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Dietary factors and patterns in relation to risk of later-onset ulcerative colitis in Chinese: A prospective study of 0.5 million people

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Summary

Background: There is limited evidence on the associations of dietary factors and patterns with risk of later-onset ulcerative colitis (UC) in Chinese adults.

Aims: To investigate the associations of dietary factors and patterns with risk of later-onset UC in Chinese.

Methods: The prospective China Kadoorie Biobank cohort study recruited 512,726 participants aged 30–79. Dietary habits were assessed using food frequency questionnaires. Dietary patterns were derived by factor analysis with a principal component method. Cox regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During a median follow-up of 12.1 years, 312 cases of newly diagnosed UC were documented (median age of diagnosis 60.1 years). Egg consumption was associated with higher risk of UC (HR for daily versus never or rarely: 2.29 [95% CI: 1.26–4.16]), while spicy food consumption was inversely associated with risk of UC (HR: 0.63 [0.45–0.88]). The traditional northern dietary pattern, characterised by high intake of wheat and low intake of rice, was associated with higher risk of UC (HR for highest vs. lowest quartile of score: 2.79 [1.93–4.05]). The

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modern dietary pattern, characterised by high intake of animal-origin foods and fruits, was associated with higher risk of UC (HR: 2.48 [1.63–3.78]). Population attributable fraction was 13.04% (7.71%–19.11%) for daily/almost daily consumption of eggs and 9.87% (1.94%–18.22%) for never/rarely consumption of spicy food.

Conclusions: The findings highlight the importance of evaluating dietary factors and patterns in the primary prevention of later-onset UC in Chinese adults.

1 | INTRODUCTION

Ulcerative colitis (UC) is one of the two major forms of chronic inflammatory bowel disease (IBD) and is characterised by frequent remission and relapse, causing chronic diarrhoea and rectal bleeding.[1,2] In 2019, the global number of IBD cases was estimated to be 4.9 million.[3] Representative studies in Western countries reported that UC accounted for ~65% of IBD.[4] While the incidence of UC is high and stable in Western countries, it is rapidly increasing in newly industrialised countries, including China.[5,6] A nationwide population-based study reported that the incidence rate of UC in urban China was 8.95 per 100,000 person-years in 2016, similar to Western countries.[7]

UC can be classified by the age of onset into paediatric-onset (≤17 years), adult-onset (18–59 years), and elderly-onset (≥60 years, the latter two classified as 'later-onset').[8] The burden of UC in older adults is increasing due to the joint impact of population ageing and an increasing incidence of later-onset UC.[9] Previous prospective studies in Western countries have shown that diet is a major modifiable risk factor for later-onset UC.[10–12] Single food items, including high consumption of red meat, soft drinks, low consumption of vegetables, and vitamin D deficiency, are associated with a higher risk of UC, while the evidence is inconclusive for other dietary factors (e.g. eggs, dairy, green tea, and fruits) and nutrients (e.g. protein, fat, and fibre).[11,13] In addition to single food items, dietary patterns, without emphasising nutrients, can depict the overall quality of a diet and provide a holistic view of food combinations, synergies, and antagonisms.[14] Therefore, assessing the associations between dietary patterns and UC risk has important public health implications. Recently, one prospective cohort study in European adults reported that a carnivorous dietary pattern (i.e. consuming high amounts of red meat, poultry, and processed meat) was associated with a higher risk of UC.[15]

The majority of previous studies, however, were conducted in Western populations. There is little prospective evidence from low- and middle-income countries, especially China, where lifestyles and dietary patterns differ appreciably from those in high-income countries. For example, Chinese cuisine is distinctive from other countries in which spices have been integral. In addition, dietary patterns in China have dramatically changed in recent decades, characterised by increased consumption of animal-origin foods (i.e. red meat and eggs) and decreased consumption of vegetables and whole grains.[16] Therefore, we examined the prospective associations of dietary factors and patterns with the risk of later-onset UC in the China Kadoorie Biobank (CKB), a large prospective cohort study of 0.5 million adults in China.

2 | MATERIALS AND METHODS

2.1 | Study population

Details of the CKB design, survey methods, and population characteristics have been described elsewhere.[17] Briefly, 512,726 participants (210,206 men and 302,520 women) aged 30–79 years were recruited into the study from 10 geographically defined localities (5 urban and 5 rural) in China during 2004–2008. Prior international, national, and regional ethical clearance was obtained, and written informed consent was obtained from all participants. At local study assessment clinics, participants completed an interviewer-administered laptop-based questionnaire on sociodemographic characteristics, smoking, alcohol consumption, diet, tea drinking, physical activity, personal and family medical history, and current medication. A range of physical measurements were recorded by trained technicians, including height, weight, hip, waist circumference, bioimpedance, lung function, blood pressure, and heart rate, using calibrated instruments with standard protocols.

2.2 | Dietary factors

In the baseline survey, dietary data was assessed by a semi-qualitative food frequency questionnaire (FFQ) covering 12 major food groups: rice, wheat products, other staple foods, meat, poultry, fish, eggs, dairy products, fresh vegetables, preserved vegetables, fresh fruit, and soybean products. In addition, participants were asked about their frequency and amount of consuming hot spicy foods in the past month. After completion of the baseline survey, ~5% of the original participants were randomly selected for two resurveys, using procedures similar to those at baseline. Additionally, the second questionnaire included frequency and amounts of major food groups consumption. This information was used to estimate the average baseline consumption across the five frequency categories and the average daily energy intake for each participant. Details about the assessment of dietary factors were reported in Appendix S1.

Two surveys were conducted to assess the reproducibility and validity of CKB FFQs, respectively (Appendix S1). To assess the reproducibility of the responses, about 5% of randomly chosen surviving participants in 10 survey sites were resurveyed between August and October of 2008.[17] To assess the validity of the FFQ, a total of 432 participants were recruited between September 2015 and August 2016 who completed 12-day and 24-h dietary recalls with FFQ.[18] Spearman's coefficient and weighted kappa indicated good reproducibility and validity of major dietary factors (Table S1).

2.3 | Endpoint ascertainment

The vital status of each participant was determined periodically through the China CDC's Disease Surveillance Points (DSP) system and the national health insurance system, supplemented by regular checks against local residential and health insurance records and by annual active confirmation through street committees or village administrators.[19] In addition, information about the occurrence of major diseases and any episodes of hospitalisation was collected through linkages, using each participant's unique national identification number, with disease registries and national health insurance claim databases, which have almost universal coverage in the study areas. All events were coded using the International Classification of Diseases, 10th revision (ICD-10), by trained staff who were blinded to baseline information and reviewed centrally for consistency.[17] The ICD-10 code was K51 for UC. Ongoing outcome adjudication studies in CKB randomly selected 132 UC cases, and the diagnosis was verified in 97% of cases, indicating good diagnostic accuracy. The present study included incident UC from enrolment until 31 December 2018, by which time a total of 56,552 (11.0%) participants had died, and 4028 (0.8%) were lost to follow-up.

2.4 | Statistical analyses

The present study excluded 56,136 participants with self-reported cancer and digestive disorders (including peptic ulcer, hepatitis or cirrhosis, and gallbladder disease), leaving 456,590 participants.

Dietary patterns were derived from the 12 major food groups and spicy food consumption at baseline using factor analysis with the principal component method.[20] A higher score indicated higher compliance with the corresponding dietary pattern. The score was divided into quartiles (Q1 to Q4 in ascending order) in urban and rural areas separately in subsequent analysis (Appendix S1).

Baseline characteristics of participants were presented as means or percentages across dietary patterns, standardised by age, sex, and region where appropriate, using multiple linear regressions for continuous variables or logistic regressions for dichotomous variables. Cox regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of incident UC associated with baseline dietary factors and dietary patterns. Subgroup analyses were conducted to examine whether the associations of dietary factors and dietary patterns with UC risk differed by baseline variables, and sensitivity analyses were conducted to investigate the robustness of the main results. Additionally, we estimated the joint impacts of these patterns on UC and conducted a stratified analysis, while the additive and multiplicative interactions of dietary patterns were quantified. Further, population-attributable fractions for protective or risk dietary factors and other five potential risk factors for UC were calculated. Details of the statistical analyses were reported in Appendix S1.

All statistical analyses were corrected for multiple testing by using Bonferroni's correction. On the basis of the total number of all statistical tests for 12 major food groups and spicy food intake variables in Chinese adults, the predefined *p*-value threshold was set to the *p*-value of 0.003846 (0.05/13). Statistical analyses were performed with Stata version 17.0 and R version 4.2.3.

3 | RESULTS

3.1 | Baseline characteristics

Overall, 58.9% of 456,590 participants were women, 43.3% were from urban areas, and the average age at recruitment was 51.8 years. During a median follow-up of 12.1 years, 312 newly diagnosed UC cases were documented, occurring between the ages of 39 and 84 (mean: 61.3 years). The crude incidence rate was 5.82 per 100,000 person-years, with a higher incidence rate in urban than in rural areas (8.11 vs. 4.10 per 100,000 person-years), and the UC incidence in urban areas in CKB was comparable with the UC incidence in urban China (8.11 vs. 8.95 per 100,000 person-years, Table S2). The incidence of UC in men was higher than that in women (rural: 6.46 vs. 3.16 per 100,000 person-years in men vs. in women; urban: 9.12 vs. 7.46 per 100,000 person-years in men vs. in women). In CKB, the peak incidence of UC was observed at slightly younger ages in urban population compared to rural population (Figure S2).

Two retained factors were identified as two dietary patterns, explaining 39% of the total variation (Tables S3–S5). The first factor, labelled as the 'traditional northern dietary pattern', featured a high intake of wheat and a low intake of rice. The second factor, labelled as 'modern dietary pattern', had high loadings of animal-origin foods and fruit.

For modern dietary pattern, participants with a higher score were younger, more likely to be male, from urban areas, had higher education levels and annual household income, and more likely to drink alcohol weekly. Meanwhile, they had higher levels of BMI and WC and were more likely to have prevalent hypertension and diabetes (Table 1).

3.2 | Associations of dietary factors with risk of UC

After adjusting for socio-demographic variables and major risk factors for UC, there was a positive association between daily egg

TABLE 1 Characteristics of participants by quartiles of two dietary pattern scores.

	Traditional northern dietary pattern				Modern dietary pattern			
Variable	Q1 (low)	Q2	Q3	Q4 (high)	Q1 (low)	Q2	Q3	Q4 (high)
Age, year	49.2 (10.1)	50.8 (10.7)	51.6 (11.0)	55.5 (10.8)	53.4 (10.8)	51.7 (10.5)	51.1 (10.6)	50.8 (10.7)
Female, %	57.9	61.1	57.7	58.8	63.5	58.0	57.4	56.5
Socioeconomic and lifestyle factors								
Urban region, %	43.5	43.0	43.4	43.2	42.9	43.3	43.4	43.5
Southern area, %	98.3	93.9	42.0	2.1	61.6	59.2	58.8	56.4
≥9 years of education, %	12.5	17.2	26.2	26.9	10.9	17.9	23.1	30.2
Household income ≥35,000 CNY/ year, %	22.4	22.0	16.1	9.7	9.3	14.8	18.9	26.9
Ever regular smoking, %								
Male	67.5	61.3	61.6	55.8	65.8	61.8	61.0	58.2
Female	2.8	2.5	2.2	1.4	3.0	2.1	1.9	1.6
Weekly drinking, %								
Male	40.3	34.6	29.7	31.1	30.1	32.5	34.3	38.2
Female	2.6	2.1	2.0	1.6	1.8	1.7	1.9	2.9
Total physical activity, MET-h/day	22.6 (14.2)	22.3 (13.8)	21.7 (13.4)	18.3 (13.8)	21.8 (13.9)	21.2 (14.3)	21 (13.9)	20.9 (13.6)
Energy intake, kcal/day	1171.1 (241.0)	1188.6 (240.3)	1334.7 (276.6)	1405.1 (234.1)	1107.1 (212.9)	1222.2 (217.4)	1298.1 (228.6)	1472.1 (262.2)
Blood pressure and anthropometry								
SBP, mm Hg	131.1 (20.7)	130.6 (21.3)	130.9 (21.9)	132.3 (21.4)	131.7 (22.3)	131.4 (21.4)	131.1 (21.1)	130.6 (20.5)
Waist circumference, cm	79 (9.3)	78.6 (9.5)	80.7 (9.7)	82.7 (9.9)	79.4 (9.7)	80.4 (9.7)	80.5 (9.7)	80.8 (9.8)
BMI, kg/m^2	23.4 (3.2)	23.2 (3.2)	23.5 (3.4)	24.5 (3.5)	23.4 (3.4)	23.7 (3.4)	23.7 (3.4)	23.8 (3.3)
Prior disease history, %								
Diabetes	4.6	5.1	6.0	7.2	4.9	5.5	5.8	6.8
Coronary heart disease	1.5	1.8	3.4	4.2	1.9	2.4	3.0	3.9
Stroke or TIA	0.9	1.2	1.9	2.7	1.6	1.8	1.7	1.7
Hypertension	10.9	11.6	11.5	11.2	9.7	11.1	11.8	12.8
Family history of diabetes	3.4	3.9	5.0	7.2	3.3	4.4	5.2	6.4
Family history of cancer	11.3	11.1	11.8	20.7	12.7	13.9	13.6	14.6

Note: Results were standardised by age, sex, and region where appropriate. Values are means (SD) or %.

Abbreviations: BMI, body mass index; CNY, unit of Chinese money Yuan; MET, metabolic equivalent of the task; Q, quartile; SBP, systolic blood pressure; TIA, transient ischaemic attack.

consumption and risk of UC and an inverse association between spicy food consumption with risk of UC. Compared with participants who never or rarely consumed eggs, the adjusted HRs were 2.13 (95% CI: 1.16–3.93) and 2.29 (1.26–4.16) for those who consumed eggs 4–6 days per week and daily, respectively (*p*-value for linear trend: <0.001; Table 2). In contrast, compared with participants who never or rarely consumed spicy food, the HRs were 0.63 (0.45–0.88) and 0.54 (0.29–1.00) for those who ate daily/almost daily and 3–5 days per week, respectively (*p*-value for linear trend: 0.001; Table 2). Additionally, compared with participants who never, rarely, or monthly consumed rice, the HR was 0.39 (0.23–0.66) for those who ate rice ≥4 days per week (*p*-value for linear trend: <0.001; Table S6). There were no clear associations between the other dietary factors and UC risk (Table S6).

The population-attributable risk (PAF) was 13.04% (7.71%–19.11%) for those who ate eggs daily or almost every day, while the PAF was 9.87% (1.94%–18.22%) for those who never or rarely ate spicy foods. This suggests that if all participants consumed fewer eggs or ate more spicy foods, approximately 13% and 10% of the incident UC cases could have been prevented during the follow-up period (Table S7). The UC risk was also attributed to general and central adiposity, defined by BMI > 28 kg/m^2 and WC > 90 cm (in men) or 85 cm (in women) (PAF: 7.80% [3.58 to 12.92%] and 7.86% [−0.31 to 17.21%], respectively).

3.3 | Associations of dietary patterns with risk of UC

There were positive associations of traditional northern and modern dietary pattern scores with risk of UC. Compared with participants in the lowest quartile scores, the adjusted HRs were 1.56 (1.06–2.28) and 2.79 (1.93–4.05) for those in the top two quartiles of traditional northern dietary pattern, respectively (*p*-value for linear trend: <0.001); the adjusted HRs were 1.76 (1.20–2.60) and 2.48 (1.63–3.78) for those in the top two quartiles of the modern dietary pattern, respectively (*p*-value for linear trend: <0.001; Table 3). Compared with non-adherence to either dietary pattern, simultaneous adherence to both patterns was associated with four times (HR: 42.04–7.84) higher UC risk, and both multiplicative and additive interactions were observed (*p*-value for interaction <0.02; Tables S8 and S9).

3.4 | Subgroup and sensitivity analyses

As shown in Figure 1, the association of egg consumption, spicy food consumption, and dietary patterns with UC risk did not differ by age, sex, education, smoking, or BMI. In sensitivity analysis, the results did not substantially change when (1) incident UC cases within the

TABLE 2 Associations of intake frequency of eggs and spicy food with risk of UC.

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Eggs consumption				
Never or rarely	14	443,915	3.2	Reference
Monthly	48	1,056,319	4.5	1.41 (0.78–2.56)
1–3 days/week	125	2,532,888	4.9	1.38 (0.79–2.41)
4–6 days/week	43	576,483	7.5	2.13 (1.16–3.93)
Dasily	82	746,899	11.0	2.29 (1.26–4.16)
p-value for linear trend[a]				<0.001
HR for 1 egg/week[b]				1.31 (1.18–1.45)
Spicy food consumption				
Never or rarely	129	1,718,887	7.5	Reference
Only occasionally	96	1,330,507	7.2	0.98 (0.75–1.29)
1–2 days/week	17	346,883	4.9	0.70 (0.42–1.17)
3–5 days/week	11	311,782	3.5	0.54 (0.29–1.00)
Daily or almost every day	59	1,648,445	3.6	0.63 (0.45–0.88)
p-value for linear trend				0.001

Note: Cox regression models were used to estimate HRs and 95% CIs. Model adjusted age at recruitment, sex, region, education level, alcohol consumption, tobacco smoking, physical activity, BMI, household income, marital status, and the log-transformed average daily energy intake and dietary patterns.

Abbreviations: BMI, body mass index; CI, confidence interval; PYAR, person-years at risk; HR, hazard ratio.

[a]Tests for the linear trend were conducted by assigning 0, 0.5, 2.0, 5.0, and 7.0 to the frequency levels from the lowest to the highest and treating the variable as a continuous variable in the Cox models. The associations for egg consumption and spicy food were significant using the Bonferroni-adjusted *p*-value threshold of 0.003846.

[b]HR for each egg increment per week was calculated by using the usual amount in the model (Appendix S1).

TABLE 3 Associations of dietary pattern scores with risk of UC.

	No. of cases	Person-time, PYAR	Incidence rate per 100,000	HR (95% CI)
Traditional northern pattern				
Q1 (low)	51	1,360,706	3.7	Reference
Q2	66	1,332,073	5.0	1.32 (0.91–1.90)
Q3	71	1,329,051	5.3	1.56 (1.06–2.28)
Q4 (high)	124	1,334,674	9.3	2.79 (1.93–4.05)
1-SD increase				1.40 (1.22–1.60)
p-value for linear trend[a]				<0.001
Modern dietary pattern				
Q1 (low)	48	1,319,960	3.6	Reference
Q2	72	1,333,786	5.4	1.54 (1.06–2.25)
Q3	80	1,340,460	6.0	1.76 (1.20–2.60)
Q4 (high)	112	1,362,299	8.2	2.48 (1.63–3.78)
1-SD increase				1.47 (1.24–1.74)
p-value for linear trend				<0.001

Note: Cox regression models were used to estimate HRs and 95% CIs. Model adjusted age at recruitment, sex, region, education level, alcohol consumption, tobacco smoking, physical activity, BMI, household income, marital status, and the log-transformed average daily energy intake.
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; PYAR, person-years at risk; Q, quartile; SD, standard deviation.
[a]Tests for linear trend were conducted by dietary pattern scores in the Cox models. The associations were significant using the Bonferroni-adjusted *p*-value threshold of 0.003846.

first 2 years of follow-up were excluded; (2) additional covariates were adjusted including hygiene-related factors, oral contraceptives, disease history, or medications related to antibiotics or NSAIDs; and (3) multivariable logistic models were used (Tables S10–S12).

4 | DISCUSSION

This is one of the largest prospective studies in China examining the associations of dietary factors and dietary patterns with risk of UC. In this study, a positive association of intake frequency of eggs and an inverse association of intake frequency of spicy food with risk of UC were found. Of the two major dietary patterns obtained in this population of Chinese adults, adherence to the traditional northern dietary pattern, characterised by high intake of wheat and low intake of rice, was associated with a higher risk of UC, while adherence to the modern dietary pattern, characterised by high intake of animal-origin foods (i.e. meat, poultry, fish, egg and dairy products) and fresh fruits, was also associated with a higher risk of UC. Our findings expanded the literature by showing novel associations of spicy food with UC risk as well as dietary patterns unique to the Chinese population.

At least 12 studies from Western and East Asian populations have examined the association of egg consumption with risk of UC. A meta-analysis involving one prospective study and nine case–control studies reported a positive association between egg intake and risk of UC in East Asians but not in Europeans.[21] However, the positive association in East Asians was based on five hospital-based case–control studies with crude assessments of egg consumption and might be subject to recall bias. Upon careful inspection of each study, the associations of egg consumption with risk of UC are inconsistent, and the number of cases ranged from 50 to 256 (median 83). Our study showed a robust and positive association between egg consumption and risk of UC. Although there is limited evidence on the possible mechanisms underlying the association between egg consumption and UC, a multifactorial process has been hypothesised and warrants further investigation. One possible explanation is that eggs contain a variety of bioactive compounds (e.g. cholesterol and choline) that can influence proinflammatory pathways and are associated with inflammation and oxidative stress, both of which are related to risk of UC.[22,23] Another possible explanation is that eggs are rich in sulphur amino acids and might increase sulphide formation in the colon. Clinical studies have shown that removing foods rich in sulphur amino acids (e.g. animal-region foods including eggs) has potential therapeutic benefits in UC patients.[24]

A novel finding of the present study is the protective association between spicy food consumption and UC risk. This finding is in line with previous reports in CKB that showed protective associations of spicy food with mortality and morbidity of major chronic diseases.[25,26] The potential mechanism underlying the protective association might relate to the main active component of chilli peppers, capsaicin (CAP). Small population-based studies and animal studies have shown the pleiotropic benefits of CAP, including anti-inflammatory, antioxidant, anti-proliferative, and metabolic effects.[27] A considerable body of evidence, mostly animal studies, showed that capsaicin had modulatory effects on the

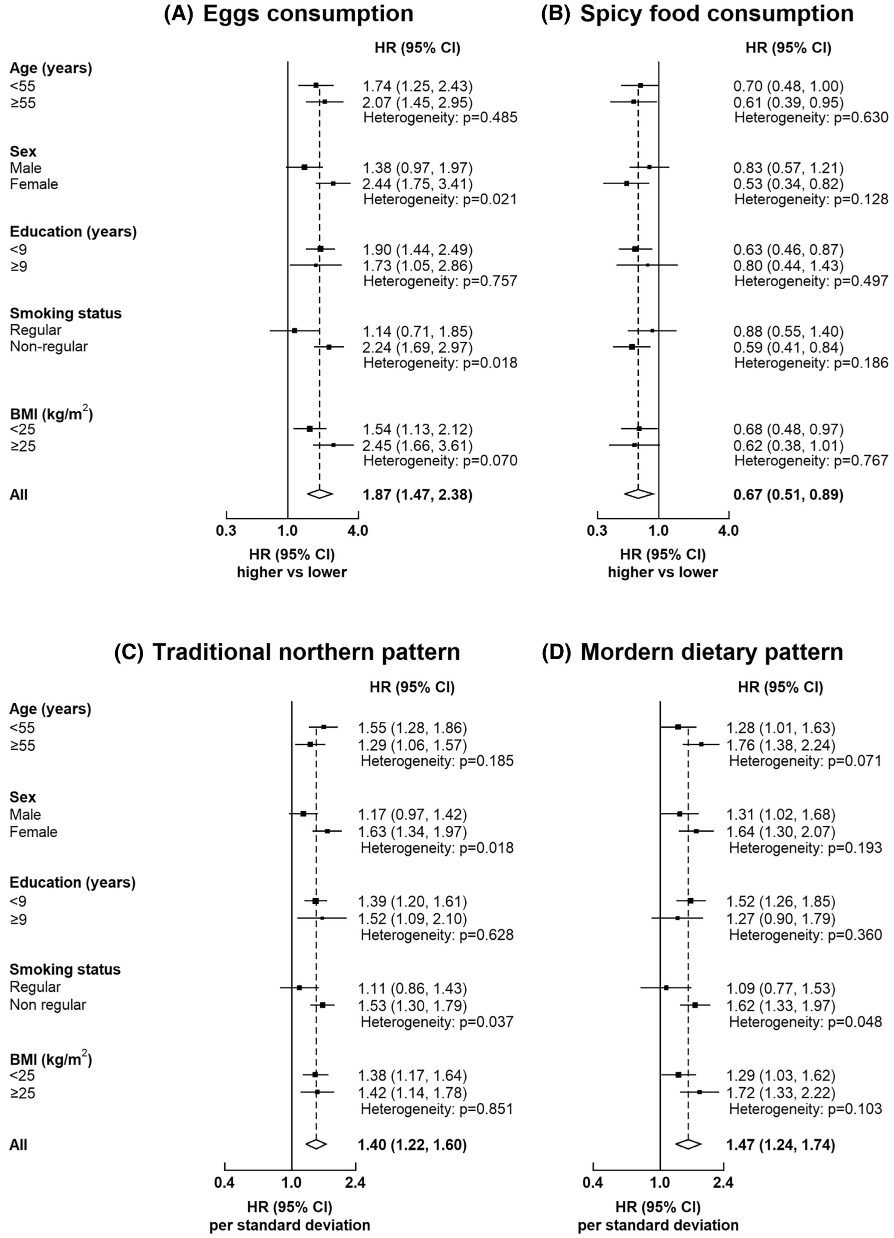

FIGURE 1 Subgroup analysis of associations of egg consumption, spicy food consumption, and two dietary patterns with risk of UC. HRs (95% CIs) were provided to compare the higher consumption frequency of both eggs and spicy food with lower consumption frequencies, and HRs (95% CIs) per standard deviation change were presented for the linear trend of dietary pattern scores. For eggs, the lower consumption frequencies were never/rarely, monthly, and 1–3 days per week; the higher consumption frequencies were 4–6 days per week or daily. For spicy food, the lower consumption frequencies were never/rarely, only occasionally, and 1–2 days per week; the higher frequencies were 3–5 days per week, almost every day or daily. Adjusted variables for Cox models included age at recruitment, sex, region, education level, alcohol consumption, tobacco smoking, physical activity, BMI, household income, marital status, and the average daily energy intake in its log-transformed. Bonferroni-adjusted *p*-value threshold for interaction was 0.003846. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

gut microbiota, targeting inflammatory diseases.[28] An analysis of 12 healthy adults in China showed that a short-term intervention of a high-dose CAP-enriched diet (10 mg/day for 2 weeks) could increase microbiota diversity and the abundance of the human gut microbiome,[29] which may be associated with the lower risk of UC.[30] Collectively, this evidence suggests that spicy food consumption may lead to an anti-inflammatory environment in the gut and could help prevent the incidence of UC.

In this Chinese population, the modern dietary pattern score was strongly correlated with a high intake of animal-origin foods and fresh fruits and was associated with a higher risk of UC. A systematic review and meta-analysis including seven case–control studies and two prospective cohorts found that adherence to Western dietary pattern was associated with increased risk of UC (RR: 2.15, 95% CI: 1.38–3.34),[31] suggesting that adopting a healthier dietary pattern may be a potential preventive strategy for UC. Recently, a prospective population-based cohort study in the north of the Netherlands, involving 125,445 individuals and documenting 224 UC patients, found that adherence to a carnivorous dietary pattern was associated with a higher risk of UC (OR: 1.11, 95% CI: 1.01–1.20).[15] Potential mechanisms for the harmful associations of the Western diet are linked to changes in the gut microbiome and epithelial barrier function, which might influence immune function and trigger pro-inflammatory.[32]

The strengths of this study include the prospective design, large and diverse study population, ability to collect detailed information on lifestyle factors, and careful adjustment for other risk factors of UC (Table S13). However, our study also has several limitations. First, we only assessed the frequency of 12 major food groups consumption and spicy food consumption in Chinese diet. Other food groups (e.g. sugar sweetened beverage consumption and intake of other processed or ultra-processed foods) that may be related to UC were not considered.[33] However, in the second resurvey of CKB, the majority of the participants (90%–99%) reported consuming carbonated drinks, other soft drinks, deep-fried foods, and Western-type fast foods <1 day/week, so the infrequent consumption in this study suggests that they were unlikely to alter the primary findings of our study. Second, the baseline FFQ included only information on consumption frequency. However, concise questions could enhance response accuracy and reduce measurement bias. In the second resurvey of approximately 25,000 participants, we collected more detailed information on food intake (both frequency and amount consumed) and found that the dietary pattern scores calculated using only frequency was highly consistent with those calculated using both frequency and amount.[34] Meanwhile, FFQ has been demonstrated as a proper and achievable method to assess long-term dietary habits, especially in middle-aged populations with strong dietary habits.[12,35] Third, there is potential misclassification of food group consumption due to recall bias. However, two prior surveys were conducted to assess the reproducibility and validity of CKB FFQs. These surveys showed good reproducibility and validity of major dietary factors (Table S1), which were comparable with other perspective studies in Western and East Asian populations (Table S14). Additionally, this misclassification may be non-differential, biasing the associations toward the null. Fourth, our findings may not be generalised to all age onset of UC, since the age of UC diagnosis in this study ranged from 39 to 84 years (median: 60.1 years). The extended follow-up period of our study facilitated the identification of new diagnoses of later-onset UC, particularly between the age 50 and 80 (Figure S2). Nevertheless, with detailed and validated data on UC diagnosis and dietary information on over 0.5 million middle-aged adults in China, our cohort provided a unique opportunity to examine the associations of diet with adult-onset and elderly-onset UC, where relative to paediatric-onset UC the overall contribution of environment is greater.[8] Furthermore, our findings were consistent in stratified analyses by age (<55 or ≥55 years, Figure 1). Fifth, ICD codes were used for the diagnosis of UC, which might be prone to misclassification. However, ongoing outcome adjudication studies in CKB showed a relatively good diagnostic accuracy of UC (97%). Sixth, although we adjusted for sociodemographic factors, behavioural factors, and other risk factors beyond diet in our multivariable models, residual confounding may still exist due to uncollected or suboptimally collected factors.

In this Chinese population, egg consumption was associated with higher risk of later-onset UC, whereas spicy food consumption was associated with lower risk. Adherence to both traditional northern dietary pattern (high intakes of wheat and low intakes of rice) and modern dietary pattern (high intakes of animal-origin food and fruits) was associated with higher risk of UC. The findings of our study emphasise the importance of evaluating dietary factors and patterns in the primary prevention of later-onset UC in adults. While interventional studies are needed to confirm these findings, the results suggest that dietary counselling aimed at reducing consumption of animal-origin food, as well as avoiding a Western dietary pattern, may help lower the risk of developing UC in Chinese adults.

AUTHOR CONTRIBUTIONS

Yuanjie Pang: Conceptualization; data curation; formal analysis; supervision; writing – original draft; writing – review and editing. **Shuyao Song:** Writing – original draft; investigation; formal analysis; writing – review and editing. **Zhiyu Wu:** Formal analysis; writing – original draft; writing – review and editing. **Jun Lv:** Conceptualization; writing – original draft; writing – review and editing. **Canqing Yu:** Data curation; investigation; writing – original draft; writing – review and editing. **Dianjianyi Sun:** Data curation; investigation; writing – original draft; writing – review and editing. **Pei Pei:** Project administration; writing – original draft; writing – review and editing. **Lang Pan:** Formal analysis; project administration; writing – original draft; writing – review and editing. **Ling Yang:** Validation; writing – original draft; writing – review and editing. **Yiping Chen:** Validation; writing – original draft; writing – review and editing. **Huaidong Du:** Project administration; writing – original draft; writing – review and editing. **Lingli Chen:** Project administration; writing – original draft; writing – review and editing. **Danile Schmidt:** Software; writing – original draft; writing – review and editing. **Daniel Avery:** Data curation; software; writing – original draft; writing – review and editing. **Liping Duan:** Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Junshi Chen:** Funding acquisition; writing – original draft; writing – review and editing. **Zhengming Chen:** Funding acquisition; writing – original draft; writing – review and editing. **Liming Li:** Conceptualization; funding acquisition; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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INVITED EDITORIAL

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Editorial: Exploring the influence of diet on later-onset ulcerative colitis—Are eggs and spicy foods the key factors in Asia? Authors' reply

We appreciate the insightful commentary from Drs. Okabayashi and Kobayashi on our paper.[1,2] Our findings underscore the significant role that diet plays in the development of later-onset ulcerative colitis (UC) in Chinese adults, suggesting that recommendations of lowering the consumption of eggs and avoiding a Western diet are important in the primary prevention of later-onset UC. Our study also provided novel evidence on the associations of spicy food and traditional northern dietary patterns with the risk of later-onset UC in Chinese.

The prospective China Kadoorie Biobank (CKB) study, one of the world's largest prospective cohort studies, recruited 0.5 million participants aged 30–79 years and followed for a median of 12.1 years with 0.8% loss to follow-up.[3] The extensive and rigorous follow-up allowed us to identify new diagnoses of later-onset UC (median age at diagnosis: 60.1 years). Moreover, this study collected comprehensive and validated data on UC diagnosis, dietary information, and other relevant risk factors,[3] providing a unique opportunity to yield reliable evidence on the associations of diet with risk of later-onset UC.

We acknowledge that it may be difficult to generalise our findings to all ages of UC onset, as the age of UC diagnosis in this study ranged from 39 to 84 years. However, the overall contribution of the environment is greater for later-onset than paediatric-onset UC.[4] Additionally, our findings, along with those of other prospective cohort studies in high-income countries, consistently demonstrate associations of potentially modifiable factors (e.g. diet and lifestyle factors) with UC in analyses stratified by age.[5,6] Furthermore, we used the Fine and Gray sub-distribution hazard model considering competing risks (non-inflammatory bowel disease [IBD]-related deaths) to evaluate the associations of egg and spicy food consumption with UC: the associations remained robust (daily vs. never or rarely: hazard ratio [HR] for egg consumption 2.30 in Fine-Gray model vs. 2.29 in our original analyses; HR for spicy food consumption 0.83 vs. 0.63).

Considering the potential onset of UC at any stage of life and the crucial role of diet in its aetiology,[7,8] further prospective cohort studies with longer follow-up, recruiting participants with younger ages, are necessary. Large-scale, general population-based observational studies utilising integrated real-world data are a promising direction. For instance, the Chinese Electronic Health Records Research in Yinzhou (CHERRY) study, integrates comprehensive healthcare data, enabling trajectory analyses of lifetime healthcare for one million Chinese adults from Ningbo City, China.[9] However, the food frequency questionnaire used by CHERRY has not been qualitatively or quantitatively validated. In addition, quantitative assessment of dietary intake may be particularly difficult earlier in life. An alternative solution may be to use biomarkers to quantify early life exposures from diet, which is a key scientific advance in ascertaining risk factors.[10] With recent breakthroughs in omics technologies, such studies are likely to be feasible and provide us with meaningful data to provide insights on prevention strategies for IBD.

AUTHOR CONTRIBUTIONS

Shuyao Song: Writing – original draft; validation; writing – review and editing; formal analysis. **Jun Lv:** Conceptualization; investigation; methodology; funding acquisition; writing – review and editing; supervision; resources. **Liming Li:** Conceptualization; investigation; funding acquisition; methodology; supervision; writing – review and editing; resources. **Yuanjie Pang:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; writing – review and editing; supervision; formal analysis; project administration; resources.

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LINKED CONTENT

This article is linked to Song et al papers. To view these articles, visit https://doi.org/10.1111/apt.17963 and https://doi.org/10.1111/apt.17983

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中国中老年人肝脏生物学年龄构建和评价

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【摘要】（969 字）

目的 在中国中老年人中构建肝脏生物学年龄，探索肝脏生物学年龄与实足年龄相关性及对全因死亡的预测能力，分析肝脏生物学年龄及其年龄加速与全因死亡和肝脏相关死亡的关联。为探索以肝脏为代表的主要器官系统特异性衰老指标提供证据。

方法 中国慢性病前瞻性研究（CKB）第三次重复调查开展于 2020-2021 年，在基线调查的 51 万余名研究对象中抽取约 5%尚存活的队列成员（25 087 名）。（1）构建肝脏生物学年龄：将数据合格研究对象随机等分为训练集和验证集。纳入脂肪衰减参数（FAP）和肝脏硬度值（LSM）2 个肝脏影像标志物，以及丙氨酸转氨酶、天冬氨酸转氨酶和γ-谷氨酰转移酶 3 个肝酶标志物，并进行对数转换，采用 Gompertz 比例风险模型，以全因死亡为训练表型构建肝脏生物学年龄。（2）计算肝脏生物学年龄与实足年龄的 Pearson 相关系数及预测误差。肝脏生物学年龄加速为肝脏生物学年龄与实足年龄回归残差。（3）以全因死亡为结局，绘制实足年龄和肝脏生物学年龄的受试者工作特征曲线（ROC），计算曲线下面积（AUC），比较对全因死亡的预测效果。（4）采用 Cox 比例风险模型分析肝脏生物学年龄及其年龄加速与全因死亡风险的前瞻性关联。采用限制性立方样条函数分析非线性关联。

结果 本研究共纳入 CKB 第三次重复调查肝超声和血生化检测数据合格的 22 773 名 45~95 岁研究对象，平均年龄 65.2 岁，女性占比 64.8%。FAP 中位数为 249.0（*IQR*: 223.0~275.0）dB/m，LSM 中位数为 6.9（*IQR*: 5.6~8.6）kPa。肝脏生物学年龄与实足年龄高度相关。在训练集和验证集中，肝脏生物学年龄与实足年龄的相关性均为 0.95，预测误差分别为 2.78 年和 2.72 年。截至 2022 年 12 月 31 日，平均随访时长 1.5 年，共观察到 307 例死亡，包括 6 例肝脏相关死亡。肝脏生物学年龄对全因死亡的预测效度大于实足年龄。在训练集和验证集中，肝脏生物学年龄 AUC 分别为 0.804（*95% CI*: 0.777~ 0.831）和 0.808（*95% CI*: 0.782~ 0.833），高于实足年龄的 0.791（*95% CI:* 0.763~0.818; P<0.05）和 0.805（*95% CI:* 0.778~0.831; P=0.54）。肝脏生物学年龄及其年龄加速与全因死亡风险的关联有统计学显著性。在全部研究对象中，肝脏生物学年龄加速每增加一个标准差（2.8 年），全因死亡风险增加 28%（*HR*=1.28, *95% CI*: 1.14~1.43），肝脏相关死亡风险增加 48%（*HR*=1.48, *95% CI*: 1.09~1.99），非肝脏相关死亡 27%（*HR*=1.27, *95% CI*: 1.14~1.42）。肝脏生物学年龄及其年龄加速与全因死亡有非线性关联（P<0.001）。

结论 基于肝脏特异性标志物构建的肝脏生物学年龄能较好拟合实足年龄，并对死亡有较好预测效果。肝脏生物学年龄有望捕获肝脏特异性衰老特征，为人体器官系统特异性衰老机制研究提供基础。

【关键词】肝脏；生物学年龄；器官系统；中国中老年人

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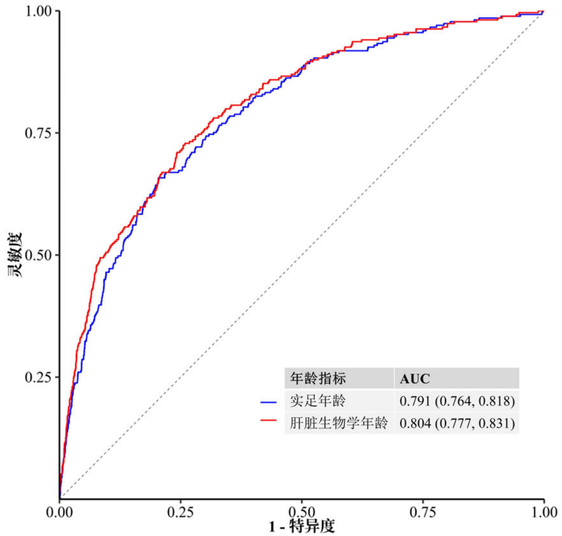
1）肝脏生物学年龄指标特征

年龄指标	均值（标准差），年	年龄加速标准差，年	与实足年龄相关系数	对实足年龄均方根误差
训练集				
实足年龄	65.26 (9.13)			
肝脏生物学年龄	64.97 (9.35)	2.84	0.953	2.78
验证集				
实足年龄	65.22 (9.01)			
肝脏生物学年龄	65.02 (9.21)	2.79	0.953	2.72

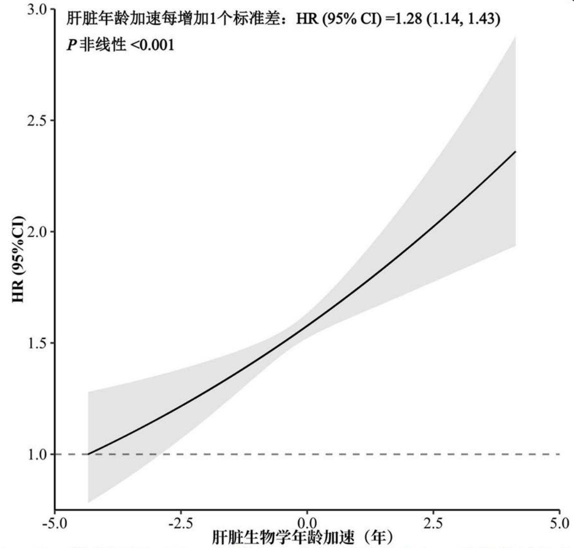
注：肝脏生物学年龄为肝脏生物标志物经自然对数转换后，采用Gompertz比例风险模型构建。肝脏生物学年龄加速为肝脏生物学年龄与实足年龄回归的残差。研究人群为CKB第三次重复调查数据合格的22 773名研究对象，随机等分为训练集和验证集。

2）肝脏生物学年龄对全因死亡的预测效度



注：AUC，受试者工作特征曲线下面积。训练集中，以全因死亡为结局，绘制实足年龄及肝脏生物学年龄的受试者工作特征曲线并计算曲线下面积，图例标注了不同颜色曲线对应指标及相应AUC值。

3）肝脏生物学年龄加速与全因死亡的非线性关联



注：CI，置信区间；HR，风险比。全部研究对象中，采用限制性立方样条函数Cox比例风险模型，选取5个节点，以全因死亡为结局，调整性别、城乡地区、禁食时间、吸烟状况、饮酒状况和受教育程度。

图　肝脏生物学年龄的指标评价

中国中老年人肝脏生物学年龄构建和评价

宋树摇 毋之钰 余灿清 孙点剑一 裴培 杜怀东 陈君石 陈铮鸣 吕筠 李立明 庞元捷 代表中国慢性病前瞻性研究项目协作组

背　景

评估人体肝脏衰老程度具有重要的科学和临床意义。本研究在中国中老年人群中构建和评价肝脏生物学年龄，为探索以肝脏为代表的主要器官系统特异性衰老指标提供证据。

研究设计

研究纳入中国慢性病前瞻性研究（CKB）第三次重复调查数据合格的22 773名研究对象，随机等分为训练集和检验集。研究基于脂肪衰减参数（FAP）、肝脏硬度值（LSM）、丙氨酸转氨酶（ALT）、天冬氨酸转氨酶（AST）和γ-谷氨酰转移酶（GGT）5个肝脏标志物，采用Gompertz比例风险模型，以全因死亡为训练表型构建肝脏生物学年龄。肝脏生物学年龄加速为肝脏生物学年龄与实足年龄回归的残差。评价肝脏生物学年龄与实足年龄相关程度，对全因死亡的预测效度，年龄加速与死亡风险的前瞻性关联。

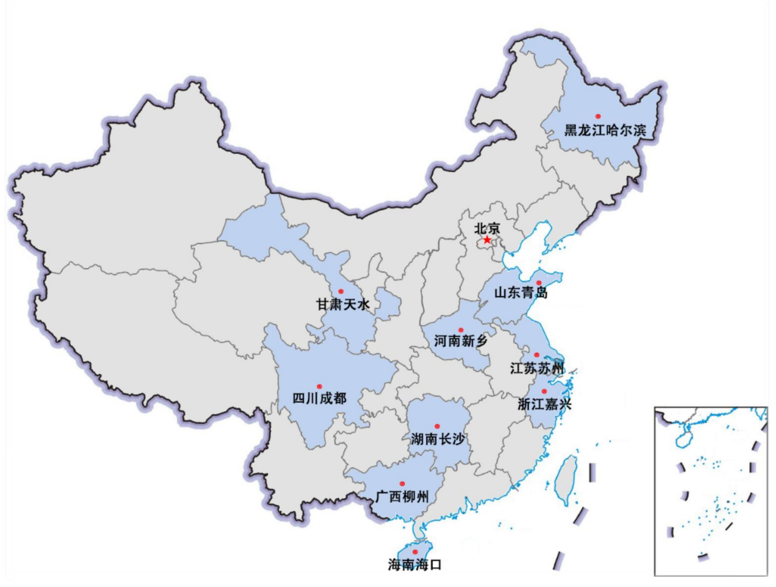


图1 CKB项目调查现场

$$\mathrm{BA}=\frac{\ln\left(\frac{\ln\left(e^{-\left(e^{xb}\gamma_1^{-1}\left(e^{\gamma_1 t}-1\right)\right)}\right)}{\gamma_0^{-1}\left(e^{\gamma_0 t}-1\right)}\right)-\beta_0}{\beta_1}$$

公式1 Gompertz比例风险模型计算肝脏生物学年龄

- BA：肝脏生物学年龄；
- x：肝脏生物标志物；
- γ_1，b：肝脏生物标志物为预测因子时模型拟合系数；
- γ_0，β_0，β_1：实足年龄为预测因子时模型拟合系数；
- t：随访时间；*e*：自然常数。

结　果

1 肝脏生物标志物基本特征

- 研究对象年龄范围为45~95岁，平均年龄65.2岁，女性占比64.8%。
- FAP中位数为249.0（*IQR*: 52.0）dB/m，LSM中位数为6.9（3.0）kPa；ALT、AST、GGT中位数分别为20.0（11.5）U/L、22.8（8.5）U/L和22.2（16.1）U/L。
- ALT和AST在男性和女性中均与全因死亡风险有非线性关联（*P*<0.05）。

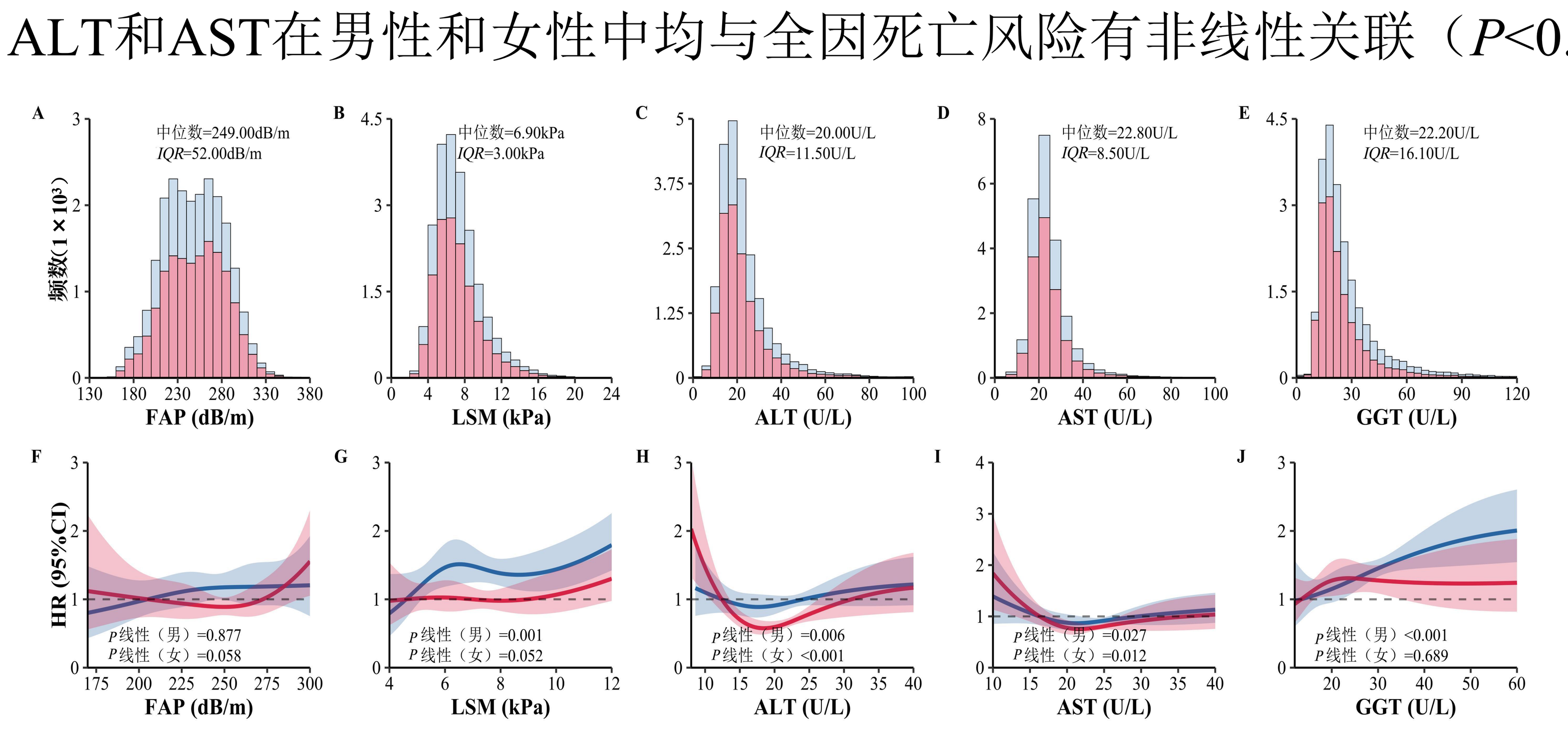


图2 肝脏生物标志物概率分布及与全因死亡的前瞻性关联

注：FAP，脂肪衰减参数；LSM，肝脏硬度值；ALT，丙氨酸转氨酶；AST，天冬氨酸转氨酶；GGT：谷氨酰转移酶。

2 肝脏生物学年龄基本特征

- 在检验集中，肝脏生物学年龄均值为65.0±9.2岁。
- 肝脏生物学年龄与实足年龄高度相关。在检验集中，肝脏生物学年龄与实足年龄的相关系数为0.95，预测误差为2.72。

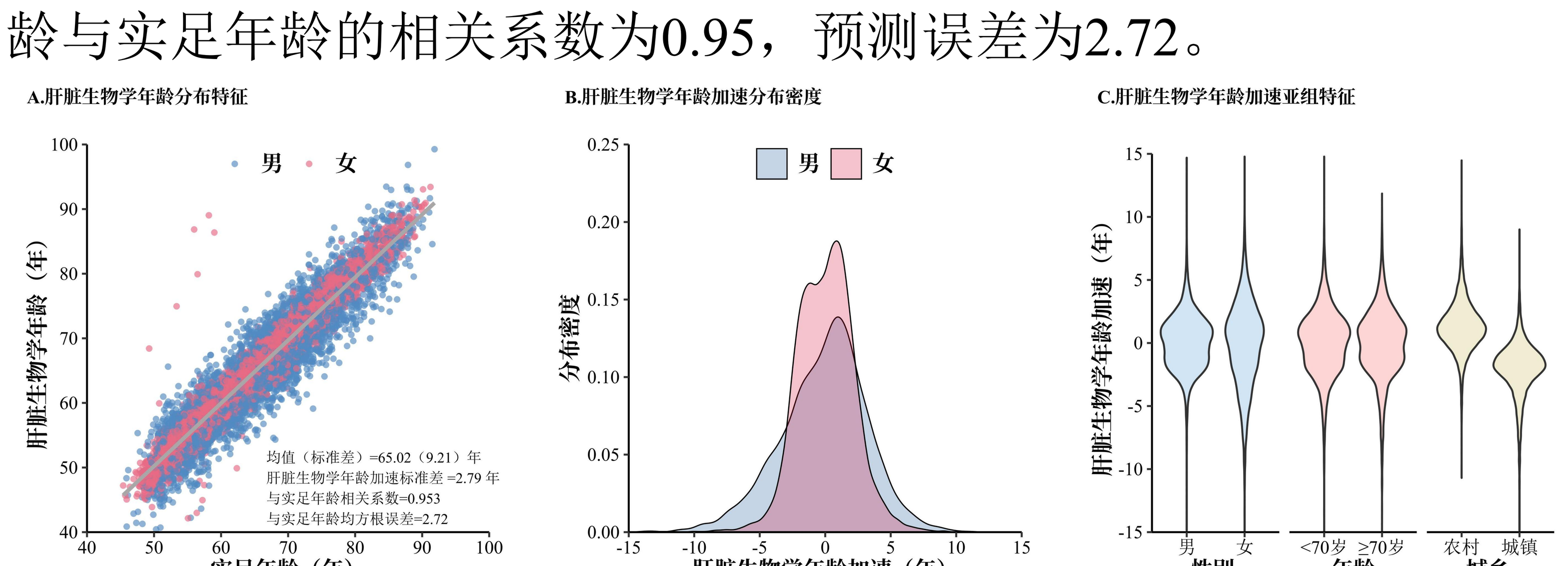


图3 肝脏生物学年龄基本特征

结　果

表1 肝脏生物学年龄加速分组的基线特征分布

	肝脏生物学年龄加速					*P*线性
	Q1（低）	Q2	Q3	Q4	Q5（高）	
年龄（标准差），岁	64.4 (9.0)	65.2 (8.9)	65.2 (9.2)	65.5 (9.1)	65.9 (9.1)	<0.001
女性，%	49.5	71.8	72.8	72.2	57.6	0.034
当前吸烟，%						
男性	54.7	54.4	56.2	54.5	57.6	0.162
女性	1.2	1.4	2.0	1.7	1.9	0.226
缺乏体力活动[a]，%	49.7	49.4	49.4	50.9	50.6	0.307
不健康体型[b]，%	16.1	15.8	18.6	16.8	19.8	0.001
进展期肝纤维化，%	4.9	10.3	15.2	17.9	28.7	<0.001
现患糖尿病，%	13.3	13.9	14.4	15.0	17.5	<0.001
自评健康良好，%	8.2	6.8	6.6	5.9	5.3	<0.001

注：Q，五分位数分组。结果适时调整年龄，性别和城乡地区。[a]缺乏体力活动指总体力活动水平排位在同年龄组、同性别人群的后50%；[b]不健康体型指BMI<20kg/m²或BMI≥30 kg/m²。

3 肝脏生物学年龄对死亡的预测效度

- 平均随访时长1.5年，共观察到307例死亡，其中6例肝脏相关死亡。
- 肝脏生物学年龄对全因死亡预测效度大于实足年龄（*P*<0.05）。
- 肝脏生物学年龄受试者工作特征曲线下面积在性别、年龄和城乡亚组分析间差异无统计学显著性（*P*>0.05）。

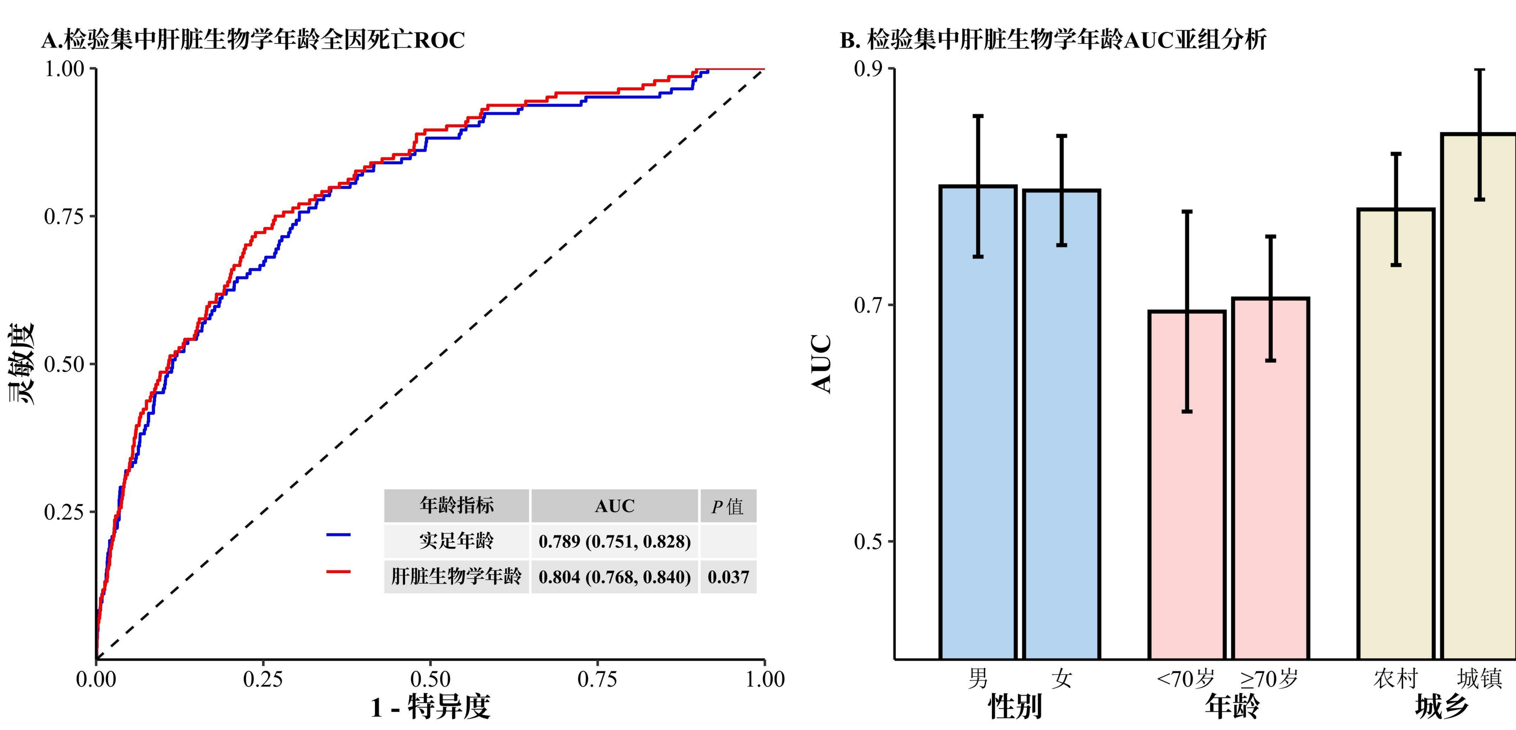


图4 肝脏生物学年龄对死亡的预测效度

注：ROC，受试者工作特征曲线；AUC，受试者工作特征曲线下面积。

4 肝脏生物学年龄加速与死亡的前瞻性关联

- 肝脏生物学年龄加速与全因死亡风险和肝脏相关死亡的关联有统计学显著性。
- 肝脏生物学年龄加速每增加一个标准差（2.8年），全因死亡风险增加20%（HR=1.20, 95% CI: 1.06~1.37），肝脏相关死亡风险增加56%（HR=1.56, 95% CI: 1.06~2.30）。
- 在女性中，肝脏生物学年龄加速与全因死亡有非线性关联（*P*<0.05）。

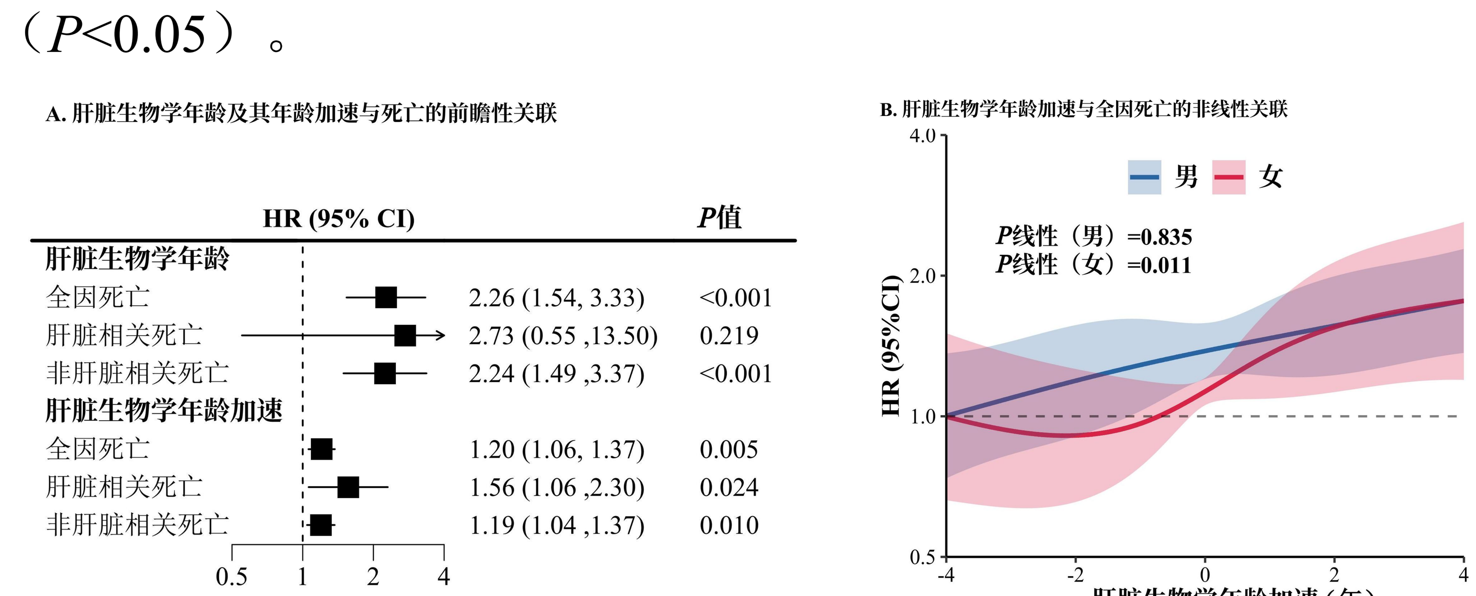


图5 肝脏生物学年龄及年龄加速与死亡的前瞻性关联

注：HR，风险比；CI，置信区间。

结　论

基于肝脏生物标志物，以死亡为训练表型构建的肝脏生物学年龄能较好拟合实足年龄，并对死亡有较好预测效果。肝脏生物学年龄有望捕获肝脏特异性衰老特征，为人体器官系统特异性衰老机制研究提供基础。

本研究由国家重点研发计划项目（2023YFC3606300）；国家自然科学基金（82192901，82192902，82192904，82192900）；中国香港Kadoorie Charitable基金资助。

北京大学

硕士研究生学位论文

题目：**生活方式与中国中老年人肝脏生物学年龄的关联研究**

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二〇二五 年 五 月

生活方式与中国中老年人肝脏生物学年龄的关联研究

摘要

【目的】 基于中国慢性病前瞻性研究（China Kadoorie Biobank, CKB）第三次重复调查数据：（1）构建中国中老年人肝脏生物学年龄；（2）探索肝脏生物学年龄与实足年龄相关性；（3）分析肝脏生物学年龄及其年龄加速与全因死亡和肝脏相关死亡的关联；（4）分析生活方式与肝脏生物学年龄及其年龄加速的关联；（5）评估肝脏生物学年龄及其年龄加速在生活方式与死亡关联中的中介作用。

【方法】 中国慢性病前瞻性研究（CKB）第三次重复调查开展于 2020-2021 年，在基线调查的 51 万余名研究对象中抽取约 5%尚存活的队列成员（25 087 名）。（1）构建肝脏生物学年龄：将数据合格研究对象随机等分为训练集和验证集。纳入脂肪衰减参数（FAP）和肝脏硬度值（LSM）2 个肝脏影像标志物，以及丙氨酸转氨酶、天冬氨酸转氨酶和 γ -谷氨酰转移酶 3 个肝酶标志物，并进行对数转换，采用 Gompertz 比例风险模型，以全因死亡为训练表型构建肝脏生物学年龄。（2）计算肝脏生物学年龄与实足年龄的 Pearson 相关系数及预测误差。肝脏生物学年龄加速为肝脏生物学年龄与实足年龄回归残差。（3）以全因死亡为结局，绘制实足年龄和肝脏生物学年龄的受试者工作特征曲线（ROC），计算曲线下面积（AUC），比较对全因死亡的预测效果。采用 Cox 比例风险模型分析肝脏生物学年龄及其年龄加速与全因死亡风险的前瞻性关联。采用限制性立方样条函数分析非线性关联。采用 Fine&Gray 竞争风险模型分析肝脏生物学年龄及其年龄加速与肝脏相关死亡风险的前瞻性关联。（4）采用一般线性模型，分析不健康生活方式与肝脏生物学年龄及其年龄加速的关联，纳入的生活方式包括现在吸烟、过量饮酒、不健康膳食摄入、低体力活动、不健康体型。（5）采用中介分析计算肝脏生物学年龄及其年龄加速介导生活方式与死亡关联的中介效应。

【结果】 本研究共纳入 CKB 第三次重复调查肝超声和血生化检测数据合格的 22 773 名 45~95 岁研究对象，平均年龄 65.2 岁，女性占比 64.8%。（1）FAP 中位数为 249.0（*IQR*: 223.0~275.0）dB/m，LSM 中位数为 6.9（*IQR*: 5.6~8.6）kPa。在训练集和验证集中，肝脏生物学年龄均值分别为 64.97 和 65.02 年，标准差分别为 9.35 和 9.21 年。（2）肝脏生物学年龄与实足年龄高度相关。在训练集和验证集中，肝脏生物学年龄与实足年龄的相关性均为 0.95，预测误差分别为 2.78 年和 2.72 年。（3）截至 2022 年 12 月 31 日，平均随访时长 1.5 年，本研究纳入的分析的研究对象中共观察到 307 例死亡，包括

6 例肝脏相关死亡。肝脏生物学年龄对全因死亡的预测效度大于实足年龄。在训练集和验证集中，肝脏生物学年龄 AUC 分别为 0.804（*95% CI*: 0.777~ 0.831）和 0.808（*95% CI*: 0.782~ 0.833）。肝脏生物学年龄及其年龄加速与全因死亡风险的关联有统计学显著性。在全部研究对象中，肝脏生物学年龄加速每增加一个标准差（2.8 年），全因死亡风险增加 28%（*HR*=1.28, *95% CI*: 1.14~1.43），肝脏相关死亡风险增加 48%（*HR*=1.48, *95% CI*: 1.09~1.99），非肝脏相关死亡 27%（*HR*=1.27, *95% CI*: 1.14~1.42）。肝脏生物学年龄及其年龄加速与全因死亡有非线性关联（P<0.001）。（4）不健康生活方式会增加肝脏生物学年龄及其年龄加速，即增加肝脏衰老。不健康生活方式得分每增加 1 分，肝脏生物学年龄加速 0.24 年（95% CI: 0.21-0.28），肝脏生物学年龄加速 0.18 年（95% CI: 0.15-0.22），均具有统计学显著性（P < 0.001）。（5）肝脏生物学年龄在不健康生活方式得分与全因死亡风险的中介效应为 8.83%，肝脏生物学年龄加速在不健康生活方式得分与全因死亡风险的中介效应为 4.89%。

【结论】基于肝脏标志物构建的肝脏生物学年龄能较好拟合实足年龄，对死亡有较好预测效果，捕获肝脏特异性衰老特征。不健康生活方式，即吸烟、过量饮酒和不健康膳食、低体力活和不健康体型，与肝脏生物学年龄及其年龄加速的增加正向关联；肝脏生物学年龄及其年龄加速可部分介导生活方式与死亡风险之间的关联。在中老年人群中应用肝脏生物学年龄，并可用于评估个体的全因死亡和肝脏相关死亡风险，作为肝脏衰老预警指标，有望有效指导人群健康管理。

【关键词】 肝脏衰老；生物学年龄；生活方式；中国中老年人

Association of lifestyles with liver biological age in Chinese middle-aged and elderly populations

ABSTRACT

Objectives: Based on the third resurvey data from the China Kadoorie Biobank (CKB), this study aimed to (1) construct Liver Age (LiverAge) in Chinese middle-aged and elderly individuals; (2) explore the correlation of LiverAge and Liver Age Acceleration (LiverAgeAccel) with chronological age (CA); (3) analyze the associations of LiverAge and LiverAgeAccel with all-cause mortality and liver-related mortality; (4) analyze the relationship between lifestyle factors and lifestyle scores with LiverAge and LiverAgeAccel , (5) assess the mediating role of LiverAge and LiverAgeAccel in the association between lifestyle factors and mortality.

Methods: The third resurvey of CKB was conducted from 2020 to 2021, extracting approximately 5% of the surviving cohort members (25,087 individuals) from over 510,000 participants in baseline. (1) To construct LiverAge, dataset was randomly divided into training and validation sets. Two liver imaging markers, Fatty Liver Parameter (FAP) and Liver Stiffness Measurement (LSM), as well as three liver enzyme markers (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase), were included and log-transformed. The Gompertz proportional hazards model was used to generate LiverAge with all-cause mortality as the training phenotype. (2) Pearson correlation coefficients and prediction errors for LiverAge and CA were calculated. LiverAgeAccel was derived as the regression residuals of biological liver age and chronological age. (3) Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated to compare predictive effectiveness for all-cause mortality. Cox proportional hazards models were employed to analyze the associations between LiverAge, LiverAgeAccel, and all-cause mortality risk. Restricted cubic spline was used to analyze non-linear associations. The Fine & Gray competing risks regression model was used to evaluated the associations of LiverAge and LiverAgeAccel with liver-related mortality risk. (4) General linear models were used to analyze the relationships between lifestyle factors and LiverAge and LiverAgeAccel. The lifestyle factors included current smoking, excessive alcohol consumption, unhealthy dietary intake, low physical activity, and unhealthy body shape. (5) Mediating analysis was conducted to calculate the mediating effects of biological liver age and its acceleration in the association between lifestyle factors and mortality.

Results: This study included 22,773 participants aged 45-95 from CKB third resurvey of the CKB with liver ultrasound and blood biochemical data, with mean age of 65.2 years and 64.8% female. (1) The median FAP was 249.0 (IQR: 223.0, 275.0) dB/m, and the median LSM was 6.9 (5.6, 8.6) kPa. In the training and validation sets, the mean biological liver age was 64.97 and 65.02 years, with standard deviations of 9.35 and 9.21 years, respectively. (2) LiverAge fitted CA well, with correlation coefficients of 0.95 in both training and validation sets and prediction errors of 2.78 years and 2.72 years, respectively. (3) As of December 31, 2022, with an average follow-up of 1.5 years, 307 deaths were observed, including 6 liver-related deaths. LiverAge had greater predictive validity for all-cause mortality than CA. In the training and validation sets, the AUC for LiverAge was 0.804 (95% CI: 0.777, 0.831) and 0.808 (0.782, 0.833), respectively. The LiverAge, LiverAgeAccel, were statistically significantly associated with the risk of all-cause mortality risk. For all participants, 1-SD HR (95% CI) of LiverAgeAccel for all-cause mortality was 1.28 (1.14, 1.43), a 48% increase in liver-related mortality risk (HR=1.48; 1.09, 1.99), and a 27% increase in non-liver-related mortality (HR=1.27; 1.14, 1.42). There were non-linear associations of LiverAge, LiverAgeAccel, with all-cause mortality (P<0.001). (4) For each point increase in unhealthy lifestyle scores, LiverAge increased 0.24 years (0.21, 0.28) and LiverAgeAccel increased 0.18 years (0.15, 0.22), both statistically significant (P<0.001). (5) The mediating effect of biological liver age in the association between unhealthy lifestyle scores and all-cause mortality risk was 8.83%, while the mediating effect of biological liver age acceleration was 4.89%.

Conclusions: The LiverAge constructed based on liver markers fits well with CA and provides good predictive effects for mortality, capturing liver-specific aging characteristics. Unhealthy lifestyle factors—smoking, excessive alcohol consumption, unhealthy diet, low physical activity, and unhealthy body shape—are positively associated with increases in LiverAge and LiverAgeAccel. LiverAge and LiverAgeAccel partially mediate the association of lifestyle factors with mortality risk. Applying biological liver age in Chinese middle-aged and elderly populations can help assess individual risks for all-cause mortality and liver-related mortality, serving as a warning indicator for liver aging and potentially guiding effective population health management.

KEY WORDS: Liver aging, Biological age, Lifestyle, Chinese middle-aged and elderly populations

目录