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Association of Multi-Dimensional Factors with Accelerating Age and Constructing a Healthy Lifestyle Index: Guangzhou Biobank Cohort Study

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Keywords
Ageing · Phenotypic age · Lifestyle

Abstract
Introduction: Ageing process is influenced by multi-dimensional factors collectively. Previous studies examined association of one separate factor with mortality without considering different manifestations of ageing process. We investigated associations of multi-dimensional factors with accelerating age (AA), a proxy to quantify ageing, in older Chinese. ***Methods:*** 9,831 participants from Guangzhou Biobank Cohort Study were included. Four exposure domains of 15 variables including demographic and socio-economic factors, lifestyle factors, stress across the life course, and common diseases were assessed. AA was calculated based on chronological age and eight biomarkers. Traditional multivariable linear and Bayesian Network (BN) models were used. ***Results:*** In both traditional and BN models, male sex, smoking, alcohol use, physical inactivity, greater waist circumference, and body mass index (BMI) were associated with higher AA, with the adjusted β (95% confidence intervals) being 2.75 (2.40–3.09), 1.31 (0.87–1.76), 1.35 (0.55–2.15), 0.64 (0.40–0.88), 0.09 (0.06–0.11), and 0.13 (0.07–0.19) years, respectively. A Healthy Lifestyle Index (HLI) was constructed including the above lifestyle factors (non-smoking, non-alcohol use, physically active, non-central, and non-general obesity) with a point assigned for each. A higher index indicates healthier lifestyle. Compared with participants with an HLI of 5, those with an HLI of 0–2 had 2.90 (2.48–3.32) years older AA. ***Conclusions:*** Male sex, smoking, alcohol use, physical inactivity, greater waist circumference, and BMI were associated with higher AA by 0.09–2.75 years, suggesting that adopting a healthy lifestyle may alleviate process of phenotypic ageing.

Introduction

In 2020, 9.3% of the global population were aged 65 years or above, and this would increase to 16% in 2050 [1]. In China, this share increased from 6.9% in 2000 to 12% in 2020 [2] and was predicted to reach 30% in 2050 [3]. Population ageing is mainly due to the longer life ex-

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pectancy and is associated with chronic diseases or disability [4], which underlies a greater burden to society. Thus, research on how to achieve healthy ageing is of great public health significance.

Conceptually, the ageing process can be considered as a dynamic equilibrium between resilience mechanisms and stressors, with the former decreasing and the latter increasing as time goes by [5]. Ageing occurs since birth, although biological ageing precedes the deterioration of physical and cognitive function by many years [5]. Ageing is influenced by multi-dimensional factors including sex, age, heredity, and environmental factors [6, 7]. Heredity accounted for 20%~30% of the variation in longevity [8], indicating that environmental factors should be more important. Previous studies reported important risk factors of longevity, including elevated blood pressure [9], smoking, higher body mass index (BMI) [10], and stress across the life course including childhood adversity and stressful life events [11]. Also, previous studies based on the Guangzhou Biobank Cohort Study (GBCS) have identified lifestyle factors associated with all-cause mortality including smoking [12], physical inactivity [13], obesity [14], and unhealthy diet [15, 16]. However, the above studies only focused on one separate factor, and used all-cause mortality as a proxy for longevity without considering different manifestations of the ageing process, i.e., some people were alive but had much worse biological profiles than expected, given their chronological age [17]. Biological age is calculated based on biological data, thus could reflect the status of tissue. Six scores of biological age have been constructed including blood biochemical prediction age [18, 19], composite proxy prediction age [20, 21], telomere clock [22, 23], DNA methylation prediction age [24], proteomic prediction age [25], and tissue and organ prediction age [26, 27]. Furthermore, different scores of biological age included various biomarkers, and of these six scores, blood biochemical prediction age was the most frequently used because it is relatively simple and readily available. We therefore examined the associations of multi-dimensional factors with phenotypic age measured by a modified indicator, i.e., accelerating age (AA) [19], using data from a well-established older Chinese cohort, GBCS.

Methods

Study Sample

GBCS is a collaborative cohort study under the Guangzhou Twelfth People's Hospital and the Universities of Hong Kong, China, and Birmingham, UK. Details of the GBCS have been described previously [28]. Briefly, participants were recruited from the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE), which is a large unofficial organization with branches in all ten districts of Guangzhou. Guangzhou permanent residents aged 50 years or above were eligible to participate, with a nominal fee of 4 RMB (about 50 US cents) per month. Baseline information was conducted using face-to-face computer-assisted questionnaire by trained nurses. This study protocol was reviewed and approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association (IRB No. N/A). All participants provided written informed consent before participation. Participants from phase 1 (2003–2004) were included in this study.

Exposures

Multi-dimensional exposures were classified into four domains including demographic and socio-economic factors, lifestyle factors, stress across the life course, and common diseases. Demographic and socio-economic factors included sex, education, occupation, and family income. According to previous studies [29–31], lifestyle factors included smoking status, alcohol use, physical activity, Dietary Approaches to Stop Hypertension (DASH) diet pattern [32], continuous sleep duration, and snoring. In sensitivity analysis, sleep duration was categorized into three groups (i.e., 7.0–8.9, <7.0, and ≥9.0 h/day) as normal, short, and long sleep duration [33].

Stress across the life course included childhood adversity and stressful life events, which were shown to be significantly associated with mortality [34] and phenotypic age [35]. Childhood adversity was defined as at least one of the following four adverse experiences during childhood: continuous separation from mother for more than a year, parents frequently quarrelling, being sent away from home due to wrongdoing, or an experience so frightening that it was thought about years afterwards [36]. Stressful life events were defined as at least one major life event in the last year including separation or divorce, unemployment or retirement, business bankruptcy, physical assault, major conflict within family, major injury or traffic accident, death of spouse, major illness or death of a close family member, major natural disaster (such as flood or drought), and loss of all sources of income or living on debt [36].

Common diseases were also considered as exposures since disease status could influence biological status, i.e., phenotypic age. Continuous variables such as BMI and waist circumference were used to define general and central obesity, respectively. In sensitivity analysis, general obesity was defined by BMI ≥28 kg/m^2 [37], and central obesity was defined by waist circumference ≥90 cm in men and ≥80 cm in women [38]. Both waist circumference and BMI were measured by trained nurses and thus bias due to self-report was unlikely. Multimorbidity was defined by the presence of any two or more of the following 20 diseases: hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, angina, rheumatic heart disease, arrhythmia, heart failure, cancer, liver disease, gastrointestinal disease, chest disease, genitourinary disease, neurological disease, eye disease, arthritis, thyroid disease, fracture history, and mental disease [39].

Outcome

The primary outcome was AA defined as the residual resulting from a linear model when regressing phenotypic age on chronological age [19], expressed in years. A positive value of AA indi-

Table 1. Accelerating age (AA, years) by characteristics in 9,831 participants of the Guangzhou Biobank Cohort Study

	Number	AA, years	
		mean (95% CI)	*p* value
Sex			
Women	6,957	−0.99 (−1.13 to −0.86)	<0.001
Men	2,874	2.41 (2.19–2.63)	
Age group, years			
50–64	5,114	0.05 (−0.11–0.22)	0.18
65–94	4,717	−0.06 (−0.23 to 0.12)	
Education			
Primary or below	4,920	−0.18 (−0.36 to −0.01)	<0.001
Middle school	4,011	0.08 (−0.10–0.26)	
College or above	899	0.65 (0.25–1.05)	
Occupation			
Manual	6,279	−0.14 (−0.30 to 0.01)	<0.001
Non-manual	3,071	0.41 (0.19–0.63)	
Others	481	−0.73 (−1.22 to −0.24)	
Family income, CNY/year			
<10,000	680	−0.24 (−0.71 to 0.23)	0.18
10,000–29999	3,318	0.12 (−0.10–0.33)	
30,000–49999	1,494	0.05 (−0.25–0.34)	
≥50,000	1,021	0.09 (−0.26–0.44)	
Don't know	3,311	−0.12 (−0.33 to 0.08)	
Smoking status			
Never	7,800	−0.60 (−0.73 to −0.47)	<0.001
Former	1,048	2.16 (1.76–2.56)	
Current	980	2.43 (2.05–2.81)	
Alcohol use			
Never	8,201	−0.28 (−0.41 to −0.15)	<0.001
Former	215	3.00 (2.06–3.94)	
Current	1,406	1.18 (0.86–1.50)	
Physical activity			
Active	6,240	−0.35 (−0.50 to −0.21)	<0.001
Moderate to inactive	3,590	0.62 (0.41–0.83)	
DASH diet pattern			
1st quantiles	3,981	−0.04 (−0.23 to 0.15)	0.68
2nd quantiles	3,288	0.09 (−0.12–0.30)	
3rd quantiles	2,498	−0.08 (−0.31 to 0.16)	
Sleep duration, hours/day			
7.0–8.9	4,698	0.03 (−0.14–0.20)	<0.001
<7.0	4,177	−0.13 (−0.32 to 0.05)	
≥9.0	812	0.63 (0.19–1.06)	
Snoring			
No	3,771	−0.44 (−0.62 to −0.25)	<0.001
Yes	4,467	0.40 (0.23–0.58)	
Don't know	1,580	−0.08 (−0.41 to 0.24)	
Childhood adversity			
No	8,495	0.04 (−0.09–0.17)	0.12
Yes	1,336	−0.27 (−0.59 to 0.05)	
Stressful life events			
No	9,104	0.03 (−0.10–0.15)	0.42
Yes	727	−0.33 (−0.72 to 0.07)	
Central obesity			
No	5,662	−0.42 (−0.57 to −0.26)	<0.001
Yes	4,169	0.57 (0.38–0.76)	
General obesity			
No	8,835	−0.19 (−0.32 to −0.07)	<0.001
Yes	996	1.70 (1.30–2.09)	
Multimorbidity			
No	2,252	−1.05 (−1.24 to −0.85)	<0.001
Yes	7,579	0.31 (0.17–0.45)	

AA was defined as the residual resulting from a linear model when regressing phenotypic age on chronological age, expressed in years, with a positive value of AA indicating an older biological profile than expected given the chronological age and a negative value indicating a younger biological profile. Phenotypic age was calculated based on participants' biological profile and chronological age. CI, confidence interval; DASH diet pattern, Dietary Approaches to Stop Hypertension diet pattern.

Table 2. Association of sex and lifestyle factors[a] with accelerating age (AA, years) in the Guangzhou Biobank Cohort Study

	Number	AA, years	
		crude β (95% CI)	adjusted β (95% CI)[b]
Sex			
Women	6,957	0.00	0.00
Men	2,874	3.40 (3.15–3.66)***	2.75 (2.40–3.09)***
Smoking status			
Never	7,800	0.00	0.00
Former	1,048	2.76 (2.38–3.15)***	0.44 (0.01–0.88)*
Current	980	3.03 (2.63–3.42)***	1.31 (0.87–1.76)***
Alcohol use			
Never	8,201	0.00	0.00
Former	215	3.28 (2.47–4.10)***	1.35 (0.55–2.15)***
Current	1,406	1.46 (1.12–1.81)***	−0.05 (−0.39 to 0.30)
Physical activity			
Active	6,240	0.00	0.00
Moderate to inactive	3,590	0.97 (0.72–1.22)***	0.64 (0.40–0.88)***
Sleep duration, hours/day	9,687	0.19 (0.10–0.28)***	0.07 (−0.02–0.16)
Snoring			
No	3,771	0.00	0.00
Yes	4,467	0.84 (0.57–1.10)***	−0.01 (−0.27 to 0.25)
Don't know	1,580	0.35 (−0.01–0.71)	0.02 (−0.33–0.36)
Waist circumference, cm	9,769	0.16 (0.14–0.17)***	0.09 (0.06–0.11)***
BMI, kg/m^2	9,799	0.30 (0.26–0.33)***	0.13 (0.07–0.19)***

AA was defined as the residual resulting from a linear model when regressing phenotypic age on chronological age, expressed in years, with a positive value of AA indicating an older biological profile than expected given the chronological age and a negative value indicating a younger biological profile. Phenotypic age was calculated based on participants' biological profile and chronological age. [a] Significant factors in the Table 1 were selected for analysis in this table. [b] All factors were mutually adjusted and additionally adjusted for education, occupation, and presence of multimorbidity. * $p < 0.05$. *** $p < 0.001$.

cated an older biological profile than expected given the chronological age, whereas a negative value indicated a younger biological profile. Phenotypic age was calculated based on a weighted linear combination score including chronological age in years and 8 biomarkers including albumin, creatinine, glucose, C-reactive protein, lymphocyte percent, mean cell volume, red cell distribution width, and white blood cell count [19]. Among them, albumin [18, 40, 41], alkaline phosphatase [18], glucose [18, 40, 41], lymphocyte percent [18], creatine [18, 40], and red cell distribution width [41] were also used to define biological age in other methods. Phenotypic age was developed according to the following formula [19]:

$$\text{Phenotypic age} = 141.50225 + \frac{\ln\left[-0.00553 \times \ln\left(1 - \text{score}\right)\right]}{0.090165}$$

Where

$$\text{Score} = 1 - e^{-e^{xb}\left[\frac{\exp(120\times\gamma)-1}{\gamma}\right]}$$

γ was 0.0076927, and

xb = −19.9067 − 0.0036 × albumin + 0.0095 × creatine + 0.1953 × glucose + 0.0954 × ln (CRP) − 0.0120 × lymphocyte percent + 0.0268 × mean cell volume + 0.3306 × red cell distribution width + 0.0554 × white blood cell count + 0.0804 × chronological age

We also dichotomized AA into presence or absence of AA over 5 years (i.e., AA ≥5 years).

Statistical Analysis

Kruskal-Wallis rank sum tests were used to compare AA by baseline characteristics. Traditional multivariable linear model was used to assess the associations of sex, lifestyle factors, waist circumference, and BMI with AA, giving adjusted regression coefficients (βs) and 95% confidence intervals (CIs). Significant lifestyle factors were used to construct a Healthy Lifestyle Index (HLI) by allocating one point for the presence of each factor and zero otherwise. A higher HLI indicated an optimal lifestyle. Variance inflation factor [42] was used to evaluate multicollinearity in regression models. We also conducted a Bayesian Network (BN) model to test the interactions and associations of multi-dimensional factors with AA over 5 years. BN model could show the conditional dependences among a set of variables based on Directed Acyclic Graph (DAG). Nodes in DAG represent variables, edges

Table 3. Association of lifestyle factors[a] with accelerating age (AA, years) in the Guangzhou Biobank Cohort Study by sex

	Men			Women		
	n	AA, years		*n*	AA, years	
		crude β (95% CI)	adjusted β (95% CI)[b]		crude β (95% CI)	adjusted β (95% CI)[b]
Smoking status						
Never	1,209	0.00	0.00	6,591	0.00	0.00
Former	867	0.82 (0.30–1.34)**	0.59 (0.06–1.12)*	181	1.18 (0.32–2.04)**	0.55 (−0.31–1.41)
Current	795	1.42 (0.89–1.96)***	1.73 (1.17–2.28)***	185	0.19 (−0.66–1.04)	0.26 (−0.58–1.10)
Alcohol use						
Never	1,861	0.00	0.00	6,340	0.00	0.00
Former	146	2.08 (1.07–3.08)***	1.54 (0.53–2.54)**	69	1.33 (−0.05–2.71)	1.04 (−0.32–2.40)
Current	860	0.35 (−0.13–0.84)	0.01 (−0.47–0.50)	546	0.04 (−0.47–0.55)	−0.15 (−0.65 to 0.35)
Physical activity						
Active	1,684	0.00	0.00	4,556	0.00	0.00
Moderate to inactive	1,190	1.00 (0.56–1.44)***	0.85 (0.41–1.29)***	2,400	0.66 (0.37–0.95)***	0.55 (0.27–0.84)***
Sleep duration, hours/day	2,838	0.17 (0.01–0.33)*	0.14 (−0.02–0.30)	6,849	0.02 (−0.08–0.13)	0.04 (−0.07–0.14)
Snoring						
No	963	0.00	0.00	2,808	0.00	0.00
Yes	1,538	0.46 (−0.02–0.94)	−0.14 (−0.63 to 0.34)	2,929	0.58 (0.27–0.88)***	0.05 (−0.26–0.35)
Don't know	373	0.49 (−0.23–1.20)	0.02 (−0.69–0.73)	1,207	0.39 (0.002–0.79)*	0.01 (−0.38–0.40)
Waist circumference, cm	2,852	0.13 (0.10–0.15)***	0.07 (0.02–0.11)**	6,917	0.14 (0.12–0.15)***	0.09 (0.06–0.12)***
BMI, kg/m^2	2,865	0.34 (0.27–0.41)***	0.17 (0.04–0.30)**	6,934	0.32 (0.28–0.36)***	0.12 (0.05–0.19)**

AA was defined as the residual resulting from a linear model when regressing phenotypic age on chronological age, expressed in years, with a positive value of AA indicating an older biological profile than expected given the chronological age and a negative value indicating a younger biological profile. Phenotypic age was calculated based on participants' biological profile and chronological age. [a] Significant factors in the Table 1 were selected for analysis in this table. [b] All factors were mutually adjusted and additionally adjusted for education, occupation, and presence of multimorbidity. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

between nodes indicate probabilistic dependencies (i.e., significant associations), and no edges indicate non-significant associations among variables [43, 44]. Statistical analysis was done using Stata version 16.0 (STATA Corp LP, College Station, TX, USA) and R program version 4.0.2 (ST Louis, MO, USA). All tests were two-sided with $p < 0.05$ as statistically significant.

Results

Of 10,413 participants recruited from 2003 to 2004, after excluding those with duplicate information ($N = 33$) and missing data on the 8 biomarkers used to calculate AA ($N = 549$), 9,831 participants with a median (interquartile range) AA of −0.71 (10.89) years were included in the current study. Table 1 shows that of the 9,831 participants, men, smokers, alcohol users, and those with manual occupation, long sleep duration, and snoring had higher AA (all $p < 0.001$). Participants with less physically active, higher education, central obesity, general obesity, and multimorbidity also had higher AA (all $p < 0.001$). No significant differences were found in AA by groups of age, family income, DASH diet pattern, childhood adversity, and stressful life events (P from 0.18 to 0.68).

Table 2 shows that after adjusting for sex, education, occupation, smoking status, alcohol use, physical activity, sleep duration, snoring, waist circumference, BMI, and presence of multimorbidity, men had higher AA by 2.75 years (95% CI: 2.40–3.09) than women. Current versus never smokers and former versus never alcohol users had higher AA, with adjusted β (95% CI) being 1.31 (0.87–1.76) and 1.35 (0.55–2.15) years, respectively. Compared with participants who were physically active, moderate to inactive participants had higher AA by 0.64 (0.40–0.88) years. Furthermore, each one unit increase in waist circumference (cm) and BMI (kg/m^2) was associated with higher AA by 0.09 (0.06–0.11) and 0.13 (0.07–0.19) years, respectively.

Table 3 shows that after similar adjustment, in men, current smoking, former alcohol use, moderate to inactivity, waist circumference, and BMI were associated with higher AA (adjusted β [95% CI] = 1.73 [1.17–2.28], 1.54

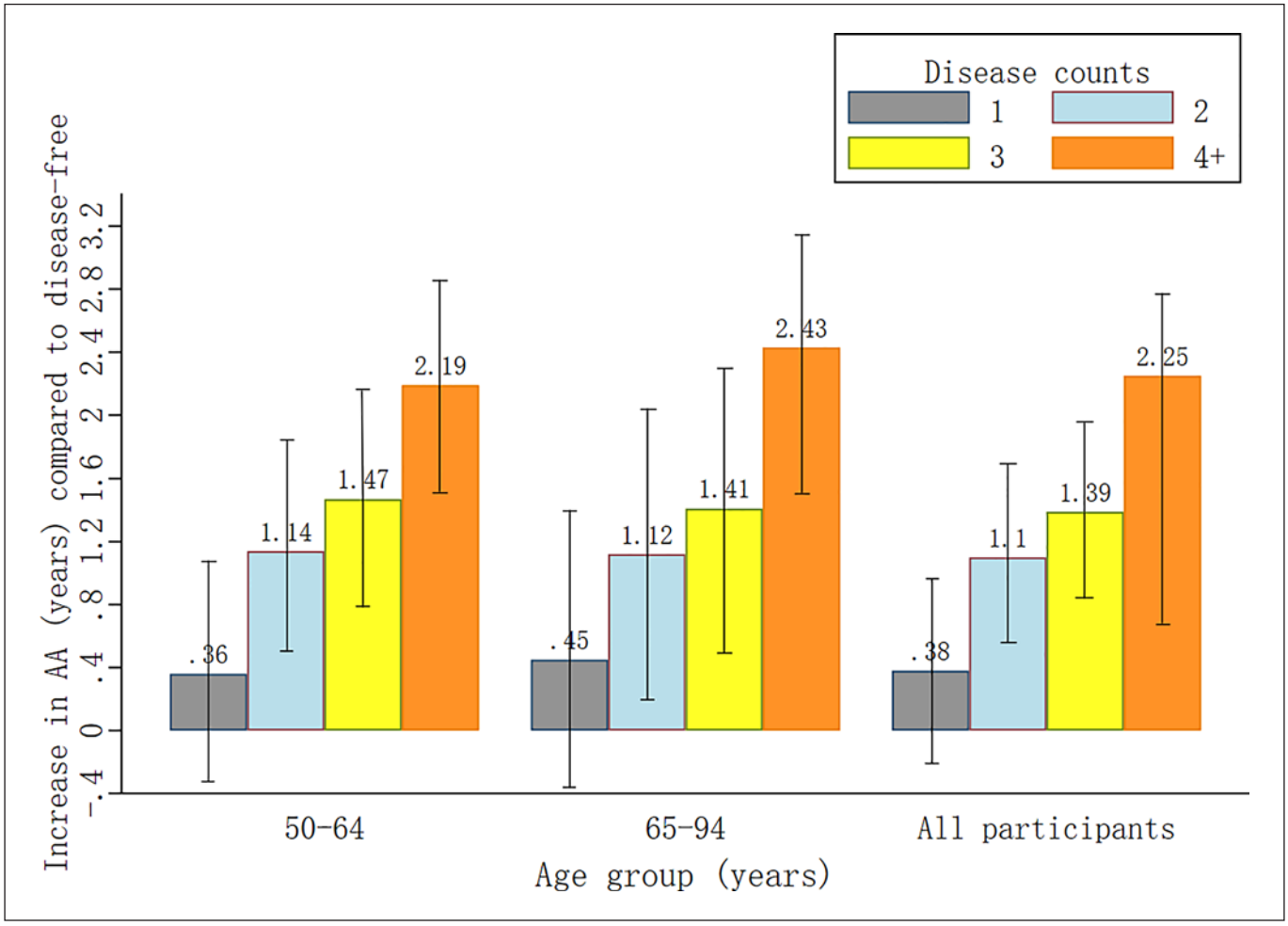

Fig. 1. Predicted increase in accelerating age (AA, years) for each disease count in the Guangzhou Biobank Cohort Study. The y-axis illustrates the increase in AA compared to participants who were disease-free. Number for disease-free, one disease, two diseases, three diseases, and four or more diseases were 377, 1,001, 1,307, 1,110, and 1,319 in participants aged 56–64 years, 211, 663, 1,074, 1,104, and 1,665 in participants aged 65–94 years, and 588, 1,664, 2,381, 2,214, and 2,984 in all participants.

[0.53–2.54], 0.85 [0.41–1.29], 0.07 [0.02–0.11], and 0.17 [0.04–0.30] years, respectively). In women, moderate to inactive activity and each one unit increase in waist circumference (cm) and BMI (kg/m^2) was associated with higher AA by 0.55 (95% CI: 0.27–0.84), 0.09 (0.06–0.12), and 0.12 (0.05–0.19) years, respectively. Online supplementary Tables 1, 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000528760) show that analysis using categorical variables of sleep duration, central, and general obesity instead of continuous variables showed similar results.

Figure 1 shows increase in AA for each disease count category by age groups. Participants with more diseases showed higher AA. In all participants, compared to those without any of the specified diseases, those with one disease and with four or more diseases were phenotypically older by 0.38 and 2.25 years. In participants aged 56–64 and 65–94 years, those with one disease had 0.36 and 0.45 years of higher AA, and those with four or more diseases had 2.19 and 2.43 years of higher AA, respectively.

The BN model identified five parent nodes in green (sex, smoking, physical activity, central obesity, and multimorbidity) as direct risk factors for AA over 5 years (Fig. 2). Men, smokers, inactive participants, those with central obesity, or multimorbidity were more likely to have AA over 5 years. Alcohol use and education were indirectly associated with AA over 5 years through physical activity and smoking, respectively (Fig. 2).

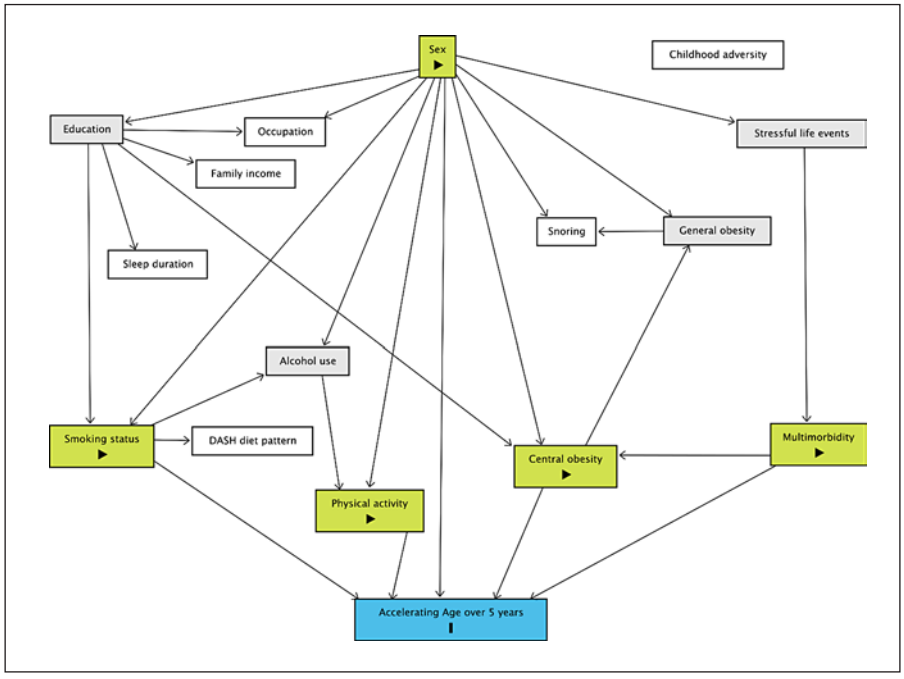

Fig. 2. Bayesian Network model on factors associated with AA over 5 years in Guangzhou Biobank Cohort Study. AA over 5 years was defined as the residual resulting from a linear model when regressing phenotypic age on chronological age was over 5 years. Phenotypic age was calculated based on participants' biological profile and chronological age. DASH diet pattern, Dietary Approaches to Stop Hypertension diet pattern.

Table 4. Association of Healthy Lifestyle Index with accelerating age (AA, years) in the Guangzhou Biobank Cohort Study

	Healthy lifestyle index, adjusted β (95% CI)[a]				*p* for trend
	5	4	3	0–2	
No. of participants	2,434	3,720	2,544	1,133	
All participants	0.00	0.86 (0.56–1.16)***	1.90 (1.57–2.22)***	2.90 (2.48–3.32)***	<0.001
Men	0.00	0.17 (−0.50–0.85)	1.29 (0.61–1.96)***	2.59 (1.86–3.32)***	<0.001
Women	0.00	1.04 (0.71–1.38)***	2.08 (1.70–2.46)***	2.83 (2.27, 3.40)***	<0.001

AA was defined as the residual resulting from a linear model when regressing phenotypic age on chronological age, expressed in years, with a positive value of AA indicating an older biological profile than expected given the chronological age and a negative value indicating a younger biological profile. Phenotypic age was calculated based on participants' biological profile and chronological age. Healthy Lifestyle Index including five factors (never smoking, never alcohol use, active physical activity, non-central obesity, and non-general obesity), with one point for the presence of each factor. [a] Adjusted for sex, education, occupation, sleep duration, snoring, and presence of multimorbidity. *** $p < 0.001$.

HLI included never smoking, non-alcohol use, physically active, non-central obesity, and non-general obesity. Table 4 shows that in all participants, compared to those with an HLI of 5, those with an HLI of 0–2 had higher AA by 2.90 (95% CI: 2.48–3.32) years, and the results were similar in men and women with the adjusted β (95% CI) being 2.59 (1.86–3.32) and 2.83 (2.27–3.40) years, respectively. A weighted HLI was calculated with the weight for smoking status, alcohol use, physical activity, central obesity and general obesity being 1.14, 1.32, 0.64, 1.53, and 1.13, respectively. A higher weighted HLI represents an unhealthier lifestyle. After adjustment for sex, education, occupation, sleep duration, snoring, and presence of multimorbidity, each point higher in weighted HLI was associated with 0.80 (β 0.80, 95% CI: 0.70–0.90) years of AA.

Discussion

In this large cohort in China, we not only identified factors associated with AA including male sex, smoking, alcohol use, physically inactivity, greater waist circumference, and BMI using both traditional and BN models but also quantified the associations of these factors with AA. We further constructed an HLI based on the above five lifestyle factors significantly associated with AA, with never smoking, never alcohol use, physically active, non-central obesity, and non-general obesity being assigned one point for each. Compared to those with an HLI score of 5, those with the lowest HLI score (0–2) had AA by 2.9 years. As the HLI is easy to calculate and interpret and all factors included can be readily accessible in the general community, it may serve as an efficient index for public health education and promotion.

We found that compared with women, men were more likely to have older AA, which was consistent with a cross-sectional study of 774 Mexico participants, showing that men had higher accelerated ageing (phenotypic age ≥4 years of their chronological age) [45]. Chinese women also had a longer life expectancy than men by about 4.5 years in 2020 [28]. A study from Korea examining the difference of life expectancy between men and women by age groups found that compared with men aged 60 years or above, women of the same age group showed a longer life expectance by 4.42 years, which accounted for about 70% of the total sex difference in life expectancy at birth between men and women [46], indicating the lifespan disparity may be mainly due to the discrepancy among the older age group. In our study, smoking was an important risk factor for higher AA, which was consistent with existing evidence, showing that smoking is a well-established risk factor for mortality [12, 47, 48]. A cross-sectional study of 2,339 participants in the USA showed that current versus never smokers had 3.55-year older phenotypic age [35]. In our results, a positive association between alcohol use and higher AA was found, which was consistent with a German cohort study of 22,469 participants, showing that relative to no/light alcohol drinking, men aged at 40 with heavy alcohol drinking had a shorter life expectancy by 3.1 years [29]. Similar results were found in another cohort study of 123,329 participants in the USA, which showed that compared with moderate alcohol consumption, heavy alcohol use of >30 g/day was associated with lower life expectancy by about 2.5 years for women and 2 years for men at age 50 [30]. We found that inactivity was associated with older phenotypic age, which was supported by the existing evidence that compared to sedentary participants, moderately and vigorously active participants at age 50 could gain additional life expectancy of approximately 4.5 and 8 years for women, and 3 and 7.5 years for men, respectively [30]. Moreover, we showed that participants with obesity had older phenotypic age. Notably, a previous US study also found that each 1-SD increase in the proportion of participants who were classified into obesity (ranging from 0 to 1) was associated with higher phenotypic age by 2.44 years [35]. Another US study also showed that higher BMI was associated with a shorter life expectancy at age 50 in both men and women [49].

A biomarker-based phenotypic age was developed by Liu et al. [19] and validated in another study of 774 Mexico participants, showing that male sex, diabetes, and long-term sleep duration were associated with ageing rapidly [45]. Our results were generally consistent with results of this Mexican study [45], except for sleep duration. We showed that compared with normal sleep duration, neither short nor long sleep duration was associated with AA, and the Mexican study showed that long sleep duration was positively associated with accelerated ageing [45]. The discrepancy might be due to the various definition for long sleep duration, i.e., 9 or more hours per day was defined as long duration in our study, while 8 or more hours per day in the Mexico study [45]. However, physical activity was not included in the analysis of the study [45].

We defined a Healthy Lifestyle Index including healthy lifestyle factors independently associated with a lower rate of ageing, which was generally consistent with studies from both western settings [29, 30] and China [31]. The Nurses' Health Study and Health Professions Follow-up Study showed that adopting a healthy lifestyle (never smoking, normal BMI, regular physical activity, moderate alcohol intake, and a healthy diet) was associated with a lower risk of all-cause mortality and longer life expectancy [30]. A prospective cohort study in German on 22,469 participants showed that adherence to never smoking, optimal BMI, no/light alcohol use, and low processed/red meat consumption was associated with an increase in life expectancy by 17.0 years in men and 13.9 years in women compared with those without these healthy lifestyles at age 40 [29]. Our previous study of 46,120 cancer patients from China also showed that compared to those adopting a healthy lifestyle including never smoking, never alcohol use, regular physical activity, sufficient sleep, and normal or high BMI, those with less than two healthy behaviours had more than twofold risk of all-cause mortality after an average follow-up of 4.3 years [31]. A cross-sectional study from USA found that

four different domains, i.e., childhood and adulthood circumstances domains, polygenic score domain, behaviour domain, and demographic domain totally accounted for 29.2% of the variance in phenotypic age, with the behaviour domain (obesity, smoking, alcohol use, and physical activity) showing the largest contribution (9.2%) [35].

Strengths of this study included the use of AA instead of chronological age or mortality which could represent biological function and quantify the ageing process. In addition to the traditional regression model, we also used the BN to explore factors that were potentially causally associated with AA. Besides, a wide variety of factors were included in our study not only including demographic, socio-economic, and common lifestyle factors but also stress across the life course and multimorbidity. Our study also had several limitations. Firstly, alkaline phosphatase was one of factors used to calculate phenotypic age [19] but not detected in our study. However, as the weight of alkaline phosphatase for mortality risk score was 0.0019 and the reference intervals of alkaline phosphatase for adults was between 50 and 120 U/L [50], the contribution of alkaline phosphatase on prediction was small. Thus, the results were unlikely to be influenced by alkaline phosphatase. Secondly, AA was firstly developed in the USA [19] and our participants had different genetic, environmental, and lifestyle background with them. But biomarker-based prediction score for biological age derived from the US population was shown to be well-replicated in different age groups in Taiwan Chinese [51]. Thirdly, the HLI was simply treated identically for easy use in community and a weighted HLI was also conducted with similar results. Further studies using different methods such as structural equation modelling to create a latent factor for healthy lifestyle may be informative. Finally, although various dimension variables were investigated, all were non-genetic factors, and genetics factors were not included. In conclusion, male sex, smoking, alcohol use, physical inactivity, greater waist circumference, and BMI were associated with higher AA by 0.09–2.75 years, suggesting that adopting a healthy lifestyle may alleviate the process of phenotypic ageing.

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Statement of Ethics

This study protocol was reviewed and approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association. All participants provided written informed consent before participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xue Liang, Lin Xu, Tai Hing Lam, Wei Sen Zhang, Feng Zhu, Ya Li Jin, Chao Qiang Jiang, and Kar Keung Cheng gave substantial contributions to conception and design, acquisition of funding and data, and interpretation of data; Xue Liang, Lin Xu, Chao Qiang Jiang, and Tai Hing Lam analysed the data; Xue Liang, Lin Xu, Chao Qiang Jiang, Tai Hing Lam, and Kar Keung Cheng drafted the article; Lin Xu, Chao Qiang Jiang, Tai Hing Lam, and Kar Keung Cheng revised it critically for important intellectual content. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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