Estimation of losses of quality-adjusted life expectancy attributed to the combination of cognitive impairment and multimorbidity among Chinese adults aged 45 years and older

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Abstract

Objectives: This study aims to estimate the losses of quality-adjusted life expectancy (QALE) due to the joint effect of cognitive impairment and multimorbidity, and further to confirm additional losses attributable to their interaction among the middle-aged and elderly Chinese.

Methods: The National Cause of Death Monitoring Data were linked with the China Health and Retirement Longitudinal Study (CHARLS). A mapping and assigning method was used to estimate health utility values, which were further used to calculate QALE. Losses of QALE were measured by comparing the differences between subgroups. And all the losses of QALE were displayed at two levels: the individual and the population level.

Results: At age 45, the individual-level and population-level losses of QALE (95% CI) attributed to the combination of cognitive impairment and multimorbidity were 7.606 (5.679, 9.566) years and 4.297 (3.425, 5.200) years. The losses (95% CI) for cognitive impairment alone were 3.104 (2.287, 3.954) years and 1.709 (1.318, 2.132) years at two levels. Similarly, the losses (95% CI) for multimorbidity alone were 3.526 (2.528, 4.556) years and 1.914 (1.235, 2.625) years at two levels. Additional losses due to their interaction were indicated by the 0.976 years of the individual-level gap and 0.674 years of the population-level gap.

Conclusion: Among the middle-aged and elderly Chinese, cognitive impairment and multimorbidity resulted in much losses of QALE, and additional QALE losses were seen due to their interaction at both individual and population levels.

Keywords: Quality-adjusted life expectancy; cognitive impairment; multimorbidity; CHARLS

Introduction

Age-associated cognitive impairment is a transition link between healthy aging and dementia with the 10% conversion rate, featuring declines in memory, attention, and cognitive function [1]. At the end of 2019, the population aged 65 and above in China accounted for 176.0 million [2]. And a large-sample, multi-region study showed that the prevalence (95% CI) of total dementia for the population aged 65 years and older in China was 5.60% (3.50%, 7.60%) in 2019 [3]. Moreover, mild cognitive impairment (MCI) is estimated >4 times more common than dementia [1, 4].

Meanwhile, age-dependent noncommunicable diseases (NCD) are proved to experience a continuous increase among the elders in the near decades [5]. Nearly 50% of the NCD burden in China occurred in people aged 65 years and older [6], while 47.5% of the elderly aged 65+ had ≥ 2 chronic conditions [7]. Multimorbidity, which is defined as the co-occurrence of two or more chronic diseases in an individual, is widely observed beyond two-thirds of older adults [8, 9]. Many patient-based studies suggested that older adults with at least two diseases were more susceptible to develop cognitive impairment [10-18]. The hypothesis that multimorbidity may increase the risk of cognitive impairment has also been verified in population-based researches [10-12, 14].

Despite the documented risk of cognitive impairment and multimorbidity to health aging, few studies have been conducted to measure how long those aging people would be expected to live less in a quality damaged state caused by this combined burden. Quality-adjusted life expectancy (QALE), as a more sensitive and comprehensive population-health measure, combines the health-related quality of life (HRQoL) with life expectancy (LE) to obtain a single summary score [19-21]. When it is hard to estimate HRQoLs directly, the mapping methods could help a lot to generate predictive utility values based on

existing health-related data [22-24]. As is widely acknowledged, QALE is better for public health surveillance among older adults compared to other health expectancy measures [20, 22]. The QALE losses demonstrated in the previous study [25, 26], could quantify the difference in disease burden due to cause-specific mortality and morbidity, and could be displayed at both individual and population levels [25]. Researches about losses of QALE quantifying the severity of the health damages are valuable for both clinical intervention assessments over a pre-determined time interval and resource optimization in public health strategies for those in high-risk groups [22, 27].

Based on the availability of CHARLS data, this study aims to 1) estimate the losses of QALE attributed to the combination of cognitive impairment and multimorbidity at both individual and population levels, and 2) confirm the additional losses of QALE due to their interaction.

Data and methods

The baseline wave (2011) of CHARLS was used for estimating the HRQoLs among participants included, and the follow-up data (2013, 2015) were used for estimating the cause-specific mortality rates of cognitive impairment and multimorbidity [28]. The detailed profile [29] and data of CHARLS published are available in the CHARLS repository, http://charls.pku.edu.cn/index/zh-cn.html.

Measurement of cognitive impairment

To judge cognitive impairment, we took the two-part brief cognition measure sets of CHARLS [30-32], similar to the imputed cognition part of the American Health and Retirement Study (HRS). The first part evaluates episodic memory through a calculation of average scores (0-10) between 10-Chinese-word immediate and delayed recalling. And the second part measures executive function based on the 11-score

sum, which is consisted of the orientation of dates (day, week, month, season, and year), serial subtracting 7 from 100 five times successively, and the item repainting the specific picture. The current study evaluated the cognitive function of the participants employing the total scores of two parts, ranging from 0 to 21 [30, 33, 34]. Therefore, the cut-off value for judgment of cognitive impairment was estimated by the receiver operating characteristic (ROC) curve analysis combining the cognitive scores (0-21) and the diagnosis of the memory-related problem included in the CHARLS.

Definition of multimorbidity

The CHARLS longitudinal study covered 14 chronic conditions diagnosed by doctors significant to the elders (including hypertension, diabetes or high blood sugar, cancer or a malignant tumor, chronic lung disease, stroke, other cardiovascular problems, emotional or psychiatric problems, arthritis, dyslipidemia, liver diseases, kidney diseases, digestive diseases, asthma, and memory-related diseases) [29]. More detailed definitions of these 14 conditions can be found in the data using documents provided on their website [35]. According to the most common approach [33], this study defined multimorbidity as a count of the number of diseases without weighting for severity [36]. Of course, we excluded the diagnosis of the memory-related problem included in the CHARLS.

Health utility value——morbidity rate

To describe the HRQoL using a summary value between 0 (for death) and 1 (for perfect health), preference-based measure——health utility value——was used to estimate the impacts of physical and mental dysfunction [37]. This study obtained the health utility values by a mapping and assigning method.

From a total of 17,224 individuals (aged 45+) included in CHARLS, random 3636 participants

answered five questions profiling health at the baseline wave (2011), which were analogous to the five dimains of the EuroQol-5 Dimensions instrument (EQ-5D). The descriptive system of ED-5D classifies people's health into 1 to 5 levels of 5 domains: anxiety/depression, pain/discomfort, usual activities, self-care, and mobility [38]. We substituted the five existing similar questions for five domains of EQ-5D, using a nonparametric mapping method rather than the mapping function [23]. And then, we estimated predictive values through an EQ-5D-5L utility database (a full set of predicted values for all 3,125 health states) for China [39]. Cronbach's alpha and confirmatory factor analyses were performed to test the reliability and validity of mapping.

To enlarge the sample size, a propensity score matching (PSM) method was used to assign health utility values to participants matched, who had no health utility values. From 17,224 individuals aged 45+, 3,600 participants had complete data of covariables and health utility values , and 11,850 participants had complete information on covariables of propensity score matching (PSM) without health utility values. Under the control of the 1:3 matching ratio and the 0.1 caliper value, 10,214 out of 11,850 participants were assigned with health utility values. The balance of the PSM-based assigning method was examined by multiple logistic regression.

Of 13,850 individuals with health utility values, 12,300 with complete information on cognition were used to estimate the average health utility values in age-specific intervals (9 five-year intervals), replacing morbidity. The bootstrapping-based estimates of confidence intervals for average health utility values were computed from 2.5^{th} to 97.5^{th} percentile, and confidence intervals for the differences of average health utility values (2.5^{th}, 97.5^{th}).

122 Cause-specific mortality rate

123 The age-specific death rate (m) was derived from the national cause of death monitoring data
124 (2011)[40]. However, age-specific death rates stratified by cognitive impairment and multimorbidity
125 were not available, so these rates were estimated through the following formulas. For example, death
126 rates for those with cognitive impairment (m_1) and those without cognitive impairment (m_0) were
127 calculated using the hazard ratio (h) of dying for cognitive impairment versus none cognitive impairment
128 and the prevalence of cognitive impairment (p) by $m_1 = \frac{hm}{hp + (1-p)}$ and $m_0 = \frac{m}{hp + (1-p)}$,
129 respectively [25]. Likewise, the death rates for the combination of cognitive impairment and
130 multimorbidity were estimated through the same formulas above. Based on the Cox proportional hazards
131 model, hazard ratios were computed. The prevalence of cognitive impairment and multimorbidity
132 obtained from the CHARLS were assessed only at the start of 45 years old.

133 QALE and losses of QALE

134 The life table of the general population was constructed with the age-specific mortality rates from
135 the national cause of death monitoring data (2011) [40]. Based on the cause-specific mortality rate, the
136 life tables of the subgroups were constructed. Let A_i be the number of the population surviving to age
137 i ($i \geq 45$). The quality-adjusted life-years (QALYs) $D_i y_i$ in the age-specific interval $[i, i+5]$
138 were calculated using the average health utility value y_i and the person-year of survival D_i in the age-
139 specific interval $[i, i+5]$ so that QALE_i at the age x was calculated by
140 $\mathrm{QALE}_i = \sum_{i \geq x} D_i y_i \Big/ A_i \quad i, x \in [45, 80]$ [21, 25]. And the confidence intervals for QALEs were
141 computed through the confidence intervals for health utility values. A completive process regarding the

142 estimation of QALE was presented in Figure 1.

143 Similar to the definition of attributable risk (AR) and population attributable risk (PAR) in
144 epidemiology [41, 42], losses of QALE could be measured at both individual and population levels [25].
145 For instance, the definition of individual-level losses of QALE due to cognitive impairment is referred
146 to as the difference in QALE between groups with and without cognitive impairment. The population-
147 level losses of QALE were considered as the difference in QALE between the group with cognitive
148 impairment and the total population. Losses of QALE due to the combination of cognitive impairment
149 and multimorbidity were estimated in the same way. And the confidence intervals for losses of QALEs
150 were computed through the confidence intervals for differences of health utility values.

151 Results

152 Characteristics of participants

153 According to the results of ROC, the cut-off value for judging cognitive impairment under both high
154 sensitivity and specificity was 8.25, and the AUC (95% CI) for this value was 0.613 (0.575, 0.650). All
155 participants (n=13,850) in this study were divided into four subgroups with another missing cognitive
156 subgroup by the combination of cognitive impairment and multimorbidity. Characteristics in these
157 subgroups were presented in Appendix Table 1. Participants figuring higher age, female,
158 divorced/separated status, lower education level, living in urban, smoking, drinking, lower BMI, and
159 multimorbidity, were more likely to be low-level-cognition. However, the characteristics described in the
160 missing cognitive subgroup were similar to the subgroups of low-level-cognition.

161 Results of the mapping and assigning values

162 Based on the results of the mapping, the Cronbach's alpha based on standardized items (α' = 0.829)
163 and the results of confirmatory factor analyses (with five eigenvalues obliquely rotated ≥ 1 corresponding
164 for the five dimensions of EQ-5D) reflected excellent reliability and validity. And the results of assigning
165 values based on PSM were examined by multiple logistic regression, showing a good balance on almost
166 all of the covariates of PSM between participants owned health utility values before and those who were
167 given health utility values after (Appendix Table 2). Except for the married or partnered status which was
168 more likely to be matched ($P = 0.028$), other covariates of PSM had no statistical significance between
169 the two groups ($P > 0.05$), particularly the differences in health utility values no significant ($P = 0.124$).

170 Quality-adjusted life expectancy (QALE)

171 The QALEs among the four subgroups were increased in turn at the same age interval (including
172 low-level-cognition with multimorbidity, high-level-cognition with multimorbidity, low-level-cognition
173 without multimorbidity, and high-level-cognition without multimorbidity). The QALEs of the missing
174 subgroup were lower than those in any high-level-cognition group. QALE results of all age intervals
175 were described in Appendix Table 3.

176 Losses of QALE

177 The differences in three trend lines among these nine age intervals showed the QALE losses at both
178 individual and population levels due to the joint effect of cognitive impairment and multimorbidity
179 (Figure 2). Among the two groups (Figure 3A): high-level-cognition without multimorbidity group and
180 low-level-cognition with multimorbidity group, the individual-level losses of QALE (95% CI) for these

people (aged 45 years) were 7.606 (5.679, 9.566) years. Analogously, the QALE losses (95% CI) for cognition impairment alone were 3.104 (2.287, 3.954) years, and the QALE losses (95% CI) for multimorbidity alone were 3.526 (2.528, 4.556) years. According to Figure 3B, the population-level losses of QALE (95% CI) between the two groups (the high-level-cognition without multimorbidity group and the general population group) were 4.297 (3.425, 5.200) years. At the same age interval, compared with the general population group, the QALE losses (95% CI) for cognition impairment alone were 1.709 (1.318, 2.132) years, and the QALE losses (95% CI) for multimorbidity alone were 1.914 (1.235, 2.625) years.

Obviously, the 0.976 (= 7.606-3.104-3.526) years for the individual-level gap showed that there were additional losses of QALE due to their interaction, with 0.674 (= 4.297-1.709-1.914) years of losses at population-level also the same. The other results at both two levels, which were described in detail in all age intervals, were shown in (Tables 1 and 2).

Discussion

The current study measured the losses of QALE due to the combination of cognitive impairment and multimorbidity, and then discovered significantly additional burden from the interaction of cognitive impairment and multimorbidity at both individual and population levels. Unlike previous studies [26, 43, 44], our consequences were confirmed by losses of QALE based on the representative sample of a country rather than patient-based clinical studies.

The three trend lines of QALE represented the aging-related health burden under the joint effect of cognitive impairment and multimorbidity (Figure 2). They declined with age owing to a decrease in life

expectancy [45, 46]. Strangely, it seemed that the health burden of participants declined because the losses of QALE at the individual level decreased by age (Table 1, Figure 3A). However, it did not mean that the exposure to the combination had a weaker influence on older generations. On the contrary, the losses at population level kept steady comparatively (Table 2, Figure 3B), which exactly confirmed that the damage due to the combination could not be weakened among the elderly population, and even had a little rising range between age from 70 to 85 years. It is worth mentioning that the losses of QALE due to the combination could be divided into three parts: only due to cognitive impairment, only due to multimorbidity, and due to the interaction of cognitive impairment and multimorbidity. According to Table 1 and Table 2, we discovered the significantly additional losses due to the interaction in all age intervals without intersecting confidence intervals after subtracting the losses due to cognitive impairment and multimorbidity from the combination losses successively.

The losses of QALE had different influences at the individual and population levels so that the losses of QALE at both two levels had different meanings. For instance, the population-level losses of QALE due to the combination of cognitive impairment and multimorbidity, the burden to the total population, estimated the maximum number of QALEs for the general population that could be attained if those who had the combination did not have the burden of this combination after the early intervention for high-risk groups in the community. The years of QALEs for the general population could be obtained more if they had never had the burden above were 4.297 and 3.456 among the seniors aged 45 and 85 years old (accounting for the QALEs of the general population 14.80% and 123.9%, respectively). As for the individual-level burden, the losses of QALE quantified the level at which the risk could be prevented or decreased for those who had both cognitive impairment and multimorbidity if they were without this combination above under specific treatment. The individual-level losses of QALE could

account for more helpfully than the population-level burden to assess therapies for diseases in clinical researches. This study indicated that more focus and early intervention should be placed on the group with both risks of cognitive impairment and multimorbidity not only for clinical individuals under treatment but also among these high-risk groups in the community.

The main innovation of this study is the method to estimate health utility values from existing health-related data without standardized scales for HRQoLs. To date, increasing preference-based HRQoL data are widely collected at the national, provinces, or lower levels. At the same time, only a few standardized measures could provide a summary index to assess health states, though most of the rest measures have similar question-settings. Previous mapping studies reported mapping functions by regression analyses to estimate or generate utility values from one standardized scale to another standardized scale [23, 24]. Firstly, this study substituted the five existing similar questions in CHARLS for five domains of EQ-5D, using a nonparametric mapping method rather than a mapping function. It is a pity that this study could not evaluate the bias of estimation due to the unavailability of observed EQ-5D-based data. However, QALEs estimated from other measures different from EQ-5D would be very similar because the variables set for "health" are closely correlated [23, 25, 47]. To some extent, the results of Cronbach's alpha and confirmatory factor analyses showed the reliability and validity of mapping. Secondly, the PSM-based assigning value method enlarged the application fields of PSM, while standard propensity score matching was used to create a highly comparable control group [48]. And the results of good balance proved the reasonable assigning value among matched groups.

People without cognitive data had the penultimate QALE. Likely, missing cognitive data lead to underestimation for describing the health burden of cognitive impairment (Appendix Table 3). A

sensitivity analysis was conducted to evaluate the impact of missing value. Unlike the analysis above that excluded participants (n=1,550) without cognitive scores, we classified these participants towards the low-cognition-level group. The new individual-level losses of QALE increased in all age intervals, which suggested that people who had missing values tended to have lower values (more severe morbidity) and that we underestimated losses of QALE at the individual level. However, there were not similar outcomes at the population level.

The main limitation refers to the definition of cognitive impairment. The definition of mild cognitive impairment (MCI) is distinguished from dementia, and the criteria for MCI are as following: cognitive decline as evidenced by self and/or informant and/or clinician report and impairment on objective cognitive tasks, and/or evidence of decline overtime on objective tasks; preserved basic activities of daily living (ADLs) (or minimal impairment in complex instrumental functions); and does not meet DSM-IV, ICD-10 criteria for a dementia syndrome [49]. However, it is difficult to diagnose by MIC in older adults from a large national epidemiological study, and CHARLS covered simple scale-based tests of cognitive function. Instead of using the definition of MCI, the ROC curve analysis was performed to generate the cut-off score for cognitive impairment in this study.

Conclusion

In conclusion, this current study measured the losses of QALE due to the joint effect of cognitive impairment and multimorbidity, which confirmed additional burden from the interaction of cognitive impairment and multimorbidity at both individual and population levels. Therefore, this study indicated that more focus and early interventions should be placed on the group with both risks of cognitive impairment and multimorbidity, and these measures should be taken not only for clinical individuals

under treatment but also among these high-risk groups in the community.

Abbreviations

QALE: Quality-Adjusted Life Expectancy; CHARLS: China Health and Retirement Longitudinal Study; CI: Confidence interval; MCI: Mild cognitive impairment; NCD: Noncommunicable diseases; HRQoL: Health-Related Quality of Life; LE: Life expectancy; HRS: Health and Retirement Study; ROC: Receiver operating characteristic curve: EQ-5D: EuroQol-5 Dimensions instrument; PSM: Propensity Score Matching; HRs: Hazard Ratios; BMI: Body mass index (kg/m^2); ADL: Activities of daily living; IADL: Instrumental activities of daily living; CESD: Centre for Epidemiology Studies-Depression Scale; SroH: Self-report of Health; SD: Standard deviation

Declarations

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Availability of data and materials

The demographic data that support the findings of this study are available from the Chinese National Bureau of Statistics. And the other data that support the findings of this study are available in the in the CHARLS repository (http://charls.pku.edu.cn/en).

Authors' contributions

SX, CK and YS contributed to the study design, data collection, data analyses. SL and YQ contributed to the literature collection, data cleaning and data analyses. DH, YZ and YY helped a lot for the interpretation of results and manuscript writing. SX was a major contributor in writing this manuscript, and CK and YS polished this manuscript finally. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The CHARLS obtained ethics approval (license number: IRB00001052-11015, IRB00001052-14030 and IRB00001052-17053) from the institutional review board of the Peking University National School of Development. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The interviewers explained the purpose of the survey before obtaining oral informed consent from the individual participants.

Consent for publication

Not applicable.

Competing interests

306 The authors declare that they have no competing interests.

307 Figure legends

308 Figure 1 The diagram for the calculation of QALE. CHARLS (2011), Baseline data of the China Health
309 and Retirement Longitudinal Study; PSM, Propensity Score Matching; HRs, Hazard Ratios; LEs, Life
310 Expectancies; QALEs, Quality-Adjusted Life Expectancies;

311 Figure 2 QALE tendency among different groups. Population-level QALE loss: the difference of
312 QALE between population with the combination of cognitive impairment and multimorbidity and the
313 general population; Individual-level QALE loss: the difference of QALE between population with the
314 combination of cognitive impairment and multimorbidity and the population without the combination.

315 Figure 3 Losses of QALE (with the corresponding 95% confidence intervals). These losses displayed
316 for cognitive impairment, for multimorbidity, and for the combination of cognitive impairment and
317 multimorbidity, which were displayed at the individual level (3A) and population level (3B).

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Figures

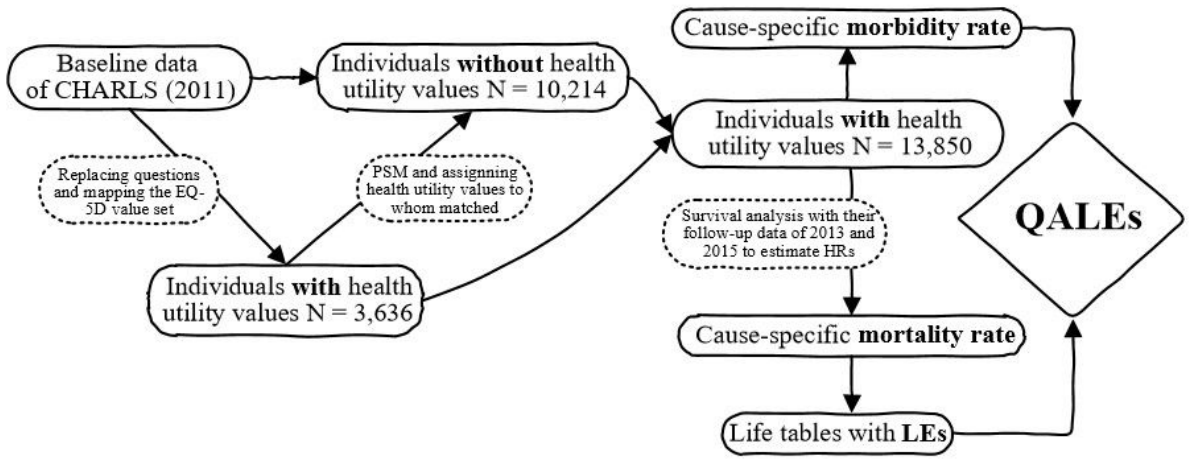

Figure 1

The diagram for the calculation of QALE. CHARLS (2011), Baseline data of the China Health and Retirement Longitudinal Study; PSM, Propensity Score Matching; HRs, Hazard Ratios; LEs, Life Expectancies; QALEs, Quality-Adjusted Life Expectancies;

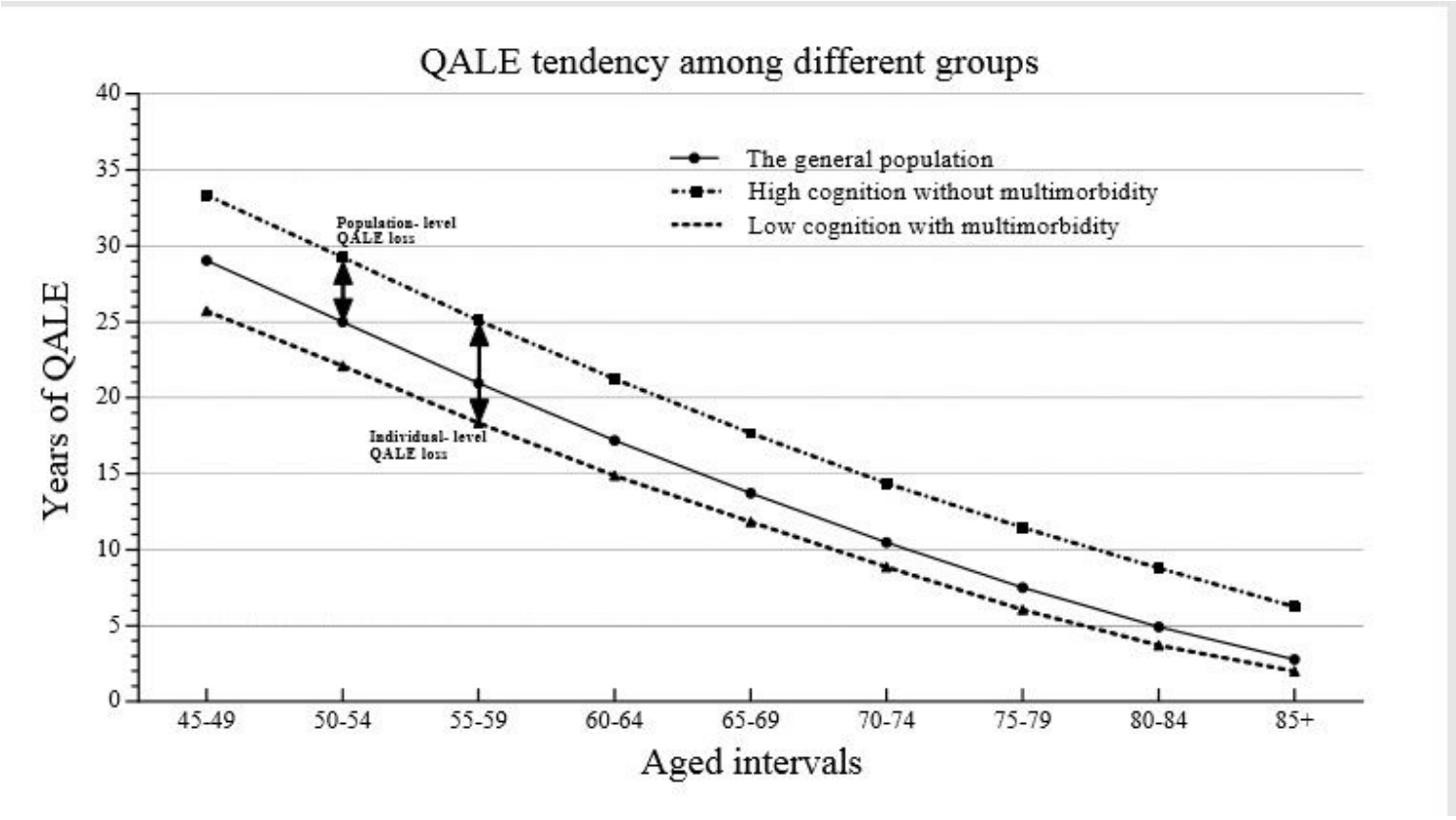

Figure 2

QALE tendency among different groups. Population-level QALE loss: the difference of QALE between population with the combination of cognitive impairment and multimorbidity and the general population; Individual-level QALE loss: the difference of QALE between population with the combination of cognitive impairment and multimorbidity and the population without the combination.

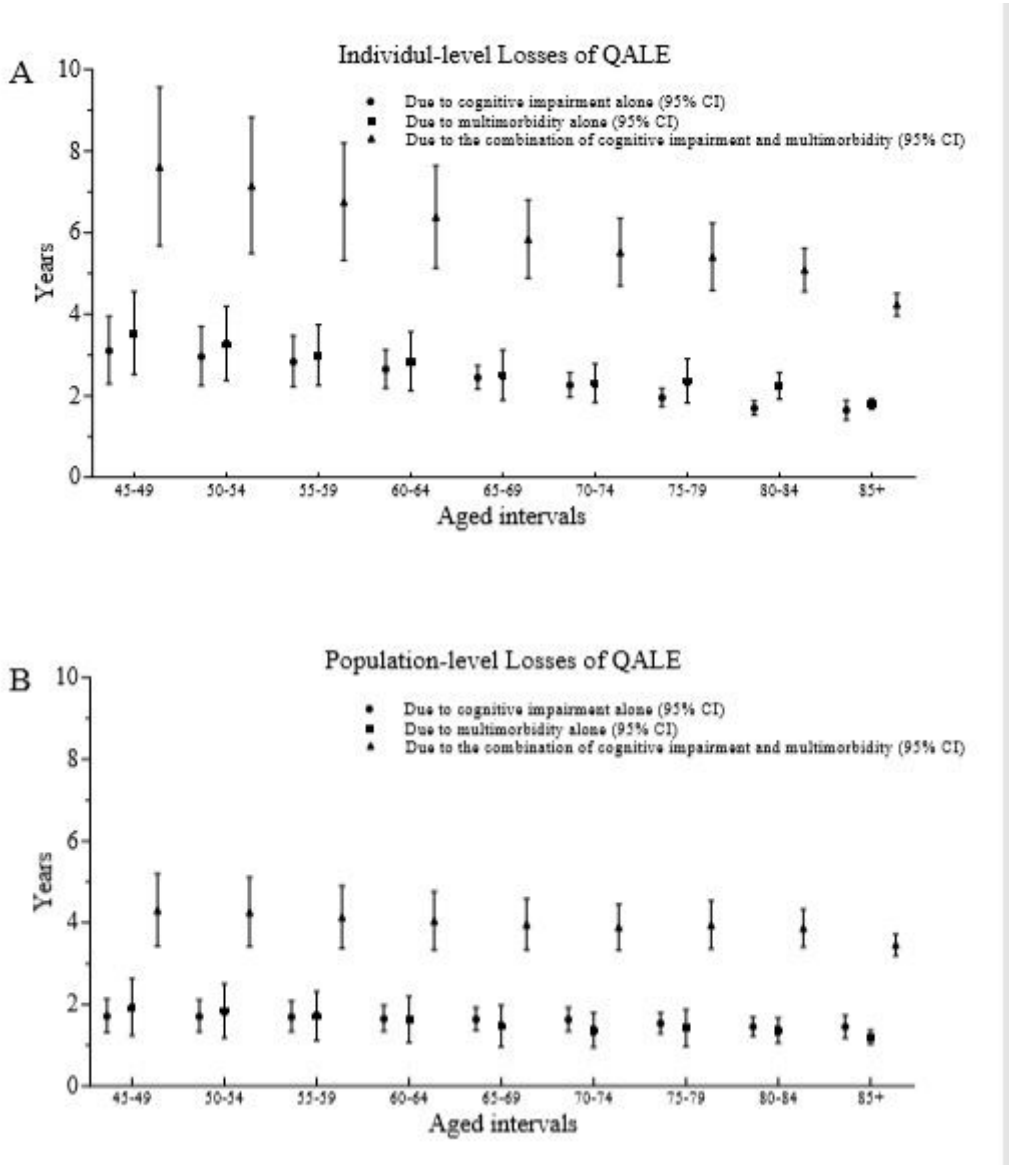

Figure 3

Losses of QALE (with the corresponding 95% confidence intervals). These losses displayed for cognitive impairment, for multimorbidity, and for the combination of cognitive impairment and multimorbidity, which were displayed at the individual level (3A) and population level (3B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixTable3.docx
- AppendixTable2.docx
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