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Expanded mosaic chromosomal alterations, frailty, and risks of all-cause and cause-specific mortality among Chinese and the UK adults: evidence from two prospective cohorts

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Abstract

Background Mosaic chromosomal alterations (mCAs) served as a novel indicator of genomic aging. We aimed to investigate the association of expanded mCAs (cell fraction ≥ 10%) with all-cause and cause-specific mortality, and to examine the joint effect of expanded mCAs and frailty index (FI), an indicator of phenotypic aging, on mortality in two large prospective cohorts.

Methods A total of 100,237 participants in the China Kadoorie Biobank (CKB) and 456,283 participants in the UK Biobank (UKB) were included, followed till Dec 31, 2023, and Nov 30, 2022, respectively. MoChA pipeline was used to detect expanded mCAs events and the subtypes. FIs were calculated using previously validated equations, with 28 items included in the CKB and 49 items in the UKB, and categorized participants into three groups: robust, prefrail, and frail. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to examine the associations of the expanded mCAs and joint categories of frailty-mCAs with all-cause and cause-specific mortality by using Cox proportional hazards models. The combined effect values of two cohorts were estimated using random-effects models by meta-analysis.

Results The prevalence of expanded mCAs in the CKB and UKB was 2.2% and 3.4%, respectively. After a median follow-up of 17.2 years in the CKB and 13.7 years in the UKB, expanded mCAs carriers had a higher risk of all-cause (HRs [95% CIs]: 1.20 [1.16, 1.24]) and risks of cause-specific mortality (HRs [95% CIs]: 1.27 [1.21, 1.34], 1.13 [1.02, 1.25], and 1.24 [1.12, 1.37] for death from cancers, circulatory diseases, and respiratory diseases, respectively). Such associations largely did not overlap with FI, especially for all-cause and cancer mortality. Joint analyses revealed that individuals with lower frailty level but with expanded mCAs had a comparable and even higher risk of cancer mortality compared to those with higher frailty level but without mCAs. Similar pattern was also found in terms of adjusted 10-year cancer mortality rates.

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Conclusions Our findings suggested that expanded mCAs were significantly associated with all-cause and cause-specific deaths and could serve as a complement to the FI in providing a more comprehensive perspective on mortality risk, especially for cancer mortality.

Keywords Mosaic chromosomal alterations, Frailty index, All-cause death, Cause-specific death, Prospective cohort study

Background

Early detection of subclinical senescence is crucial for empowering personalized preventive strategies for chronic disease and alleviating the escalating disease burden posed by population aging. Evidence suggests that biological age provides a more reliable assessment of human aging compared to chronological age [1–3]. Among the various indicators of biological aging, mosaic chromosomal alterations (mCAs) have been extensively studied in recent years. The peripheral blood mCAs represent a group of large-scale structural alterations detected in a fraction of peripheral leukocytes and serve as an indicator of genomic aging [4, 5]. The proportion of affected cells exceeding 10% signifies the accumulation of such mCAs in leukocytes, a phenomenon known as expanded mCAs [6, 7]. Previous studies have found the associations of mCAs with age-related diseases and all-cause mortality [8–13]. However, few studies have explored its association with cause-specific deaths, particularly among the general population in East Asia.

Phenotypic aging represents another dimension of biological aging, focusing more on the individual's physical characteristics and functioning [1, 14]. The frailty index (FI), a widely utilized method for assessing phenotypic aging, has been validated as a predictor of mortality [15–17]. Mechanistically, genomic aging may be one of the molecular basis of phenotypic aging, while phenotypic aging may in turn exacerbate genomic damage [18, 19]. However, genomic aging is not always accompanied by perceivable phenotypic aging in an individual, and vice versa [20–22]. Therefore, given the assumption of an existing association between mCAs and mortality, we hypothesized that the mCAs, especially expanded mCAs, could complement the FI in population stratification for mortality risk. However, no studies have yet provided relevant evidence.

Therefore, based on the two populations with different genetic and environmental backgrounds, China Kadoorie Biobank (CKB) and UK Biobank (UKB), we aimed to investigate the prospective associations of expanded mCAs with all-cause and cause-specific mortality, and to examine the joint effect of expanded mCAs and FI on mortality.

Methods

Study design

The CKB and UKB are multicenter prospective cohort studies, each enrolling over 500,000 participants. The CKB enrolled adults aged 30–79 years from 5 urban and 5 rural areas across China from 2004 to 2008, while the UKB recruited adults aged 40–69 years recruited between 2006 and 2010 across 22 assessment sites in England, Scotland, and Wales. All participants reported detailed information about their demographics, lifestyles, medical histories, and current medical conditions at enrollment and underwent physical measurements. Blood samples were collected for all participants at baseline. Further details of the CKB and UKB have been described elsewhere [23–25].

Both one-fifth of the CKB participants and almost all the UKB participants were genotyped using two Affymetrix arrays customized for each respective cohort [26, 27]. The initial CKB array selected ~ 33,000 participants as a nested case–control study, including ~ 14,000 cardiovascular disease (CVD) cases, ~ 5000 chronic obstructive pulmonary disease (COPD) hospitalizations, ~ 10,000 CVD controls, and ~ 4000 randomly selected individuals who had attended the second resurvey. The updated CKB array included a further ~ 72,000 randomly selected samples [26].

Detection of expanded mCAs

Detection of the mCAs in the CKB and UKB has been described previously [8, 28]. Mosaic Chromosomal Alterations (MoChA) pipeline [8, 29] (https://github.com/freeseek/mocha) was followed to detect mCAs events, including mCAs on autosomes (categorized into three subtypes: copy-neutral loss of heterozygosity [CN-LOH], gain, and loss), and the loss of X and Y chromosomes (LOX/LOY). In brief, the log R ratio (LRR) and B-allele frequency (BAF) were calculated based on genotyping intensity data and Eagle2 [30] was used for long-range phasing. The mCAs calling process was based on phased genotypes and detected BAF imbalances across haplotypes, which enhanced the detection of mCAs at low cell fractions. The cell fractions for each mCAs event were estimated based on the deviation of the BAF from 0.5, except in cases where algorithmic issues prevented

such estimation. Participants with cell fraction of any mCAs ≥ 10% were considered as expanded mCAs carriers, indicating amplified mutations [6, 7].

We included 100,298 individuals who had baseline data and passed the genotyping quality control procedure in the CKB [26, 28]. A total of 482,413 participants from the updated mCAs dataset (Return ID 3094 generated from UKB application 19808[14]) were included. Participants who had missing data, implausible data, or loss to follow-up (detailed exclusion criteria are shown in Additional file 1: Fig. S1) were further excluded. Finally, 100,237 participants in the CKB and 456,283 participants in the UKB were included in the current study.

Construction of frailty index

The frailty statuses of the study participants were assessed using FIs that were previously constructed and validated following a standard procedure in the CKB and UKB, respectively [31, 32]. Based on the cumulative deficit model of frailty [33], items of deficits were given a value between 0 (no deficits) to 1 (deficits). The FIs were calculated as the ratio of the sum of deficit values to the total number of deficit items. In the CKB study, we used 28 health-related variables obtained from the baseline survey (Additional file 1: Table S1) to calculate the FI, which categorized participants into three groups: robust (FI ≤ 0.1), prefrail (0.1 < FI < 0.25), and frail (FI ≥ 0.25). In the UKB study, 49 baseline variables were identified as FI items (Additional file 1: Table S2), and cut-offs of 0.12 and 0.24 were used to divide participants into the same 3 categories as the CKB [34, 35]. For each participant, a deficit with a missing value was excluded from both the numerator and the denominator.

Ascertainment of deaths

The vital statuses of CKB participants were followed up using linkage to national death registry systems, with annual active follow-up until Dec 31, 2023. Causes of death were further supplemented by medical records reviews and verbal autopsies using validated instruments. Detailed death data for UKB participants before Nov 30, 2022, were received from National Health Service (NHS) England for participants in England and Wales and the NHS Central Register for participants in Scotland. All deaths were coded according to the 10th revision of the International Classification of Diseases (ICD-10). The primary outcomes were all-cause mortality and cause-specific mortality, including cancers (C00–C97), circulatory diseases (I00–I99), respiratory diseases (J00–J99), solid cancers (C00–C80, C97), and hematological malignancies (C81–C96). These causes accounted for approximately 85% and 75% of all deaths in the CKB and UKB populations, respectively (Additional file 1: Table S3).

Statistical analysis

Person-years at risk were calculated from the enrollment to the earliest occurrence of death, loss to follow-up, or global censoring. We used stratified Cox proportional hazard models, with age as the underlying time scale, to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of expanded mCAs with risks of all-cause and cause-specific mortality. Participants without expanded mCAs were the reference groups. Models were stratified by age group (every 5 years), gender (male; female), and study region (CKB: 10 regions; UKB: 3 assessment centers) and were adjusted for ethnicity (only in UKB: white; mixed; Asian; black; others), genotyping sampling group (only in CKB: CVD cases; COPD cases; CVD controls; randomly selected individuals for the initial array; randomly selected individuals for the updated array), genotyping array (two types), top 10 principal components (continuous), sociodemographic characteristics (CKB: occupation [agricultural or industrial; retirement; non-agricultural or industrial; others], highest education [primary school or lower; middle or high school; college or higher], and household income [< 10,000 yuan; 10,000–19,999 yuan; ≥ 20,000 yuan]; UKB: multiple deprivation index [continuous]), tobacco smoking (non-smoker; former smoker who had stopped for reasons other than illness; and current smoker or former smoker who had stopped because of illness), alcohol consumption (non-drinker; former drinker; weekly drinker but not daily; daily drinker), and healthy diet habits (yes: eating vegetables or fruits every day and not eating red meat every day; no). Details of the CKB and UKB baseline survey questionnaire are available online [36, 37]. A meta-analysis combining the CKB and UKB results was conducted to estimate the effects using random-effects models, and *P* values for heterogeneity between the two cohorts were reported.

Stratified analyses were conducted to estimate whether the associations between expanded mCAs and mortality differed across frailty status. Similarly, we performed heterogeneity tests between the different frailty groups and provided the combined HRs and 95% CIs of two populations for each group. To investigate the effect modification of frailty in the associations of expanded mCAs with mortality, we estimated the additive and multiplicative interactions between frailty status and expanded mCAs separately among the two populations. We further conducted joint analyses by categorizing participants into six groups based on frailty and mCAs status, with robust participants without expanded mCAs as the reference group.

The distributions of time-to-death by frailty status and joint groups were separately presented using adjusted

survival curves. Using direct standardization, survival curves were adjusted for age, gender, and study regions. To take competing risks into account, cause-specific Cox regression models were used.

Sensitivity analyses were conducted in a subcohort of the CKB, in which participants who were selected for genotyping as COPD or CVD cases were excluded ($n = 19{,}173$). All tests were two-tailed, and $P < 0.05$ was considered significant. Statistical analyses and plots were conducted using R (v4.3.3). Specifically, the R packages "*survival*," "*riskRegression*," "*adjustedCurves*," and "*meta*" were employed to conduct Cox regression analyses, cause-specific Cox regression analyses, adjusted survival probability analyses, and meta analyses, respectively. We tested multiplicative and additive interactions using the "*lmtest*" and "*interactionR*" packages, respectively. Additionally, the R packages "*ggplot2*" and "*forestplot*" were used to draw forest plots and adjusted survival curves.

Results

Study population and expanded mCAs distribution

The mean age at the enrollment was 53.7 ± 11.0 years for the 100,237 participants in the CKB and 56.6 ± 8.1 years for the 456,283 participants in the UKB, respectively. The corresponding proportions of male were 42.7% and 45.8%. A total of 2152 (2.2%) participants in the CKB population were identified as expanded mCAs carriers, while 15,443 (3.4%) individuals carried expanded mCAs in the UKB, accounting for 37.1% and 22.6% of all carriers in each population (Tables 1 and 2, Additional file 1: Table S4). Expanded mCAs carriers in both populations were found to be older, more likely to be male, and current smokers compared to participants without expanded mCAs (Tables 1 and 2). Additionally, retired participants and former drinkers had a higher prevalence of expanded mCAs in the CKB (Table 1). The white, more deprived, daily drinkers, and participants without a healthy diet among the UKB population were more likely to be expanded carriers (Table 2). Furthermore, there was a significant increase in the prevalence of expanded mCAs with advancing frailty status in the UKB (P for trend < 0.001). A similar trend could be observed in the CKB though the statistical test was not significant (P for trend = 0.298). No significant association was found between expanded mCAs and frailty status in the multinomial logistic regression analysis (Additional file 1: Table S5). Baseline characteristics stratified by frailty status for two cohorts were shown in Additional file 1: Tables S6 and S7.

Associations of expanded mCAs with death

The median (interquartile range) follow-ups of the CKB and UKB were 17.2 (15.7–18.2) and 13.7 (13.0–14.4) years, respectively. In the CKB, a total of 25,966 deaths (25.9% of the 100,237 participants) were identified, including 5484 (21.1%) from cancers, 13,641 (52.5%) from circulatory diseases, and 3194 (12.3%) from respiratory diseases. The UKB recorded 39,418 deaths (8.6% of the 456,283 participants), with 19,117 (48.5%) from cancers, 8257 (20.9%) from circulatory diseases, and 2814 (7.1%) from respiratory diseases (Additional file 1: Table S3).

The associations of expanded mCAs with both all-cause and cause-specific mortality were consistent across the two cohort. The combined HR (95% CI) for all-cause mortality was 1.20 (1.16, 1.24). For mortality from other specific causes, HRs (95% CIs) were (from the strongest to the weakest) 1.27 (1.21, 1.34) for cancers, 1.24 (1.12, 1.37) for respiratory diseases, and 1.13 (1.02, 1.25) for circulatory diseases (Table 3). Associations of chromosome-specific expanded mCAs and three autosomal mCAs subtypes with all-cause and cause-specific mortality were shown in Additional file 1: Tables S8–S10. In brief, the elevated mortality risk associated with autosomal mCAs was primarily driven by circulatory and respiratory diseases, while LOY and LOX were mainly associated with respiratory diseases and cancers mortality, respectively. As for specific autosomes, expanded mCAs on chr13, chr12, and chr8 showed the strongest associations with cancer, circulatory, and respiratory mortality, respectively, with consistent effects across both cohorts (P for heterogeneity > 0.05). Subtype-specific analyses revealed that CN-LOH and loss were primarily associated with circulatory mortality, whereas gain increased risks of both cancer and circulatory deaths. We further subclassified cancer mortality into solid cancer mortality and hematological malignancy mortality and found that expanded mCAs were associated with increased risks of both. As expected, the associations were stronger for hematological malignancies in both CKB and UKB (Additional file 1: Table S11).

The stratified analyses by frailty status indicated that (Fig. 1, Additional file 1: Table S12), among the UKB population, expanded mCAs were significantly associated with all-cause mortality in each frailty status, with approximate effect values (P for heterogeneity = 0.351). While in the CKB, the elevated risks were only observed in prefrail and frail population (P for heterogeneity = 0.049). For cause-specific death, the association pattern in the two cohort for cancer mortality was similar with that for all-cause mortality. No replicated significant associations were found between the two populations for circulatory disease mortality, and for respiratory diseases mortality, a consistent significant association was observed only in the robust population. Sensitivity analyses in the subcohort of the CKB were not materially altered (Additional file 1: Table S13).

Table 1 Baseline characteristics of CKB participants ($n = 100,237$) by expanded mCAs status

	With expanded mCAs ($N = 2152$) *n* (%)	Without expanded mCAs ($N = 98,085$) *n* (%)	*P*
Age, mean ± s.d	59.9 ± 11.2	53.6 ± 11.0	< 2E − 16
Gender			
Male	1401 (3.3)	41,425 (96.7)	< 2E − 16
Female	751 (1.3)	56,660 (98.7)	
Region			
North area	851 (2.0)	41,844 (98.0)	
South area	1301 (2.3)	56,241 (97.7)	0.073
Highest education			
Primary school or lower	1204 (2.3)	52,038 (97.7)	
Middle or high school	807 (2.0)	40,230 (98.0)	0.576
College or higher	141 (2.4)	5817 (97.6)	0.870
Occupation			
Agricultural or industrial	921 (1.7)	51,835 (98.3)	
Retirement	762 (4.0)	18,459 (96.0)	1.18E − 07
Non-agricultural or industrial[a]	366 (1.7)	21,037 (98.3)	0.917
Others[b]	103 (1.5)	6754 (98.5)	0.393
Household income			
< 10,000 yuan	664 (2.1)	30,424 (97.9)	
10,000–19,999 yuan	657 (2.2)	29,467 (97.8)	0.655
≥ 20,000 yuan	831 (2.1)	38,194 (97.9)	0.729
Smoking status			
Non-smoker	1036 (1.6)	64,755 (98.4)	
Former smoker	115 (3.6)	3103 (96.4)	0.598
Current smoker[c]	1001 (3.2)	30,227 (96.8)	0.003
Alcohol consumption			
Non-drinker	1528 (1.9)	78,669 (98.1)	
Former drinker	211 (4.6)	4409 (95.4)	1.52E − 04
Weekly drinker but not daily	127 (2.2)	5721 (97.8)	0.535
Daily drinker	286 (3.0)	9286 (97.0)	0.859
Healthy diet[d]			
No	793 (2.3)	33,901 (97.7)	
Yes	1359 (2.1)	64,184 (97.9)	0.382
Frailty status[e]			
Robust	971 (1.8)	53,004 (98.2)	
Prefrail	1071 (2.5)	41,546 (97.5)	0.356
Frail	110 (3.0)	3535 (97.0)	0.467

All *P* values were adjusted for age (continuous), gender (male, female), and 10 study regions in CKB using logistic regression, as appropriate. [a]Non-agricultural or industrial workers included administrator, professional and technical workers, sales and service staff, and domestic workers. [b]Other workers included self-employed, unemployed, and others who could not be classified into any other groups. [c]Current smokers included former smokers who had stopped smoking because of illness. [d]A healthy diet referred to eating vegetables or fruits every day and not eating red meat every day. [e]The *P* value for linear trend test (adjusted for age, gender, and regions) of the expanded mCAs prevalence across frailty status was 0.298

CKB China Kadoorie Biobank, *mCAs* mosaic chromosomal alterations

Joint effects of expanded mCAs and frailty status

We also estimated the joint effects of expanded mCAs and FI on the mortality, with the risks of all-cause and cause-specific mortality increased as both mCAs-related risk and frailty-related risk increased (Fig. 2, Additional file 1: Table S14). In both CKB and UKB, positive additive interactions were observed between expanded mCAs and prefrailty on all-cause mortality, with relative excess risk due to interaction (RERI) was 0.22 (95% CI: 0.02, 0.41) and attributable proportion due to interaction (AP) was 0.12 (0.01, 0.21) in the CKB, and the corresponding values were 0.16 (0.05, 0.27) and 0.09 (0.03,

Table 2 Baseline characteristics of UKB participants ($n=456,283$) by expanded mCAs status

	With expanded mCAs ($N=15,443$) *n* (%)	Without expanded mCAs ($N=440,840$) *n* (%)	*P*
Age, mean ± s.d	63.0 ± 5.5	56.3 ± 8.1	< 2E − 16
Gender			
Male	13,368 (6.4)	195,746 (93.6)	< 2E − 16
Female	2075 (0.8)	245,094 (99.2)	
Assessment center			
England	13,729 (3.4)	389,752 (96.6)	
Scotland	1077 (3.2)	32,648 (96.8)	0.690
Wales	637 (3.3)	18,440 (96.7)	0.217
Ethnicity			
White	15,021 (3.5)	416,242 (96.5)	
Mixed	48 (1.9)	2521 (98.1)	0.781
Asian	172 (1.8)	9566 (98.2)	2.74E − 09
Black	80 (1.2)	6791 (98.8)	1.16E − 06
Others	122 (2.1)	5720 (97.9)	0.001
Multiple deprivation index, mean ± sd	17.2 ± 14.0	17.1 ± 13.9	6.42E − 07
Smoking status			
Non-smoker	5478 (2.2)	245,060 (97.8)	
Former smoker	6163 (4.2)	139,737 (95.8)	< 2E − 16
Current smoker[a]	3802 (6.4)	56,043 (93.6)	< 2E − 16
Alcohol consumption			
Non-drinker	2932 (2.4)	119,483 (97.6)	
Former drinker	597 (3.7)	15,466 (96.3)	0.001
Weekly drinker but not daily	7292 (3.2)	217,098 (96.8)	0.177
Daily drinker	4622 (4.9)	88,793 (95.1)	1.38E − 13
Healthy diet[b]			
No	606 (4.6)	12,675 (95.4)	
Yes	14,837 (3.3)	428,165 (96.7)	3.22E − 06
Frailty status[c]			
Robust	7918 (3.1)	247,671 (96.9)	
Prefrail	6246 (3.7)	162,619 (96.3)	0.008
Frail	1279 (4.0)	30,550 (96.0)	2.24E − 04

All *P* values were adjusted for age (continuous), gender (male, female), and 3 assessment centers of UKB using logistic regression, as appropriate. [a]Current smokers included former smokers who had stopped smoking because of illness. [b]A healthy diet referred to eating vegetables or fruits every day and not eating red meat every day. [c]The *P* value for linear trend test (adjusted for age, gender, and assessment centers) of the expanded mCAs prevalence across frailty status was 5.11E − 05

UKB UK Biobank, *mCAs* mosaic chromosomal alteration

0.15) in the UKB. A positive additive interaction was also found between mCAs and frailty on all-cause mortality in the CKB (RERI [95% CI] = 0.70 [0.07, 1.46]; AP [95% CI] = 0.21 [0.01, 0.35]). Multiplicative interaction was significant only for respiratory disease mortality in the UKB ($P=0.019$) (Additional file 1: Table S15).

The survival probability of expanded mCAs carriers (darker solid lines) decreased more rapidly over time in comparison to participants without expanded mCAs (lighter solid lines) across all frailty categories (Fig. 3). Also, adjusted 10-year all-cause mortality rates among expanded mCAs carriers within each frailty groups were higher than participants without expanded mCAs (Additional file 1: Table S16).

Notably, joint analyses suggested that expanded mCAs carriers have a nominally higher risk of cancer mortality compared to those who had higher frailty levels but without expanded mCAs (Fig. 2, Additional file 1: Table S14). Adjusted cancer survival curves illustrated that, in both populations, the absolute risks of cancer mortality among individuals with lower frail levels but with mCAs were comparable to that among individuals with higher frail levels but without mCAs (Fig. 3). Similar pattern was also found in terms of adjusted 10-year cancer mortality

Table 3 Associations of expanded mCAs with all-cause and cause-specific deaths among CKB and UKB population

	No. expanded mCAs/*N*	All-cause deaths		Cancers		Circulatory diseases		Respiratory diseases	
		No. deaths (crude mortality)	HRs (95% CIs)	No. deaths (crude mortality)	HRs (95% CIs)	No. deaths (crude mortality)	HRs (95% CIs)	No. deaths (crude mortality)	HRs (95% CIs)
CKB	2152/100,237	25,966 (16.77)	1.19 (1.12, 1.27)	5484 (3.54)	1.25 (1.08, 1.44)	13,641 (8.81)	1.19 (1.09, 1.30)	3194 (2.06)	1.20 (1.01, 1.42)
UKB	15,443/456,283	39,418 (6.45)	1.20 (1.16, 1.25)	19,117 (3.13)	1.28 (1.21, 1.35)	8257 (1.35)	1.08 (0.99, 1.17)	2814 (0.46)	1.27 (1.12, 1.44)
Combined	–	–	1.20 (1.16, 1.24)	–	1.27 (1.21, 1.34)	–	1.13 (1.02, 1.25)	–	1.24 (1.12, 1.37)
P for heterogeneity	–	–	0.848	–	0.750	–	0.102	–	0.597

The crude mortality rates referred to the number of deaths in the given population per 1000 person-years. Cox proportional hazard models were stratified by age in the 5-year interval, gender (male and female), and region (10 regions in CKB and 3 assessment centers in UKB), and adjusted for ethnicity (only in UKB), genotyping sampling group (only in CKB), genotyping array, top 10 principal components, sociodemographic characteristics (occupation, highest education, and household income in CKB, multiple deprivation index in UKB), tobacco smoking, alcohol consumption, and diet habits. The combined HRs were derived from meta-analysis using random effect models

mCAs mosaic chromosomal alterations, *HR* hazard ratios, *CI* confidence interval, *CKB* China Kadoorie Biobank, *UKB* UK Biobank

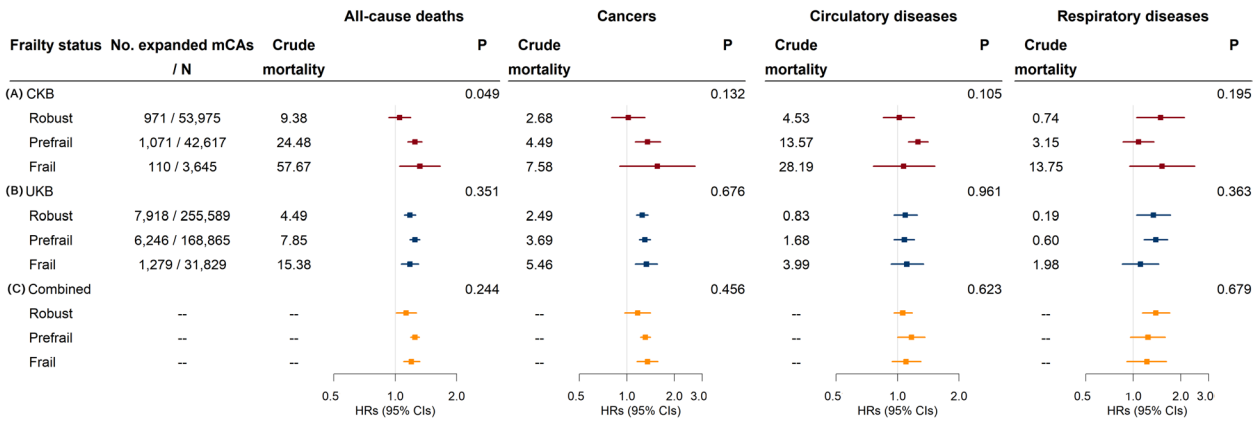

Fig. 1 Associations of expanded mCAs with all-cause and cause-specific deaths by frailty status among (**A**) CKB, (**B**) UKB, and (**C**) combined population. The crude mortality rates referred to the number of deaths in the given population per 1000 person-years. Adjusted covariates in the models were consistent with models in Table 3

rates, especially for hematological malignancy: significant differences were observed in the UKB (0.42% vs. 0.23% [robust and mCA + vs. prefrail and mCA −]; 0.58% vs. 0.28% [prefrail and mCA + vs. frail and mCA −]), with marginally significant differences in CKB (Table 4, Additional file 1: Tables S17 and S18). These findings were not observed for deaths related to cardiovascular and respiratory diseases (Figs. 2 and 3, Additional file 1: Table S16).

Discussion

In the current study of two community-based population from China and the UK, we found that expanded mCAs, an indicator of genomic aging, was significantly associated with increased risks of all-cause, cancer, circulatory, and respiratory diseases mortality. Besides, such associations showed minimal overlap with FI, an indicator of phenotypic aging, especially for all-cause mortality and death from cancers. More importantly, we noted that, compared with individuals with higher frailty level but without expanded mCAs, individuals with lower frailty level but with mCAs had a comparable and even higher risk of any cancers, solid and hematological malignancies mortality.

The mCAs represented a manifestation of cellular genomic instability and a hallmark of premature cellular aging [18]. The mCAs has been associated with increased risks of a range of age-related adverse health outcomes [13], which could potentially elevate the mortality risk for carriers. Evidence suggested that the association between mCAs and mortality varied across populations with different affected cell proportion [9, 12]. Sano et al. observed a 1.31-fold risk of circulatory disease mortality among LOY carriers with cell fractions ≥ 40% based on the UKB male population and

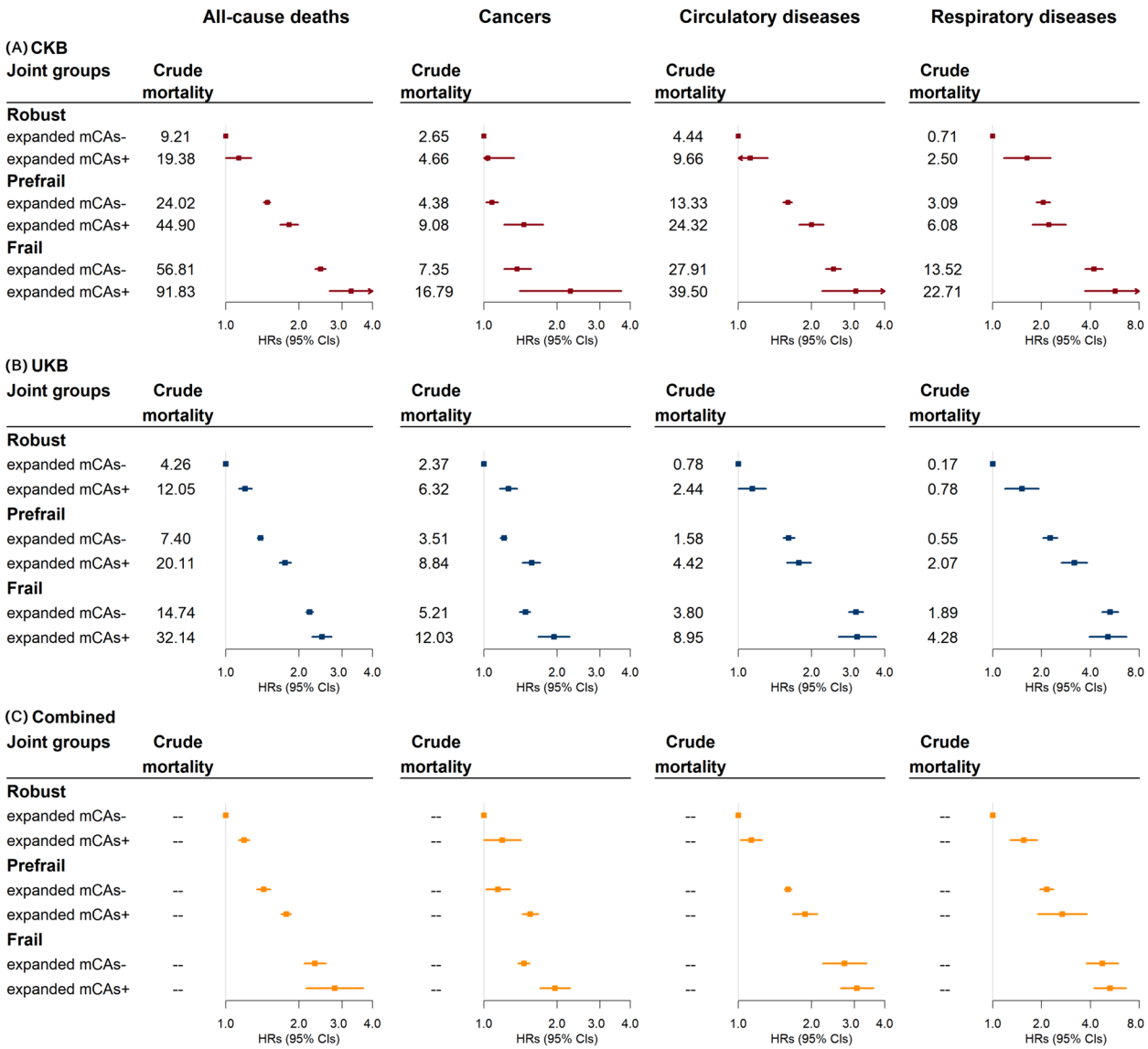

Fig. 2 Forest plot of all-cause and cause-specific deaths according to joint groups of frailty status and expanded mCAs among (**A**) CKB, (**B**) UKB, and (**C**) combined population. The crude mortality rates referred to the number of deaths in the given population per 1000 person-years. Adjusted covariates in the models were consistent with models in Table 3

validated this process in mice [38]. In the current study, we focused on mCAs with cell fractions ≥ 10% and validated its previously reported associations with the increased risks of all-cause mortality and cancer mortality [8–12, 39, 40] in a Chinese population. Limited evidence exists on mortality from cardiovascular and respiratory diseases, with no association between autosomal mCAs and cardiovascular mortality (including coronary artery disease and ischemic stroke) observed in the BioBank Japan study [9]. Our study found a significant association of expanded autosomal mCAs with death from any circulatory diseases in both the Chinese and UK populations (Additional file 1: Table S8). Subtype-specific analyses further demonstrated significant combined associations for all three subtypes (loss, gain, and CN-LOH) across the two populations (Additional file 1: Table S10). A marginal association of expanded LOY and circulatory disease mortality was observed, while no significant association was found for LOX. The observed divergent associations might stem from differences in the gene functions affected by specific mCAs and sex-specific mechanisms of immune modulation. For instance, autosomal mCAs involve key inflammatory genes such as *TET2* (on chr4) and *JAK2* (on chr9).

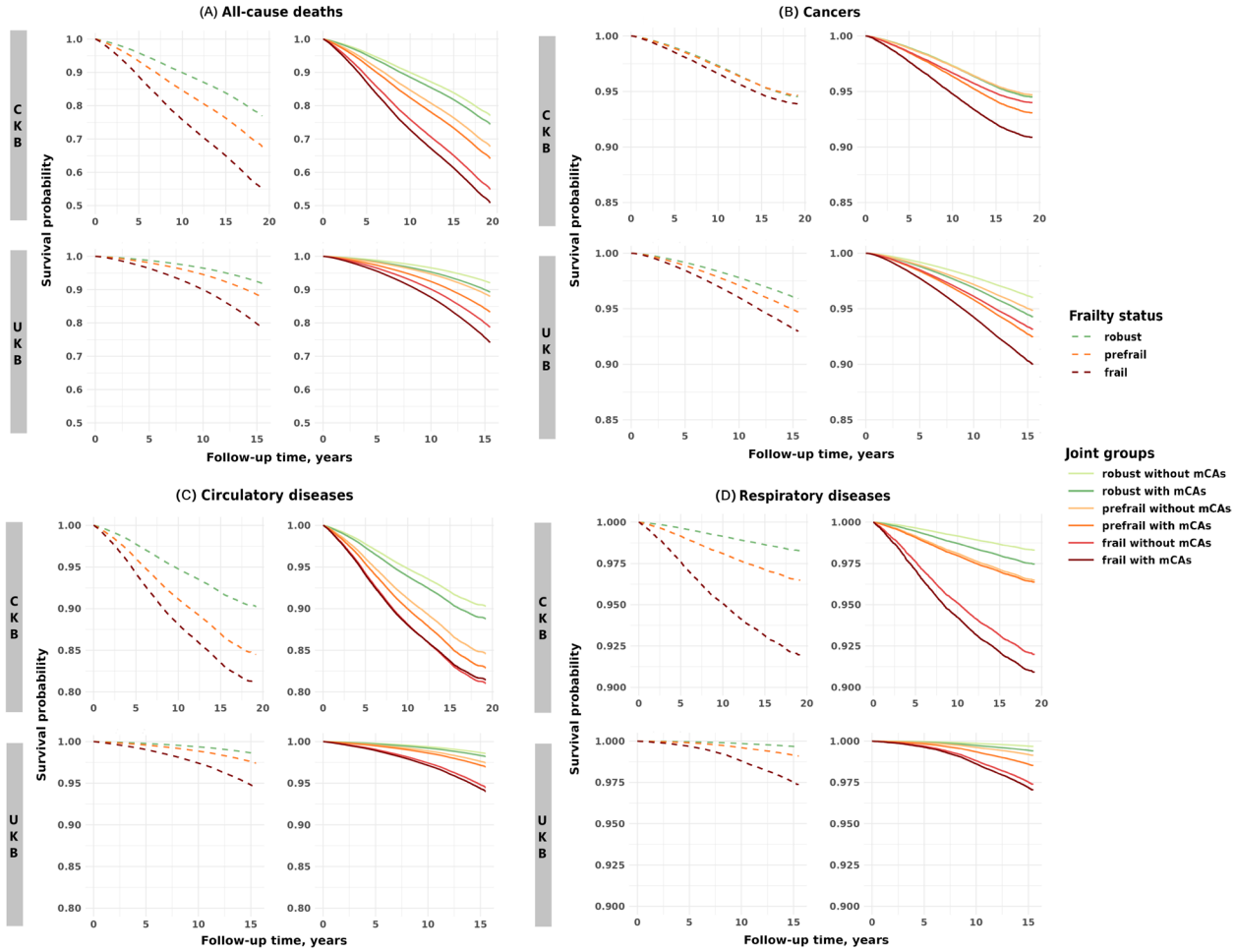

Fig. 3 Adjusted survival curves for (**A**) all-cause and (**B**–**D**) cause-specific deaths stratified by frailty status and frailty-mCAs joint groups among CKB and UKB population. Cause-specific Cox regression models were developed for cause-specific deaths, to account for competing risks. All models were adjusted for age in the 5-year interval, gender (male and female), and regions (10 regions in CKB and 3 assessment centers in UKB). Adjusted survival curves were estimated and depicted using direct standardization by frailty status (dotted lines) and frailty-mCAs joint groups (solid lines), respectively. mCAs, mosaic chromosomal alterations; CKB, China Kadoorie Biobank; UKB, UK Biobank

Consistently, significant associations between these two chromosomes with circulatory mortality were observed in this study (Additional file 1: Table S9). While LOY carries genes critical for maintaining cellular function and suppressing inflammation, such as the Y-linked gene (*UTY*) [41], the phenotypic impact of LOX, however, is often obscured by the compensatory mechanism of random X-chromosome inactivation in females, making its association more challenging to detect in large-scale cohorts [42]. In addition, the present study provided novel evidence on the association between expanded mCAs and death from respiratory diseases, one of the prominent cause of death in low- and middle-income countries [43, 44].

Another important dimension of biological aging, the FI, was a well-established predictor of all-cause mortality that could reflect phenotypic aging [16, 17, 32]. Although the FI has already included numerous clinically health-related items, we still revealed associations between expanded mCAs and all-cause death in both prefrail and frail individuals, indicating that genomic aging and phenotypic aging had largely distinct effects with minimal overlap. Among population with perceptible similar frailty conditions, detecting imperceptible expanded mCAs could further identify population with higher risk of death.

Previous studies also found significantly higher risks of cause-specific mortality in prefrail and frail population [16, 45]. However, these associations exhibited variation across different causes of death. A meta-analysis pooled 56 prospective cohort studies or clinical trials reported that frail adults had a significantly higher risk of mortality from CVD, respiratory illness, and cancer, with the HRs (95% CIs) of 2.64 (2.20, 3.17), 4.91 (2.97, 8.12), and 1.97

Table 4 Adjusted 10-year cancer mortality rates (%) and 95% CIs by frailty status and frailty-mCAs joint groups among CKB and UKB population

Groups		Any cancers		Solid cancers		Hematological malignancies	
		Adjusted mortality (95% CIs), %		Adjusted mortality (95% CIs), %		Adjusted mortality (95% CIs), %	
CKB							
Robust	mCAs −	2.66 (2.53, 2.79)	2.65 (2.52, 2.79)	2.53 (2.40, 2.65)	2.53 (2.40, 2.66)	0.13 (0.10, 0.16)	0.12 (0.10, 0.15)
	mCAs +		2.72 (2.10, 3.34)		2.44 (1.85, 3.03)		0.27 (0.07, 0.48)
Prefrail	mCAs −	2.75 (2.63, 2.87)	2.72 (2.59, 2.84)	2.63 (2.51, 2.75)	2.60 (2.48, 2.72)	0.12 (0.09, 0.15)	0.12 (0.09, 0.14)
	mCAs +		3.63 (3.01, 4.26)		3.35 (2.75, 3.95)		0.30 (0.09, 0.50)
Frail	mCAs −	3.39 (3.01, 3.77)	3.33 (2.94, 3.71)	3.26 (2.89, 3.64)	3.20 (2.82, 3.57)	0.12 (0.05, 0.20)	0.13 (0.05, 0.21)
	mCAs +		5.21 (2.97, 7.46)		5.16 (2.94, 7.38)		< 0.01
UKB							
Robust	mCAs −	2.19 (2.14, 2.25)	2.14 (2.09, 2.19)	2.00 (1.95, 2.05)	1.96 (1.91, 2.01)	0.20 (0.18, 0.21)	0.18 (0.17, 0.20)
	mCAs +		3.11 (2.88, 3.35)		2.66 (2.44, 2.88)		0.42 (0.33, 0.51)
Prefrail	mCAs −	2.89 (2.82, 2.96)	2.81 (2.74, 2.88)	2.64 (2.57, 2.70)	2.58 (2.52, 2.65)	0.25 (0.23, 0.27)	0.23 (0.21, 0.25)
	mCAs +		4.19 (3.88, 4.50)		3.55 (3.26, 3.84)		0.58 (0.47, 0.70)
Frail	mCAs −	3.98 (3.82, 4.15)	3.88 (3.71, 4.05)	3.67 (3.51, 3.83)	3.60 (3.44, 3.76)	0.31 (0.26, 0.36)	0.28 (0.23, 0.32)
	mCAs +		5.75 (4.95, 6.55)		4.91 (4.16, 5.66)		0.78 (0.49, 1.07)

Cause-specific Cox regression models were used to account for competing risks. Model adjustments were the same as models in Fig. 3. Adjusted 10-year mortality rates were estimated using direct standardization by frailty status and frailty-mCAs joint groups, respectively

CI confidence interval, *mCAs* mosaic chromosomal alterations, *CKB* China Kadoorie Biobank, *UKB* UK Biobank

(1.50, 2.57), respectively [16]. Similarly, we observed an almost threefold and over a fivefold increased risk of death from circulatory and respiratory diseases respectively among the frail group in both the CKB and UKB populations, whereas the increased risk of cancer mortality was merely 50%, markedly lower than the risks associated with the above causes of death (Additional file 1: Table S19). In contrast, stratified analyses in the current study revealed robust associations of expanded mCAs with death from cancers among prefrail and frail participants, but not from circulatory and respiratory diseases. Cancer is vulnerable to genome instability, with the accumulation of somatic mutations being the underlying mechanism of its development [46, 47]. The relationship between expanded mCAs, a category of somatic mutations with a large impact on genome stability, and cancer mortality has been reported previously; however, no prior studies have investigated the independent effect of mCAs on the FI. Our study suggested that expanded mCAs might compensate for the lack of the traditional FI and provide additional insights on cancer mortality. The additional detection of genomic aging alongside phenotypic aging could identify individuals with biologically accelerated aging more accurately, namely those at higher risk of mortality, and guide preventive interventions and clinical decisions. With the decreasing cost of genotyping and sequencing, such strategies are becoming increasingly cost-effective.

We further explored the effect modification between phenotypic aging and genomic aging and found a possible additive interaction between expanded mCAs and FI for all-cause mortality. The underlying mechanism of this interaction remains unclear; however, the synergistic effect of these two aging on mortality risk may be biologically plausible. The expanded mCAs indicated genomic instability, potentially resulting in protein destabilization, epigenetic alterations, and enhanced the secretion of aging-associated cytokines such as IL-6 and TNF-α [5, 18, 48]. This may accelerate the functional decline and frail status at the organism level. Conversely, frail individuals could be more susceptible to chronic inflammation and immunosenescence that could be exacerbated by mCAs [5, 6], due to biological vulnerability, resulting the increased risks of death from infections and other non-infectious age-related chronic diseases. Specifically, immunosenescence marked by eroded T-cell diversity and exhausted adaptive immunity could be intensified by clonal expansion of immune cells, creating a vicious cycle of immune dysregulation and organismal aging [49]. However, with the limited number of cases, the present study did not observe the mutually validated effect modifications between expanded mCAs and FI in the two study populations for cause-specific deaths. Therefore, further studies are still necessary.

The present study, to the best of our knowledge, was the first to combine FI with expanded mCAs and quantitatively estimated their separate and joint effects on all-cause and multiple cause-specific mortality across two different ethnic populations with wide ranges of

age, diverse geographical regions, and heterogeneous profiles. Moreover, the consistency of these findings across both populations enhanced the generalizability of our conclusions. Our study also came with a number of limitations. First, both the FI and the mCAs status were dynamic states, known to change over time, typically trending towards worsening rather than improvement [50, 51]. Therefore, in our populations with long follow-up periods, estimating the associations of FI and mCAs status solely at baseline might underestimate their associations with mortality. In addition, although we utilized validated FI, the clinical information included in the current index was partially obtained from baseline self-reported questionnaires in both populations, potentially existing recall inaccuracy. Third, even though the present study has been based on two extraordinarily large cohorts, the sample size was still insufficient to further classify the more-nuanced endpoints and explore potential interactions. Further validation should be conducted by other studies.

Conclusions

In conclusion, our study presented evidence from two community-based populations in China and the UK, suggesting that expanded mCAs carriers were at a significantly greater risk of all-cause and cause-specific deaths. Additionally, our results indicated, for the first time, that expanded mCAs might serve as a complementary indicator to the FI, particularly in overcoming its limitation in the estimation of cancer mortality risk. Considering both FI and expanded mCAs might provide a more comprehensive perspective on mortality risk, especially for cancer mortality. Further studies are warranted to replicate the results and investigate the shared and different mechanisms of phenotypic and genomic aging, which is essential for clarifying their causal interplay.

Abbreviations

AP	Attributable proportion due to interaction
BAF	B-allele frequency
CI	Confidence interval
CKB	China Kadoorie Biobank
CN-LOH	Copy-neutral loss of heterozygosity
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
FI	Frailty index
HR	Hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
ID	Identity document
LOX	Loss of X chromosomes
LOY	Loss of Y chromosomes
LRR	Log R ratio
mCAs	Mosaic chromosomal alterations
MoChA	Mosaic chromosomal alterations pipeline
NHS	National Health Service
RERI	Relative excess risk due to interaction
UKB	UK Biobank
ULSAM	Uppsala Longitudinal Study of Adult Men

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04452-w.

Additional file 1: Text S1, Tables S1–S19, and Fig. S1. Text S1 Members of the China Kadoorie Biobank Collaborative Group. Table S1 List of frailty index items included in the CKB. Table S2 List of frailty index items included in the UKB. Table S3 The distribution of death causes among CKB and UKB. Table S4 The number (prevalence) of carriers and expanded mCAs carriers among CKB and UKB. Table S5 Associations of expanded mCAs with frailty status among CKB and UKB. Table S6 Baseline characteristics of CKB participants by frailty status. Table S7 Baseline characteristics of UKB participants by frailty status. Table S8 Associations of expanded mCAs categories with all-cause and cause-specific deaths among CKB and UKB. Table S9 Associations of expanded mCAs on 22 autosomes with all-cause and cause-specific deaths among CKB and UKB. Table S10 Associations of expanded autosomal mCAs subtypes with all-cause and cause-specific deaths among CKB and UKB. Table S11 Associations of expanded mCAs with solid cancers and hematological malignancies by frailty status among CKB and UKB. Table S12 The HRs and 95% CIs of all-cause and cause-specific mortality associated with expanded mCAs by frailty status among CKB and UKB. Table S13 Associations of expanded mCAs with all-cause, cancer, and cause-specific cancer mortality by frailty status in a subcohort of the CKB. Table S14 The HRs and 95% CIs of all-cause and cause-specific deaths according to joint groups of frailty status and expanded mCAs among CKB and UKB. Table S15 Additive and multiplicative interactions between frailty status and expanded mCAs on all-cause and cause-specific deaths among CKB and UKB. Table S16 Adjusted 10-year all-cause, circulatory diseases, and respiratory diseases mortality rates and 95% CIs by frailty status and frailty-mCAs joint groups among CKB and UKB. Table S17 Adjusted 10-year cancer mortality rates and 95% CIs by frailty status and frailty-mCAs joint groups in a subcohort of the CKB. Table S18 Differences and 95% CIs in adjusted 10-year cancer mortality rates between different frailty-mCAs joint groups among CKB and UKB. Table S19 Associations of frailty index with all-cause and cause-specific deaths among CKB and UKB. Fig. S1 Flow chart of the study.

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Authors' contributions

D.S. and M.S. conceived of and designed the paper. L.L., Z.C., and J.C., as the members of the CKB steering committee, designed and supervised the CKB study obtained funding, and, together with J.L., C.Y., P.P., L.Y., I.Y.M., R.G.W., Y.C., H.D., X.Y. and M.W. acquired the data. M.S., Z.S. and Y.Z. analyzed the data, M.S. wrote the first draft of the manuscript. D.S., C.T., G.G. and Y.H. helped to interpret the results, and contributed to the critical revision of the manuscript for important intellectual content and approved the final version. All authors read and approved the final manuscript. D.S. is the guarantor.

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Data availability

The China Kadoorie Biobank (CKB) is a global resource for the investigation of lifestyle, environmental, blood biochemical and genetic factors as determinants of common diseases. The CKB study group is committed to making the cohort data available to the scientific community in China, the UK and worldwide to advance knowledge about the causes, prevention and treatment of disease. For detailed information on what data is currently available to open access users and how to apply for it, visit: https://www.ckbiobank.org/data-access. Researchers who are interested in obtaining the raw data from the China Kadoorie Biobank study that underlines this paper should contact ckbaccess@ndph.ox.ac.uk. This research has been conducted using the UK Biobank Resource under Application Number 86473. The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk).

Declarations

Ethics approval and consent to participate

The CKB complies with all the required ethical standards for medical research on human subjects, approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (Oxford, UK). The UKB study was approved by the National Information Governance Board for Health and Social Care in England and Wales, the Community Health Index Advisory Group in Scotland, and the North West Multicenter Research Ethics Committee. Written informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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