



Association of lifestyles and multimorbidity with mortality among individuals aged 60 years or older: Two prospective cohort studies

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ABSTRACT

Lifestyles are associated with all-cause mortality, yet limited research has explored the association in the elderly population with multimorbidity. We aim to investigate the impact of adopting a healthy lifestyle on reducing the risk of all-cause mortality in older individuals with or without multimorbidity in both China and UK. This prospective study included 29,451 and 173,503 older adults aged 60 and over from Chinese Longitudinal Healthy Longevity Survey (CLHLS) and UK Biobank. Lifestyles and multimorbidity were categorized into three groups, respectively. Cox proportional hazards regression was used to estimate the Hazard Ratios (HRs), 95% confidence intervals (95% CIs), and dose-response for all-cause mortality in relation to lifestyles and multimorbidity, as well as the combination of both factors. During a mean follow-up period of 4.7 years in CLHLS and 12.14 years in UK Biobank, we observed 21,540 and 20,720 deaths, respectively. For participants with two or more conditions, compared to those with an unhealthy lifestyle, adopting a healthy lifestyle was associated with a 27%–41% and 22%–42% reduction in mortality risk in the CLHLS and UK Biobank, respectively; Similarly, for individuals without multimorbidity, this reduction ranged from 18% to 41%. Among participants with multimorbidity, individuals with an unhealthy lifestyle had a higher mortality risk compared to those maintaining a healthy lifestyle, with HRs of 1.15 (95% CI: 1.00, 1.32) and 1.27 (95% CI: 1.16, 1.39) for two conditions, and 1.24 (95% CI: 1.06, 1.45) and 1.73 (95% CI: 1.56, 1.91) for three or more conditions in CLHLS and UK Biobank, respectively. Adherence to a healthy lifestyle can yield comparable mortality benefits for older individuals, regardless of their multimorbidity status. Furthermore, maintaining a healthy lifestyle can alleviate the mortality risks linked to a higher number of diseases.

1. Introduction

The life expectancy has increased with economic and healthcare improvements, and the world has entered a phase of increased population ageing (Beard et al., 2016; Jiang & Jiang, 2021; Partridge et al., 2018). At the same time, 55%–98% of older adults suffer from multiple diseases in their later life (Tazzeo et al., 2021). Multimorbidity is generally understood to be the presence of two or more chronic conditions in one individual (Barnett et al., 2012; Tinetti et al., 2012). Multimorbidity is linked to reduced quality of life (Marengoni et al., 2011), increased disability (Dugravot et al., 2020) and higher mortality rates (Hanlon et al., 2018). It also leads to significant healthcare utilization,

longer hospital stays, and the need for complex medication regimens (Skou et al., 2022).

Individuals over 60 years old, especially those over 80, experience a higher prevalence of multiple conditions and more intense symptoms (Forman et al., 2018; MacMahon, 2018). Emerging evidence emphasize the significance of integrating healthy lifestyle, including being physically active, having a healthy diet, maintaining a fit body weight, abstinence from smoking and moderate alcohol consumption in multimorbidity management (Chudasama et al., 2020; Freisling et al., 2020; Han et al., 2021; Xie et al., 2022). Previous studies have reported that healthy lifestyles have benefits for older individuals with multimorbidity, such as delaying cognitive decline and attenuating dementia

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risk (Jin et al., 2023; Xing et al., 2024; Xiong et al., 2023).

However, there are several significant gaps in evidence that should be addressed. Firstly, the majority of previous studies have concentrated on specific conditions like cardiovascular diseases (Jin et al., 2023; Xie et al., 2022) or cancers (Freisling et al., 2020). However, the reality of multimorbidity in older adults is multi-systemic, encompassing a range of issues including lung, stomach, eye, and other diseases (Marengoni et al., 2020). Secondly, current research has primarily focused on neurodegenerative diseases, neglecting to explore the association between lifestyles and mortality in the population aged 60 years or older with multimorbidity. Moreover, variations in cultural and social customs, economies and medical services, dietary habits and lifestyles across countries (e.g. China and the UK), have led to inconsistent results in prior studies regarding whether a healthy lifestyle yields similar benefits, thus limiting the generalizability of findings (Li et al., 2018; Sun, Yu, et al., 2022; Zhang et al., 2021).

Hence, there is a need for further exploration to address the unresolved issues mentioned above. In this study, we performed analyses using data from two cohort studies in China and UK to mutually verify the relationship between healthy lifestyle factors and mortality among older individuals, both with and without multimorbidity.

2. Methods

2.1. Study population

We used data from Chinese Longitudinal Healthy Longevity Survey (CLHLS) and UK Biobank. The CLHLS is a prospective cohort study of the Chinese population aged 60 years or over. CLHLS recruited participants from half of the counties and city districts in 23 Chinese provinces by multistage cluster sampling (Lv et al., 2018). All participants who voluntarily agreed to participate were attempted to be interviewed in the 806 cities and counties. Participants were enrolled in 7 waves of 1998, 2000, 2002, 2005, 2008–09, 2011–12, 2014 and have been followed up ever since. We excluded the 2000 survey due to missing height data and instead incorporated data from 6 waves into our analysis. Information about lifestyles, medical history and physical measurements were collected by the CLHLS investigators (Ji et al., 2020; Yu et al., 2022). In this study, among the 38,252 participants recruited from 6 waves, we first excluded 151 participants under 60 years old. Among the remaining participants, 6568 lost to follow-up and 2082 with missing data related to lifestyles and multimorbidity were excluded, resulting in a final inclusion of 29,451 (77.3%) participants (Figure S1).

UK Biobank consisted of a total of 502,413 participants, aged between 38 and 73, who were recruited through postal invitations from 2006 to 2010 (Sudlow et al., 2015). Participants attended one of 22 assessment centers across England, Scotland, and Wales. Comprehensive data collection methods were utilized, including completion of a touchscreen questionnaire, a nurse-led interview, physical measurements, and provision of biological samples (Littlejohns et al., 2020). All participants provided written informed consent for the collection, analysis, and linkage of their data with hospital admissions, cancer registries, and death registries. In this study, we first excluded 284,946 participants under 60 years old. Among the remaining participants, we excluded 411 lost to follow-up and 43,553 with missing data related to lifestyles and multimorbidity, leading to a final inclusion of 173,503 (79.7%) participants (Figure S1). The main characteristics of the exclude participants from CLHLS and UK Biobank were provided in Table S1.

2.2. Assessment of healthy lifestyles

According to previous cohort studies (Dhana et al., 2022; Jia et al., 2023; Jin et al., 2021; Sun et al., 2021, 2022), five healthy lifestyles were included in this study: physical activity, dietary patterns, BMI, smoking and alcohol consumption. Physical activity was categorized as regular, sometimes, and rarely. In CLHLS, physical activity was defined by two

questions (Yin et al., 2023): “Do you do exercises regularly at present?” and “Did you do exercises regularly in the past?”. If the participants answered “yes” to both questions, the physical activity was defined as “regular”; conversely, if they answered “no” to both, it was classified as “rarely”. Responses falling outside these categories were defined as “sometimes”. In UK Biobank, physical activity quantified as the total number of days spent on walking, moderate, and vigorous activities per month. Referring to the restricted cubic spline plot illustrating the relationship between physical activity days and mortality (Figure S2), along with findings from previous studies (Aly & Yeung, 2023; Chekroud et al., 2018; Chudasama et al., 2019; Dos Santos et al., 2022; Lee et al., 2022; Melzer et al., 2010), we categorized individuals engaging in 0–3 days of physical activity as “rarely”, 4–12 days as “sometimes”, and 13 or more days as “regular”.

Dietary pattern was categorized as unhealthy, moderate, and healthy. In CLHLS, dietary pattern scores were constructed from intake frequency of vegetables, fruit, tea, bean products and fish, with a higher score indicating better diet quality (Yan et al., 2022). In UK Biobank, consistent with previous studies (Lourida et al., 2019; Malik et al., 2021), dietary pattern scores were defined by intake frequency of vegetables, fruits, whole grains, fish, refined grains, unprocessed and processed meats. A healthy dietary pattern was defined as the adequate consumption of at least four of seven specified food groups. A detailed definition was provided in Table S2.

According to the guidelines (Chen & Lu, 2004; Kushner & Ryan, 2014), BMI was categorized into four group in both CLHLS (underweight: BMI <18.5 kg/m², normal: 18.5 ≤ BMI <24.0 kg/m², overweight: 24.0 ≤ BMI <28.0 kg/m², obese: BMI ≥28.0 kg/m²) and UK Biobank (underweight: BMI <18.5 kg/m², normal: 18.5 ≤ BMI <25.0 kg/m², overweight: 25.0 ≤ BMI <30.0 kg/m², obese: BMI ≥30.0 kg/m²). In the absence of height measurements during the 1998 and 2002 baseline surveys in CLHLS, knee height was utilized to estimate participants' height. We applied a validated equation (Zhang et al., 1998) to compute height (men, height = 67.78 + 2.01*knee height; women, height = 74.08 + 1.81*knee height).

Based on prior studies (Han et al., 2022; Jin et al., 2021) and self-reported questionnaires in baseline, smoking status was categorized as current, former or never. According to WHO guideline (Organization, 2000) and prior studies (Bradbury et al., 2020; Han et al., 2022; Liu et al., 2018), low risk of alcohol consumption is characterized by a daily intake of less than 21 g for female and less than 41 g for male. Thus, alcohol consumption is categorized into three categories: never (0 g), moderate (1–40 g for males; 1–20 g for females) and excess (≥41 g for males; ≥21 g for females).

These five lifestyles are scored within the range of 0–2 points each, with a total score ranging from 0 to 10 points. The criteria and detailed information regarding these scores can be found in Table S2. Ultimately, participants were categorized into three groups according to their scores: healthy (7–10), moderate (5–6), and unhealthy (≤4) lifestyles.

2.3. Assessment of multimorbidity

All conditions were self-reported and hospital diagnosed, which included hypertension, diabetes, cardiovascular diseases (CVDs), stroke, chronic obstructive pulmonary disease (COPD), cancers, tuberculosis, cataract, glaucoma, and gastric or duodenal ulcer. Hypertension was also determined by participants' systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg. The definition of multimorbidity entailed the coexistence of a minimum of two conditions within a single individual. To assess the severity of multimorbidity, we classified as no multimorbidity (zero or one condition), two conditions, and three or more conditions.

2.4. Assessment of outcome

We used all-cause mortality as primary outcome. In CLHLS, deaths

were recorded between 1998 and 2019, reported by the next of kin (Ji et al., 2020). The follow-up period continued until December 31, 2019, in cases where the outcome had not occurred by that time. In UK Biobank, death data were sourced from the National Health Service Information Centre and the National Health Service Central in England, Scotland, and Wales. The follow-up period extended from March 21, 2006, to October 31, 2021, and concluded on September 30, 2021, for England and Wales and October 30, 2021, for Scotland (Sudlow et al., 2015).

2.5. Assessment of covariates

We used baseline questionnaires to assess the following potential confounders: baseline age, sex, ethnicity, region, education levels, marital status, self-reported of co-residence, primary source of income, overall health, denture-wearing and loneliness. Regarding the classification of ethnicity, individuals were categorized as Han or others in CLHLS, and as White or others in UK Biobank. Based on years of schooling and degree, education levels were categorized into college, senior, junior or primary and less. According to the map of China and the UK, we divided region into South China, North China, West China in CLHLS, and England, Scotland or Wales in UK Biobank. Further details regarding the assessment of these factors can be found on the CLHLS website (<https://opendata.pku.edu.cn/dataverse/CHADS>) and UK Biobank website (<http://www.ukbiobank.ac.uk>).

2.6. Statistical analysis

Details of missing covariates was presented in Table S3. To account for missing values of covariates, multiple imputation by chained equations (MICE) method was used, and 5 datasets were created through imputation process. All variables, including the outcomes, were included in the multiple imputation model, ensuring a comprehensive imputation of missing values. Baseline characteristics are presented as the mean (standard deviation [SD]) for continuous variables and number (percentage [%]) for categorical variables.

The relationship of lifestyles, multimorbidity and their combination with all-cause mortality were explored using Cox proportional hazard models with time. We examined the proportional hazards assumption by creating a cross product of follow-up time and lifestyles, multimorbidity and their combination. For each covariate, the Cox proportional hazards assumption was evaluated with Kaplan–Meier curves, and no major violations were observed. In the analysis, several covariates were adjusted for. In model 1, adjustments were made for baseline age (continuous), sex (male or female); In model 2, adjustments were additionally made for ethnicity (CLHLS: Han or others; UK Biobank: White or others), region (CLHLS: South China, North China or West China; UK Biobank: England, Scotland or Wales), education levels (college, senior, junior or primary and less), marital status (married or others), co-residence (living alone or no alone), primary source of income (employed, pension or others), overall health (good, fair or bad), denture-wearing (yes or no) and loneliness (yes or no). In individual analyses of lifestyle and multimorbidity, lifestyles and multimorbidity were adjusted mutually.

We examine the potential non-linear association of lifestyles scores and the multimorbidity with all-cause mortality by Cox proportional hazards analysis through restricted cubic spline with knots placed at 10th, 50th and 90th percentiles. In addition, we performed subgroups and interaction analyses to examine the association of healthy lifestyles with all-cause mortality among participants with multimorbidity. Given that the maximum age of participants in CLHLS was 120 years and in UK Biobank was 73 years, participants in CLHLS were categorized into three groups: 60 to 69, 70 to 79 or ≥ 80 years, whereas in UK Biobank, they were divided into two groups: 60 to 69 or ≥ 70 years. The subgroups were categorized by age (60–69, 70–79 or ≥ 80 years), sex (male or female), ethnicity (CLHLS: Han or others; UK-Biobank: White or others),

region (CLHLS: South China, North China or West China; UK Biobank: England, Scotland or Wales) and education levels (college, senior, junior or primary and less).

We performed several sensitivity analyses to verify the stability of the results. Firstly, we excluded the participants with multiple imputations to examine the effects of missing data. Secondly, we excluded the 1998 and 2002 waves in CLHLS to exclude the influence of estimated body height on the BMI. Thirdly, we excluded participants who died within the first one or two years of follow-up to reduce potential reverse causality. Fourthly, to confirm the stability of the lifestyle classification, we redefined an additional categorization: healthy (7–10 points), moderate (4–6 points), and unhealthy (≤ 3 points). Fifthly, we excluded one or two lifestyle factors to recalculate lifestyle scores and redefined lifestyle groupings. Finally, we included the excluded participants in the analysis. We assigned a score of 0 to missing corresponding lifestyles information. Participants with missing information on multimorbidity were considered as not having these conditions. Additionally, those who were lost to follow-up were not included in the analysis.

Analyses were performed using R version 4.2.3 (Survival analysis, ggplot2, forest plot and the rms package, etc.). Statistical tests were two-sided, and p values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 showed the baseline characteristics in CLHLS and UK Biobank. Among the 29,415 participants in CLHLS, the mean age at baseline was 87.6 (SD 11.8) years, with 58.4% being female. Out of these, 5725 (17.9%), 11,549 (39.2%) and 12,627 (42.9%) followed a healthy, moderate and unhealthy lifestyle, respectively. Multimorbidity was identified in 6675 participants (22.7%), with 4925 (16.7%) having two conditions and 1750 (6.0%) experiencing three or more conditions. Hypertension (54.1%) was the most prevalent condition, followed by cataracts (12.2%). Participants followed a healthy lifestyle in CLHLS were generally younger, with higher level of education, a greater likelihood of having a pension, more likely to live with family members, less likely to report feeling lonely, have better overall health, and a higher rate of denture wearers. It was noteworthy that participants with multimorbidity had a higher proportion adhering to a healthy lifestyle (Table S3).

In UK Biobank, involving 173,503 participants, the mean age at baseline was 64.1 (SD 2.8) years and 50.3% were female (Table 1). Among these, 93,047 (53.6%), 58,500 (33.7%) and 21,956 (12.7%) adhered to a healthy, moderate and unhealthy lifestyle, respectively. Out of these participants, 45,499 (26.2%) had multimorbidity, comprising 35,603 (20.5%) with two conditions and 9896 (5.7%) with three or more conditions. In contrast to CLHLS, participants who with multimorbidity have a higher proportion of unhealthy lifestyle adherence (Table S3). Compared to those included in this study, we observed that excluded participants were more likely to be female and have lower education levels in UK Biobank, while in CLHLS, the basic characteristics remained almost consistent (Table S1).

3.2. Risk of all-cause mortality in relation to lifestyles

Over a mean follow-up period of 4.7 years with a total of 138,702 person-years, we recorded 21,540 deaths in CLHLS. In UK Biobank, we recorded 20,720 deaths over 12.14 years with a total of 2107,144 person-years.

According to the results of Cox proportional hazard analysis with restricted cubic spline, we observed a significantly association for lower risk of mortality with increasing lifestyles scores (Figure S3). Compared to the participants who followed an unhealthy lifestyle, adhering to a healthy lifestyle would reduce 20% (HR: 0.80; 95% CI: 0.77, 0.84) and

Table 1
Baseline characteristics in CLHLS and UK Biobank according to lifestyles groups.

Characteristic	CLHLS Lifestyles				UK Biobank Lifestyles			
	Total	Healthy	Moderate	Unhealthy	Total	Healthy	Moderate	Unhealthy
Participate, n (%)	29,451 (100.0)	5275 (17.9)	11,549 (39.2)	12,627 (42.9)	173,503 (100.0)	93,047 (53.6)	58,500 (33.7)	21,956 (12.7)
Age (years), mean (SD)	87.6 (11.8)	84.9 (12.0)	87.6 (11.8)	88.8 (11.6)	64.1 (2.8)	64.1 (2.9)	64.1 (2.9)	63.9 (2.8)
60-69, n (%)	3299 (11.2)	789 (14.9)	1302 (11.3)	1208 (9.6)	171,602 (98.9)	91,999 (98.9)	57,841 (98.9)	21,762 (99.1)
70-79, n (%)	4042 (13.7)	1012 (19.1)	1583 (13.7)	1447 (11.5)	1901 (1.1)	1048 (1.1)	659 (1.1)	194 (0.9)
≥80, n (%)	22,110 (75.1)	3474 (66.0)	8664 (75.0)	9972 (78.9)				
Female, n (%)	17,217 (58.4)	2888 (54.7)	7054 (61.0)	7275 (57.6)	87,288 (50.3)	52,393 (56.3)	27,194 (46.4)	7701 (35.1)
Ethnicity, n (%)								
Han/White	27,339 (93.1)	5034 (95.6)	10,824 (93.8)	11,481 (91.2)	168,125 (96.9)	90,158 (96.9)	56,470 (96.5)	21,497 (97.9)
Others	2021 (6.9)	229 (4.4)	682 (6.2)	1110 (8.8)	5378 (3.1)	2889 (3.1)	2030 (3.5)	459 (2.1)
Region, n (%)								
North China/Scotland	7806 (26.5)	1608 (30.5)	3164 (27.4)	3034 (24.0)	11,725 (6.8)	6025 (6.5)	4020 (6.9)	1680 (7.6)
South China/England	17,718 (60.2)	3079 (58.4)	6915 (59.9)	7724 (61.2)	155,176 (89.4)	83,762 (90.0)	52,129 (89.1)	19,285 (87.9)
West China/Wales	3927 (13.3)	588 (11.1)	1470 (12.7)	1869 (14.8)	6602 (3.8)	3260 (3.5)	2351 (4.0)	991 (4.5)
Education level, n (%)								
College	502 (1.7)	218 (4.1)	182 (1.6)	102 (0.8)	49,376 (28.8)	31,195 (33.8)	14,153 (24.5)	4028 (18.6)
Senior	747 (2.6)	293 (5.6)	274 (2.4)	180 (1.6)	40,487 (23.5)	21,422 (23.2)	13,897 (24.0)	5168 (23.8)
Junior	1278 (4.3)	391 (7.4)	472 (4.1)	415 (3.2)	40,373 (23.6)	21,397 (23.2)	13,859 (24.0)	5117 (23.5)
Primary and less	26,881 (91.4)	4366 (82.9)	10,601 (91.9)	11,914 (94.4)	41,464 (24.1)	18,163 (19.8)	15,909 (27.5)	7392 (34.1)
Marital status, n (%)								
Married	8289 (28.1)	1903 (36.0)	3244 (28.1)	3142 (24.8)	128,580 (94.5)	70,688 (95.3)	42,669 (93.8)	15,223 (92.7)
Others	21,147 (71.9)	3370 (64.0)	8297 (71.9)	9480 (75.2)	7429 (5.5)	3444 (4.7)	2783 (6.2)	1202 (7.3)
Primary source of income, n (%)								
Employed	2424 (8.2)	292 (5.5)	948 (8.2)	1184 (9.4)	36,142 (20.8)	18,327 (19.7)	12,827 (21.9)	4988 (22.7)
Pension	4317 (14.7)	1704 (32.3)	1650 (14.3)	963 (7.6)	131,042 (75.7)	72,243 (77.8)	43,395 (74.3)	15,404 (70.3)
Others	22,703 (77.1)	3279 (62.2)	8949 (77.5)	10,475 (83)	5982 (3.5)	2303 (2.5)	2170 (3.8)	1509 (7.0)
Overall health, n (%)								
Good	14,331 (53.1)	3195 (63.1)	5746 (54.1)	5390 (47.8)	131,249 (75.9)	77,975 (84.0)	40,914 (70.2)	12,360 (56.5)
Fair	9143 (33.9)	1489 (29.4)	3628 (34.2)	4026 (35.9)	35,313 (20.4)	13,441 (14.4)	14,693 (25.2)	7179 (32.8)
Bad	3476 (13.0)	382 (7.5)	1248 (11.7)	1846 (16.3)	6485 (3.7)	1457 (1.6)	2702 (4.6)	2326 (10.7)
Denture-wearing, n (%)	6924 (23.5)	1770 (33.6)	2805 (24.3)	2349 (18.5)	46,527 (26.8)	20,416 (22.0)	17,937 (30.7)	8174 (37.3)
Living alone, n (%)	3940 (13.3)	568 (10.7)	1557 (13.4)	1815 (14.3)	38,312 (22.2)	19,727 (21.3)	13,138 (22.6)	5447 (25.1)
Loneliness, n (%)	8292 (31.7)	1237 (24.7)	3214 (31.1)	3841 (35.4)	25,152 (14.6)	11,462 (12.4)	9451 (16.3)	4267 (19.7)
Physical activity, n (%)								
Regular	6173 (21.0)	3272 (62.0)	2355 (20.4)	546 (4.3)	65,321 (37.6)	48,018 (51.6)	14,643 (25.0)	2660 (12.1)
Sometimes	3515 (11.9)	876 (16.6)	1652 (14.3)	987 (7.8)	97,896 (56.4)	43,942 (47.2)	39,538 (67.6)	14,416 (65.7)
Rarely	19,763 (67.1)	1127 (21.4)	7542 (65.3)	11,094 (87.9)	10,286 (6.0)	1087 (1.2)	4319 (7.4)	4880 (22.2)
Diet pattern, n (%)								
Healthy	6459 (22.0)	3109 (59.0)	2552 (22.1)	798 (6.3)	78,619 (45.3)	60,482 (65.0)	16,536 (28.3)	1601 (7.3)
Moderate	11,119 (37.7)	1675 (31.7)	4968 (43.0)	4476 (35.4)	68,234 (39.3)	29,361 (31.6)	29,850 (51.0)	9023 (41.1)
Unhealthy	11,873 (40.3)	491 (9.3)	4029 (34.9)	7353 (58.3)	26,650 (15.4)	3204 (3.4)	12,114 (21.7)	11,332 (51.6)
BMI, n (%)								
Underweight	12,059 (41.0)	342 (6.5)	2844 (24.6)	8873 (70.2)	752 (0.4)	221 (0.2)	326 (0.6)	205 (1.0)
Normal	13,582 (46.0)	4263 (80.8)	7171 (62.1)	2148 (17.0)	52,027 (30.0)	42,537 (45.7)	8061 (13.7)	1429 (6.5)
Overweight	2837 (9.6)	582 (11.0)	1226 (10.6)	1029 (8.1)	79,264 (45.7)	43,118 (46.4)	28,598 (48.9)	7548 (34.3)
Obese	973 (3.4)	88 (1.7)	308 (2.7)	577 (4.7)	41,460 (23.9)	7171 (7.7)	21,515 (36.8)	12,774 (58.2)
Smoking, n (%)								
Current	5506 (18.7)	307 (5.8)	1360 (11.8)	3839 (30.4)	13,849 (8.0)	1468 (1.6)	5915 (10.1)	6466 (29.4)
Former	3910 (13.3)	607 (11.5)	1428 (12.4)	1875 (14.9)	73,295 (42.2)	29,084 (31.2)	31,592 (54.0)	12,619 (57.5)
Never	20,035 (68.0)	4361 (82.7)	8761 (75.8)	6913 (54.7)	86,359 (49.8)	62,495 (67.2)	20,993 (35.9)	2871 (13.1)
Alcohol consumption, n (%)								
Never	23,430 (79.5)	4182 (79.3)	9596 (83.1)	9652 (76.4)	50,438 (29.0)	20,886 (22.4)	21,624 (37.0)	7928 (36.1)
Moderate	2805 (9.5)	936 (17.7)	1122 (9.7)	747 (5.9)	101,555 (58.6)	69,858 (75.1)	27,714 (47.3)	3983 (18.1)
Excess	3216 (11.0)	157 (3.0)	831 (7.2)	2228 (17.7)	21,510 (12.4)	2303 (2.5)	9162 (15.7)	10,045 (45.8)
Diseases, n (%)								
Hypertension	15,955 (54.1)	2921 (55.3)	6377 (55.2)	6657 (52.7)	117,967 (67.9)	58,599 (62.9)	42,314 (72.3)	17,054 (77.6)
Diabetes	513 (1.7)	169 (3.2)	190 (1.6)	154 (1.2)	12,015 (6.9)	3943 (4.2)	5239 (8.9)	2833 (12.9)
CVDs	2209 (7.5)	550 (10.4)	908 (7.9)	751 (6.0)	13,340 (7.7)	5201 (5.6)	5316 (9.1)	2823 (12.8)
Stroke	1282 (4.4)	270 (5.1)	532 (4.6)	480 (3.8)	10,895 (6.3)	4716 (5.1)	4121 (7.0)	2058 (9.4)
COPD	3300 (11.1)	536 (10.1)	1217 (10.5)	1547 (12.2)	4093 (2.4)	1210 (1.3)	1655 (2.8)	1228 (5.6)
Tuberculosis	186 (0.6)	28 (0.5)	61 (0.5)	97 (0.8)	1342 (0.8)	690 (0.7)	460 (0.8)	192 (0.9)
Cataract	3607 (12.2)	681 (12.9)	1448 (12.5)	1478 (11.7)	4734 (2.7)	2549 (2.7)	1579 (2.7)	606 (2.8)
Glaucoma	649 (2.2)	96 (1.8)	256 (2.2)	297 (2.4)	3151 (1.8)	1703 (1.8)	1064 (1.8)	384 (1.7)
Cancer	112 (0.4)	20 (0.4)	49 (0.4)	43 (0.3)	21,726 (12.5)	11,928 (12.8)	7177 (12.2)	2621 (11.9)
Gastric or duodenal ulcer	1288 (4.4)	241 (4.6)	478 (4.1)	569 (4.5)	1474 (0.8)	611 (0.7)	573 (1.0)	290 (1.3)
Multimorbidity, n (%)								
No multimorbidity	22,776 (77.3)	3954 (75.0)	8921 (77.2)	9901 (78.4)	128,004 (73.8)	73,105 (78.6)	41,137 (70.3)	13,762 (62.7)
2 conditions	4925 (16.7)	927 (17.5)	1937 (16.8)	2061 (16.3)	35,603 (20.5)	16,579 (17.8)	13,272 (22.7)	5752 (26.2)
≥3 conditions	1750 (6.0)	394 (7.5)	691 (6.0)	665 (5.3)	9896 (5.7)	3363 (3.6)	4091 (7.0)	2442 (11.1)

41% (HR: 0.59; 95% CI: 0.57, 0.61) risk of all-cause mortality in CLHLS and UK Biobank. Every one-point increase in lifestyle score reduces the risk of death by 5% (HR: 0.95; 95% CI: 0.94, 0.96) and 11% (HR: 0.89; 95% CI: 0.88, 0.89) in CLHLS and UK Biobank, respectively (Table 2).

The associations of physical activity, dietary pattern, BMI, smoking, and alcohol consumption with all-cause mortality were presented in Table S5 to S6. Individuals who were physically active, maintained a healthy dietary pattern, overweight or never smoking had a 4%–51% lower risk of all-cause mortality compared with their counterparts in both CLHLS and UK Biobank. In UK Biobank, we found that participants who consumed excessive alcohol had 20% higher risk of all-cause mortality. Meanwhile, participants who were underweight had a 13%–87% higher risk of all-cause mortality in both CLHLS and UK Biobank, respectively.

3.3. Risk of all-cause mortality in relation to multimorbidity

According to the restricted cubic spline, we found that an increased number of conditions was linked to higher risk of mortality (Figure S3). Compared to participants without multimorbidity, those with three or more conditions had HRs of 1.19 (95%CI: 1.12, 1.26) in CLHLS, 1.88 (95%CI: 1.80, 1.97) in UK Biobank, and 1.67 (95%CI: 1.61, 1.72) in pooled for all-cause mortality (Table 2).

3.4. Risk of all-cause mortality in relation to lifestyles across multimorbidity status

Fig. 1 and Figure S4 showed the HRs (95% CI) and dose-response relationship between healthy lifestyle and mortality across three categories of multimorbidity status. We found that maintaining a moderate lifestyle significantly reduced the risk of mortality. Compared to those leading unhealthy lifestyles, individuals in CLHLS and UK Biobank who adopted moderate lifestyles had a 11%–27%, 14%–25% and 15%–26% lower risk of all-cause mortality when dealing with zero or one, two and three or more conditions, respectively. Continued enhancements in adopting a healthier lifestyle led to more significant reductions in mortality risk across three categories of multimorbidity status. Compared to an unhealthy lifestyle in both CLHLS and UK Biobank, participants who adopted a healthy lifestyle could reduce the risk of mortality by 27% (HR: 0.73; 95% CI: 0.66, 0.81) to 41% (HR: 0.59; 95% CI: 0.55, 0.64) for those with two conditions, and 22% (HR: 0.78; 95% CI: 0.66, 0.92) to 42% (HR: 0.58; 95% CI: 0.52, 0.64) for those with three or more conditions, respectively; In comparison, this reduction ranged from 18% (HR: 0.82; 95% CI: 0.79, 0.86) to 41% (HR: 0.59; 95% CI: 0.56, 0.62) for individuals without multimorbidity.

Risk of all-cause mortality in relation to both lifestyles and multimorbidity among participants with multimorbidity.

To further evaluate the combined effect of healthy lifestyle and multimorbidity on all-cause mortality among participants with multimorbidity, the findings are presented in Table 3 and Table S7. We found that in comparison to individuals who followed a healthy lifestyle and had three or more conditions, those with an unhealthy lifestyle, regardless of the presence of multiple conditions, had a higher risk of mortality, with HRs of 1.15 (95% CI: 1.00, 1.32) and 1.27 (95% CI: 1.16, 1.39) for participants with two conditions, and 1.24 (95% CI: 1.06, 1.45) and 1.73 (95% CI: 1.56, 1.91) for those with three or more conditions in CLHLS and UK Biobank, respectively.

3.5. Subgroups and sensitivity analyses

Consistent findings were observed among participants with multimorbidity when stratified by age, sex, education level, ethnicity and region (Figure S5). Notably, among female participants both in CLHLS and pooled, and aged 60–69 years in pooled, a stronger association was found between higher lifestyle scores and a reduced risk of mortality (P interaction <0.05). Tables S8 to S10 and Figure S6 to S8 presents results

Table 2

Hazard ratios (95% CIs) of lifestyles and multimorbidity with all-cause mortality.

Group of lifestyles or multimorbidity	Incident rate per 1000 person years	Cases/N	Hazard ratio (95% CI)	
			Model 1*	Model 2*
Lifestyles				
CLHLS, N = 29,451				
Unhealthy	179.8	9969/12627	1 (reference)	1 (reference)
Moderate	150.1	8259/11549	0.87 [0.85, 0.90]	0.88 [0.86, 0.91]
Healthy	117.1	3312/5275	0.77 [0.74, 0.81]	0.80 [0.77, 0.84]
Each 1-point increment			0.94 [0.94, 0.95]	0.95 [0.94, 0.96]
UK Biobank, N = 173,503				
Unhealthy	18.0	4630/21956	1 (reference)	1 (reference)
Moderate	11.1	7840/58500	0.62 [0.60, 0.64]	0.74 [0.71, 0.77]
Healthy	7.2	8250/93047	0.42 [0.40, 0.44]	0.59 [0.57, 0.61]
Each 1-point increment			0.82 [0.82, 0.83]	0.89 [0.88, 0.89]
Pooled, N = 202,954				
Unhealthy	46.7	14599/34583	1 (reference)	1 (reference)
Moderate	21.1	16099/70049	0.74 [0.73, 0.76]	0.82 [0.80, 0.83]
Healthy	9.8	11562/98322	0.50 [0.49, 0.51]	0.64 [0.62, 0.66]
Each 1-point increment			0.86 [0.86, 0.87]	0.91 [0.90, 0.91]
Multimorbidity				
CLHLS, N = 29,451				
No multimorbidity	152.8	16686/22776	1 (reference)	1 (reference)
2 conditions	161.6	3582/4925	1.11 [1.07, 1.15]	1.10 [1.06, 1.14]
≥3 conditions	171.8	1272/1750	1.22 [1.15, 1.29]	1.19 [1.12, 1.26]
Each 1-condition increment			1.06 [1.05, 1.08]	1.05 [1.04, 1.07]
UK Biobank, N = 173,503				
No multimorbidity	7.6	12054/128004	1 (reference)	1 (reference)
2 conditions	14.0	5934/35603	1.66 [1.61, 1.72]	1.41 [1.37, 1.46]
≥3 conditions	24.5	2732/9896	2.80 [2.68, 2.92]	1.88 [1.80, 1.97]
Each 1-condition increment			1.47 [1.45, 1.49]	1.28 [1.26, 1.30]
Pooled, N = 202,954				
No multimorbidity	17.1	28740/150780	1 (reference)	1 (reference)
2 conditions	21.3	9516/40528	1.36 [1.32, 1.39]	1.29 [1.26, 1.32]
≥3 conditions	33.7	4004/11646	1.95 [1.88, 2.01]	1.67 [1.61, 1.72]
Each 1-condition increment			1.23 [1.22, 1.25]	1.17 [1.15, 1.18]

†Model 1 was adjusted for baseline age (continuous) and sex (male or female).
 †Model 2 was additionally adjusted for ethnicity (CLHLS: Han or others; UK Biobank: White or others), region (CLHLS: South China, North China or West China; UK Biobank: England, Scotland or Wales), education levels (college, senior, junior or primary and less), marital status (married or others), co-residence (living alone or no alone), primary source of income (employed, pension or others), overall health (good, fair or bad), denture-wearing (yes or no) and loneliness (yes or no). Lifestyles and multimorbidity were adjusted mutually.

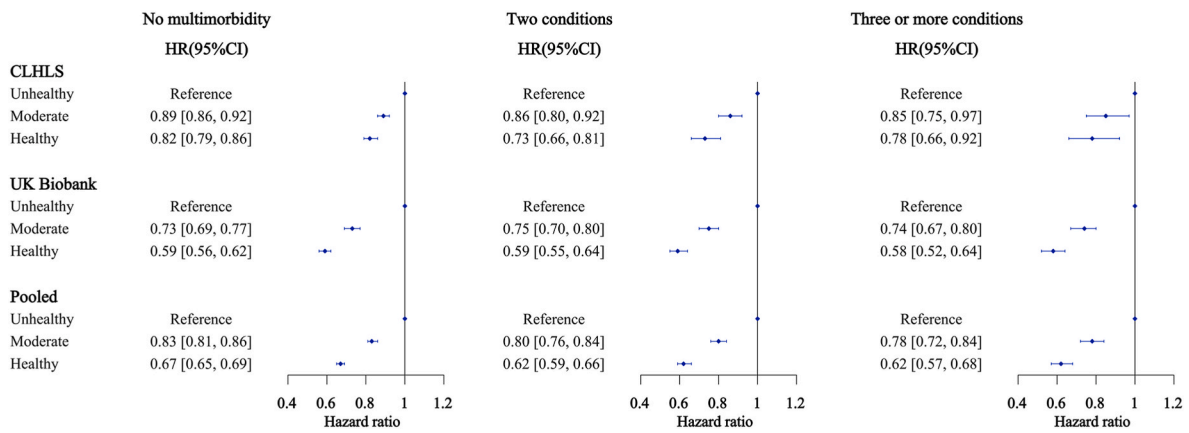


Fig. 1. Association of lifestyles and multimorbidity with all-cause mortality. Data were adjusted for ethnicity (CLHLS: Han or others; UK Biobank: White or others), region (CLHLS: South China, North China or West China; UK Biobank: England, Scotland or Wales), education levels (college, senior, junior or primary and less), marital status (married or others), co-residence (living alone or no alone), primary source of income (employed, pension or others), overall health (good, fair or bad), denture-wearing (yes or no) and loneliness (yes or no).

Table 3

Hazard ratios (95% CIs) of combination of lifestyles and multimorbidity with all-cause mortality among participants with multimorbidity.

Multimorbidity	Lifestyles	Incident rate per 1000 person years	Cases/N	Hazard ratio (95% CI)	
				Model 1†	Model 2‡
CLHLS, N = 6675					
≥3 conditions	Healthy	135.4	250/394	1 (reference)	1 (reference)
	Moderate	159.4	483/691	1.14 [0.98, 1.33]	1.07 [0.92, 1.25]
	Unhealthy	213.5	539/665	1.41 [1.21, 1.63]	1.24 [1.06, 1.45]
2 conditions	Healthy	111.0	537/927	0.84 [0.73, 0.98]	0.83 [0.72, 0.97]
	Moderate	157.1	1397/1937	1.06 [0.92, 1.21]	0.99 [0.86, 1.13]
	Unhealthy	195.4	1648/2061	1.27 [1.11, 1.45]	1.15 [1.00, 1.32]
UK Biobank, N = 45,499					
≥3 conditions	Healthy	16.4	646/3363	1 (reference)	1 (reference)
	Moderate	24.3	1122/4091	1.50 [1.36, 1.66]	1.28 [1.16, 1.41]
	Unhealthy	37.4	964/2442	2.41 [2.18, 2.66]	1.73 [1.56, 1.91]
2 conditions	Healthy	10.4	2085/16579	0.67 [0.62, 0.73]	0.75 [0.69, 0.82]
	Moderate	15.0	2367/13272	0.96 [0.88, 1.04]	0.95 [0.87, 1.04]
	Unhealthy	22.5	1482/5752	1.44 [1.31, 1.58]	1.27 [1.16, 1.39]
Pooled, N = 52,174					
≥3 conditions	Healthy	21.7	896/3757	1 (reference)	1 (reference)
	Moderate	32.6	1605/4782	1.40 [1.29, 1.52]	1.22 [1.13, 1.33]
	Unhealthy	53.1	1503/3107	2.01 [1.85, 2.19]	1.54 [1.41, 1.68]
2 conditions	Healthy	12.8	2622/17506	0.69 [0.64, 0.74]	0.74 [0.69, 0.80]
	Moderate	22.6	3764/15209	1.01 [0.94, 1.09]	0.97 [0.90, 1.04]
	Unhealthy	42.2	3130/7813	1.44 [1.34, 1.55]	1.24 [1.15, 1.34]

†Model 1 was adjusted for baseline age (continuous) and sex (male or female).

‡Model 2 was additionally adjusted for ethnicity (CLHLS: Han or others; UK Biobank: White or others), region (CLHLS: South China, North China or West China; UK Biobank: England, Scotland or Wales), education levels (college, senior, junior or primary and less), marital status (married or others), co-residence (living alone or no alone), primary source of income (employed, pension or others), overall health (good, fair or bad), denture-wearing (yes or no) and loneliness (yes or no).

from sensitivity analyses, which were largely consistent with main findings. However, the effects were slightly attenuated when excluding alcohol consumption factor in CLHLS (Tables S8) and excluding smoking and alcohol consumption factor in UK Biobank (Figure S8).

4. Discussion

In our analysis of two prospective population-based cohort studies, we investigated the relationships between lifestyles and all-cause mortality across various multimorbidity statuses. The results indicated that adherence to a healthy lifestyle can offer comparable health benefits to older individuals, regardless of the presence of multiple health conditions. In the population with multimorbidity, adhering to a healthy lifestyle can counteract the mortality risks associated with an increasing number of diseases. Our results have important implications for public health and provide valuable supplementary evidence for clinical practice, demonstrating that even older individuals with multimorbidity can

experience comparable beneficial effects by adhering to healthier lifestyle behaviors.

Our results are generally consistent with previous studies from different age group (Li et al., 2014, 2020; Sun et al., 2021; Wang et al., 2023; Zhang, Li, et al., 2022). We found that each 1-score increment with lifestyle factors, older individuals had a lower risk of all-cause mortality. While the specific lifestyle factors considered in each study varied slightly, the consistent outcome across most studies indicated beneficial effects on all-cause mortality by adopting healthy lifestyles. In our study, the protective effect of lifestyle was primarily driven by regular physical activity, healthy dietary pattern, never smoking and maintaining an overweight body weight, which underscored the significance of these four factors for the elderly. However, the association between alcohol intake, smoking and mortality was less consistent. Consistent with previous studies (Han et al., 2022; Liu et al., 2018), we found that excessive and never alcohol consumption was risk factor for all-cause mortality in UK Biobank, and non-significant association was

found in CLHLS. This variation may be attributed to the lower overall alcohol consumption in CLHLS (Chudasama et al., 2020). Additionally, we observed that in the CLHLS study, individuals with quit smoking seemed to exhibit an elevated risk of mortality. In contrast, the findings from the UK Biobank indicated the opposite trend. This could be associated with variations in age distribution and follow-up duration. The CLHLS participants are older and have a relatively short follow-up period, potentially leading to mortality before the protective effects of smoking cessation can be realized (Sun, Liu, et al., 2022). Conversely, the UK Biobank cohort, being younger with a longer follow-up, might reveal the long-term protective effects of quitting smoking. In our sensitivity analysis, we excluded smoking and alcohol consumption and reanalyzed the data and found that the outcomes were nearly consistent.

Most previous studies were conducted in the general populations (Chudasama et al., 2020; Fan et al., 2022; Freisling et al., 2020). Nevertheless, there has been limited evidence regarding the connection between adopting healthy lifestyles and the risk of mortality in individuals with multimorbidity. Previous studies (Fan et al., 2022; Luque-Fernandez et al., 2020) demonstrated the significant impact of multimorbidity on all-cause mortality, revealing an elevated mortality risk with each additional disease, particularly among individuals with multimorbidity. In our study, we discovered that older individuals with multimorbidity had a lower risk of all-cause mortality if they maintained a healthy lifestyle. Previous studies (Chen et al., 2023; Chudasama et al., 2020) of multimorbidity have focused more on chronic diseases such as cardiovascular disease, but our study also focused on common diseases including lung, stomach, eye, and other diseases. Furthermore, we found that the benefits of adopting healthy lifestyles were similar between individuals with and without multimorbidity. Both groups experienced similar protective effects from adopting a healthy lifestyle, older individuals with multimorbidity could achieve significant health benefits by adhering to a moderate lifestyle. These results imply that older individuals with multimorbidity may not need to make drastic changes to their unhealthy habits. This approach is advantageous for older people as it acknowledges the challenge of changing long-standing habits. Making modest adjustments to some of these habits can still yield substantial health benefits.

In the population with multimorbidity, we found that adhering to a healthy lifestyle can counteract the mortality risks associated with an increasing number of diseases. We observed that among participants with multimorbidity in CLHLS and pooled, females had a greater reduction in risk for each-1 point increment in healthy lifestyle scores compared to males. This may indicate that females who had multimorbidity may gain more benefits by adhering to healthier lifestyles than males. Besides, we found that among participants with multimorbidity, those who engaged in regular physical activity had a lower risk of all-cause mortality. This result was comparable to the conclusions reached in previous studies (Chudasama et al., 2019; He et al., 2021; Zhang, Duan, et al., 2022) and emphasized that the negative effects of multimorbidity on lifespan might be mitigated by physical activity. In addition, we observed that maintaining overweight was associated with a lower risk of all-cause mortality, regardless of multimorbidity status. And participants with multimorbidity who were underweight had the highest risk of all-cause mortality in both UK Biobank and CLHLS. This could be explained by the reduced height observed among older individuals. This decrease in height may result in an elevated BMI, consequently contributing to a greater proportion of individuals falling into the overweight category (Hannan et al., 2012; Holt et al., 2023; Peter et al., 2014). Our finding was consistent with a cohort study in China (Lv et al., 2022). Furthermore, for older individuals dealing with multimorbidity, being overweight may serve as an indicator of better nutritional status. In this context, the advantages of enhanced nutrition could outweigh the potential disadvantages associated with a higher BMI (Kramer et al., 2013).

Our study included two prospective cohorts from different countries (China and UK). And we observed differences between them. In the

CLHLS cohort, the highest proportion of participants followed an unhealthy lifestyle, while in the UK Biobank cohort, the majority adhered to a healthy lifestyle. Additionally, the average age of UK Biobank participants was over 20 years younger than those in CLHLS, and participants in CLHLS had lower educational levels. This might be due to regional disparities, as more CLHLS participants lived in rural areas compared to the predominantly urban residency of UK Biobank participants (Maxwell et al., 2021; Zhang et al., 2017; Zhao et al., 2020). Despite these variations, our study revealed consistent associations between lifestyle factors, multimorbidity, and all-cause mortality across both cohorts, as indicated by similar hazard ratios presented in Tables 2 and 3. We demonstrated that in both middle-income country such as China and high-income country like the UK, adhering to a healthy lifestyle was equally essential for older individuals with and without multimorbidity. In both cohorts, we observed that among the five lifestyle factors, regular physical activity has the greatest on reducing mortality. Hence, public health policies can concentrate on this highly accepted and low-cost risk factor.

4.1. Strengths and limitations

This study has several strengths, such as its prospective design, a substantial sample size, inclusion of participants from both the young elderly and the elderly population from UK and China, and comprehensive collection of lifestyle information. The detailed data allowed us to find out whether the risk of all-cause mortality in a multimorbidity population could be reduced by adhering to a healthy lifestyle. However, the study has several limitations. Firstly, information on lifestyle factors was obtained through self-reports using straightforward questions. Consequently, some specific details like the types of alcohol consumed and the nature of physical activities were not assessed. Nevertheless, the use of simple questions may decrease the chances of misclassification of exposures and could enhance the translation of public health information, especially for elderly individuals of advanced age. Secondly, people may have changed their lifestyle after diagnosis of diseases. Nevertheless, even if the lifestyle has changed at baseline among individuals with multimorbidity, our results remain relevant for clinical practice in assessing future mortality risk. Thirdly, the height data for 1998 and 2002 waves in CLHLS were calculated based on knee height, potentially introducing bias in height measurements. However, we addressed this issue by excluding these two waves, and our findings remained consistent. Fourthly, The UK Biobank and CHLHS datasets may not accurately represent the sampling population. However, it's important to note that valid assessments of exposure-disease relationships can still be conducted without a representative population (Ebrahim & Davey Smith, 2013; Fry et al., 2017). Furthermore, due to variations in local norms and participant demographics, the questionnaires utilized in the cohorts from China and the UK differ, resulting in varied definitions of healthy lifestyle factors, such as physical activity. However, we defined lifestyles according to previous studies (Chudasama et al., 2020; Jin et al., 2021; Sun, Liu, et al., 2022), enabling us to distinguish between individuals with healthy and unhealthy lifestyles. Notably, despite these variations, our analysis revealed consistent HRs across both cohorts. Prior studies have also indicated that while definitions of healthy lifestyles may vary, the validation of results within specific local contexts remains broadly applicable (Bian et al., 2024; Jin et al., 2023; Zhang, Pan, et al., 2022). Nonetheless, it's essential to acknowledge that these methods of assessing healthy lifestyles may introduce bias. Fifthly, in the UK Biobank, the maximum age of participant was restricted to 73 years old due to database limitations, resulting in a contrast with the average age of CLHLS. However, our subgroup analyses revealed no age-related interactions. However, expanding the upper age limit for UK Biobank data is crucial to facilitate research on older populations. Sixthly, due to missing data on death records reviewed by professionals in CLHLS, the association of healthy lifestyle and cause-specific mortality was not evaluated. Seventhly, like other

traditional observational cohort studies, the possibility of residual confounding due to unmeasured or unknown factors cannot be entirely eliminated. For instance, specific geographic and environmental variables might also influence the outcomes of this study. Nevertheless, only an exceptionally potent unmeasured risk factor for mortality, coupled with a significant imbalance in prevalence among exposure groups, could explain such strong findings (Lee, 2011; Schneeweiss, 2006).

5. Conclusion

The present study demonstrates that adherence to a healthy lifestyle can yield similar health benefits for older individuals, regardless of whether they have multiple health conditions or not. Moreover, maintaining a healthy lifestyle can mitigate the mortality risks linked to an increasing number of diseases. Our findings offer valuable additional support for clinical practice.

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Ethical statement

This study was approved by the Biomedical Ethics Committee, Peking University (IRB00001052-13074). All CLHLS participants provided written informed consent. All UK Biobank participants signed informed consent before information collection and the study has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

Availability of data and materials

The CLHLS data can be found at Peking University Open Research Data (<https://opendata.pku.edu.cn/dataverse/CHADS>). The data used in the present study can be made available through reasonable request to PKU Open data. The UK Biobank data support the findings of this study are available at www.ukbiobank.ac.uk/, subject to registration and application process.

CRediT authorship contribution statement

Jianfeng Zhong: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Lianhong Chen:** Writing – review & editing, Software, Methodology. **Chengping Li:** Writing – review & editing, Software, Methodology, Conceptualization. **Jing Li:** Writing – review & editing, Software, Methodology. **Yingying Niu:** Software, Methodology. **Xuerui Bai:** Software, Methodology. **Huiyan Wen:** Software, Methodology. **Zhiquan Diao:** Software, Methodology. **Haoyu Yan:** Software, Methodology. **Miao Xu:** Software, Methodology. **Wenqi Huang:** Software, Methodology. **Zhitong Xu:** Methodology. **Xiaofeng Liang:** Validation, Supervision. **Dan Liu:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

All authors declare that they have no other competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ssmph.2024.101673>.

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