion

This is the first longitudinal study to demonstrate the bidirectional association between cognitive function and oral health in the same ageing population. Oral health and cognitive function are reciprocally linked by a positive feedback loop. Such a positive reciprocal relationship suggests the opportunities and potential gains for developing an integrated approach to inform interventions that simultaneously promote cognitive enhancement and oral health.

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Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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Table 1. Baseline characteristics of study participants by quintile of general cognitive function (range 0-100), ELSA (n = 5477), 2004-2014.

	Quintile of cognitive function					
Characteristics:	1075	1078	1084	1097	1059	p-value
Cognition function score, mean (SD)	29.08 (7.75)	41.03 (1.92)	47.00 (1.61)	53.04 (1.92)	62.72 (5.31)	<0.001
Age in years, mean (SD)	67.76 (9.72)	64.37 (9.28)	62.71 (8.46)	61.17 (7.75)	59.55 (6.79)	<0.001
Sex, male (%)						0.010
	496 (46.1)	491 (45.5)	477 (44.0)	461 (42.0)	417 (39.4)	
Married (%)	622 (57.9)	735 (68.2)	766 (70.7)	796 (72.6)	766 (72.3)	<0.001
Educational level (%)						<0.001
Degree or equivalent	77 (7.2)	132 (12.3)	185 (17.1)	255 (23.3)	410 (38.8)	
Some qualification	517 (48.2)	611 (56.8)	667 (61.5)	669 (61.2)	579 (54.7)	
No qualification	479 (44.6)	332 (30.9)	232 (21.4)	170 (15.5)	69 (6.5)	
Lowest wealth quintile (%)	206 (21.1)	129 (12.8)	102 (10.2)	80 (7.7)	72 (7.1)	<0.001
No. of cardiovascular condition (%)						<0.001
0	274 (28.2)	304 (33.1)	331 (35.9)	364 (39.9)	358 (40.9)	
1	285 (29.3)	300 (32.7)	284 (30.8)	300 (32.9)	309 (35.3)	
2	242 (24.9)	165 (18.0)	197 (21.4)	161 (17.6)	133 (15.2)	
≥ 3	171 (17.6)	149 (16.2)	110 (11.9)	88 (9.6)	76 (8.7)	
No. of non-cardiovascular condition (%)						<0.001
0	335 (34.5)	379 (41.3)	380 (41.2)	409 (44.8)	419 (47.8)	
1	401 (41.3)	350 (38.1)	351 (38.1)	304 (33.3)	325 (37.1)	
2	165 (17.0)	136 (14.8)	140 (15.2)	152 (16.6)	105 (12.0)	
≥ 3	71 (7.3)	53 (5.8)	51 (5.5)	48 (5.3)	27 (3.1)	
smoking status (%)						<0.001
Never smoker	408 (38.0)	415 (38.5)	410 (37.9)	448 (40.8)	473 (44.7)	
Ex-smoker	493 (45.9)	504 (46.8)	510 (47.1)	521 (47.5)	478 (45.1)	
Current smoker	174 (16.2)	159 (14.7)	163 (15.1)	128 (11.7)	108 (10.2)	
Daily or almost daily alcohol consumption (%)	229 (21.3)	311 (28.8)	359 (33.1)	399 (36.4)	500 (47.2)	<0.001

Weekly physical exercise, moderate/vigorous (%)	665 (61.9)	807 (74.9)	820 (75.8)	911 (83.1)	922 (87.2)	<0.001
CESD symptoms ≥ 4 (%)	208 (19.5)	148 (13.8)	123 (11.4)	106 (9.7)	81 (7.7)	<0.001
BMI, mean (SD)	28.25 (4.81)	28.17 (4.88)	27.97 (4.90)	28.02 (4.92)	27.50 (4.91)	0.032
C-reactive protein level, mean (SD)	3.89 (5.50)	3.55 (5.25)	3.27 (4.63)	3.12 (4.91)	3.10 (5.60)	0.027
Dental visit (%)						<0.001
Regular	289 (52.9)	332 (63.6)	347 (67.6)	398 (73.6)	399 (77.9)	
Occasional	127 (23.3)	124 (23.8)	99 (19.3)	89 (16.5)	91 (17.8)	
Never	130 (23.8)	66 (12.6)	67 (13.1)	54 (10.0)	22 (4.3)	
Teeth condition (%)						<0.001
Edentulous	234 (21.8)	141 (13.1)	112 (10.3)	77 (7.0)	48 (4.5)	
Teeth + denture	363 (33.8)	340 (31.5)	302 (27.9)	265 (24.2)	218 (20.6)	
Teeth only	478 (44.5)	597 (55.4)	669 (61.8)	755 (68.8)	792 (74.9)	
Self-rated oral health (%)						0.002
Poor	46 (4.3)	48 (4.5)	37 (3.4)	34 (3.1)	25 (2.4)	
Fair	176 (16.4)	149 (13.8)	131 (12.1)	136 (12.4)	124 (11.7)	
Good	424 (39.4)	427 (39.6)	399 (36.8)	428 (39.0)	421 (39.8)	
Very good	301 (28.0)	302 (28.0)	365 (33.7)	330 (30.1)	320 (30.2)	
Excellent	128 (11.9)	152 (14.1)	152 (14.0)	169 (15.4)	169 (16.0)	
Dental health related quality of life (%)	111 (10.3)	100 (9.3)	80 (7.4)	70 (6.4)	64 (6.0)	0.001

Note: frequency (%) is reported unless specified; SD, standard deviation; CESD, Center for Epidemiological Studies Depression; BMI, body mass index.

a. Cognitive function scores theoretical range is 0-100, with weighted score 0-50 to memory test and 0-50 to executive function test. Grouped by quintiles as follows: quintile 1 (lowest), 0-37; quintile 2, 38-44; quintile 3, 45-50; quintile 4, 51-56; quintile 5, 57-86.

b. P-value for trend for dichotomous and continuous variables; otherwise P-value for heterogeneity.

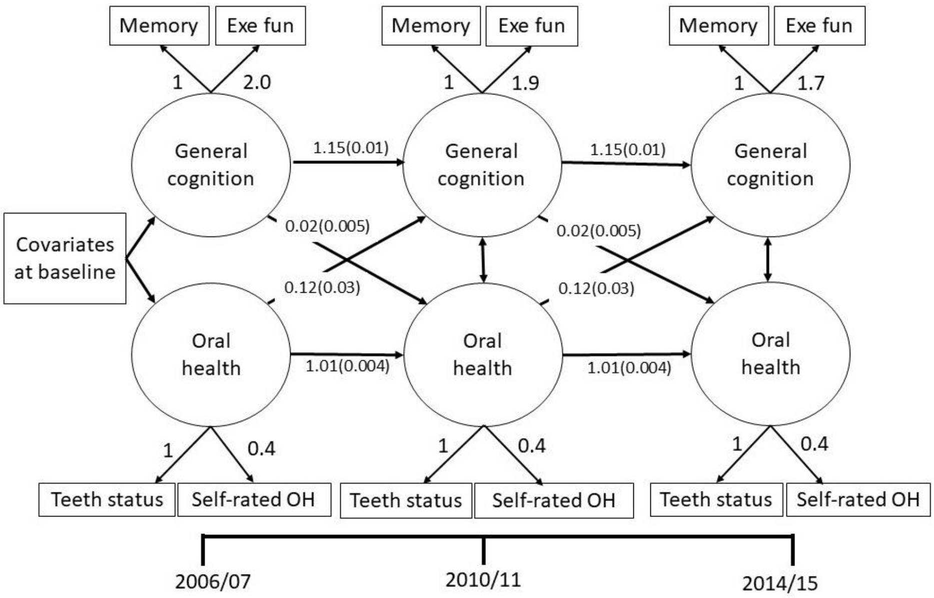
Table 2. Coefficient estimates for the bidirectional longitudinal association between cognitive function (CF) and oral health (OH), ELSA (n = 5477), 2004-2014.

	Models adjusted by				
	unadjusted	demographics[a]	demographics and comorbidities[b]	demographics and health behaviour[c]	fully adjusted[d]
Model 1[e]					
predictive associations					
CF->CF	1.13 (0.02)***	1.14 (0.01)***	1.13 (0.01)***	1.15 (0.01)***	1.14 (0.01)***
CF->OH	0.005 (0.003)	0.03 (0.005)***	0.03 (0.005)***	0.02 (0.005)***	0.02 (0.005)***
OH->CF	0.08 (0.03)**	0.17 (0.03)***	0.16 (0.03)***	0.12 (0.03)***	0.11 (0.03)***
OH->OH	1.00 (0.004)***	1.01 (0.004)***	1.01 (0.004)***	1.01 (0.004)	1.01 (0.004)***
residual correlations					
CF2<->OH2	ns	-0.12 (0.03)***	-0.11 (0.03)***	-0.09 (0.03)**	-0.09 (0.03)**
CF3<->OH3	ns	-0.18 (0.04)***	-0.16 (0.04)***	-0.11 (0.04)**	-0.11 (0.04)*
Model 2[e]					
predictive associations					
CF->CF	1.14 (0.02)***	1.16 (0.01)***	1.16 (0.01)***	1.17 (0.01)***	1.16 (0.01)***
CF->OIDP	0.03 (0.007)***	0.03 (0.01)***	0.03 (0.01)***	0.02 (0.01)**	0.02 (0.01)*
OIDP->CF	0.40 (0.07)***	0.15 (0.04)***	0.12 (0.04)***	0.08 (0.04)*	0.07 (0.04)*
OIDP->OIDP	0.63 (0.03)***	0.48 (0.02)***	0.48 (0.02)***	0.47 (0.02)***	0.47 (0.02)***
residual correlations					
CF2<->OIDP2	-0.29 (0.07)***	-0.17 (0.06)**	-0.16 (0.06)**	-0.13 (0.06)*	-0.13 (0.06)*
CF3<->OIDP3	ns	ns	ns	ns	ns

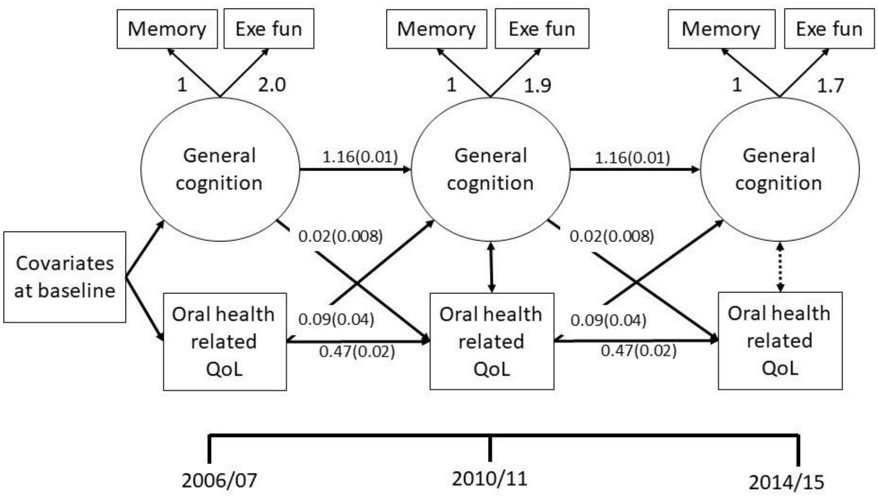
Note: ***p-value<0.001; *p-value<0.05

a. Demographics include age, sex, marital status, education qualification, and total wealth.
b. Comorbidities comprised of number of cardiovascular and non-cardiovascular conditions and CESD depression score.
c. Health behaviours comprised alcohol intake, smoking status, weekly physical activity, dentist visit, C-reactive protein, and body mass index.
d. Adjustment for all the covariates listed above.
e. Model 1: oral health measure in latent model as 'oral health'; Model 2: oral health measured by oral related quality of life using OIDP

Figure 1. Pathway diagram of the structural equation models: (a) cognitive function vs oral health, and (b) cognitive function vs oral health related qualify of life. Depiction of the main findings of the study using three time points bivariate autoregressive cross-lagged structural equation model testing the longitudinal association between cognitive function and oral health, in 2006/07, 2010/11, and 2014/15. Observed variables are presented in rectangles, and latent variables are presented in circles. Solid line with bolded estimates indicates associations. OH = oral health; QoL = quality of life.



a)



b)