Healthy lifestyle in late-life, longevity genes, and life expectancy among older adults: a 20-year, population-based, prospective cohort study

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Summary

Background Lifestyle and longevity genes have different and important roles in the human lifespan; however, the association between a healthy lifestyle in late-life and life expectancy mediated by genetic risk is yet to be elucidated. We aimed to investigate the associations of healthy lifestyle in late-life and genetic risk with life expectancy among older adults.

Methods A weighted healthy lifestyle score was constructed from the following variables: current non-smoking, non-harmful alcohol consumption, regular physical activity, and a healthy diet. Participants were recruited from the Chinese Longitudinal Healthy Longevity Survey, a prospective community-based cohort study that took place between 1998 and 2018. Eligible participants were aged 65 years and older with available information on lifestyle factors at baseline, and then were categorised into unhealthy (bottom tertile of the weighted healthy lifestyle score), intermediate (middle tertile), and healthy (top tertile) lifestyle groups. A genetic risk score was constructed based on 11 lifespan loci among 9633 participants, divided by the median and classified into low and high genetic risk groups. Stratified Cox proportional hazard regression was used to estimate the interaction between genetic and lifestyle factors on all-cause mortality risk.

Findings Between Jan 13, 1998, and Dec 31, 2018, 36164 adults aged 65 years and older were recruited, among whom a total of 27462 deaths were documented during a median follow-up of 3·12 years (IQR 1·62–5·94) and included in the lifestyle association analysis. Compared with the unhealthy lifestyle category, participants in the healthy lifestyle group had a lower all-cause mortality risk (hazard ratio [HR] 0·56 [95% CI 0·54–0·57]; p<0·0001). The highest mortality risk was observed in individuals in the high genetic risk and unhealthy lifestyle group (HR 1·80 [95% CI 1·63–1·98]; p<0·0001). The absolute risk reduction was greater for participants in the high genetic risk group. A healthy lifestyle was associated with a gain of 3·84 years (95% CI 3·05–4·64) at the age of 65 years in the low genetic risk group, and 4·35 years (3·70–5·06) in the high genetic risk group.

Interpretation A healthy lifestyle, even in late-life, was associated with lower mortality risk and longer life expectancy among Chinese older adults, highlighting the importance of a healthy lifestyle in extending the lifespan, especially for individuals with high genetic risk.

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Introduction

According to the World Bank, the number of individuals aged 65 years or older has been gradually rising worldwide over the past several decades, with this population accounting for 13·5% of the total population in China.[1,2] The promotion of healthy ageing is of high importance to individual and social health. Compelling data have shown that adherence to a healthy lifestyle, including abstinence from smoking and drinking, being physically active, and having a healthy diet, decreases the risk of chronic disease and all-cause mortality.[3,4] In addition to attenuating chronic disease and mortality risk, emerging evidence suggests that following a healthier lifestyle at a younger age is related to longer life expectancy.[5] Moreover, successful modification of these lifestyle factors at midlife

is also associated with a longer life expectancy free of major chronic diseases such as diabetes, cardiovascular disease, and cancer.[6] However, most of these studies were done with younger adults with an age range of 30–79 years, and the effects of individual and combined lifestyle behaviours in late-life on mortality risk and life expectancy among older adults remains unclear.

Life expectancy, as a complex trait, is also influenced by genetic factors. Twin studies[7,8] have shown that the heritability of longevity is approximately 20–30%, and this proportion increases with age to up to approximately 40% for long-lived individuals who survive beyond the age of 85 years.[9] In the past decade, genome-wide association studies have identified several genetic variants affecting the human lifespan.[10–12] Previous studies used a single

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Research in context

Evidence before this study

We systematically searched PubMed, Web of Science, and Google Scholar for articles published from database inception to April 15, 2023, using the search terms ("healthy lifestyle" OR "lifestyle") AND ("genetic risk" OR "genetic" OR "genetic factors") AND ("mortality" OR "life expectancy" OR "life span" OR "life years"), with no language restrictions. Previous studies on the effect of adopting a healthy lifestyle on mortality risk and life expectancy were mainly conducted among young and middle-aged populations; data from older adults are relatively scarce. Both genetic and lifestyle factors are known to play a pivotal role on lifespan, and the extent to which the benefits of healthy lifestyle can offset the genetic risk of lifespan among Chinese older adults remains unclear.

Added value of this study

Our data show that in this nationwide, diverse sample of older adults (aged ≥65 years) from 23 provincial-level

administrative regions across China, adoption of a healthy lifestyle in late-life could extend life-years. The greater risk reduction in mortality and life-year gains associated with a healthy lifestyle occurred in individuals with high genetic risk of a shorter lifespan, suggesting that adoption of a healthier lifestyle in late-life, particularly the practice of physical activity, could attenuate the deleterious effect of genetic factors on mortality risk.

Implications of all the available evidence

Lifestyle modification and promotion of a healthy lifestyle in late-life can contribute to reduction of the mortality burden, prevention of early mortality, and promotion of healthy ageing. These findings can be used for health education and health promotion in primary care settings and in clinical practice.

candidate gene to assess the effect of interactions between genetics and some lifestyle factors on all-cause mortality in old age.[13,14] However, such studies were limited by the fact that little genetic information can be gleaned from a single genetic variant, and the effects of a single variant on longevity are too small for comprehensive assessments. Therefore, the construction of the weighted genetic risk score combined the cumulative effect of multiple risk alleles to improve the estimation of an individual's genetic susceptibility to a complex disease.[10] On the basis of the genetic risk score, a previous study estimated combined effects of ambient air pollutants and genetic susceptibility on mortality risk.[15] However, whether and to what extent the benefits of a healthy lifestyle apply to people with different genetic risks to short lifespan is not yet clear. To contribute additional data on this topic, using data from a 20-year, population-based cohort of individuals aged 65 years and older included in the Chinese Longitudinal Healthy Longevity Survey, we aimed to assess the association between adherence to a healthy lifestyle and all-cause mortality, and we further investigated the interaction between healthy lifestyle and genetic variations on mortality risk.

See **Online** for appendix 2

Methods

Study design and participants

A detailed description and assessment of the Chinese Longitudinal Healthy Longevity Survey data quality has been reported elsewhere.[16] The Chinese Longitudinal Healthy Longevity Survey is a dynamic population-based prospective cohort study that was initially launched on Jan 13, 1998, with seven follow-up interviews conducted in 2000, 2002, 2005, 2008–09, 2011–12, 2014, and 2017–18. Participants were recruited via the unequal probability multistage sampling method from countries and cities in

23 provincial-level administrative regions of China. In each wave of follow-up interviews, participants provided information on several variables, such as demographic characteristics, socioeconomic status, behavioural factors, and health-related factors via face-to-face interview conducted in the local community or participants' home. Deceased participants were replaced by new participants of the same sex within the same 5-year age range.

For this study, 44 612 participants in the Chinese Longitudinal Healthy Longevity Survey were recruited between Jan 13, 1998, and Nov 14, 2014. Participants for whom only baseline information was available or who were lost to follow-up at any timepoint (n=7156); with missing information on lifestyle score at baseline (n=999); or younger than 65 years at recruitment (n=293) were excluded, leaving 36 164 participants who were included in the lifestyle association analysis. In the joint association between healthy lifestyle and genetic risk analysis, 9633 participants with available genetic data were included (appendix 2 p 29).

The Chinese Longitudinal Healthy Longevity Survey received approval from the Ethics Committee of Peking University (reference IRB00001052–13074). All participants or their legal representatives provided written informed consent during the face-to-face interview.

Procedures

Lifestyle factors at baseline were assessed by trained local research staff via the baseline questionnaire. We created a healthy lifestyle score based on four factors associated with healthy longevity, described in WHO's Decade of Healthy Ageing Baseline Report[17] and previous literature:[18–23] current non-smoking status, non-harmful alcohol consumption, being physically active, and following a healthy diet. Each component was given a

score of 0 or 1, with 1 representing the healthy behaviour category. Detailed information is provided in the appendix 2 (pp 3–5, 7–8). Sex data were self-reported, with the options of female or male provided. Current non-smoking was defined as never having smoked or having quit smoking for at least 30 years.[18,19] Non-harmful alcohol consumption was defined as a daily alcohol consumption of less than 41 g for women and less than 61 g for men, according to WHO's International guide for monitoring alcohol consumption and related harm.[20] For physical activity, we assessed the frequency of participation in nine different activities: regular exercise (aerobic and anaerobic), housework tasks, personal outdoor activities, gardening, rearing domestic animals or pets, reading, playing cards or mahjong, watching television or listening to the radio, and attending social activities (appendix 2 p 3).[21] The frequency of "almost every day" was scored as 2, "occasionally" was scored as 1, and "rarely or never" was scored as 0. A total physical activity score was calculated by the sum of these nine activities, and further standardised on a 0 to 1 scale. Dietary intake was estimated with a standardised food frequency questionnaire with acceptable reproducibility and validity, which included nine commonly consumed food groups in the Chinese diet: fresh vegetables, fresh fruit, legumes, meat, eggs, fish and seafood, salty vegetables (ie, preserved in soy sauce or salt for a long and varied amount of time), tea, and garlic.[22,23] Because insufficient total daily protein intake and imbalance in protein synthesis and degradation was observed with ageing among Chinese older adults, especially the oldest old (≥80 years), for the purposes of this study, consumption of protein-rich foods such as fish, meat, legumes, and eggs was considered as a healthy lifestyle choice.[24] A total dietary score was computed in the same way as physical activity (standardised on a 0 to 1 scale). The physical activity or diet intake were deemed ideal if the total physical activity score or total diet score in the top 40% of the cohort distribution in line with previous studies.[4]

All component scores were summed to obtain the healthy lifestyle score ranging from 0 to 4, with a higher index indicating a healthier lifestyle. We further constructed a weighted healthy lifestyle score based on the four lifestyle factors using the equation:

$$\text{weighted healthy lifestyle score} = \frac{(\beta_1 \times \text{factor 1} + \beta_2 \times \text{factor 2} + \beta_3 \times \text{factor 3} + \beta_4 \times \text{factor 4})}{(\text{sum of the } \beta \text{ coefficient})}$$

The weighted healthy lifestyle score was subsequently categorised into three lifestyle groups: unhealthy (bottom tertile of the weighted healthy lifestyle score), intermediate (middle tertile), and healthy lifestyle (top tertile).

According to the genome-wide association study results of the Chinese Longitudinal Healthy Longevity Survey, a replication study was carried out among 13 228 individuals using a well designed, customised chip targeting 27 656 longevity and its related traits single nucleotide polymorphisms (SNPs). Twelve SNPs were found to be associated with life expectancy. Detailed information on SNPs selection and the genotyping process used in the Chinese Longitudinal Healthy Longevity Survey study has been published previously.[10] In this study, we included 11 of 12 SNPs, with one SNP (rs3803304) failing genotyping that did not meet the quality control requirements. Details regarding the selected SNPs are provided in the appendix 2 (p 9). Individual SNPs were coded as 0, 1, and 2 according to the number of effect alleles associated with longevity. Calculation of the weight coefficient for each SNP has been previously reported.[10] The genetic risk score was formulated as the sum of the number of effect alleles at each locus multiplied by the respective weight coefficient, with a higher genetic risk score indicating increased years of life. Participants were divided into low and high genetic risk for lifespan according to the median of genetic risk score.

Outcomes

Mortality outcomes were ascertained from official death certificates if available, or reported by close family members of the participants, the local physicians, or local residential committees.[25] Person-years of follow-up were calculated from inclusion in the study to the date of death or to the last follow-up interview for each study participant, whichever came first. Loss to follow-up was defined as participants becoming unreachable after at least three attempts at contact. Survival time was defined as the time from the baseline survey to death or loss to follow-up.

Statistical analysis and covariates

A series of covariates were identified according to the available literature. Data on age, sex, area of residence (urban or rural), educational attainment at any level (<1 year or ≥1 year), source of income (independent or dependent), marital status (married or not married), living pattern (ie, living with family members, living alone or in a nursing home), activities of daily living status, self-reported health status, and prevalence of major chronic conditions were collected via standardised questionnaires administered by trained staff (appendix 2 pp 4–5).

Baseline characteristics of participants were described as mean (SD) or median (IQR) for continuous variables and counts (percentages) for categorical variables. Age-adjusted and sex-adjusted mortality rate per 1000 person-years was calculated using Poisson regression.

Entry time-stratified Cox proportional hazard models with the duration of follow-up as the time metric were applied to estimate hazard ratios (HRs) and their 95% CIs of all-cause mortality, with the lower category of healthy lifestyle score or genetic risk score as the reference. Proportional hazards assumptions were not violated

when assessed using Schoenfeld residuals (p>0·05). We selected potential covariates on the basis of a minimally sufficient adjustment set identified in a directed acyclic graph (appendix 2 p 30), availability of data, and consistency with previously published studies on the topic. Two models were constructed to test the association of healthy lifestyle and genetic risk with all-cause mortality risk: model 1 adjusted for age (continuous) and sex (categorical; male or female); and model 2 for age and sex, and further adjusted for area of residence, educational attainment, source of income, marital status, and living pattern.

We performed a trend test by modelling the median of the healthy lifestyle score or genetic risk score of each category as a continuous variable. Potential non-linear relationships of all-cause mortality risk associated with a healthy lifestyle score and genetic risk score were assessed by restricted cubic splines with the smallest Akaike's information criterion advising on the number and placement of knots. Moreover, we investigated the combined effects of a healthy lifestyle score and genetic risk score on all-cause mortality, with the lowest genetic risk and healthy lifestyle as the reference. We further explored the potential interaction between healthy lifestyle score and genetic risk score. Multiplicative interaction was evaluated via a likelihood ratio test with comparison of the results with and without the interaction term in the full model. Relative excess risk due to interaction, attributable proportion due to the interaction, and synergy index were used to test additive interaction.

The absolute risk reductions in the 3-year cumulative mortality rate were computed between the lifestyle groups classified as unhealthy or healthy to evaluate the benefits of adherence to a healthy lifestyle. Years of life gained with healthy lifestyle were estimated as the differences of areas under the survival curves based on fully adjusted Cox proportional hazard models with age as the underlying timescale (appendix 2 p 6). 95% CIs for absolute risk reductions and years of life gained were derived by drawing 1000 bootstrap samples from the estimation dataset.

To examine the robustness of our results, we performed sensitivity analyses by: (1) excluding first-year deaths after the baseline survey; (2) excluding participants with self-reported poor health status; (3) excluding participants who died as a result of an accident; (4) further adjusting for cognitive function status; (5) further adjusting for activities of daily living status and physical performance status; (6) further adjusting for history of chronic disease; (7) further adjusting for $PM_{2.5}$ exposure; (8) setting chronological age instead of time-on-study as the primary timescale; and (9) conducting one-sample univariable and multivariable mendelian randomisation study analyses to establish the causal link between healthy lifestyle and all-cause mortality (to avoid directional causation). Stratified analyses were performed to estimate the HRs within subgroups, and interaction terms with healthy lifestyle score were tested in the fully adjusted models.

All statistical analyses were done with SAS software (version 9.4) and R software (version 4.2.1). A two-sided p value of less than 0·05 indicated statistical significance.
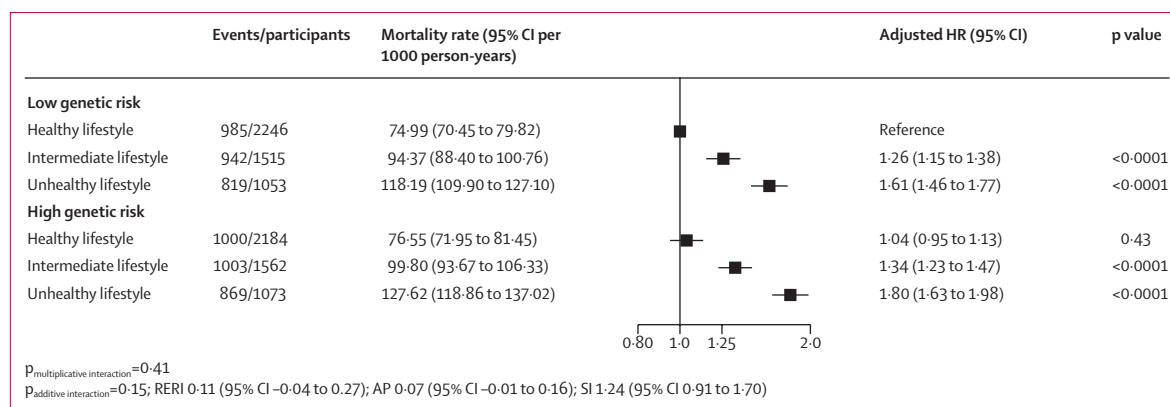
Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	All participants (n=36 164)	Participants with genetic information (n=9633)
Age, years	90·0 (81·0–99·0)	83·0 (73·0–92·0)
Sex		
Male	14 866 (41·1%)	4483 (46·5%)
Female	21 298 (58·9%)	5150 (53·5%)
Area of residence		
Urban	14 066 (38·9%)	3152 (32·7%)
Rural	22 098 (61·1%)	6481 (67·3%)
Educational attainment		
<1 year	23 978 (66·3%)	5716 (59·3%)
≥1 year	12 186 (33·7%)	3917 (40·7%)
Source of income*		
Dependent	28 275 (78·2%)	6767 (70·2%)
Independent	7889 (21·8%)	2866 (29·8%)
Marital status		
Not married	26 219 (72·5%)	5620 (58·3%)
Married	9945 (27·5%)	4013 (41·7%)
Living pattern		
With family members	31 475 (87·0%)	8211 (85·2%)
Alone or in nursing home	4689 (13·0%)	1422 (14·8%)
Ethnicity		
Han Chinese	33 740 (93·3%)	9009 (93·5%)
Other	2424 (6·7%)	624 (6·5%)
Current smoker		
No	25 513 (70·5%)	6504 (67·5%)
Yes	10 651 (29·5%)	3129 (32·5%)
Harmful alcohol consumption		
No	31 936 (88·3%)	8246 (85·6%)
Yes	4228 (11·7%)	1387 (14·4%)
Physical activity level†		
Non-ideal	21 966 (60·7%)	4330 (44·9%)
Ideal	14 198 (39·3%)	5303 (55·1%)
Dietary intake†		
Non-ideal	24 413 (67·5%)	5678 (58·9%)
Ideal	11 751 (32·5%)	3955 (41·1%)

Data are median (IQR) or n (%). Percentages may not add up to 100% due to rounding. *Source of income was assessed with the question "do you have your own income?". †For physical activity and dietary intake, the frequency of "not every month, but sometimes/never (rarely or never)" was scored 0, "not every week, but at least once a month" was scored 1, and "almost every day/not every day, but at least once a week" was scored 2. Ideal physical activity or dietary intake was defined as the top 40% of the population distribution.

Table: Baseline characteristics

	Events/participants	Mortality rate (95% CI per 1000 person-years)		Adjusted HR (95% CI)	p value
Low genetic risk					
Healthy lifestyle	985/2246	74·99 (70·45 to 79·82)		Reference	
Intermediate lifestyle	942/1515	94·37 (88·40 to 100·76)		1·26 (1·15 to 1·38)	<0·0001
Unhealthy lifestyle	819/1053	118·19 (109·90 to 127·10)		1·61 (1·46 to 1·77)	<0·0001
High genetic risk					
Healthy lifestyle	1000/2184	76·55 (71·95 to 81·45)		1·04 (0·95 to 1·13)	0·43
Intermediate lifestyle	1003/1562	99·80 (93·67 to 106·33)		1·34 (1·23 to 1·47)	<0·0001
Unhealthy lifestyle	869/1073	127·62 (118·86 to 137·02)		1·80 (1·63 to 1·98)	<0·0001

0·80 1·0 1·25 2·0

$p_{multiplicative\ interaction}$=0·41

$p_{additive\ interaction}$=0·15; RERI 0·11 (95% CI –0·04 to 0·27); AP 0·07 (95% CI –0·01 to 0·16); SI 1·24 (95% CI 0·91 to 1·70)

Figure 1: Joint association of genetic risk and healthy lifestyle with risk of all-cause mortality

The overall genetic risk of mortality was divided by the median and classified into low and high genetic risk groups. Weighted healthy lifestyle score was classified as unhealthy (the bottom tertile of the weighted healthy lifestyle score), intermediate (the middle tertile), or healthy lifestyle (the top tertile). For these comparisons, participants with a low genetic risk and healthy lifestyle served as the reference group. AP=attributable proportion due to the interaction. HR=hazard ratio. RERI=relative excess risk due to interaction. SI=synergy index.

Results

Between Jan 13, 1998, and Dec 31, 2018, a total of 27462 deaths among 36164 people were documented during a median follow-up of 3·12 years (IQR 1·62–5·94; 158680 person-years), and were included in the lifestyle association analysis. The genetic association analysis included 9633 participants, among whom 5618 deaths were recorded during a median follow-up of 5·57 years (IQR 3·07–9·54; 63130 person-years). The baseline characteristics of the study population are shown in the table and in the appendix 2 (pp 10–11), and characteristics according to healthy lifestyle and genetic risk category are presented in the appendix 2 (pp 12–16).

The healthy lifestyle score followed a normal distribution (appendix 2 p 31). Participants with a healthy lifestyle were more likely to be young, male, married, with an independent income source, living in an urban area, and with higher literacy (≥1 year of educational attainment; appendix 2 pp 12–16). An increased healthy lifestyle score was significantly associated with a lower risk of all-cause mortality with a non-linear dose-response relation ($p_{overall}$<0·0001; $p_{non-linear}$<0·0001; appendix 2 p 32). Compared with an unhealthy lifestyle, a healthy lifestyle was associated with lower all-cause mortality risk (HR 0·56 [95% CI 0·54–0·57]; p<0·0001; appendix 2 p 17).

The genetic risk score also followed a normal distribution (appendix 2 p 31), and the baseline characteristics of the participants in each genetic risk stratum were generally similar (appendix 2 pp 12–16). The adjusted HR of mortality risk of the high genetic risk group was 1·07 (95% CI 1·01–1·13; p=0·013) compared with those in low genetic risk group (appendix 2 p 18). The mortality risk increased across the range of genetic risk scores ($p_{overall}$<0·0001; $p_{non-linear}$=0·035; appendix 2 p 32).

When genetic risk and healthy lifestyle were combined, the overall risk of mortality increased as both genetic risk and unhealthy lifestyle increased (figure 1). Specifically, age-adjusted and sex-adjusted mortality rate

per 1000 person-years ranged from 74·99 (95% CI 70·45–79·82) for participants in the low genetic risk and healthy lifestyle category, to 127·62 (95% CI 118·86–137·02) for participants in the high genetic risk and unhealthy lifestyle category. Participants in the high genetic risk and unhealthy lifestyle category had the highest mortality risk (HR 1·80 [95% CI 1·63–1·98]; p<0·0001). Participants in the healthy lifestyle group had significantly lower adjusted cumulative mortality rates than those in the unhealthy lifestyle group, with an adjusted HR of 0·60 (95% CI 0·54–0·67) in participants at a low genetic risk and 0·59 (0·54–0·66) in participants at a high genetic risk (figure 2). No statistically significant additive or multiplicative interactions were observed.

Adjusted cumulative mortality rate according to genetic risk and healthy lifestyle was plotted. Standardised 3-year mortality rates in all participants were 47·32% (95% CI 46·50–48·13) for those in the unhealthy lifestyle category versus 30·72% (95% CI 30·02–31·41) for those in the healthy lifestyle category (appendix 2 p 33). Among participants with high genetic risk, the standardised 3-year mortality rates were 19·03% (95% CI 17·61–20·44) among those with a unhealthy lifestyle and 11·75% (95% CI 10·90–12·60) among those with a healthy lifestyle. A similar trend was observed in low genetic risk group (figure 3).

Life expectancy at the age of 65 years was longer for participants in the intermediate (2·14 years [95% CI 1·98–2·30]) and healthy lifestyle category (4·51 years [4·17–4·89]) than for participants in the unhealthy lifestyle category (appendix 2 p 34). Moreover, we estimated that a change from the unhealthy lifestyle category to the healthy lifestyle category was associated with an additional 3·84 years (95% CI 3·05–4·64) of life expectancy in the low genetic risk group and 4·35 years (3·70–5·06) in the high genetic risk group at 65 years (figure 4). Stronger beneficial effects were also observed for ideal physical

activity levels in overall participants and in different genetic risk groups (appendix 2 pp 19, 35–36).

Sensitivity analyses results are shown in the appendix 2 (pp 20–28). The association between healthy lifestyle and all-cause mortality was robust and stable in all sensitivity analyses. Similar findings were observed when excluding individuals with activities of daily living status and physical performance disability or excluding individuals with chronic disease (data not shown). The association estimates were strongest in oldest-old (≥80 years) women and urban participants (appendix 2 p 37).

Discussion

In this population-based cohort of Chinese older adults, we found that adhering to a healthy lifestyle substantially reduced mortality risk and moderately prolonged life expectancy. The greater risk reduction in mortality and life-year gain associated with a healthy lifestyle occurred among those with high genetic risk of short lifespan. Among individual lifestyle factors, ideal physical activity has the greatest effect on reducing mortality. Our study provides strong evidence of the benefits of a healthy lifestyle for mortality prevention and postponement in a general population, but especially for those at high genetic risk of short lifespan.

Although several studies have reported that a healthy lifestyle was related to a reduced risk of major health conditions in older people,[26–28] the benefits of a healthy lifestyle on lifespan have not yet been as widely investigated. Results from the Kungsholmen Project[29] indicated that participants aged 75 years and older with a healthy lifestyle versus unhealthy lifestyle behaviours gained an additional 5·4 years in life expectancy. Another study found that a healthy lifestyle was associated with an increased life expectancy after middle age (≥40 years old). The benefits persisted beyond the age of 85 years and were also apparent regardless of the presence of a major comorbidity or multimorbidity at each life stage since middle age.[30] Similarly, our analyses showed that a healthy lifestyle was associated with a reduction in all-cause mortality risk, and the potential benefits of a healthy lifestyle on lifetime gain persisted up to the age of 100 years (figure 4).

In addition to lifestyle behaviours, genetic factors have a pivotal role in all-cause mortality. Several studies investigating the potential interactions between different diet components and candidate genes for mortality risk,
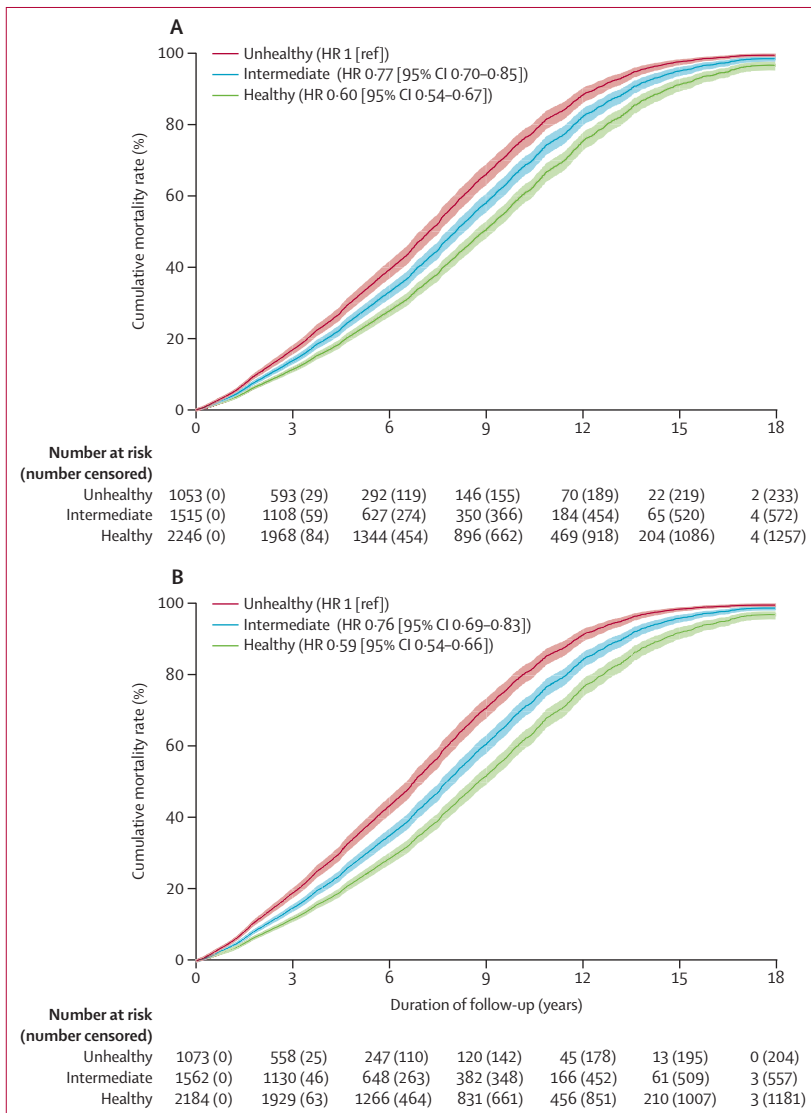
Figure 2: Cumulative mortality rate according to lifestyle categories in different genetic risk groups
Solid lines represent point estimates and shaded areas show 95% CIs. The overall genetic risk of mortality was divided by the median and classified into low genetic risk group (A) and high genetic risk group (B). Weighted healthy lifestyle score was classified into unhealthy (the bottom tertile of the weighted healthy lifestyle score), intermediate (the middle tertile), and healthy lifestyle (the top tertile). Models were adjusted for entry time, age, sex, area of residence, educational attainment, source of income, marital status, and living pattern, which was adjusted and performed on population averages for each covariate. HR=hazard ratio.
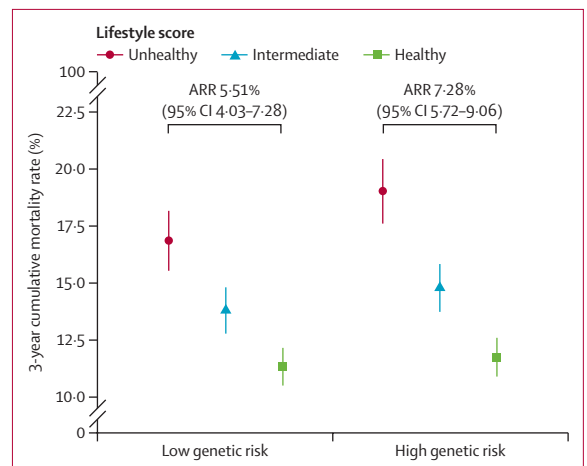
Figure 3: Adjusted 3-year cumulative mortality rate according to lifestyle in different genetic risk groups
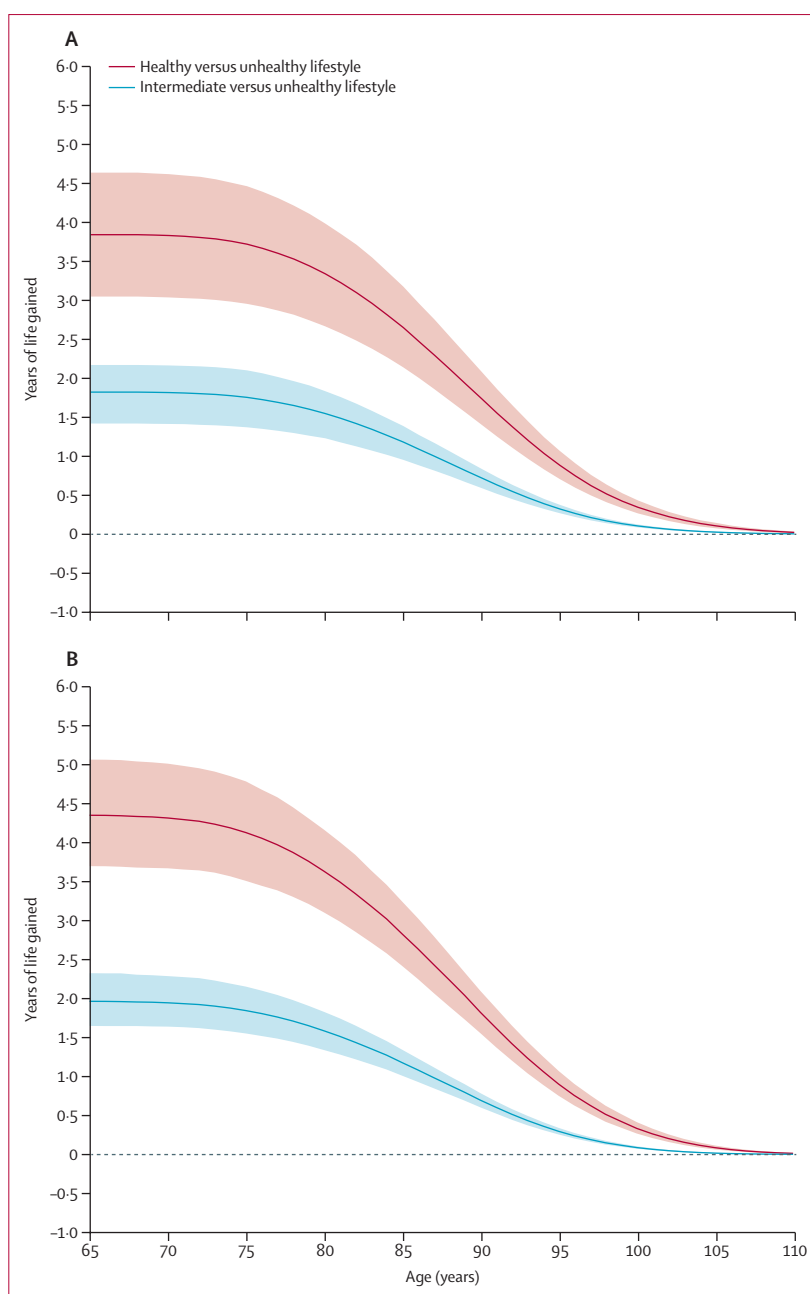Standardised to means of entry time, age, sex, area of residence, educational attainment, source of income, current marital status, and living pattern within the study population. Error bars refer to 95% CI of 3-year cumulative mortality rate. ARR=absolute risk reduction.

such as the *APOE* and *FOXO* genes,[13,14] found that a healthy dietary intake might attenuate the negative effects of genetic risk on lifespan. However, very few studies have quantified potential interactions between aggregated genetic risk and overall lifestyle on all-cause mortality risk. We combined the estimated effects of 11 SNPs associated with lifespan to construct the genetic risk score, and the overall healthy lifestyle score was derived from four modifiable lifestyle factors. Compared with participants with low genetic risk, the beneficial effects of adhering to a healthy lifestyle were more pronounced for those with high genetic risk, who had the greater 3-year absolute risk reduction of all-cause mortality and life-years gain. However, the mechanisms behind the observed results are not fully understood. Further research is needed to provide biological insights into the joint effects between genetic risk and combined lifestyle factors on all-cause mortality among Chinese older adults.

Greater efforts to address health problems associated with ageing could support healthy longevity for populations worldwide. At the national level, laws, regulations, and policies should be tailored to older adults with consideration of their individual health characteristics and nutritional status. At the individual level, approaches should be taken to strengthen health education on following a healthy lifestyle and promote active ageing and self-health management of older adults. For example, a study with adults older than 65 years in Spain suggested that interventions to improve subjective wellbeing can promote the maintenance of a healthy lifestyle and therefore contribute to reducing mortality risk.[31]

Another previous study[4] including two nationwide adult cohorts (the US National Health and Nutrition Examination Survey and the UK Biobank database) found no mediation of lifestyle on the association between socioeconomic status and all-cause mortality in the US cohort, but did report a stronger association between lifestyle and health outcomes in participants with low socioeconomic status in the UK cohort.[4] In our study, we observed that the estimated effect of following a healthy lifestyle on reducing mortality risk was larger among participants living in urban areas than in rural areas. The possible reasons for the inconsistent findings might partly be attributed to a difference in the definition of socioeconomic status and lifestyle factors as well as the population characteristics.

Strengths of this study are its large sample size and the strict and comprehensive data collection. We estimated the interaction of a healthy lifestyle and genetic risk on all-cause mortality and life-year gains from adherence to a healthy lifestyle among Chinese older adults. Our results were robust to a variety of sensitivity analyses, and individual lifestyle factors were evaluated. Nevertheless, our study has several potential limitations that should be investigated in future research. First, misclassification errors, which tend to

Figure 4: **Gain in years of life associated with healthy lifestyle in different genetic risk groups**
Solid lines represent point estimates and shaded areas show 95% CIs. The overall genetic risk of mortality was divided by the median and classified into the low genetic risk group (A) and high genetic risk group (B). Weighted healthy lifestyle score was classified into unhealthy (the bottom tertile of the weighted healthy lifestyle score), intermediate (the middle tertile), and healthy lifestyle (the top tertile). Models were adjusted for entry time, age, sex, area of residence, educational attainment, source of income, marital status, and living pattern.

overestimate or underestimate the lifestyle–mortality association, might exist because self-reported data were used to assess lifestyle factors.[32,33] Second, unlike most studies, BMI was not included in the healthy lifestyle score in this study, given the concern that the BMI cutoff points used in previous studies might not be appropriate for the older adults, and that the optimal

range of BMI for older adults is still unclear.[3,34] Third, changes in lifestyle factors over the follow-up period were not evaluated. Fourth, the dietary data collected were insufficient to estimate total energy intake; consequently, we were unable to adjust our models for energy intake. Moreover, the diet score might not exactly reflect overall healthy dietary behaviours, and unavailable information on dietary intake, such as cooking procedures, total energy intake, and diet quality, could lead to a misclassification bias. Additionally, in contrast to some previous studies,[35,36] meat consumption was regarded as a healthy diet pattern in this study; therefore, the application of the healthy lifestyle score constructed in this study should be used with appropriate adjustment to other populations. Fifth, although we adjusted for a range of covariates, we could not rule out the possibility of residual confounding by some uncontrolled factors (eg, social drinking, xenobiotics and drug use, and chronic pain), which could bias the lifestyle–mortality association. Sixth, although the explanation rate of the genetic risk score constructed from 11 longevity-related SNPs for lifespan in our study was comparable with some previous studies,[37,38] studies that compute genetic risk score of lifespan by capturing a full spectrum of genomic variants are still needed to improve risk classification among Chinese older adults. Seventh, the proportion of oldest-old was about 80% in this study, with a loss to follow-up rate of 16%, which was consistent with a similar study carried out in Europe.[39] Eighth, due to heterogeneity of genetic backgrounds across ancestry, our results were restricted to Chinese older adults, so generalisation to other ethnicities should be done cautiously. Finally, due to missing data on death records reviewed by professionals, the association of healthy lifestyle and cause-specific mortality was not evaluated.

In conclusion, our findings support the hypothesis that adherence to a healthy lifestyle could substantially reduce the risk of all-cause mortality in Chinese older adults, and that a healthy lifestyle could attenuate the deleterious effect of genetic factors on lifespan. Lifestyle modifications could have a greater effect on individuals with a high genetic risk of short lifespan than in those with low genetic risk.

Contributors
YLv and XS conceived and designed the study and hold responsibility for the integrity of the data and the accuracy of the data analysis. JW did the statistical analysis and data interpretation and drafted the manuscript. CC, YLv, and XS accessed and verified the data. All authors critically revised the manuscript, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
The datasets used and analysed are available from the Peking University Open Research Data website (https://opendata.pku.edu.cn/dataverse/CHADS), but restrictions apply to the availability of genetic sequence data; interested researchers can contact the corresponding authors for further information.

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