Multimorbidity patterns and association with mortality in 0.5 million Chinese adults

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Abstract

Background: Few studies have assessed the relationship between multimorbidity patterns and mortality risk in the Chinese population. We aimed to identify multimorbidity patterns and examined the associations of multimorbidity patterns and the number of chronic diseases with the risk of mortality among Chinese middle-aged and older adults.

Methods: We used data from the China Kadoorie Biobank and included 512,723 participants aged 30 to 79 years. Multimorbidity was defined as the presence of two or more of the 15 chronic diseases collected by self-report or physical examination at baseline. Multimorbidity patterns were identified using hierarchical cluster analysis. Cox regression was used to estimate the associations of multimorbidity patterns and the number of chronic diseases with all-cause and cause-specific mortality.

Results: Overall, 15.8% of participants had multimorbidity. The prevalence of multimorbidity increased with age and was higher in urban than rural participants. Four multimorbidity patterns were identified, including cardiometabolic multimorbidity (diabetes, coronary heart disease, stroke, and hypertension), respiratory multimorbidity (tuberculosis, asthma, and chronic obstructive pulmonary disease), gastrointestinal and hepatorenal multimorbidity (gallstone disease, chronic kidney disease, cirrhosis, peptic ulcer, and cancer), and mental and arthritis multimorbidity (neurasthenia, psychiatric disorder, and rheumatoid arthritis). During a median of 10.8 years of follow-up, 49,371 deaths occurred. Compared with participants without multimorbidity, cardiometabolic multimorbidity (hazard ratios [HR] = 2.20, 95% confidence intervals [CI]: 2.14–2.26) and respiratory multimorbidity (HR = 2.13, 95% CI:1.97–2.31) demonstrated relatively higher risks of mortality, followed by gastrointestinal and hepatorenal multimorbidity (HR = 1.33, 95% CI:1.22–1.46). The mortality risk increased by 36% (HR = 1.36, 95% CI: 1.35–1.37) with every additional disease.

Conclusion: Cardiometabolic multimorbidity and respiratory multimorbidity posed the highest threat on mortality risk and deserved particular attention in Chinese adults.

Keywords: Multimorbidity; Pattern; Mortality; Chinese

Introduction

Multimorbidity is often defined as the coexistence of two or more chronic diseases in an individual. Although the prevalence of multimorbidity increases with age, it was reported that more than half of people with multimorbidity were <65 years.[1] Multimorbidity leads to increased risk of functional decline,[2] polypharmacy,[3] disability[4] hospitalization,[5] and mortality,[6] posing a heavy medical burden on the health care system. The prevalence of multimorbidity increases with the number of single chronic diseases.

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However, some chronic diseases often do not cluster randomly. Chronic diseases that co-occur may share common underlying risk factors. Alternatively, one disease may arise as the consequence of another chronic condition or treatment.[7,8] Identification of multimorbidity patterns helps provide clues for prevention and treatment of disease as well as improvement of prognosis.

A systematic review of 14 studies conducted in Europe and the US has identified 97 disease patterns.[9] Despite heterogeneity in multimorbidity patterns across studies due to the diversity of the study population, diseases included, and statistical methods, three common multimorbidity patterns were observed, including cardiovascular and metabolic diseases, mental health problems, and musculoskeletal disorders. These findings may not be generalizable to the Chinese population, which has a different disease spectrum from that of the Western population. However, only a few studies have examined multimorbidity patterns in the Chinese population,[10-12] most of which were conducted among older adults.

Existing evidence has shown an increased risk of mortality with an increase in the number of diseases.[2,13,14] However, the single count of diseases may not reflect the impacts of disease severity or disease combinations on mortality risk.[15] Several studies, mainly from the Western population, have found that specific combinations of multimorbidity patterns may show different associations with risks of mortality.[6,8] However, no such evidence was available in the Chinese population.

This study aimed to identify multimorbidity patterns among 0.5 million Chinese middle-aged and older adults and to assess the associations of multimorbidity patterns and the number of chronic diseases with all-cause and cause-specific mortality.

Methods

Ethics approval

Ethics approval was obtained from the Oxford University Tropical Research Ethics Committee (Approval No. 025-04) and the Chinese Center for Disease Control and Prevention Ethical Review Committee (Approval No. 005/2004). All participants provided written informed consent.

Study design and participants

We used data from the China Kadoorie Biobank (CKB). Detailed information on the CKB study has been published elsewhere.[16] In brief, 512,725 participants aged 30 to 79 years were recruited from ten (five urban and five rural) study areas across China during 2004 to 2008. At baseline, an interviewer-administered laptop-based questionnaire survey was undertaken by trained health workers to collect information on sociodemographic factors, dietary and lifestyle factors, personal and family medical history. Physical measurements were undertaken for each participant, and a 10-mL blood sample was collected for long-term storage. Prebronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured by trained staff following standard proce-dures.[17] In the present study, we excluded two participants with missing values for body mass index (BMI), leaving 512,723 participants in the final analysis.

Assessment of chronic disease status

At baseline survey, information about medical history was obtained through self-reported chronic diseases diagnosed by a doctor, supplemented by physical examination or blood test. In this study, we included 15 chronic diseases, namely, hypertension, diabetes, coronary heart disease, stroke or transient ischemic attack, tuberculosis, asthma, chronic obstructive pulmonary disease (COPD), gallstone diseases, peptic ulcer, cirrhosis/chronic hepatitis, chronic kidney disease, cancer, neurasthenia, psychiatric disorder, and rheumatoid arthritis.

Prevalent hypertension was defined as measured systolic blood pressure ≥140 mmHg, or measured diastolic blood pressure ≥90 mmHg, or self-reported doctor-diagnosed hypertension, or self-reported use of antihypertensive medication at baseline. Prevalent diabetes was defined as measured fasting blood glucose ≥7.0 mmol/L, measured non-fasting blood glucose ≥11.1 mmol/L, or self-reported doctor-diagnosed diabetes. Prevalent COPD was defined as the measured ratio of $FEV_1/FVC < 0.7$ or self-reported doctor-diagnosed COPD at baseline. Past year major depression episode (MDE) and generalized anxiety disorder (GAD) at baseline were assessed using the Chinese version of the computerized Composite International Diagnostic Inventory-short form by face-to-face interviews.[18] A psychiatric disorder was defined as a self-reported doctor diagnosed psychiatric disorder, or MDE, or GAD. Participants presented with two or more of the 15 chronic diseases mentioned above were defined as having multimorbidity.

Assessment of covariates

The covariates, including sociodemographic characteristics (age, sex, and education level), lifestyle factors (smoking status; alcohol consumption; dietary intake of fresh fruits, vegetables, and red meat; and physical activity), were gathered by baseline questionnaire. Information on physical activity was obtained by asking participants about their usual type and duration of activities in occupational, commuting, domestic, and leisure-time related domains in the past 12 months.[19] Total physical activity level was calculated by multiplying the metabolic equivalent tasks (METs) value for each activity by hours spent on that activity per day and summing the MET-hours for all activities. Trained staff measured weight, height, and waist and hip circumference by using calibrated instruments. BMI was calculated as weight in kilograms divided by height in meters squared.

Ascertainment of mortality

The death information of cohort members during follow-up was mainly obtained from linkages with China's Disease Surveillance Points system[20] death registries and local residential records, supplemented by active confir-

mation by visiting community. The causes of death were coded by the International Classification of Diseases tenth revision (ICD-10). The primary outcome used in this study was death from all causes. The secondary outcomes were cause-specific deaths from cardiovascular diseases (CVD, ICD-10 codes: I20–I25, I60–I69), respiratory diseases (J00–J99), cancer (C00–C97), and other causes.

Statistical analysis

Baseline characteristics of all participants were presented as means or percentages by the number of chronic diseases (0, 1, 2, 3, and ≥4), adjusting for age, sex, and area, when appropriate. The linear trend test was performed by treating the number of chronic diseases as a continuous variable. The prevalence of participants with different numbers of chronic diseases (0, 1, 2, 3, and ≥4) among different age groups was plotted.

We employed hierarchical cluster analysis, a commonly used exploratory method, to classify participants into different multimorbidity patterns. Participants within the same cluster showed similar characteristics, whereas participants of different clusters were distinct from each other. Each chronic disease can only belong to one cluster. Yule's Q distance was used to measure the dissimilarity between chronic diseases. Wald's distance, which provides minimum variances by minimizing the sum of squares between the two clusters, was used to measure the distance between clusters. Dendrograms were plotted to visualize the aggregation of chronic diseases. The number of multimorbidity patterns extracted was balanced through dendrogram and clinical significance. Characteristics of participants across identified multimorbidity patterns were also presented, after adjusting for age, sex, and area, when appropriate. Considering the possible diversity of multimorbidity patterns across subgroups, we also plotted dendrograms by sex (men and women), baseline age (<60 years and ≥60 years), and region (urban area and rural area).

The observed/expected (O/E) ratios were used to identify multimorbidity dyads with the highest possibility to co-occur rather than by chance. The expected prevalence of multimorbidity pairs was calculated by multiplying the prevalence of these two diseases.[21] If the O/E ratio was >1, there exists a positive association for the disease pair. The higher the O/E ratio, the stronger the association.[22]

Person-years at risk were calculated from the baseline date to death, loss to follow-up, or December 31, 2017, whichever came first. Cox proportional hazards models, with age as the underlying timescale, were used to estimate the associations of number of chronic diseases, multimorbidity patterns, as well as multimorbidity dyads with all-cause and cause-specific mortality. The results were presented with hazard ratios (HRs) and 95% confidence intervals (CIs). The models were stratified by baseline age (5-year intervals), sex, and ten areas. Multivariable models were adjusted for baseline age, education level, smoking status, alcohol consumption, intake frequency of fresh fruits, vegetables, and red meat, physical activity, BMI, and waist circumference.

All analyses were carried out using Stata (version 15.0, StataCorp LP, College Station, TX, USA) and R version 4.0.4. The level of statistical significance was set at two-tailed $P < 0.05$.

Results

Characteristics of the study participants by number of chronic diseases

Of all participants included, the mean ± standard deviation of age was 52.0 ± 10.7 years; 59.0% (302,521/ 512,723) were women and 44.1% (226,192/512,723) lived in urban areas [Table 1]. The number (%) of participants with 0, 1, 2, 3, and ≥4 chronic diseases was 246,309 (48.0%), 185,330 (36.2%), 61,800 (12.1%), 14,997 (2.9%), and 4287 (0.8%), respectively. Participants with more chronic diseases were more likely to be older and live in urban areas. They also tended to be heavy drinkers, engage in lower levels of physical activity, and have higher values of BMI and waist circumference (P value for trend <0.05). Of the 15 types of chronic diseases, hypertension had the highest prevalence [35.2% (180,588/ 512,723)], followed by COPD [7.2% (37,057/512,723)], gallstone disease [6.0% (30,997/512,723)], and diabetes [5.9% (30,300/ 512,723)].

Overall, 15.8% (81,084/512,723) of participants had multimorbidity. The prevalence of multimorbidity increased steadily with age, with 6.4% (14,697/230,390) among participants aged <50 years, 17.0% (26,733/ 157,616) among 50 to 59 years, and 31.8% (39,654/ 124,717) among ≥60 years [Supplementary Figure 1, http://links.lww.com/CM9/A932]. The multimorbidity prevalence was higher in urban 18.7% (42,358/ 226,192) than rural participants 13.5% (38,726/ 286,531), and similar in men 16.3% (34,336/210,202) and women 15.5% (46,748/ 302,521).

Multimorbidity patterns

Among all participants, we identified four patterns of multimorbidity, namely, cardiometabolic multimorbidity [6.0% (30,868/512,723); diabetes, coronary heart disease, stroke, and hypertension], respiratory multimorbidity [0.4% (2120/512,723); tuberculosis, asthma, and COPD], gastrointestinal and hepatorenal multimorbidity [0.8% (4324/512,723); gallstone disease, chronic kidney disease, cirrhosis, peptic ulcer, and cancers], and mental and arthritis multimorbidity [0.2% (827/512,723); neurasthenia, psychiatric disorder, and rheumatoid arthritis) [Figure 1 and Table 2]. Besides, 1042 (0.2%) participants had more than two patterns of multimorbidity, 41,903 (8.2%) participants had no specific patterns of multimorbidity, and 431,639 (84.2%) participants did not have multimorbidity. Participants with mental and arthritis multimorbidity were more likely to be women [80.4% (665/827)], while participants with respiratory multimorbidity were more likely to be men [56.8% (1204/ 2120)]. Participants with cardiovascular multimorbidity had a lower level of physical activity and higher values of BMI and waist circumference [Table 2].

Table 1: Baseline characteristics of participants by the number of chronic diseases.

Parameters	N of chronic diseases						*P* value for trend
	Total	0	1	2	3	≥4	
Number (%) of participants	512,723	246,309 (48.0)	185,330 (36.1)	61,800 (12.1)	14,997 (2.9)	4287 (0.8)	–
Socio-demographic factors							
Age (years)	52.0 (10.7)	48.1 (9.6)	54.1 (10.3)	58.4 (9.8)	61.1 (9.0)	63.1 (8.3)	<0.001
Women (%)	59.0	60.9	57.1	56.9	59.2	62.4	<0.001
Urban area (%)	44.1	43.0	42.0	49.0	59.4	73.4	<0.001
Middle school and higher (%)	49.2	49.2	48.8	49.5	51.8	55.7	<0.001
Lifestyle factors							
Male daily smoker[*] (%)	67.7	68.1	67.2	67.5	67.1	69.1	0.016
Female daily smoker[*] (%)	2.8	2.8	2.9	2.8	3.1	3.0	0.094
Male heavy drinker[†] (%)	24.6	21.7	26.3	28.2	28.6	31.8	<0.001
Female heavy drinker[†] (%)	1.5	1.4	1.6	1.7	1.7	1.7	<0.001
Eat fruits daily (%)	18.8	19.0	18.5	18.8	19.5	20.1	0.795
Eat vegetables daily (%)	94.8	94.8	94.8	94.7	95.0	95.1	0.761
Eat red meat 1–6 days/week (%)	53.4	54.0	53.1	52.4	52.5	53.3	<0.001
Physical activity (MET h/day)	21.1	21.7	21.1	19.4	18.4	17.8	<0.001
BMI (kg/m^2)	23.7	23.0	24.1	24.4	24.7	25.0	<0.001
Waist circumference (cm)	80.3	78.5	81.4	82.7	83.7	84.5	<0.001
Prevalence of chronic diseases (%)							
Hypertension	35.2	0	63.0	77.6	83.1	86.0	<0.001
Diabetes	5.9	0	4.6	23.0	35.7	45.3	<0.001
Coronary heart disease	3.0	0	1.8	9.1	20.9	36.0	<0.001
Stroke or transient ischemic attack	1.7	0	0.7	6.3	12.6	19.5	<0.001
Tuberculosis	1.5	0	1.6	4.3	8.2	13.2	<0.001
Asthma	0.5	0	0.4	1.8	5.3	11.8	<0.001
COPD	7.2	0	8.5	22.9	34.5	44.7	<0.001
Gallstone disease	6.0	0	6.8	19.4	32.6	47.6	<0.001
Peptic ulcer	3.9	0	4.8	12.1	20.0	29.7	<0.001
Cirrhosis/chronic hepatitis	1.2	0	1.4	4.0	8.0	14.5	<0.001
Chronic kidney disease	1.5	0	1.5	4.6	8.8	17.2	<0.001
Cancer	0.5	0	0.6	1.5	2.4	4.1	<0.001
Neurasthenia	1.1	0	1.0	3.5	7.9	17.7	<0.001
Psychiatric disorder	1.1	0	1.2	4.1	8.6	16.5	<0.001
Rheumatic arthritis	2.1	0	2.1	6.5	12.5	23.2	<0.001

Data are presented as *n* (%), mean (standard deviation), mean or percentage. [*] Included former smokers who had quit smoking due to illness. [†] Heavy drinker refers to participants who drank >30 g/day pure alcohol for men or >15 g/day pure alcohol for women or those who had quit drinking. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; MET: Metabolic equivalent tasks.

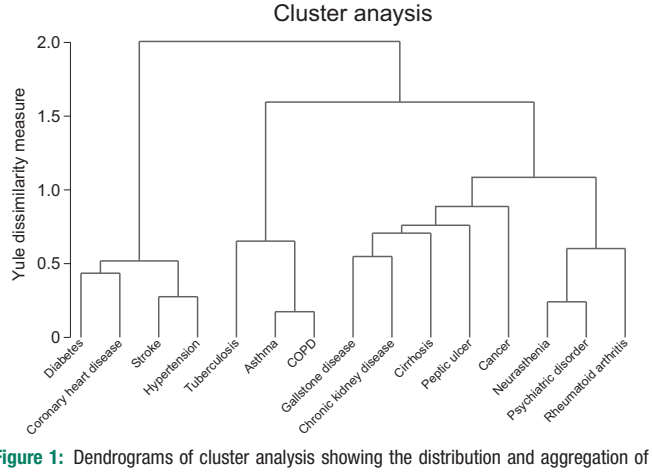

Figure 1: Dendrograms of cluster analysis showing the distribution and aggregation of chronic diseases. COPD: Chronic obstructive pulmonary disease.

The patterns of multimorbidity demonstrated some variations across subgroups [Supplementary Figures 2–4, http://links.lww.com/CM9/A932]. The patterns in men, rural residents, and those aged <60 years mirrored those in the overall population. Whereas for women, urban residents, and participants aged ≥60 years, cardiovascular multimorbidity remained stable, but the other three patterns were not exactly the same as those in the overall participants. Asthma usually co-occurred with COPD, while tuberculosis usually co-occurred with cirrhosis. Other digestive and hepatorenal diseases are often clustered with mental diseases and arthritis.

Among all the multimorbidity dyads, the multimorbidity pairs with the highest O/E ratios were psychiatric disorder and neurasthenia (O/E ratio = 8.00), followed by asthma and COPD (O/E ratio = 6.00) [Table 3].

Association of multimorbidity patterns with mortality

Over a median of 10.8 years (total person years: 5,551,974) of follow-up, 49,371 deaths occurred, including 18,421

Table 2: Baseline characteristics of participants by multimorbidity patterns.

Parameters	Total	With no multimorbidity	Cardiometabolic multimorbidity	Respiratory multimorbidity	Gastrointestinal and hepatorenal multimorbidity	Mental and arthritis multimorbidity	With ≥2 patterns of multimorbidity	With no specific patterns of multimorbidity
Number (%) of participants	512,723	431,639 (84.2)	30,868 (6.0)	2120 (0.4)	4324 (0.8)	827 (0.2)	1042 (0.2)	41,903 (8.2)
Socio-demographic factors								
Age (years)	52.0 (10.7)	50.7 (10.3)	61.0 (8.8)	59.6 (10.4)	54.2 (10.1)	53.2 (9.8)	62.8 (8.8)	58.3 (9.9)
Women (%)	59.0	59.3	58.6	43.2	60.5	80.4	62.5	56.8
Urban area (%)	44.1	42.6	60.0	50.3	52.1	57.1	77.4	45.9
Middle school and higher (%)	49.2	49.0	49.9	50.3	53.2	54.5	56.6	50.0
Lifestyle factors								
Male daily smoker* (%)	67.7	67.7	66.4	69.1	67.4	62.4	73.0	68.2
Female daily smoker* %)	2.8	2.8	2.5	3.6	3.5	2.8	2.6	3.0
Male heavy drinker† (%)	24.6	23.9	30.7	24.7	25.3	24.4	31.6	26.7
Female heavy drinker† (%)	1.5	1.5	1.5	1.7	1.9	2.8	0.7	1.7
Eat fruits daily (%)	18.8	18.8	17.8	19.3	22.0	20.5	20.6	19.7
Eat vegetables daily (%)	94.8	94.8	95.1	94.3	94.7	91.7	95.1	94.5
Eat red meat 1 – 6 days/week (%)	53.4	53.6	52.7	52.4	51.2	51.1	51.7	52.7
Physical activity (MET h/day)	21.1	21.4	18.3	18.6	19.8	20.1	17.9	19.9
BMI (kg/m^2)	23.7	23.5	25.3	22.5	23.4	23.2	24.7	24.0
Waist circumference (cm)	80.3	79.8	85.4	78.0	79.8	79.1	84.1	81.3
Prevalence of chronic diseases (%)								
Hypertension	35.2	28.2	94.5	28.1	26.7	27.5	77.7	69.5
Diabetes	5.9	2.0	58.5	2.5	3.1	4.6	43.1	5.9
Coronary heart disease	3.0	0.8	20.1	2.0	3.2	5.1	31.1	3.4
Stroke or transient ischemic attack	1.7	0.3	16.5	0.4	0.4	0.8	12.9	0.8
Tuberculosis	1.5	0.7	1.5	47.2	1.9	1.4	11.8	5.9
Asthma	0.5	0.2	0.5	55.5	0.4	1.0	18.8	1.8
COPD	7.2	3.8	7.3	97.9	7.8	10.7	34.4	31.0
Gallstone disease	6.0	3.0	8.2	6.8	75.5	10.7	54.2	25.4
Peptic ulcer	3.9	2.2	3.2	5.3	59.6	9.6	35.4	15.2
Cirrhosis/chronic hepatitis	1.2	0.6	1.2	1.8	25.2	2.3	18.9	5.0
Chronic kidney disease	1.5	0.7	2.0	1.5	22.5	2.4	23.2	5.8
Cancer	0.5	0.3	0.5	0.5	8.3	0.4	5.4	1.9
Neurasthenia	1.1	0.5	1.4	1.8	2.6	73.4	16.1	5.6
Psychiatric disorder	1.1	0.5	1.9	1.9	2.2	59.9	17.0	6.7
Rheumatic arthritis	2.1	0.9	2.7	3.1	3.8	56.5	17.3	11.1

Data are presented as *n* (%), mean (standard deviation), mean or percentage. * Included former smokers who had quit smoking due to illness. † Heavy drinker refers to participants who drank >30 g/day pure alcohol for men or >15 g/day pure alcohol for women or those previous heavy drinkers who had quit drinking. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; MET: Metabolic equivalent tasks.

deaths from CVD, 4652 deaths from respiratory diseases, 15,750 deaths from cancer, and 10,548 deaths from other causes. For disease pairs, compared with participants with no multimorbidity, participants with co-occurrence of cirrhosis and cancer had the highest risk of mortality (HR = 5.09, 95% CI: 3.40–7.61), followed by those with diabetes and stroke (HR = 3.41, 95% CI: 3.15–3.68) [Table 3].

Further analyses by the patterns we derived showed that, compared with participants with no multimorbidity, cardiometabolic multimorbidity (HR = 2.20, 95% CI: 2.14–2.26) and respiratory multimorbidity (HR = 2.13, 95% CI: 1.97–2.31) had relatively higher risks of mortality, followed by gastrointestinal and hepatorenal multimorbidity (HR = 1.33, 95% CI: 1.22–1.46). No statistically significant increased mortality risk was found for participants with mental and arthritis multimorbidity (HR = 1.18, 95% CI: 0.93–1.50), possibly due to the small number of deaths [Table 4]. Participants with two or more patterns of multimorbidity had ~2-fold increased risk of mortality (HR = 2.21, 95% CI: 1.98–2.48), whereas participants of no specific pattern of multimorbidity had 46% higher risk (HR = 1.46, 95% CI: 1.42–1.50). In the analyses of cause-specific mortality, participants with cardiometabolic multimorbidity had the highest risk of death from CVD, followed by those with respiratory multimorbidity [Table 5]. For death from respiratory diseases, participants with respiratory multimorbidity had the highest risk, followed by those with cardiometabolic multimorbidity. For deaths from cancer, participants with gastrointestinal and hepatorenal multimorbidity had the highest risk.

Association of number of chronic diseases with mortality

We observed a graded increased risk of the number of chronic diseases with all-cause mortality. The mortality risk increased by 36% (HR = 1.36, 95% CI: 1.35–1.37) with every additional disease [Table 4]. Compared with participants without any aforementioned chronic diseases, the multivariable-adjusted HRs for those with 1, 2, 3, and ≥4 diseases were 1.59 (1.55–1.63), 2.25 (2.19–2.31), 2.69 (2.59–2.80), and 3.19 (3.01–3.38), respectively.

Discussion

In our cohort of 0.5 million Chinese adults, 15.8% of participants had multimorbidity. The prevalence of multimorbidity increased with age and was higher in urban than rural participants. We identified four multimorbidity

Table 3: Observed and expected prevalence of chronic disease pairs and association with mortality.

Parameters	No. of disease pairs	Observed prevalence (%)	Expected prevalence (%)	Ratio O/E	Deaths	Mortality (deaths/ 1000 PYs)	HR (95% CI)
Cardiometabolic multimorbidity							
Diabetes + hypertension	18,220	3.55	2.08	1.71	4686	25.9	2.32 (2.24–2.39)
Chronic heart disease + hypertension	9574	1.87	1.06	1.76	2567	26.8	1.82 (1.74–1.90)
Stroke + hypertension	6814	1.33	0.61	2.18	2614	42.0	2.65 (2.54–2.76)
Diabetes + chronic heart disease	2699	0.53	0.18	2.94	870	33.4	2.42 (2.25–2.60)
Diabetes + stroke	1537	0.30	0.10	3.00	689	51.6	3.41 (3.15–3.68)
Chronic heart disease + stroke	1227	0.24	0.05	4.80	489	43.9	2.63 (2.39–2.88)
Respiratory multimorbidity							
Tuberculosis + COPD	1240	0.24	0.11	2.18	430	36.3	1.98 (1.80–2.18)
Asthma + COPD	1240	0.24	0.04	6.00	377	30.7	2.36 (2.13–2.62)
Tuberculosis + asthma	121	0.02	0.01	2.00	44	38.0	2.61 (1.94–3.51)
Gastrointestinal and hepatorenal multimorbidity							
Gallstone disease + peptic ulcer	2247	0.44	0.24	1.83	218	9.0	0.99 (0.87–1.13)
Gallstone disease + kidney disease	1082	0.21	0.09	2.33	121	10.5	1.38 (1.15–1.65)
Gallstone disease + cirrhosis	733	0.14	0.07	2.00	144	19.1	2.17 (1.84–2.56)
Kidney disease + peptic ulcer	523	0.10	0.06	1.67	61	10.9	1.42 (1.10–1.83)
Peptic ulcer + cirrhosis	362	0.07	0.05	1.40	79	22.0	2.26 (1.81–2.83)
Gallstone disease + cancers	213	0.04	0.03	1.33	63	31.2	3.22 (2.52–4.13)
Kidney disease + cirrhosis	169	0.03	0.02	1.50	31	17.5	2.02 (1.42–2.87)
Peptic ulcer + cancers	143	0.03	0.02	1.50	44	32.8	2.60 (1.93–3.49)
Cirrhosis + cancers	54	0.01	0.01	1.00	24	51.7	5.09 (3.40–7.61)
Kidney disease + cancers	51	0.01	0.01	1.00	13	27.5	2.14 (1.24–3.70)
Mental and arthritis multimorbidity							
Neurasthenia + rheumatic arthritis	449	0.09	0.02	4.50	51	10.2	1.18 (0.89–1.55)
Psychiatric disorder + neurasthenia	416	0.08	0.01	8.00	34	7.3	1.38 (0.98–1.93)
Psychiatric disorder + rheumatic arthritis	249	0.05	0.02	2.50	33	11.7	1.92 (1.36–2.70)

All models were stratified by age, sex, and area. A multivariable model was adjusted for age (years), education level (no formal school, primary school, middle school, high school, college, or university or higher), smoking status (non-smoker; former smoker who had stopped for reasons other than illness; current smoker or former smoker who had stopped for illness with 1–14,15–24, or ≥25 cigarettes/day), alcohol consumption (not weekly drinker, ex-regular drinker; weekly but not a daily drinker; daily drinker with 1–14 g, 15–29 g, 30–59 g, or ≥60 g pure alcohol/day), intake frequency of fresh fruits, vegetables, and red meat (days/week, values were assigned according to the midpoint value of intake frequency: never or rarely = 0, monthly = 0.5, 1–3 days/week = 2, 4–6 days/week = 5, or daily = 7), physical activity (MET h/day), BMI (kg/m^2), and waist circumference (cm). BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CI: Confidence intervals; HR: Hazard ratios; MET: Metabolic equivalent tasks; O/E: Observed/ expected; PY: Person year.

Table 4: Association of patterns of multimorbidity and number of chronic diseases with mortality.

Parameters	Deaths	Mortality (deaths/1000 PYs)	HR (95% CI)
Patterns of multimorbidity			
With no multimorbidity	31,854	6.7	1.00
Cardiometabolic multimorbidity	8330	27.3	2.20 (2.14–2.26)
Respiratory multimorbidity	656	31.6	2.13 (1.97–2.31)
Gastrointestinal and hepatorenal multimorbidity	501	10.9	1.33 (1.22–1.46)
Mental and arthritis multimorbidity	67	7.2	1.18 (0.93–1.50)
With ≥2 patterns of multimorbidity	309	30.2	2.21 (1.98–2.48)
With no specific patterns of multimorbidity	7654	17.4	1.46 (1.42–1.50)
Number of chronic diseases			
0	11,117	4.1	1.00
1	20,737	10.4	1.59 (1.55–1.63)
2	12,284	19.2	2.25 (2.19–2.31)
3	3871	25.8	2.69 (2.59–2.80)
≥4	1362	32.6	3.19 (3.01–3.38)
Any	49,371	8.9	1.36 (1.35–1.37)

All models were stratified by age, sex, and area. Multivariable models were adjusted for the same covariates as those in Table 3. CI: Confidence intervals; HR: Hazard ratios; PY: Person year.

Table 5: Association of patterns of multimorbidity with cause-specific mortality.

Parameters	Deaths	Mortality (deaths/1000 PYs)	HR (95% CI)
Death from cardiovascular disease			
With no multimorbidity	10,894	2.3	1.00
Cardiometabolic multimorbidity	4458	14.6	2.98 (2.87–3.10)
Respiratory multimorbidity	141	6.8	1.34 (1.13–1.58)
Gastrointestinal and hepatorenal multimorbidity	89	1.9	0.73 (0.59–0.90)
Mental and arthritis multimorbidity	23	2.5	1.29 (0.86–1.95)
With ≥2 patterns of multimorbidity	129	12.6	2.47 (2.08–2.95)
With no specific patterns of multimorbidity	2687	6.1	1.45 (1.39–1.52)
Death from respiratory diseases			
With no multimorbidity	2565	0.5	1.00
Cardiometabolic multimorbidity	545	1.8	1.87 (1.70–2.06)
Respiratory multimorbidity	261	12.6	7.16 (6.28–8.16)
Gastrointestinal and hepatorenal multimorbidity	44	1.0	1.21 (0.89–1.63)
Mental and arthritis multimorbidity	6	0.6	1.47 (0.66–3.27)
With ≥2 patterns of multimorbidity	46	4.5	3.38 (2.52–4.55)
With no specific patterns of multimorbidity	1185	2.7	2.23 (2.08–2.39)
Death from cancer			
With no multimorbidity	11,498	2.4	1.00
Cardiometabolic multimorbidity	1513	5.0	1.12 (1.06–1.18)
Respiratory multimorbidity	146	7.0	1.34 (1.14–1.58)
Gastrointestinal and hepatorenal multimorbidity	247	5.4	1.74 (1.53–1.98)
Mental and arthritis multimorbidity	19	2.0	0.83 (0.53–1.31)
With ≥2 patterns of multimorbidity	73	7.1	1.44 (1.15–1.82)
With no specific patterns of multimorbidity	2254	5.1	1.23 (1.17–1.29)
Death from other causes			
With no multimorbidity	6897	1.5	1.00
Cardiometabolic multimorbidity	1814	6.0	2.71 (2.56–2.87)
Respiratory multimorbidity	108	5.2	1.84 (1.52–2.22)
Gastrointestinal and hepatorenal multimorbidity	121	2.6	1.57 (1.31–1.88)
Mental and arthritis multimorbidity	19	2.0	1.52 (0.97–2.38)
With ≥2 patterns of multimorbidity	61	6.0	2.51 (1.95–3.24)
With no specific patterns of multimorbidity	1528	3.5	1.48 (1.39–1.56)

All models were stratified by age, sex, and area. Multivariable models were adjusted for the same covariates as those in Table 3. CI: Confidence intervals; HR: Hazard ratios; PY: Person year.

patterns, including cardiometabolic multimorbidity, respiratory multimorbidity, gastrointestinal and hepatorenal multimorbidity, and mental and arthritis multimorbidity. Of the four multimorbidity patterns identified, cardiometabolic multimorbidity was the most common pattern in the current population. Individuals with cardiometabolic and respiratory multimorbidity had the highest risk of mortality.

Comparison with other studies

Previous studies found that multimorbidity prevalence varied from 6.4% to 76.5% among Chinese people aged 60 and older in the communities.[23,24] Comparing multimorbidity prevalence with other studies was difficult due to the inconsistency of participants' characteristics, the number and types of chronic diseases considered, and the cut-off used to define multimorbidity. Our study showed that the prevalence of multimorbidity increased with age, with the prevalence of 6.4% in <50 years, 17.0% in 50 to 59 years, and 31.8% in ≥60 years. Although older adults had a higher prevalence of multimorbidity, in line with previous studies, multimorbidity was not a privilege for older adults.[1,25] In line with findings from The China Health and Retirement Survey (CHARLS),[10] we also found that urban participants had a higher multimorbidity prevalence than rural participants. This urban-rural difference may be explained by the high prevalence of chronic diseases or the high detection rate owing to better access to medical care services among urban residents. Some studies showed that women had higher prevalence of multimorbidity than men.[10,26] However, we did not find significant gender differences for multimorbidity prevalence.

In line with other studies,[13,14] we found a dose-response relationship between the number of chronic diseases and mortality. A meta-analysis of 26 studies, mainly conducted in European and US populations and older adults aged ≥65 years, showed that the HRs (95% CIs) were 1.73 (1.41–2.13) and 2.72 (1.81–4.08) for participants with ≥2 and ≥3 diseases, respectively, when compared with those without multimorbidity.[14] A report of UK Biobank, with 0.5 million participants aged 37 to 73 years, showed that compared with participants without long-term conditions, the 7-year mortality risk (HRs [95%CIs]) were 1.46

(1.38–1.54), 1.77 (1.68–1.87), 2.14 (2.01–2.28), and 2.79 (2.61–2.98) for those with 1, 2, 3, and 4 long-term conditions, respectively.[13]

We extracted four types of multimorbidity patterns. Consistent with previous studies, we observed a little variation across sub-populations by age, sex, and region.[10,26] Most of the multimorbidity patterns found in our study have been documented in previous studies. The cardiometabolic multimorbidity, characterized by coronary heart disease, diabetes, hypertension, and stroke, was probably one of the most common patterns identified by researchers,[9,12,27,28] and was also the most stable pattern across different subgroups in our study. We found that participants with cardiometabolic multimorbidity had the highest risk of mortality (HR = 2.20); consistently, all disease pairs within this pattern had HRs ranging from 1.82 to 3.41. Results from the Emerging Risk Factors Collaboration of 91 cohorts showed that any combination of cardiometabolic multimorbidity had multiplicative mortality risk, and the HRs for participants with 1, 2, and 3 cardiometabolic diseases were about 2, 4, and 8, respectively.[29] The longitudinal studies of the National Health Interview Survey in America and the Swedish National Study on Aging and Care also showed, when compared with other patterns, cardiometabolic patterns posed the highest threat on mortality.[8,28]

Few previous studies have observed respiratory multimorbidity. The Global Burden of Disease Study 2019 showed that COPD, behind ischemic heart disease and stroke, was the third most common cause of death in China.[30] Tuberculosis and asthma also pose a high medical burden in the Chinese population.[31,32] Our study found that the respiratory multimorbidity, including COPD, tuberculosis, and asthma, carried a similar higher mortality risk to cardiometabolic multimorbidity. A study of National Health Interview Survey among US older adults identified a similar "respiratory condition" class (including emphysema/COPD, asthma, and arthritis) which had a relatively high mortality risk (HR = 2.14; 95% CI: 1.87–2.46), following the "complex cardiometabolic" group (HR = 5.30; 95% CI: 4.52–6.22).[28]

The mental and arthritis multimorbidity mainly included neurasthenia, psychiatric disorder, and arthritis, and sometimes co-occurred with digestive diseases. Previous literature also reported similar patterns like "mental-articular pattern,"[33] "mental-musculoskeletal pattern,"[4] or "mental and somatic multimorbidity."[34] A study in the US reported that neuropsychiatric class had about two fold increased mortality risk.[6] We did not find a statistically significant association between mental and arthritis multimorbidity and mortality, but we found that dyad of psychiatric disorder and rheumatic arthritis had a 92% increased risk of mortality.

The gastrointestinal and hepatorenal multimorbidity, characterized by diseases of the digestive system and cancer, was less reported in previous studies. The CHARLS study, similar to ours, identified two distinct patterns of "stomach-arthritis cluster" and "hepatorenal cluster."[10] The coexistence of digestive diseases may be due to the high prevalence of gastrointestinal diseases, liver diseases, and kidney diseases in China.[30] The common pathways may include unhealthy dietary habits, other immunology factors, and biological mechanisms.[35] Alternatively, one disease may be the consequence of the other. We demonstrated that, overall, gastrointestinal and hepatorenal multimorbidity carried a 33% increased risk of mortality than those without multimorbidity. While the dyads, including cirrhosis or cancer, had a relatively high mortality risk, with the HRs ranging from 2.1 to 5.1. However, there were no comparable studies.

Strength and Limitations

The strengths of the present study included its prospective design, large sample size, long-time follow-up, and a broad range of multi-system and prevalent chronic diseases. To our knowledge, this is by far the first study in China to comprehensively examine the association of both the number of chronic diseases and the patterns of multi-morbidity with mortality in middle-aged and older adults. Some limitations need to be mentioned. First, we used baseline disease information, which may change during follow-up. However, a previous study of our research team showed that the multimorbidity patterns at baseline and the second resurvey were relatively consistent.[36] Participants enrolled at baseline were more likely to be survivors since those with high-fatality diseases may have died before the survey. Therefore, the current patterns identified possibly reflect multimorbidity patterns among long-term survivors. Second, disease status information was mainly from self-report, which may cause under-reporting of undiagnosed conditions. However, this bias was likely to be non-differential, and thus drove the associations toward the null. Third, although the baseline survey inquired about common diseases of multi-systems, the number of diseases included was still limited, which may affect the results of the analyses.

Conclusions

In our prospective study of 0.5 million Chinese adults, we identified four multimorbidity patterns, namely, cardiometabolic multimorbidity, respiratory multimorbidity, gastrointestinal and hepatorenal multimorbidity, and mental and arthritis multimorbidity. Cardiometabolic multimorbidity was the predominant pattern among Chinese adults. Cardiometabolic multimorbidity and respiratory multimorbidity carried the highest mortality risk and deserved particular attention. Our study highlighted the importance of preventing the occurrence of multimorbidity, especially by targeting shared risk factors, managing patients with multiple chronic diseases, and reinforcing the need to develop clinical guidelines focusing on multimorbidity. Future studies are warranted to explore the possible mechanisms of co-occurring multiple chronic diseases.

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Conflicts of interest

None.

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