Methods

Study design

The CKB is a large-scale nationwide prospective cohort of 512 725 participants aged 30-79 years at enrollment. Participants were recruited from ten geographically defined areas across China (five urban and five rural) to retain diversity in disease patterns and risk exposures. All participants provided written informed consent, completed interviewer-administered laptop-based questionnaires, and had physical measurements taken in the 2004-08 baseline survey. Besides long-term outcome follow-up for all participants, periodic resurveys were conducted in 2008 and between 2013-14 in a random sample of about 5% surviving participants. Details of the study design and survey methods have been reported previously1. The study protocol was approved by the Ethics Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK).

We excluded participants who reported medical histories of heart disease (n=15 472), stroke (n=7 657), or cancer (n=2 385) at baseline. We also excluded those who had a self-reported history of diabetes or screen-detected diabetes, defined as measured fasting blood glucose ≥7.0 mmol/L or random blood glucose ≥11.1 mmol/L at baseline (n=26 162). Participants with missing data for body mass index (BMI, n=2) were also excluded, leaving 461 047 participants in the present analysis.

In line with the previous studies2-6, we limited cardiometabolic diseases (CMD) to ischemic heart disease (IHD), stroke, and type 2 diabetes (T2DM). Given the differences in the pathogenesis of hemorrhagic stroke (HS) and ischemic stroke (IS), and a sizeable proportion of HS among the Chinese population than that among the Western population, the study is clearly restricted to IS. Cardiometabolic multimorbidity (CMM) was defined as occurring at least two of the above-mentioned diseases.

Assessment of lifestyle factors and other covariates

Lifestyle factors of interest were assessed through baseline questionnaires and physical measurements. We asked the frequency, type, and amount of tobacco smoked per day for ever smokers (former and current). Former smokers were additionally asked about the years since quitting and the reason for quitting. Questions about alcohol consumption included typical drinking frequency, type of alcoholic beverage consumed habitually, and volume of alcohol consumed on a typical drinking day in the past 12 months. For physical activity, the usual type and duration of occupational, commuting, domestic, and leisure time–related activities in the past 12 months were collected. To calculated daily total physical activity level, we multiplied the metabolic equivalent of tasks (METs) for each activity by the hour spent on that activity and summed the MET-hours for all activities7. We assessed habitual intakes of 12 conventional food groups in the past year via a validated qualitative food frequency questionnaire8. Weight, height, and waist circumference were measured by trained staff using well-calibrated instruments. BMI was calculated as weight in kilograms divided by height in meters squared.

A range of covariates was also assessed through the baseline questionnaire, including socio-demographic characteristics, personal and family medical history, and women's reproductive information. Participants who had at least one parent suffering from chronic heart disease, stroke, or diabetes were considered as having a CMD family history. Of those, participants who reported at least one parent suffering from at least two of the CMDs were considered as having a CMM family history. Prevalent hypertension was defined as measured systolic blood pressure ≥140 mmHg, measured diastolic blood pressure ≥90 mmHg, a self-reported diagnosis of hypertension, or antihypertensive medication use at baseline.

Definition of high-risk lifestyle

We considered five lifestyle factors, including smoking, alcohol drinking, dietary habits, physical activity, and body shape; their associations with cardiovascular disease, diabetes, and mortality are well established in our population8-10. For smoking, we assigned current smokers and former smokers who quitted because of illness to the high-risk group. For alcohol drinking, the high-risk group was defined as those who drank ≥30 g/d of pure alcohol or having stopped drinking habit. Former smokers and drinkers were included in the high-risk group to avoid a misleadingly elevated risk for the reference group. For physical activity, we defined the high-risk group as those who engaged in a sex- and age- (<50 years, 50–59 years, and ≥60 years) specific lower half of total physical activity. For dietary habit, according to the Chinese Dietary Guidelines11 and previous findings in our population12, we defined unhealthy dietary habits as non-daily eating of vegetables, fruits, and eggs, and eating red meat daily or less than weekly. For body shape, both BMI and waist circumference (WC) were considered to reflect energy balance13. Participants having BMI <18.5 or ≥28.0 kg/m2 or having waist circumference ≥90 cm (men) / 85 cm (women) were considered as high risk, which emphasizes avoidance of extremely high or low weight and abdominal obesity. The number of high-risk lifestyle factors was counted, ranging from 0 to 5.

Follow-up for CMD and death

Incident cases of interest and death were identified through the linkage with the disease and mortality registries and national health insurance claim database, supplemented with local residential records and annual active confirmation. Causes of death were ascertained chiefly by death certificates and supplemented by reviews of medical records and verbal autopsy using validated instruments. All events were coded to the International Classification of Diseases, 10th Revision (ICD-10) by trained staff blinded to baseline information.

In the present analysis, IHD and IS were defined by code I20 to I25 and I63, respectively. For T2DM, we included cases coded as E11 and E14. Other cases clearly defined as non-T2DM were excluded. Since 2014, medical records of incident IHD and IS cases were retrieved and reviewed by qualified cardiovascular specialists blinded to study assay. By October 2018, of 33 515 retrieved medical records of IHD cases and 34 758 retrieved medical records of IS cases, the diagnosis was confirmed in 87.9% of IHD cases and 91.5% of IS cases. The medical records of a random sample of 831 diabetic cases were retrieved and reviewed, of which 98.6% were confirmed for diagnosis. Therefore, we did not conduct further adjudication for diabetes.

Statistical methods

Participants were considered at risk from the enrollment to death, loss to follow-up, or Dec 31, 2017, whichever came first. Changes of dichotomized lifestyles by the number of CMD occurred between 2004-08 baseline and 2013-14 resurvey were analyzed with adjustment for age, sex, and study area, as appropriate (Supplementary methods).

In the following association analyses, age was the time scale, and the models were stratified by age in the 5-y interval and study area, and adjusted for sex, education, marital status, menopausal status (women only), and parental family history of CMM. We first used Cox proportional hazards model to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of high-risk lifestyle factors (individual or combined) with first CMD (FCMD), CMM, and all-cause death. In the analyses of individual lifestyle factors, the model included five lifestyle factors simultaneously. The number of high-risk lifestyle factors was entered the model as a categorical variable, with 0-1 high-risk lifestyle factors being the reference group; this variable was also entered a separate model as an ordinal variable to assess the associations of per 1-factor increase with events of interest.

We further used a multi-state model to assess the role of both individual and combined lifestyle factors in the temporal disease progression from baseline (free of CMD) to FCMD, CMM, and death14. Five transitions were constructed based on the natural history of CMM and previous study3 (**Figure 1**): (A) baseline healthy to FCMD; (B) FCMD to CMM; (C) baseline healthy to death from a disease other than CMD; (D) FCMD to death from any causes; (E) CMM to death from any causes. For participants who entered different stages on the same date, we calculated the entering date of the theoretically prior stage as the entering date of the latter stage minus 0.5-d. For example, for participants who died of FCMD, the date of occurring the FCMD equals the date of death minus 0.5-d.

To show the impact of high-risk lifestyle factors on temporal progression visually, we predicted the probabilities of becoming FCMD survivor, CMM survivor, dying without CMD, dying with FCMD, dying with CMM from the enrollment to the longest follow-up. Probabilities were separately obtained for participants who had 0-1 high-risk lifestyle factors and 5 high-risk lifestyle factors, with all covariates being set to an average level of CKB population in the present analysis.

Several sensitivity analyses for the multi-state analyses were conducted: (1) calculating the entering date of the prior stage using different time intervals (0.5-d, 0.5-y, 1-y, 3-y, 5-y) for participants who entered different stages on the same day; (2) additionally adjusting for hypertension at baseline; (3) including participants who had previously diagnosed heart disease, stroke, or diabetes, and assigning them to FCMD or CMM stage according to their CMD status at baseline; (4) excluding the events occurring in the first two years follow-up; (5) in addition to the predefined five transitions, adding another transition from the baseline directly to CMM.

The multi-state analyses were further stratified according to sex, age, residence area, family history of CMD, and hypertension. The interactions were tested by using the likelihood ratio test comparing models with and without a cross-product term.

All statistical tests were two-tailed, and P<0.05 indicated statistical significance. The multi-state model was performed using R (version 3.5.3), and all other statistical analyses were performed using Stata (version 14, StataCorp).

Results

The mean age of 461 047 participants was 51.2±10.5 years. Of those, 41.0% were male, and 42.3% were urban population. During a median follow-up of 11.2 years (interquartile range 10.2-12.1 years; total person-years [PYs] 5 032 900), 82 060 participants experienced at least one CMD, with a crude incidence rate of CMD 175.07 per 10 000 PYs (Figure 1). Of all the incident CMD patients, 13 303 (transition B, 434.58/10 000PYs) developed CMM, and afterward, 2 627 (transition E, 666.37/10 000PYs) died from any causes; 11 243 (transition C, 367.29/10 000PYs) died without experiencing CMM. Overall, men were more likely than women to have high-risk lifestyles, with 55.4% of men and 17.1% of women having three or more high-risk lifestyle factors (**Supplementary Table 1 and Table 2**). Participants with CMM who survived or died afterward were more likely to be older, urban residences, hypertensive, and have more high-risk lifestyle factors. Among 22 965 participants who participated in both the 2004-08 baseline and 2013-14 resurvey, most had not changed their risk level of lifestyles. Participants between different CMD status group exhibited no distinct difference in the changes of lifestyles (**Supplementary Table3**).

Cox regression analyses

All five high-risk lifestyle factors were associated with increased risk of FCMD, CMM, and all-cause death (**Table 1**). Body shape defined by BMI and waist circumference had the strongest associations with both FCMD and CMM (HRs [95%CIs]: 1.42 [1.40-1.44] and 1.64 [1.58-1.70]). While smoking had the strongest association with death, with HR (95%CI) of 1.35 (1.31-1.38). Upward trends were observed for risks of FCMD, CMD, and death with an increasing number of high-risk lifestyle factors; the corresponding HRs (95%CIs) per 1-factor increase was 1.20 (1.19-1.21), 1.29 (1.27-1.32), and 1.23 (1.21-1.24). Generally, the effect estimates of association were slightly stronger for CMM than that for FCMD.

Multi-state analyses

Multi-state analyses got the same result for the transition from baseline (free of CMD) to FCMD as Cox regression analyses, but further decomposed the roles of high-risk lifestyle factors in the temporal trajectories of CMM (**Figure 2**). The impacts of smoking, unhealthy dietary habits, and unhealthy body shape on the transition to FCMD were stronger than that on the transition to subsequent CMM. The effect estimates of five lifestyle factors were similar for the transition from FCMD to death and that from CMM to death. Besides, the strength of associations of smoking, excessive drinking, and physical inactivity with mortality outcome (either from healthy, FCMD, or CMM) was greater than that of incidence outcome. In contrast, the unhealthy body shape was the opposite.

When lifestyle factors were combined, gradients in associations were observed between the number of high-risk lifestyle factors and all five transitions (**Figure 3**). Also, we observed a stronger association of the number of lifestyle factors with the transition from healthy to FCMD versus the subsequent transition to CMM, and similar effect estimates of the associations with mortality outcome (either from FCMD or CMM). In contrast to participants with zero or one high-risk factor, the adjusted HRs (95% CIs) for those with five high-risk factors were 2.21 (2.09, 2.34), 1.65 (1.46, 1.87), 2.11 (1.92, 2.32), 1.60 (1.40, 1.82), and 1.32 (1.00, 1.73) for transitions A – E, respectively.

At the longest follow-up of 13.5 years, given the average level of covariates in the CKB population, 15.2%, 1.7%, and 1.3% of participants with 0-1 high-risk lifestyle factors at baseline were predicted to develop at least one CMD (after that, survived or died), CMM (after that, survived or died), and die with CMD (including FCMD and CMM) (**Figure 4**). In contrast, having five high-risk lifestyle factors approximately doubled the risk of developing CMD (30.6%), tripled the risk of CMM (5.5%), and tripled the risk of death with CMD (4.1%).

The effect estimates for the associations of four or five high-risk lifestyle factors with transitions from baseline to FCMD and from FCMD to CMM were slightly attenuated after additionally adjusting for hypertension. Other sensitivity analyses did not substantially alter the results. (**Supplementary Table 4, Supplementary Table 5**).

Stratified analyses

Although several statistically significant interactions were found in stratified analyses, there was no clinically meaningful difference between predefined groups (**Supplementary Figure 1, Supplementary Figure 2**). Some factors, if indeed modified the associations, had different impacts on five transitions. In contrast, we observed similar impacts of age on the transitions between high-risk lifestyle factors and morbidity transitions. Taking those with 0-1 high-risk lifestyle factors as the reference, the associations of having 4-5 factors with incidence transitions were stronger among younger participants.

Supplementary methods

Changes in lifestyle factors between baseline and resurvey

This analysis was based on the 25 038 participants who participated in the resurvey during 2013-14. We excluded participants who reported medical histories of heart disease (n=712), stroke (n=220), or cancer (n=100) at baseline. We also excluded those who had a self-reported history of diabetes or screen-detected diabetes, defined as measured fasting blood glucose ≥7.0 mmol/L or random blood glucose ≥11.1 mmol/L at baseline (n=1 041). After these exclusions, 22 965 participants remained in the present analysis.

We calculated the difference in total physical activity level (measured by the metabolic equivalent of task hours per day) between the 2004-08 baseline and 2013-14 resurvey. Other lifestyle factors were dichotomized based on the criteria of high-risk lifestyle in the primary analysis. Changes in lifestyle factors between baseline and resurvey were classified into stable (at the same risk level), better (from high-risk to low-risk lifestyle), and worse (from low-risk to high-risk lifestyle). The proportions (95% confidence intervals) of change in lifestyle factors and means (standard deviations) of difference in total physical activity by cardiometabolic disease status at 2013-14 resurvey were calculated using direct standardization to age in the 5-y interval, sex, and study area of CKB population, as appropriate.

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