Sun et al. BMC Public Health (2024) 24:3516
https://doi.org/10.1186/s12889-024-21072-w

BMC Public Health

RESEARCH

Open Access

Dynamic relations between longitudinal morphological, behavioral, and emotional indicators and cognitive impairment: evidence from the Chinese Longitudinal Healthy Longevity Survey

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Abstract

Background We aimed to assess the effects of body mass index (BMI), activities of daily living (ADL), and subjective well-being (SWB) on cognitive impairment and propose dynamic risk prediction models for aging cognitive decline.

Methods We leveraged the Chinese Longitudinal Healthy Longevity Survey from 1998 to 2018. Cognitive status was measured using the Chinese Mini-Mental State Examination. We employed repeated measures correlation to assess associations, linear mixed-effect models to characterize the longitudinal changes, and Cox proportional hazard regression to model survival time. Dynamic predictive models were established based on the Bayesian joint model and deep learning approach named dynamic-DeepHit. Marginal structural Cox models were adopted to control for time-varying confounding factors and assess effect sizes.

Results ADL, SWB, and BMI showed protective effects on cognitive impairment after controlling observed confounding factors, with respective direct hazard ratios of 0.756 (0.741, 0.771), 0.912 (0.902, 0.921), and 0.919 (0.909, 0.929). Dynamic risk predictive models manifested high accuracy (best AUC = 0.89). ADL was endowed with the best predictive capability, although the combination of BMI, ADL, and SWB showed the most remarkable performance.

Conclusions BMI, ADL, and SWB are protective factors for cognitive impairment. A dynamic prediction model using these indicators can efficiently identify vulnerable individuals with high accuracy.

Keywords Aging cognitive impairment, Dynamic risk prediction, Bayesian joint model, Deep survival model, Longitudinal causal inference, Body mass index, Activities of daily living, Subjective well-being

Background

The rapid escalation of aging has become a crucial global concern, entailing daunting challenges that place a substantial burden, especially within the realm of public health [1]. With the proportion of individuals aged 60 and above reaching 18.7% in 2020 [2], China has emerged as the nation with the largest and most rapidly expanding population of older adults, signifying the significant growth of aging demographics.

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Despite significant achievements, the increasingly aging society still causes great challenges, including labor shortages, expanding government spending, and inadequate and unevenly distributed health care systems [3]. Compared to physical needs, the mental health of older adults has not received sufficient attention [4]. Older adults are susceptible to a series of mental and psychological problems, and cognitive impairment is a common example. It is estimated that there are approximately 36 million people suffering from cognitive impairment worldwide, and this number is expected to reach 115 million by 2050 [5]. Half of patients with mild cognitive impairment will develop severe impairment or even dementia within 5 years [6]. A better understanding of risk factors is necessary to ameliorate this problem.

The decline in cognitive abilities during the aging process is associated with changes in various physiological, behavioral, and psychological indicators, including body mass index (BMI), a common-used morphological indicator associated with multiple physical disorders [7–9]; activities of daily living (ADL), measuring the functional ability in living and participating activities out of their own intention and preference [10]; and subjective well-being (SWB), representing the participant's emotional status by capturing self-judgments of overall life satisfaction and fulfillment. However, there are still drawbacks, even leading to controversies on the effect sizes. First, previous studies usually model the longitudinal and survival outcomes separately [11–13], ignoring the dynamic interaction between time-varying indicators and cognition decline during aging process. Since the common-used Cox proportional hazard model assumes the proportional odds of hazard functions to be constant over time, the estimates may be biased [14] when tackling longitudinal covariates due to the existence of multiple time-fixed and time-varying confounding factors. For example, the role of BMI is particularly confusing, as some reported that a decline in BMI is an alarm of cognitive disorders [3, 15–21], while others suggested that lower BMI decreases the risk of cognitive impairment [22, 23]. Besides, previous studies lacked an evaluation of the predictive ability of these indicators for cognitive impairment. In particular, the valuable information contained within the longitudinal history will be disregarded, while the dynamic changes observed between follow-up periods often serve as crucial indicators for disease onset.

To overcome the above drawbacks, in this study, we aimed to conduct a comprehensive assessment on the effect of BMI, ADL, and SWB in cognitive decline, and establish dynamic predictive models for cognitive impairment using these longitudinal indicators. Inspired by the idea of triangulation evidence [24], in this study, we integrated diverse methods to assess the effects of risk factors and use the identified factors to establish dynamic risk prediction models for cognitive impairment, using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) [25, 26], a long-term, large-scale Chinese cohort study. We leveraged a linear mixed-effect model (LMM), repeated measures correlation (rmcorr), time-dependent Cox regression, and Bayesian joint model to examine the association of BMI, ADL, and SWB with cognitive impairment. We further evaluated hazard ratios (HRs) using a marginal structural Cox model (Cox-MSM) to control for observed time-varying confounding. In addition to the effect assessment, we employed the Bayesian joint model and a deep learning-based dynamic survival model to evaluate the predictive performance using the longitudinal history of these indicators.

Methods

Study design and participants

The baseline survey of CLHLS was conducted in 1998, with follow-up surveys with replacement for deceased participants in the following 7 waves, conducted in 2000, 2002, 2005, 2008–2009, 2011–2012, 2014, and 2017–2018, in randomly selected about half of the counties and city districts of 23 out of 31 Chinese provinces. Participants over 80 were recruited in the first two waves, and older adults aged 65–79 were included since 2002. Covering areas of around 85% of the total population of China, CLHLS has the largest coverage, the longest tracking time, the most complete data, and the greatest social influence in the field of longevity health in China. Details about the CLHLS design have been outlined [25, 26]. We compiled all CLHLS records from 1998 to 2018 and imposed the following screening criteria. We excluded the following participants and records: (a) records without cognitive information; (b) subjects diagnosed with cognitive impairment or dementia at enrollment; (c) follow-up records of subjects after they were diagnosed with cognitive impairment; (d) subjects with only one measurement before diagnosed or censoring (including those who were enrolled for the first time in 2018). 20,148 samples with 57,302 records were included in this study. Details of the participants included in each wave can be found in Supplementary Table S1-S2.

Measurements

Several demographic characteristics at enrollment were included as time-invariant covariates, including sex, baseline age, residence, education, occupation before retirement, and marital status (Table 1). Following previous studies [27, 28], given the relatively low level of education among Chinese older adults, education was classified into two categories: illiterate and literate, according to whether they have been educated in school.

Table 1 Descriptive statistics of baseline demographic characteristics and indicator values

	Case (outcome = 1)	Control (outcome = 0)	All	Difference between groups[a]
Sex				
Female (0)	70.94%	47.67%	54.61%	$P < 0.001$
Male (1)	29.06%	52.33%	45.39%	
Age (at enrollment)				
≤ 70 (1)	3.56%	22.91%	17.14%	$P < 0.001$
71 ~ 80 (2)	11.75%	24.78%	20.90%	
81 ~ 90 (3)	32.03%	33.17%	32.83%	
> 90 (4)	52.66%	19.14%	29.13%	
mean	89.35	80.31	83.63	
Resident				
Rural (0)	65.83%	57.33%	57.33%	$P < 0.001$
Urban (1)	34.17%	42.67%	42.67%	
Education				
Illiterate (0)	79.47%	50.41%	59.06%	$P < 0.001$
Literate (1)	20.53%	49.59%	40.94%	
Mean years	0.99	2.81	2.22	
Occupation				
Physical (0)	97.06%	89.31%	91.63%	$P < 0.001$
Mental (1)	2.94%	10.69%	8.37%	
Marital status				
Never married (0)	1.00%	1.20%	1.14%	$P < 0.001$
Married but currently single (1)	80.87%	54.20%	62.16%	
Currently married (2)	18.13%	44.60%	36.71%	$P < 0.001$
ADL				
Mean	11.38	11.81	11.57	$P < 0.001$
SWB				
Mean	28.74	30.38	29.94	$P < 0.001$
BMI				
Mean	19.58	20.89	20.42	$P < 0.001$
Sample Size	6,008 (29.82%)	14,140 (70.18%)	20,148	
Number of records	16,178	41,124	57,302	

[a] Details about the test for difference between case and control group in baseline are shown in Supplementary Table S6

Baseline ages were divided into four groups: 65–70, 71–80, 81–90, and above 90.

BMI was calculated by dividing the participant's weight (in kilograms) by the square of their height (in meters). For the first four waves without records on height, height was converted from knee height (height = 0.6778 + 2.01 × knee height for men and height = 0.7408 + 1.81 × knee height for women) [29, 30] or interpolated from the average of the two most recent height measurements.

We used Katz scale to assess the basic ADL, where each respondent was asked about their ability to perform the daily activities of bathing, dressing, toileting, indoor mobility, bowel control, and eating (Supplementary Table S3). Scores were assigned based on their reported completion of these activities using a three-point scale (2: independent; 1: partial limited or requiring assistance from one person; 0: totally limited or requiring assistance from two or more people) [31, 32]. ADL is the sum of each item, ranging from 0 to 12, and higher score represents better ability.

SWB was measured using a five-point Likert scale with eight items covering life satisfaction, positive emotions (optimism, happiness, personal control, and conscientiousness), and negative emotions (anxiety, loneliness, and uselessness) (Supplementary Table S4). Life satisfaction was assessed from 1 (very bad) to 5 (very good). The answers for positive emotions were coded from 1 (never) to 5 (always), while negative items were reversely coded [13, 33, 34]. SWB is the sum across all items, with the maximum 40, and higher score indicates more positive SWB.

Cognitive status was measured using the Chinese Mini-Mental State Examination (CMMSE) [35], revised from the commonly used Mini-Mental State Examination (MMSE) [36] to adapt to the Chinese population (Supplementary Table S5). The final score varied from 0 to 30, with a lower score representing worse cognitive ability. Previous studies have revealed that education has a significant effect on scores on the CMMSE, and cut-off scores are recommended to vary accordingly [35, 37, 38]. Since most of the participants had received little or no education, individuals with scores lower than 18 were identified as cognitive impairment patients, following previous analysis on cognitive impairment using CLHLS [39, 40].

Longitudinal indicators including BMI, ADL, and SWB, as well as cognitive status were assessed at each follow-up. For time-invariant demographic covariates, measurements at enrollment were used only.

Association analysis

We utilized LMM to describe overall trends in longitudinal covariates. In addition to the conventionally used Pearson and Spearman correlations, we used rmcorr [41], a longitudinal correlation coefficient based on analysis of covariance (ANCOVA), to determine the relationships between CMMSE scores and longitudinal indicators (ADL, SWB, and BMI). Both time-invariant (using baseline information only) and time-dependent Cox proportional hazard regressions were used to assess the effects of covariates on cognitive impairment risk, where the latter is assumed the covariate's effect on the outcome is constant over the follow-up time to meet the requirement of proportional hazards assumption [42].

The joint model is a statistical framework integrating both longitudinal and survival submodels by imposing an association function $g(\cdot)$ to link the longitudinal responses in the LMM as explanatory covariates in survival analysis [43]. To simplify the model, we assumed that the hazard function at each time related to the current value of longitudinal variables and HR remained the same for each time point. Therefore, we adopt the following model:

$$y_i(t) = m_i(t) + \varepsilon_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t_i + \varepsilon_i(t)$$

$$h(t|\boldsymbol{w}_i, M_i(t)) = h_0(t)e^{\gamma^{T}w_i + \alpha g[m_i(t)]} = h_0(t)e^{\gamma^{T}w_i + \alpha m_i(t)}$$

Where $y_i(t)$ represents the observed longitudinal response at time t for individual i, $m_i(t)$ is the part that can be explained by the LMM, $\boldsymbol{w}_i$ stands for the baseline time-independent covariates (baseline demographic characteristics mentioned in "Measurements" section) of individual i, and $h(t)$ represents the hazard function. BMI, ADL, and SWB were used as single longitudinal response separately in three joint models.

We conducted stratified tenfold cross-validation to evaluate the prediction performance of the baseline Cox model and Bayesian joint models (see Methodology Appendix). Time-dependent areas under the receiver operating characteristic curves (AUCs) for baseline Cox models were examined using both incident sensitivity and cumulative sensitivity [44]. The AUCs of joint models are predicted in time window $(t, t + \Delta t)$ using longitudinal history from inclusion until time t for those who survive at time t.

Cox regression, LMM, and rmcorr were conducted using the R packages survival, nlme, and rmcorr. The Bayesian joint model was established using the R package JMbayes, which uses Markov chain Monte Carlo (MCMC) algorithms to attain the posterior estimation of the joint model. All of the reported probabilities are two-sided.

Deep learning-based dynamic predictive model

The Bayesian joint model confronted tricky problems in computation when coping with a large sample size and multivariate longitudinal outcomes. Therefore, we introduce dynamic-DeepHit, a deep learning-based approach to predict the cumulative incidence function (CIF) according to the longitudinal history [45]. It utilizes a recurrent neural network (RNN) module, a gated recurrent unit (GRU), and a temporal attention mechanism to extract the longitudinal features and assign weights to different measurements. The extracted features are then imported to train a feed-forward network by minimizing the total loss function, which is defined as a combination of a log-likelihood loss to capture the first hitting time, a ranking loss to adapt the requirement of concordance, and an RNN prediction loss to enhance the ability of longitudinal feature extraction. The time-dependent concordance index (C-index) $C(t, \Delta t)$ [45] was used to examine the discrimination performance of dynamic-DeepHit, defined by comparing two participants' estimated CIFs at time $t + \Delta t$ based on the longitudinal history from baseline to time t. We implemented the deep learning-based analysis with TensorFlow 1.13, and details can be found in the methodology Appendix.

Longitudinal causal inference with the marginal structure cox model

We resorted to the Cox-MSM [46, 47] to inspect whether the correlation between these indicators and cognitive ability could be attributed to causality, which mimic the conditions of a randomized controlled trial by reweighting the observed data. A longitudinal indicator's (e.g., ADL) direct effect on cognitive impairment was evaluated by imposing stabilized inverse-probability weights (IPWs) on each sample, with baseline demographic characteristics as time-fixed covariates V_i and two other indicators as time-varying confounding L_{ij} (e.g., SWB and BMI). For each time point $t_{i,k}$ of individual i, we used lagged history of exposure $\overline{A}_{i,k-1}$ from time $t_{i,0}$ to the nearest previous time $t_{i,k-1}$, and full history of other time-varying confounding $\overline{\boldsymbol{L}}_{i,k}$ from time $t_{i,0}$ to the current time $t_{i,k}$, and the stabilized IPW are estimated as

$$sw_{ij} = \prod_{k=0}^{j} \frac{p\left(A_{i,k}|\overline{A}_{i,k-1}, \boldsymbol{V}_i\right)}{p\left(A_{i,k}|\overline{A}_{i,k-1}, \overline{\boldsymbol{L}}_{i,k}, \boldsymbol{V}_i\right)},$$

where the probability density $p(\cdot)$ was estimated via generalized estimating equation (GEE) models. The weighted "pseudo-population" was then fitted into Cox-MSMs [48] so that the average causal HR could be estimated. The causal analysis was implemented with the R package IPW [49, 50].

Results

Descriptive analysis

A total of 20,148 samples were included in the analysis. As shown in Table 1, in the case (cognitive impairment) group, the proportions of women, people living in rural areas, illiterate people, people with manual labor occupations, and people who were single were all higher than those in the control group ($P < 0.001$). The participants ending up with cognitive impairment also had a higher average age ($P < 0.001$). Compared to the case group, participants in the control group had a higher BMI, ADL, and SWB as well ($P < 0.001$). Significant test details are shown in Supplementary Table S6.

We first used measurements at baseline to conduct a time-invariant correlation analysis. Various factors were revealed to be related to cognitive impairment (Supplementary Table S6, Supplementary Figure S1), and these factors were also interrelated (Supplementary Figure S2). Generally, single people with older age, less education, lower BMI, living in rural areas and less engaged in mental labor were more likely to suffer from cognitive impairment. Insufficient ability to perform daily activities and depressed mood were also related to an increased risk of cognitive impairment.

Figure 1 shows the changes in BMI, ADL, and SWB for all participants. A dramatical decreasing trend in ADL can be observed in the case group, while the overall trend in control group remained almost constant. Repeated-measurement correlation analysis (Supplementary Table S7, Supplementary Figure S3) further supported the positive association between ADL and cognitive status [rmcorr r = 0.360, $P < 0.001$]. A positive correlation also existed between SWB and cognitive status [rmcorr r = 0.163, $P < 0.001$]. SWB decreased over time in the case group, whereas it remained fairly stable in the control group. Although BMI exhibited an increasing trend over time in both groups, the mean value remained higher in the control group, with a slight positive correlation

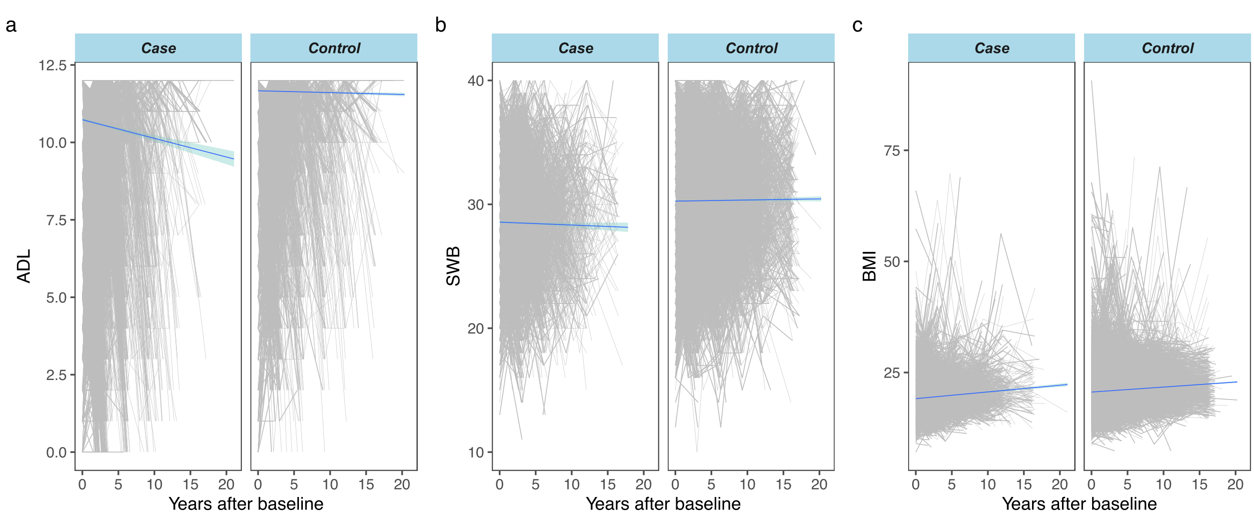

Fig. 1 Changes and correlations of longitudinal covariates over years. Changes in ADL (**a**), SWB (**b**), and BMI (**c**) after baseline. The gray lines represent the trajectories of each individual, the blue line represents the average trend estimated through the linear mixed-effect model, and the cyan shading represents the confidence interval of the average trend. ADL: ability of daily living; BMI: body mass index; SWB: subjective well-being

reported between BMI and CMMSE score [rmcorr r = 0.032, $P < 0.001$].

Bayesian joint models show remarkable discriminant performance

In Bayesian joint model (Table 2), higher BMI, ADL and SWB all manifested protective effects on cognitive impairment. Older adults with a lower BMI, weaker ability to perform daily activities, and more negative affect were associated with a higher risk of cognitive impairment.

All three indicators show remarkable discriminant abilities in cross-validation (Fig. 2a-b), especially when longitudinal records of the past 10 years were used to predict the status in the next 2 years, and the AUC reached 0.89 (Fig. 2b). To our surprise, using fewer historical records or predicting in a longer time window will not reduce the accuracy monotonically. This is likely to be attributed to a decrease in sample size when modeling and evaluating over a longer time period. Overall, the morphological, behavioral, and emotional indicators exhibit a substantial and enduring ability to discriminate cognitive impairment, with ADL emerging as the most informative predictor.

Deep survival models suggest indicator interaction

Despite the theoretical feasibility, the Bayesian joint models failed to model the three longitudinal indicators simultaneously due to computational burdens. As a complement, dynamic-DeepHit, involving baseline demographic characteristics and the combinations of three longitudinal indicators as predictors, was introduced to further examine how the longitudinal indicators incorporate each other. As shown in Fig. 2c, the collaboration of all three indicators manifested a considerable prediction accuracy (with the maximum C-index reaching 0.87). Compared to the benchmark, ADL, BMI, and SWB all boosted the model's discriminant ability, while ADL made the most remarkable contribution, similar to the findings in the joint model. While mood status alone demonstrated relatively weak predictive power for cognitive decline, the addition of SWB yielded greater improvement in prediction performance compared to the inclusion of BMI when ADL was already present in the model. This finding suggested potential interactions among mood, motor ability, and cognition.

Marginal structure cox models estimate effect sizes by controlling observed confounding

Both baseline (Fig. 3a) and time-dependent Cox models (Fig. 3b) manifested the protective effects of ADL, SWB, and BMI. However, the existence of coactions among these factors, as indicated by the dynamic-DeepHit models above, might damage the effect estimation.

As a consequence, we then explored the direct effect of each longitudinal indicator by adopting Cox-MSMs to

Table 2 Dynamic associations measured by the Bayesian joint model [a]

	BMI		ADL		SWB	
	coefficient	***P* value**[b]	**coefficient**	***P* value**	**coefficient**	***P* value**
Sex	-0.127 (-0.195, -0.062)	< 0.001	-0.038 (-0.100, 0.031)	0.253	-0.160 (-0.226, -0.097)	< 0.001
Age	1.058 (1.019, 1.094)	< 0.001	0.907 (0.873, 0.941)	< 0.001	1.058 (1.017, 1.098)	< 0.001
Residence	0.000 (-0.053, 0.056)	0.998	-0.075 (-0.132, -0.022)	0.007	0.007 (-0.052, 0.064)	0.832
Education	-0.456 (-0.540, -0.380)	< 0.001	-0.434 (-0.510, -0.357)	< 0.001	-0.463 (-0.546, -0.384)	< 0.001
Occupation	-0.417 (-0.575, -0.274)	< 0.001	-0.543 (-0.709, -0.379)	< 0.001	-0.439 (-0.603, -0.282)	< 0.001
Marital status	-0.319 (-0.397, -0.252)	< 0.001	-0.350 (-0.418, -0.273)	< 0.001	-0.329 (-0.398, -0.248)	< 0.001
Dynamic association	-0.172 (-0.214, -0.126)	< 0.001	-2.866 (-2.980, -2.745)	< 0.001	-0.325 (-0.365, -0.302)	< 0.001
Sample size	19,424		19,566		19,193	
Total number of records	54,268		55,247		50,244	

[a] There are 20,000 iterations in each joint model with the first 3000 iterations for burn-in. Default priors are used. The dynamic association in the table corresponds to the coefficients of BMI, ADL, and SWB. Min–max normalized ADL and SWB, and z-score normalized BMI are used to facilitate model convergence. The values in parentheses correspond to 95% confidence intervals

[b] *P* values are calculated as $2 \times \min\{P(\theta > 0), P(\theta < 0)\}$, where θ represents the corresponding regression coefficient in the joint model

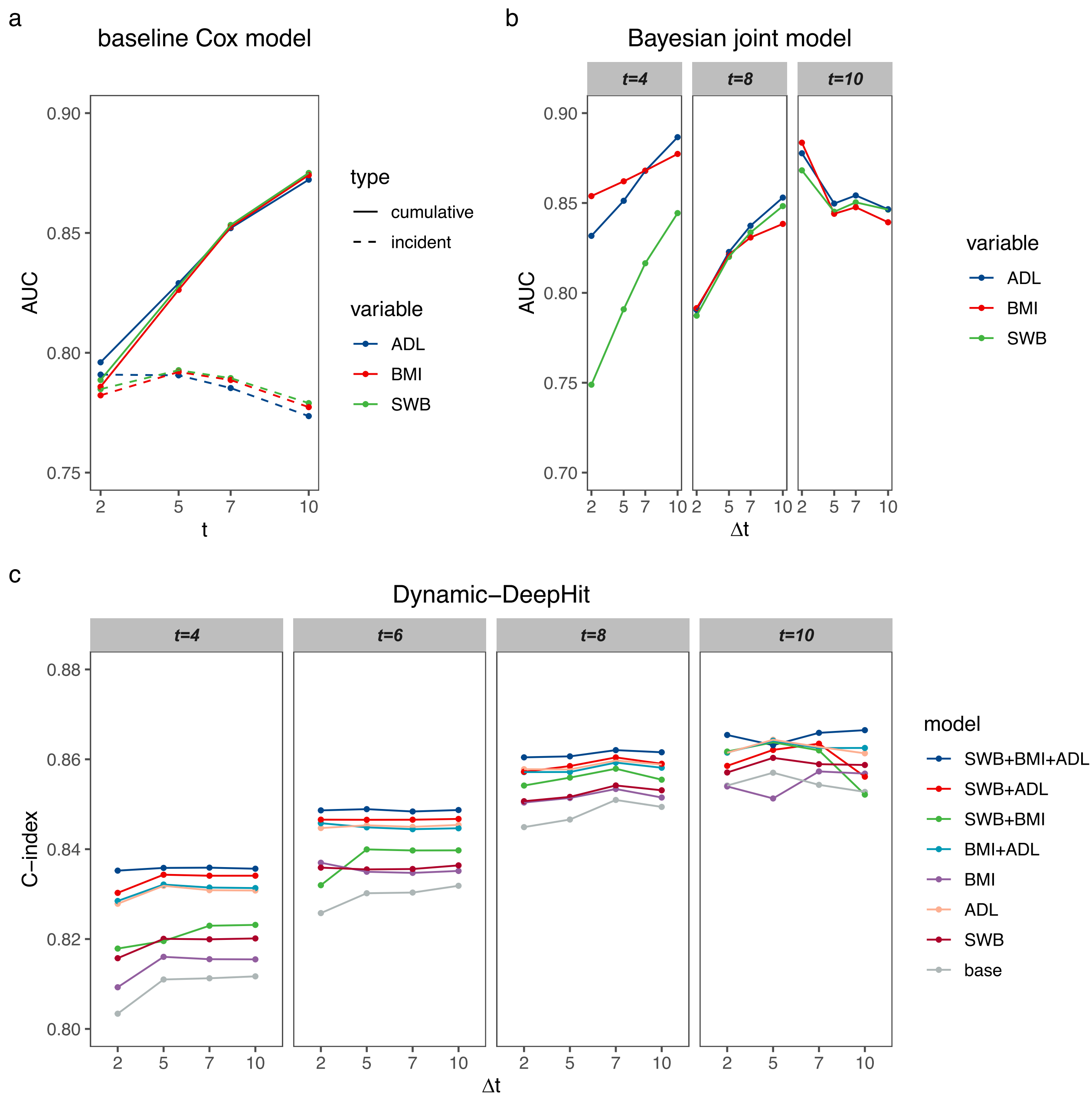

Fig. 2 Prediction performance of baseline Cox models (**a**), Bayesian joint models (**b**), and dynamic-DeepHit (**c**). **a** The prediction AUCs of the baseline Cox model in tenfold cross-validation. The horizontal axis is the prediction time (year). Time-dependent AUCs for both incident sensitivity (solid) and cumulative sensitivity (dashed) are shown. **b** The prediction AUCs of the joint model. The AUCs are predicted at time $t + \Delta t$ (prediction time) using measurements until time t (collection time) for those who survive at time t after inclusion. The horizontal axis is the evaluated time interval Δt, and the vertical axis is the mean AUC of the tenfold cross-validation. The caption shows the collection time (t), i.e., t=4 means using measurement history till the 4th year after baseline. **c.** The dynamic C-index of dynamic-DeepHit, estimated at time $t + \Delta t$ (prediction time) based on the longitudinal history from baseline to time t (collection time). The horizontal axis is the evaluated time interval Δt, and the vertical axis is the mean AUC of the tenfold cross-validation. The caption shows the collection time (t), i.e., t=4 means using measurement history till the 4th year after baseline. Cross validation is conducted among subjects with records on all three indicators at baseline for baseline model, and among subjects with at least twice records for Bayesian joint model and dynamic-DeepHit. Subjects with cognitive impairment at enrollment were removed, as well as the follow-up records of other subjects after they were diagnosed with cognitive impairment. ADL: ability of daily living; BMI: body mass index; SWB: subjective well-being; CI: cognitive impairment. Benchmark: dynamic-DeepHit with baseline demographic characteristics only

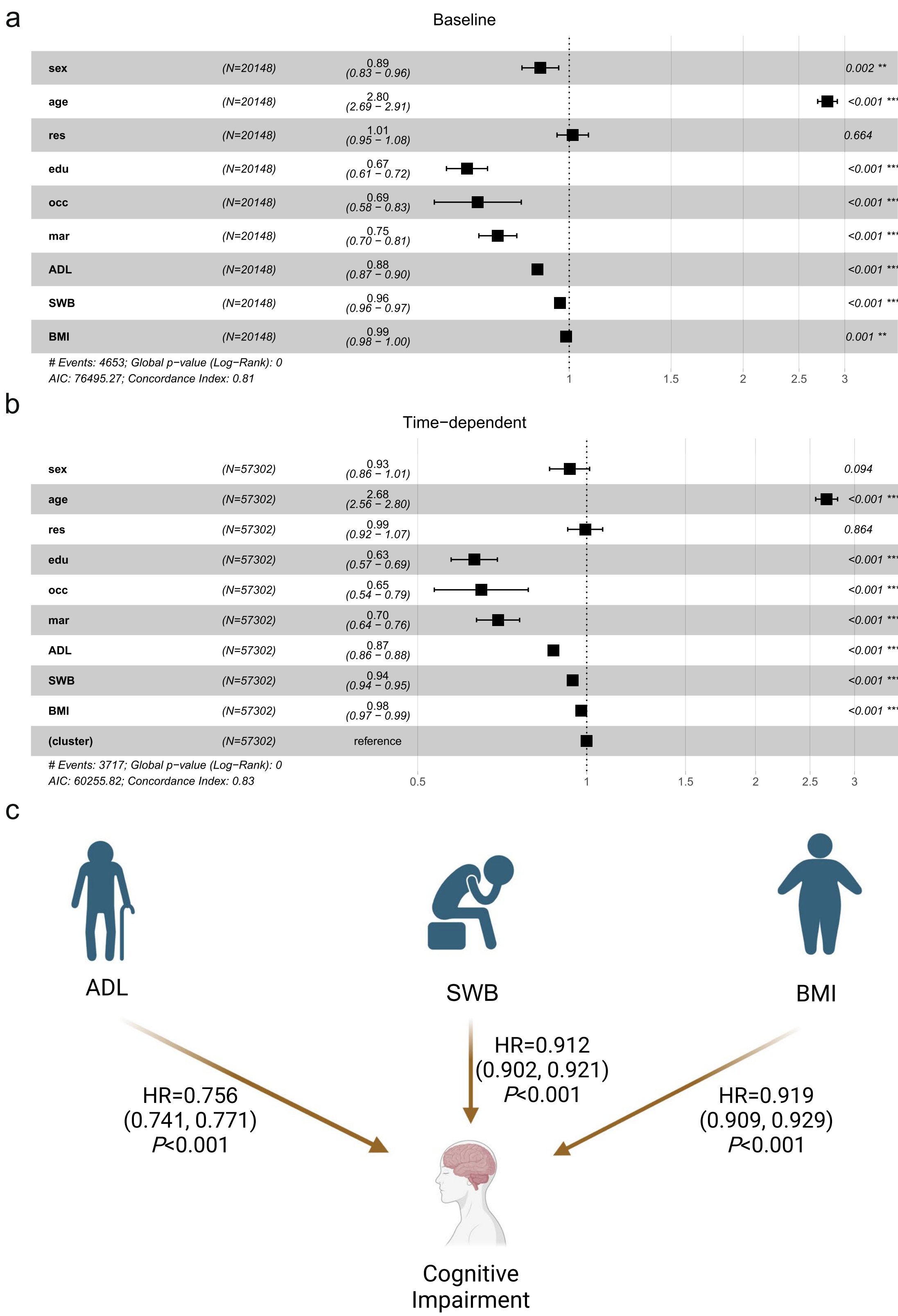

Fig. 3 Results of the time-invariant Cox model for baseline data (**a**), time-dependent Cox model using longitudinal covariates (**b**), and marginal structural Cox models (Cox-MSMs) (**c**). The scale represents the HRs and corresponding 95% confidence intervals. Figure 3c illustrates the direct effect of each longitudinal indicator by controlling baseline demographic characteristics and the other two indicators, estimated through MSMs. res: residence, edu: education level, occ: occupation, mar: marital status, ADL: ability of daily living; BMI: body mass index; SWB: subjective well-being

control both static and time-varying confounding. When evaluating a particular indicator's effect, we regarded other covariates and indicators as confounding to calculate the stabilized IPW. All three indicators suggested significant direct effects, with respective direct hazard ratios of 0.756 (0.741, 0.771), 0.912 (0.902, 0.921), and 0.919 (0.909, 0.929) (Fig. 3c). ADL showed the strongest protective effect.

The results provided evidence of causality under the assumption of no unobserved confounding, which indicated that longitudinal morphological, behavioral, and emotional indicators could be regarded not only as predictors but also as potential treatment targets, discussed thoroughly in the discussion section.

Subgroup analyses

Employing Bayesian joint model (Supplementary Tables S8-S13) and Cox-MSMs (Supplementary Table S14), we conducted subgroup analysis according to sex and baseline age to explore population heterogeneity. Both models reveal that the effects of BMI, ADL, and SWB are larger in younger older adults (baseline age ≤ 80) compared to those with advanced ages. Besides, it is also supported by both models that ADL shows more remarkable protective effects on cognition in males while BMI's effect is slightly larger in females. The sex differences in the impact of SWB on cognition seem to be somewhat complex. The joint model shows that males are more sensitive to changes in SWB, while the Cox-MSM indicates that the impacts are similar for both sexes, with a slightly stronger effect for females. This difference may arise from the age distribution difference between two sexes: the female sample has a larger proportion of individuals with advanced ages, who tend to be less sensitive to SWB, which leads to a smaller effect size of SWB on females estimated in the joint model. This bias is eliminated in the confounder-adjusted MSM, where the age imbalance is accounted and adjusted.

The above subgrouping based on baseline age is still insufficient to capture dynamic progression with age. The loess-smoothed trends in BMI, ADL, and SWB with ages in different age groups (Supplementary Figure S4-S5) show that the control group had higher mean levels of the three indicators than the case group (excluding subjects with very advanced age like age above 110, where the very limited sample size damage the stabilization of curve estimation), the differences in BMI between control and case groups tend to diminish slightly with age, while an obvious increasing trend in ADL. The results are consistent with the average trend with age in both groups estimated by linear or non-parametric mixed-effect model (with a random-effect term for each subject, Supplementary Figure S6-S7). As an observational study, the results still confront the risk of bias due to other confounding.

There is an interesting comparison between models fitting on ages (Supplementary Figure S6-S7) and models fitting on years after enrollment (Fig. 1, Supplementary Figure S8-S9). Though both models show higher ADL, SWB, and BMI in control group, there are noticeable differences in trend. It reminds us that the longitudinal changes we observed are actually the result of the integrated effects of two factors: the aging process of individual and the temporal changes in socio-economic conditions. Further research is still needed to better understand the factors influencing cognitive changes during the aging process.

Discussion

It is widely acknowledged that physical, behavioral, psychological, and cognitive status link each other tightly during the aging process. Our work supported the idea that older adults with weaker ADL ability and more negative emotional affect are at a higher risk of cognitive impairment and identified higher BMI as a protective factor for cognitive ability. The cross-validation results of the Bayesian joint models and dynamic-DeepHit show that the three indicators, ADL in particular, are easily assessed and well-informed predictors of cognitive decline. The decrease in BMI, ADL, and SWB is a sign of cognitive decline for aging people, making it possible to identify vulnerable populations and take measures to prevent deterioration in time.

The correlations between predictors may bias the inference and cause misleading explanations. For example, women seem to be at a higher risk of cognitive impairment than men, yet the higher rate of cognitive impairment in women may actually result from their higher life expectancy or relatively fewer educational opportunities instead of mere sex differences. We resorted MSMs to control measured confounding factors and identify each indicator's direct effect magnitudes.

The role of BMI in cognition decline is extremely controversial, with some supporting higher BMI as a protective factor for cognition [3, 15–21], while others reported the opposite [22, 23]. A pattern of initial increasing BMI followed by declining BMI was found to be associated with dementia [51], while another research suggested that BMI stability reduced risk of poor cognitive outcomes [52]. However, previous studies are mainly association studies without adjusting for possible confounders. Cox-MSMs controlling longitudinal measured confounding reveal that higher BMI has a slight protective effect on cognition. Although it is not possible to give a full conclusion of causality, our analysis provides clues for the existence of causality under the assumption of no unobserved confounding.

Although the conclusion of causality from observational studies should be regarded with caution and needs more evidence from triangulation [53], the protective effects of BMI, ADL, and SWB on cognitive impairment supported the idea of preventing cognitive decline via nonpharmacological interventions, such as emotion therapy or morphological management. Some particular negative emotions, such as loneliness and depression, were reported to be linked to cognitive decline in older adults [54–56]. Recent studies revealed that positive beliefs promoted patients to recover from mild cognitive impairment [57], and aging brains showed more remarkable emotional carryover effects (emotional inertia) after exposure to negative socioemotional events, which affected activity patterns in regions such as the posterior cingulate cortex (PCC), resulting in an increased risk of neurodegenerative diseases [58].

The strengths of this research are obvious. The CLHLS is so far the largest study with the longest follow-up on the health of older adults in China, geographically widespread and fully representative of the Chinese population. In particular, in addition to the baseline information, we fully exploited time-varying data during the follow-ups. Besides, accounting for the influence of potential confounding and temporal changes, following the idea of triangulation [59], we examined the longitudinal morphological, behavioral, and emotional indicators' effects on cognitive decline via several different approaches, including employing joint model integrating longitudinal and survival models, as well as MSMs controlling time-varying confounding. Finally, we assessed and compared predictive ability of these indicators and their combinations on cognitive decline using dynamic risk prediction models implemented with Bayesian joint models and deep neural networks, which integrated time-varying information efficiently and achieved remarkable accuracy.

However, the analysis still has some drawbacks. The use of the longitudinal model brings computational burdens, especially for large sample sizes and limited follow-up times. Issues such as participants' death, failure in follow-up, and measurement errors reduce the number of longitudinal records. Despite showing the features of missing at random, simple culling of missing data still affects the robustness of the results. The use of imputation methods introduces potential bias as well. For example, the missing height data in the first four waves were conversed from keen height, making the measurement of BMI not uniform, which damage the accuracy of the longitudinal modelling. Besides, due to the presence of unobserved confounding, identifying the causal effects in a time-varying process is still tricky. Pathophysiological changes during biological degeneration significantly contribute to the process of cognitive decline, and represent an important confounding variable in the analysis. Incorporating additional information, such as genetic anchors, and approaches such as time-varying Mendelian randomization [60] can avoid the interference of unmeasured confounding and strengthen causal inference.

Conclusion

In conclusion, evidence from a large-scale, long-term cohort study supports that changes in ADL, SWB, and BMI are closely associated with cognitive decline in older Chinese adults. By controlling for time-fixed and time-varying confounding factors, ADL, SWB, and BMI all showed significant protective effects on cognitive decline. Using longitudinal history, Bayesian joint models and deep survival models manifest a remarkable predictive performance on cognitive impairment. The integration of three indicators boosts the performance, and ADL is the most informative predictor.

Abbreviations

BMI	Body mass index
ADL	Activities of daily life
SWB	Subjective well-being
CLHLS	Chinese Longitudinal Healthy Longevity Survey
MSM	Marginal structure model
LMM	Linear mixed-effect model
AUC	Area under the receiver operating characteristic curve
IPW	Inverse-probability weights
GEE	Generalized estimating equation
RNN	Recurrent neural network
GRU	Gated recurrent unit
CIF	Cumulative incidence function
rmcorr	Repeated measure correlation coefficient

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-21072-w.

Supplementary Material 1

Acknowledgements

The computations in this paper were run on the Siyuan-1 cluster supported by the Centre for High Performance Computing at Shanghai Jiao Tong University.

Authors' contributions

JS and YZ designed the study. JS conducted the analysis and wrote the manuscript. LD helped manage the data. YZ supervised and sponsored the study. JS, LD, QL, JZ, and YZ discussed and revised the manuscript.

Funding

The work was supported by the National Natural Science Foundation of China (11901387) and Shanghai Jiao Tong University "Jiaotong Star" Plan Medical Engineering Cross Research Project (20230103, YG2021QN07). The supporters had no role in the design, analysis, interpretation, or publication of this study.

Data availability

The CLHLS dataset is available at https://agingcenter.duke.edu/CLHLS.

Declarations

Ethics approval and consent to participate
The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052–13074), and all participants or their proxy respondents provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 4 September 2023 Accepted: 11 December 2024
Published online: 18 December 2024

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