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Exploring multimorbidity profiles in middle-aged inpatients: a network-based comparative study of China and the United Kingdom

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Abstract

Background Multimorbidity is better prevented in younger ages than in older ages. This study aims to identify the differences in comorbidity patterns in middle-aged inpatients from China and the United Kingdom (UK).

Methods We utilized 184,133 and 180,497 baseline hospitalization records in middle-aged populations (40–59 years) from Shaanxi, China, and UK Biobank. Logistic regression was used to calculate odds ratios and *P* values for 43,110 unique comorbidity patterns in Chinese inpatients and 21,026 unique comorbidity patterns in UK inpatients. We included the statistically significant (*P* values adjusted by Bonferroni correction) and common comorbidity patterns (the pattern with prevalence > 1/10,000 in each dataset) and employed network analysis to construct multimorbidity networks and compare feature differences in multimorbidity networks for Chinese and UK inpatients, respectively. We defined hub diseases as diseases having the top 10 highest number of unique comorbidity patterns in the multimorbidity network.

Results We reported that 57.12% of Chinese inpatients had multimorbidity, substantially higher than 30.39% of UK inpatients. The complete multimorbidity network for Chinese inpatients consisted of 1367 comorbidities of 341 diseases and was 2.93 × more complex than that of 467 comorbidities of 215 diseases in the UK. In males, the complexity of the multimorbidity network in China was 2.69 × more than their UK counterparts, while the ratio was 2.63 × in females. Comorbidities associated with hub diseases represented 68.26% of comorbidity frequencies in the complete multimorbidity network in Chinese inpatients and 55.61% in UK inpatients. Essential hypertension, dyslipidemia, type 2 diabetes mellitus, and gastritis and duodenitis were the hub diseases in both populations. The Chinese inpatients consistently demonstrated a higher frequency of comorbidities related to circulatory and endocrine/nutritional/metabolic diseases. In the UK, aside from these comorbidities, comorbidities related to digestive and genitourinary diseases were also prevalent, particularly the latter among female inpatients.

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Conclusions Chinese inpatients exhibit higher multimorbidity prevalence and more complex networks compared to their UK counterparts. Multimorbidity with circulatory and endocrine/nutritional/metabolic diseases among both Chinese and UK inpatients necessitates tailored surveillance, prevention, and intervention approaches. Targeted interventions for digestive and genitourinary diseases are warranted for the UK.

Keywords Multimorbidity, Comorbidity, Network analysis, Middle-aged, Inpatients, China, United Kingdom

Background

Multimorbidity, affecting 33.1% of adults globally in 2021, is a significant and rapidly growing public health concern worldwide [1, 2], with rising prevalence in England [3], Southern Europe [4], and China [5]. Multimorbidity leads to polypharmacy and adverse drug events [1, 6]. Furthermore, managing and treating multimorbidity puts a substantial strain on healthcare resources and increases health expenditure [1, 6, 7]. The World Health Organization recognizes the magnitude of the global multimorbidity challenge and has prioritized the goal of reducing the burden of multimorbidity [7].

Preventing multimorbidity in younger age is a more effective and economically viable strategy than treating it in older age. Elderly individuals with multimorbidity experience worse clinical outcomes, lower quality of life, reduced functionality, and increased hospitalization and mortality compared to single-disease counterparts [1, 6]. The likelihood of poor health status and limited physical capacity in the elderly increases by 3–9 times with multimorbidity [4]. Interventions in the early stages of life can reduce the subsequent disease burden of multimorbidity in later life stages. Middle age may be the perfect stage of life for prevention and early intervention, as severe chronic ailments are either absent or only in their early stages of development. Prevention and treatment for multimorbidity are much more efficient in this stage of life. Comprehending multimorbidity patterns in middle-aged populations has crucial implications for effective interventions that may reduce the subsequent disease and economic burden of multimorbidity [8, 9].

The current research on multimorbidity is riddled with significant knowledge gaps, despite numerous efforts. Existing studies are largely limited to developed countries, with only limited research from developing countries [10–13]. Besides, the current research has focused on older adults [14–16] but not the younger middle-aged population. More importantly, most existing studies have focused on a small group of chronic diseases, with limited exploration of multimorbidity on a wider spectrum of diseases, except only a handful of studies in South-west China [17], Denmark [11], America [12], and Austria [13]. To date, no studies comprehensively compared comorbidity patterns at a population level between developed and developing countries.

Complex disease interactions significantly influence diagnosis and treatment and pivotal inpatient care. Untangling these less-understood relationships is crucial [13, 18]. Our study employed network analysis, an innovative tool revealing intricate interconnections among diseases [10–13]. We used this approach to construct multimorbidity networks in China and the UK, identifying hub diseases with numerous comorbidity patterns. This innovation enhances our understanding of disease interactions and enables the development of targeted surveillance and prevention strategies, benefiting clinical practice.

Our study aims to compare the comorbidity patterns among inpatients in China and the United Kingdom (UK) to enhance the understanding of the differences in disease profiles in these countries. We facilitate the comparison based on two sizable population datasets in middle-aged populations from Northwest China and the UK-Biobank. The diagnosis of diseases is according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) [19]. We included 14 systematic chapters on diseases and used sophisticated network analysis to develop multimorbidity networks, compare comorbidity patterns, and identify hub diseases between China and the UK [13]. Our findings are pivotal in global healthcare by highlighting disease disparities across countries with different economic development statuses. Our study will inform decision-makers to understand regional health challenges and endorse targeted strategies for multimorbidity prevention and treatment. Our findings will also guide global health institutes and governments, aiding in the formulation of more effective multimorbidity prevention strategies, thereby reducing both disease and economic burden caused by multimorbidity.

Methods

Study participants

Our study drew on data from two population studies from China and the UK. Both studies utilized the same disease diagnosis measure (ICD-10) [19]. The Chinese population initially recruited 678,666 participants in Shaanxi province, China (1998–2018), with 1,058,398 hospitalization records from the Centralized Hospital Medical Records (CHMRs) system [20]. The UK-Biobank

population initially recruited 502,414 participants from the National Health Service (2006–2010), with 2,372,119 hospitalization records linked to the Hospital Episode Statistics (HES) [21]. The baseline was the date of the first record for each participant. ICD-10 codes were grouped into 22 chapters (Additional File 1: Table S1) [19]. Recruitment procedures and other details are documented elsewhere [20, 22] and presented in Additional File 2: Figure S1-S2.

Inclusion and exclusion criteria

We employed consistent inclusion criteria for both datasets, requiring (1) baseline records of each inpatient, (2) health records with ICD-10 codes, and (3) records with ages ranging from 40 to 59 years (middle-aged). The exclusion criteria were as follows: health records only with ICD-10 codes from chapters 15–22, as these correspond to congenital diseases, injury, poisoning, pregnancy, childbirth and the puerperium, and others. Only records with ICD-10 codes from chapters 1–14 were included [10] (Additional File 2: Figure S1-S2).

Study population and subpopulations

Inclusion and exclusion criteria yielded 184,133 Chinese hospitalization records and 180,497 UK hospitalization records. We further stratified our dataset by sex, examining comorbidities among males (China: 103,334 inpatients, UK: 79,652 inpatients) and females (China: 80,799 inpatients, UK: 100,845 inpatients) (Additional File 1: Table S2).

Study indicators

Disease categories were identified using 3-character codes of the ICD-10 system. In Chinese inpatients, 929 diseases (854 in males, 819 in females) were recorded, and in UK inpatients, 834 diseases (724 in males, 736 in females) were recorded (Additional File 3).

Definition of comorbidity and multimorbidity

We defined “comorbidity” as the coexistence of disorders in addition to a primary disease. The “comorbidity pattern” refers to the presence of exactly two diseases, whereas multimorbidity indicates the presence of two or more diseases in the same individual [1].

Construction of multimorbidity network

The basic elements of the networks are nodes (diseases) and edges (coexistence of disease) that connect nodes within the networks. In the initial analysis, 43,110 unique comorbidity patterns emerged for the Chinese middle-aged inpatients (30,209 among males, 26,554 among females), and in the UK, 21,026 unique comorbidity patterns were found (12,887 among males, 13,197 among

females). For disease associations, logistic regression models calculated odds ratios (ORs) for each comorbidity pattern (edge). Edges were selected based on criteria: (1) $OR > 1$; (2) $P\text{-value} < 0.05/N$ (N =the number of patterns satisfying $OR > 1$, Bonferroni correction applied [23]); (3) patterns with prevalence $> 1/10,000$ in each dataset were included, while patterns with the lower prevalence were excluded (Additional File 2: Figure S3-S6).

Hub diseases and associated multimorbidity network

The overall disease network encompassed all comorbidity patterns that satisfied the specified criteria for the entire study population (Additional File 2: Figure S3, S5). The same disease network was constructed in males and females to obtain sex-specific disease networks (Additional File 2: Figure S4, S6). Employing the degree network metric [24], we identified the top ten diseases with the most connections within the network, defining them as Hub diseases. If two diseases displayed the same degree, the diseases with a higher prevalence would be given the preference. The networks formed by comorbidities linked to the Hub diseases were defined as Hub diseases’ associated networks.

Multimorbidity network metric

We obtained seven main metrics for each node: degree [24], maximal clique centrality (MCC) [25], closeness centrality (Clo_Cen) [24], clustering coefficient (Clu_Coe) [24], betweenness centrality (Bet_Cen) [24], pageranks [26], and eigencentrality [24] (the explanation of network metrics can be seen in Additional File 1: Additional Text). Node size was determined by degree, while edge thickness varied proportionally to OR values. Nodes were color-coded based on ICD-10 chapters. Additional File 3 provided detailed node metrics and OR values of edges.

Statistical analysis

The proportion of each disease and comorbidity pattern was calculated. Age was measured by mean \pm standard deviation (mean \pm SD). Analyses were conducted using R 4.1.0 and Python 2020.1.3, and Cytoscape and Gephi were utilized for network diagram and metric analysis. Microsoft Excel and GraphPad Prism 9.3.1 were used to create stacked bar charts, line charts, and violin plots.

Results

Sociodemographic characteristics of the Chinese and UK inpatients

In the Chinese inpatients, the mean age of the overall, male, and female inpatients was 48.45 (SD \pm 5.29), 48.27 (SD \pm 5.31), and 48.67 (SD \pm 5.27), respectively, and the proportion of females was 43.88%. In comparison, the

UK inpatients were older with the corresponding ages of 51.53 (SD ± 5.27), 51.82 (SD ± 5.26), and 51.30 (SD ± 5.26) years and had a higher proportion of females (55.87%) (Additional File 1: Table S2).

Disease profile in Chinese and UK inpatients

The per-capita disease diagnoses increased with age in both Chinese and UK inpatients (Fig. 1), but the counts were consistently higher in Chinese inpatients than in UK inpatients across all ages. The overall per-capita disease diagnoses in the Chinese inpatients were 2.35/person, which was higher than that of the UK counterparts (1.44/person). In Chinese inpatients, circulatory diseases dominated (0.62/person), followed by digestive (0.39/person) and endocrine/nutritional/metabolic diseases (0.27/person). In comparison, in UK inpatients, digestive diseases dominated (0.34/person), followed by genitourinary (0.27/person) and circulatory diseases (0.21/person) (Additional File 1: Table S3).

The disease profiles were similar when stratified by sex in China. In the UK, musculoskeletal diseases were

among the top three most common disease categories for both sexes (Additional File 1: Table S3).

Multimorbidity profile in Chinese and UK inpatients

We found that 57.12% of Chinese inpatients were diagnosed with multimorbidity (≥ 2 diseases), while in the UK, it was much lower (30.39%) (Table 1). Notably, among the Chinese inpatients, the proportion of multimorbidity was higher than the proportion of a single disease in all age groups, whereas the opposite was observed in the UK inpatients (Fig. 2). Notably, the proportion of multimorbidity in both males and females followed a similar trend in both inpatient groups, although males tended to have a higher multimorbidity proportion than females.

Multimorbidity networks in overall Chinese and UK inpatients

The complete multimorbidity network in Chinese inpatients was almost three times more complex than in UK inpatients (Fig. 3a). The Chinese multimorbidity network consisted of 341 diseases (nodes), which contributed to

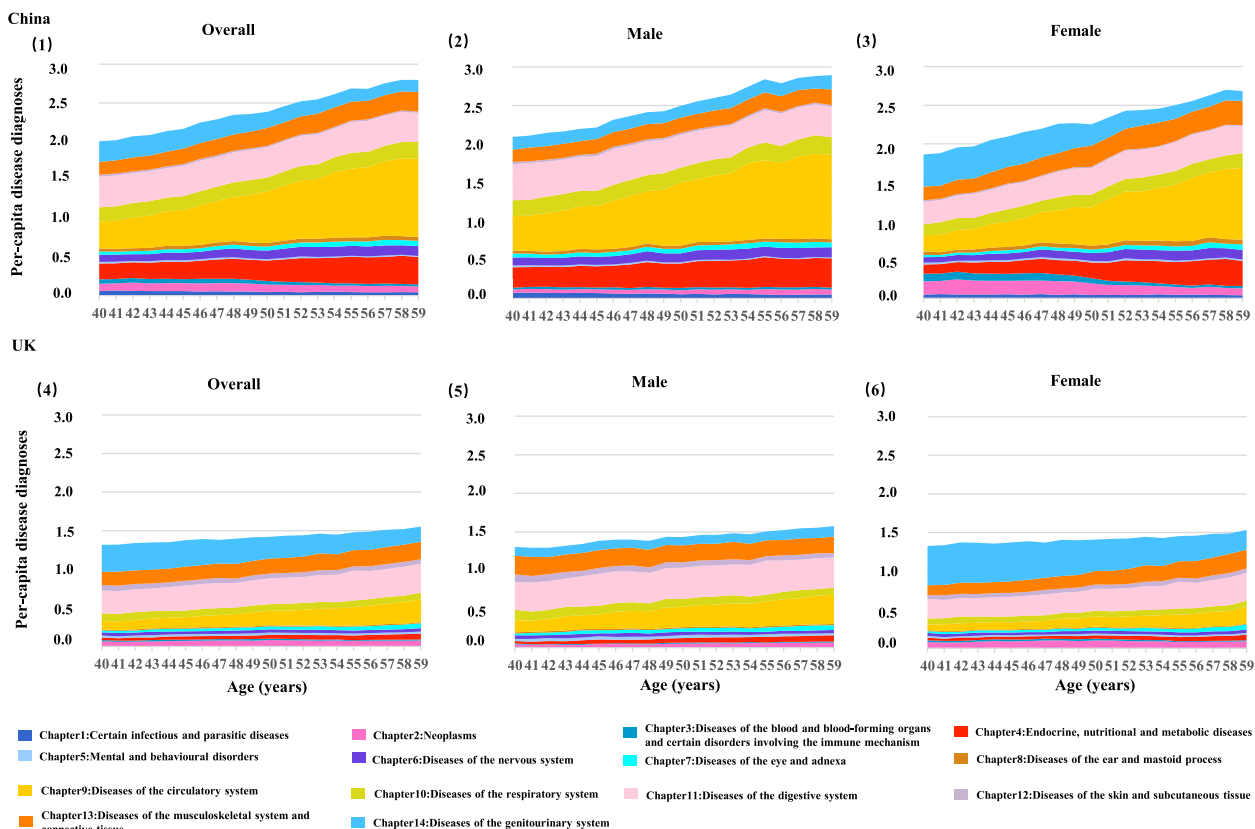


Fig. 1 Stacked bar chart of per-capita disease diagnoses according to ICD-10 (chapters 1–14) among the Chinese and UK inpatients. The x-axis represents age (from 40 to 59 years, unit: years), and the y-axis represents the per-capita disease diagnoses. The color of each bar represents disease systematic chapters

Table 1 The number of health records, disease and multimorbidity diagnoses, and characteristics of complete multimorbidity network and hub diseases’ associated network in the Chinese and UK inpatients

	Chinese inpatients			UK inpatients		
	Overall	Male	Female	Overall	Male	Female
Number of health records	184,133	103,334	80,799	180,497	79,652	100,845
Number of diseases and diagnoses	341/440,702	320/237,746	297/169,760	215/221,470	215/101,683	187/119,214
Number of inpatients with a single disease (% of the total number of inpatients)	78,963 (42.88%)	42,871 (41.49%)	36,092 (44.67%)	125,648 (69.61%)	54,840 (68.85%)	70,808 (70.21%)
Number of inpatients with multimorbidity (≥ 2 conditions) (% of the total number of inpatients)	105,170 (57.12%)	60,463 (58.51%)	44,707 (55.33%)	54,849 (30.39%)	25,812 (31.15%)	30,037 (29.79%)
Number of nodes and edges in the complete multimorbidity network	341 1367	320 1179	297 990	215 467	215 438	187 377
Number of nodes and edges in hub diseases’ associated network (% of the complete multimorbidity network)	193 (56.60%), 483 (35.33%)	173 (54.06%), 410 (34.78%)	160 (53.87%), 347 (35.05%)	95 (44.19%), 176 (37.69%)	73 (33.95%), 154 (35.16%)	79 (42.25%), 141 (37.40%)
Frequency of comorbidity patterns in the complete multimorbidity network	287,195	174,985	99,086	50,375	24,180	25,508
Frequency of comorbidity patterns in hub diseases’ associated network (% of the complete multimorbidity network)	196,064 (68.26%)	128,025 (73.16%)	64,403 (65.00%)	28,014 (55.61%)	13,094 (54.15%)	14,034 (55.02%)

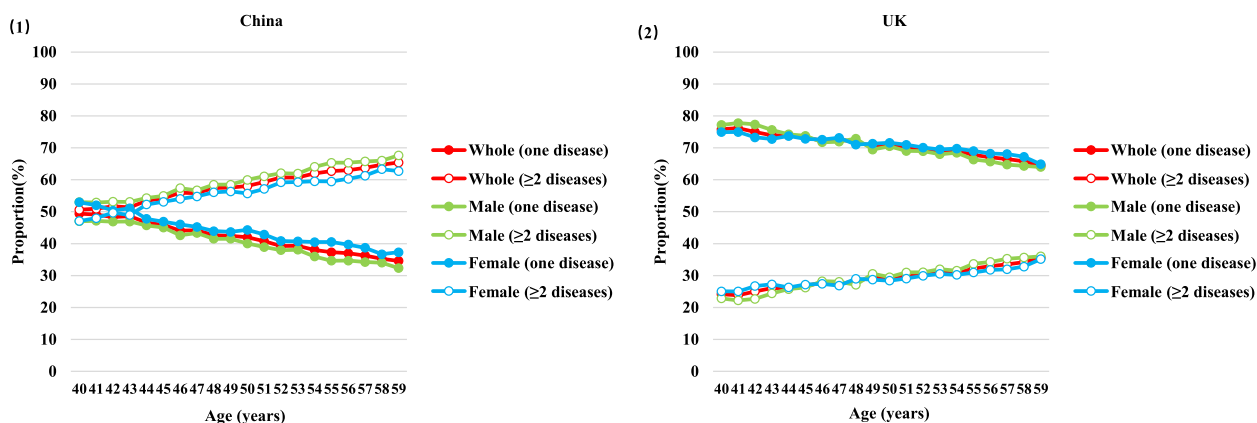


Fig. 2 The proportion of single disease and multimorbidity, stratified by overall, male, and female inpatients in China and the UK

1367 pairs of comorbidity patterns (edges), whereas the UK multimorbidity network consisted of 215 diseases and 467 pairs of comorbidity patterns (Additional File 1: Table S4-S6, Additional File 3). In Chinese inpatients, circulatory, endocrine/nutritional/metabolic, and digestive diseases-related comorbidities were most prevalent, while in UK, the most prevalent were circulatory, digestive, and genitourinary-related comorbidities (Additional File 2: Figure S7.1–7.2). Among Chinese inpatients, the most common comorbidity was essential hypertension/cerebral infarction comorbidity (I10 + I63, 6596/287,195), whereas duodenitis/diaphragmatic hernia comorbidity (K29 + K44, 1524/50,375) was the most common comorbidity in UK inpatients (Additional File 1: Table S7).

The most common comorbidities shared between the Chinese and UK inpatients were all essential hypertension (I10)-related comorbidities (with dyslipidemia, E78; type 2 diabetes mellitus, E11; chronic ischemic heart disease, I25). Several comorbidities were very specific among Chinese inpatients. These included essential hypertension (I10)-related comorbidities (with cerebral infarction, I63; heart failure, I50), liver diseases (K76)-related comorbidities (with essential hypertension; I10, dyslipidemia, E78; type 2 diabetes mellitus, E11), and other heart-related (I25 + I50) and endocrinological comorbidities (E11 + E78). Comparatively, UK-specific comorbidities included gastritis/duodenitis (K29)-related comorbidities (with a diaphragmatic

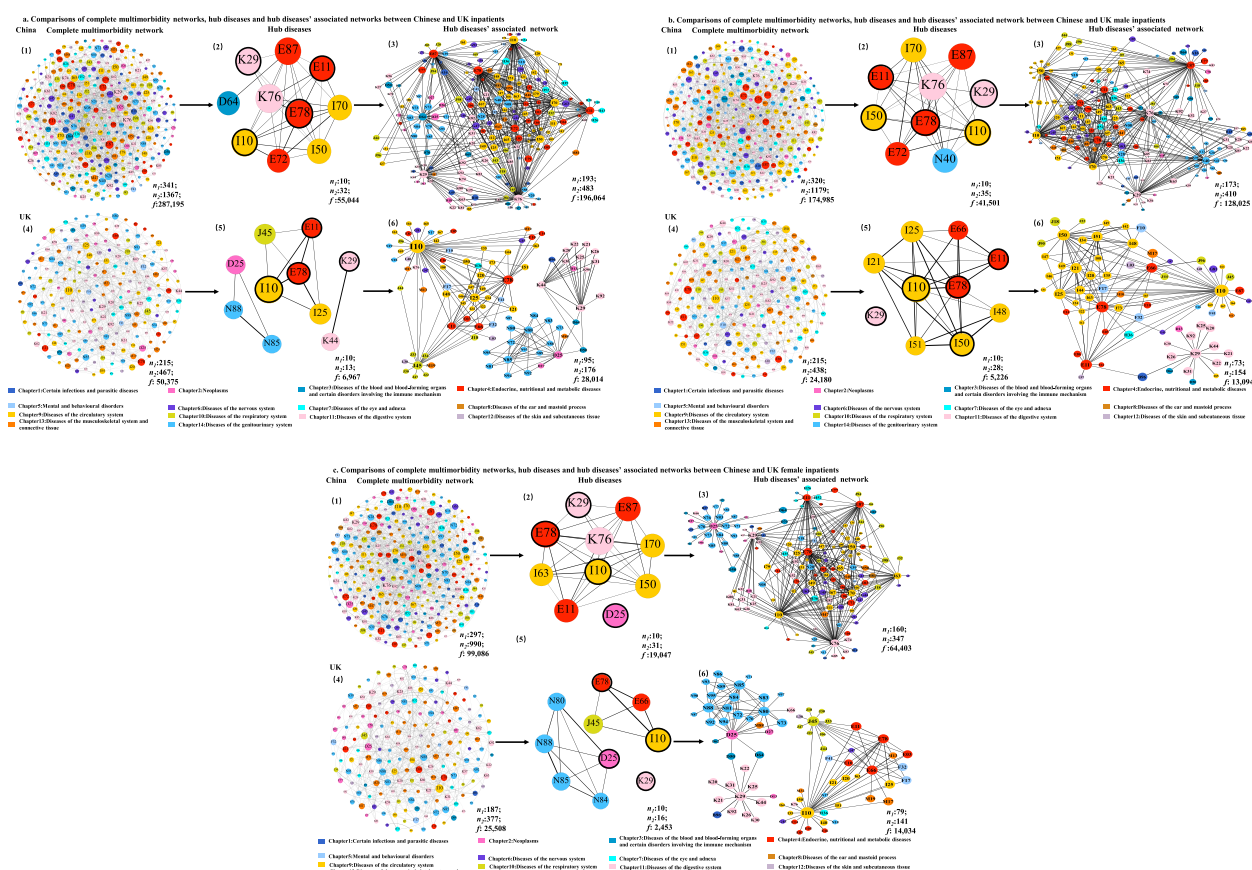


Fig. 3 **a** Comparisons of complete multimorbidity networks, hub diseases, and hub diseases' associated network between Chinese and UK inpatients. **b** Comparisons of complete multimorbidity networks, hub diseases, and hub diseases' associated network between Chinese and UK male inpatients. **c** Comparisons of complete multimorbidity networks, hub diseases, and hub diseases' associated network between Chinese and UK female inpatients. We presented the diseases in ICD-10 codes. Different colors denote different disease systematic chapters in the figure legend. The hub diseases between the Chinese and UK inpatients were highlighted in bold circles. n_1 : The number of nodes in the corresponding networks. n_2 : The number of edges in the corresponding networks. f : The total frequency of comorbidity patterns in the corresponding networks. The color of node was marked by according to disease systematic chapters. Disease name with ICD-10 codes (listed by alphabetical order): D25: Leiomyoma of uterus, D64: Other anemias, E11: Type 2 diabetes mellitus, E66: Obesity, E72: Other disorders of amino-acid metabolism, E78: Dyslipidemia, E87: Other disorders of fluid, electrolyte and acid–base balance, I10: Essential hypertension, I21: Acute myocardial infarction, I25: Chronic ischemic heart disease, I48: Atrial fibrillation and flutter, I50: Heart failure, I51: Complications and ill-defined descriptions of heart disease, I63: Cerebral infarction, I70: Atherosclerosis, J45: Asthma, K29: Gastritis and duodenitis, K44: Diaphragmatic hernia, K76: Other diseases of liver, N40: Hyperplasia of prostate, N80: Endometriosis, N84: Polyp of female genital tract, N85: Other noninflammatory disorders of cervix uteri, N88: Other noninflammatory disorders of uterus, except cervix

hernia, K44; gastroesophageal reflux disease, K21), musculoskeletal and connective tissue-related comorbidities (M17+M23), and digestive-related (K21+K44), heart-related (I20+I25), and genitourinary comorbidities (N84+N92) (Fig. 4 and Additional File 1: Table S7).

We identified ten hub diseases each from the Chinese and UK inpatients. Dyslipidemia (E78), type 2 diabetes (E11), essential hypertension (I10), and gastritis and duodenitis (K29) were overlapped hub diseases from the two populations. In Chinese inpatients, anemias (D64), disorders of fluid, electrolyte, acid–base balance (E87), amino-acid metabolism (E72), atherosclerosis (I70), heart

failure (I50), and liver diseases (K76) were specific hub diseases (Additional File 1: Table S8). Comorbidities covered by its *hub diseases' associated network* represented 35.33% (483/1367) of unique comorbidity patterns and 68.26% (196,046/287,195) of frequency of comorbidities in the complete network. In UK inpatients, leiomyoma of the uterus (D25), chronic ischemic heart disease (I25), asthma (J45), noninflammatory disorders of cervix uteri (N88), and uterus, except cervix (N85), were specific hub diseases. Comorbidities covered by its *hub diseases' associated network* represented 37.69% (176/467) of unique comorbidity patterns and 55.61% (28,014/50,375)

of frequency of comorbidities in the complete network (Fig. 3a, Table 1, Additional File 1: Table S4).

Multimorbidity networks in Chinese and UK male inpatients

The complete multimorbidity network in Chinese male inpatients was 2.69 times more complex than in UK male inpatients (Fig. 3b, Additional File 1: Table S4, Additional File 3, China: 320 diseases/1,179 comorbidities; UK: 215 diseases/438 comorbidities). In Chinese inpatients, circulatory, endocrine/nutritional/metabolic, and digestive diseases-related comorbidities were most prevalent, while in UK, the most prevalent were circulatory, digestive, and musculoskeletal diseases-related comorbidities (Additional File 2: Figure S7.1–7.2). Among Chinese male inpatients, the most common comorbidity was essential hypertension/cerebral infarction comorbidity (I10 + I63, 4598/174,985), whereas dyslipidemia/essential hypertension comorbidity (E78 + I10, 900/24,180) was the most common in UK male inpatients (Additional File 1: Table S7).

Notably, the three most common comorbidities shared between the Chinese and UK male inpatients were identical to those of the overall inpatients, and so were the China-specific comorbidities. On the contrary, common UK-specific comorbidities in males included gastritis/duodenitis (K29)-related comorbidities (with a diaphragmatic hernia, K44; gastroesophageal reflux disease, K21), other digestive-related comorbidity (K21 + K44), chronic ischemic heart disease (I25)-related comorbidities (with dyslipidemia, E78; angina pectoris, I20), gonarthrosis/internal derangement of knee (M17 + M23), and angina pectoris/essential hypertension (I20 + I10) (Fig. 4 and Additional File 1: Table S7).

For hub diseases, dyslipidemia (E78), type 2 diabetes (E11), essential hypertension (I10), gastritis and duodenitis (K29), and heart failure (I50) overlapped in both Chinese and UK males. In Chinese inpatients, disorders of fluid, electrolyte, and acid–base balance (E87), disorders of amino-acid metabolism (E72), atherosclerosis (I70),

liver diseases (K76), and hyperplasia of the prostate (N40) were specific hub diseases (Additional File 1: Table S8). Comorbidities covered by its hub diseases’ associated network represented 34.78% (410/1179) of unique comorbidity patterns and 73.16% (128,025/174,985) of frequency of comorbidities in the complete network. In UK inpatients, heart-related diseases including acute myocardial infarction (I21), chronic ischemic heart disease (I25), atrial fibrillation and flutter (I48), complications and ill-defined descriptions of heart disease (I51), and obesity (E66) were specific hub diseases. Comorbidities covered by its hub diseases’ associated network represented 35.16% (154/438) of unique comorbidity patterns and 54.15% (13,094/24,180) of frequency of comorbidities in the complete network (Fig. 3b, Table 1, Additional File 1: Table S4).

Multimorbidity networks in Chinese and UK female inpatients

The complete multimorbidity network in Chinese female inpatients was 2.63 times more complex than in UK female inpatients (Fig. 3c, Additional File 1: Table S4, Additional File 3, China: 297 diseases/990 comorbidities; UK: 187 diseases/377 comorbidities). In Chinese inpatients, circulatory, metabolic, and genitourinary diseases-related comorbidities were most prevalent, while in UK, the most prevalent were circulatory, digestive, and genitourinary diseases-related comorbidities (Additional File 2: Figure S7.1–7.2). Among Chinese female inpatients, the most common comorbidity was chronic ischemic heart disease/heart failure comorbidity (I25 + I50, 2221/99,086), whereas polyp of female genital tract/excessive, frequent, and irregular menstruation (N84 + N92, 817/25,508) was the most common in UK female inpatients.

Among the top ten most common comorbidities among Chinese and UK female inpatients, there were no overlapped comorbidities. Among Chinese inpatients, the most common group of specific comorbidities was essential hypertension (I10)-related comorbidities (with

(See figure on next page.)

Fig. 4 Overlapped and country-specific multimorbidity network patterns constructed based on the top 10 most prevalent comorbidities in overall, male, and female inpatients. In the brackets, the first number indicates ratio of the total frequency of comorbidity patterns in China-specific network and the total frequency of comorbidity patterns in the Chinese complete multimorbidity network, whereas the second number represents the corresponding ratio in the UK. The color of node was marked according to disease systematic chapters. We listed the diseases name with corresponding ICD-10 codes: D25: Leiomyoma of uterus, E11: Type 2 diabetes mellitus, E78: Dyslipidemia, G99: Other disorders of nervous system in diseases classified elsewhere, I10: Essential hypertension, I20: Angina pectoris, I25: Chronic ischemic heart disease, I50: Heart failure, I63: Cerebral infarction, I84: Hemorrhoids, J45: Asthma, K21: Gastroesophageal reflux disease, K29: Gastritis and duodenitis, K44: Diaphragmatic hernia, K62: Other diseases of anus and rectum, K76: Other diseases of liver, M17: Gonarthrosis [arthrosis of knee], M23: Internal derangement of knee, M47: Spondylosis, N39: Other disorders of urinary system, N72: Inflammatory disease of cervix uteri, N81: Female genital prolapse, N84: Polyp of female genital tract, N85: Other noninflammatory disorders of uterus, except cervix, N92: Excessive, frequent and irregular menstruation, N94: Pain and other conditions associated with female genital organs and menstrual cycle, N95: Menopausal and other perimenopausal disorders

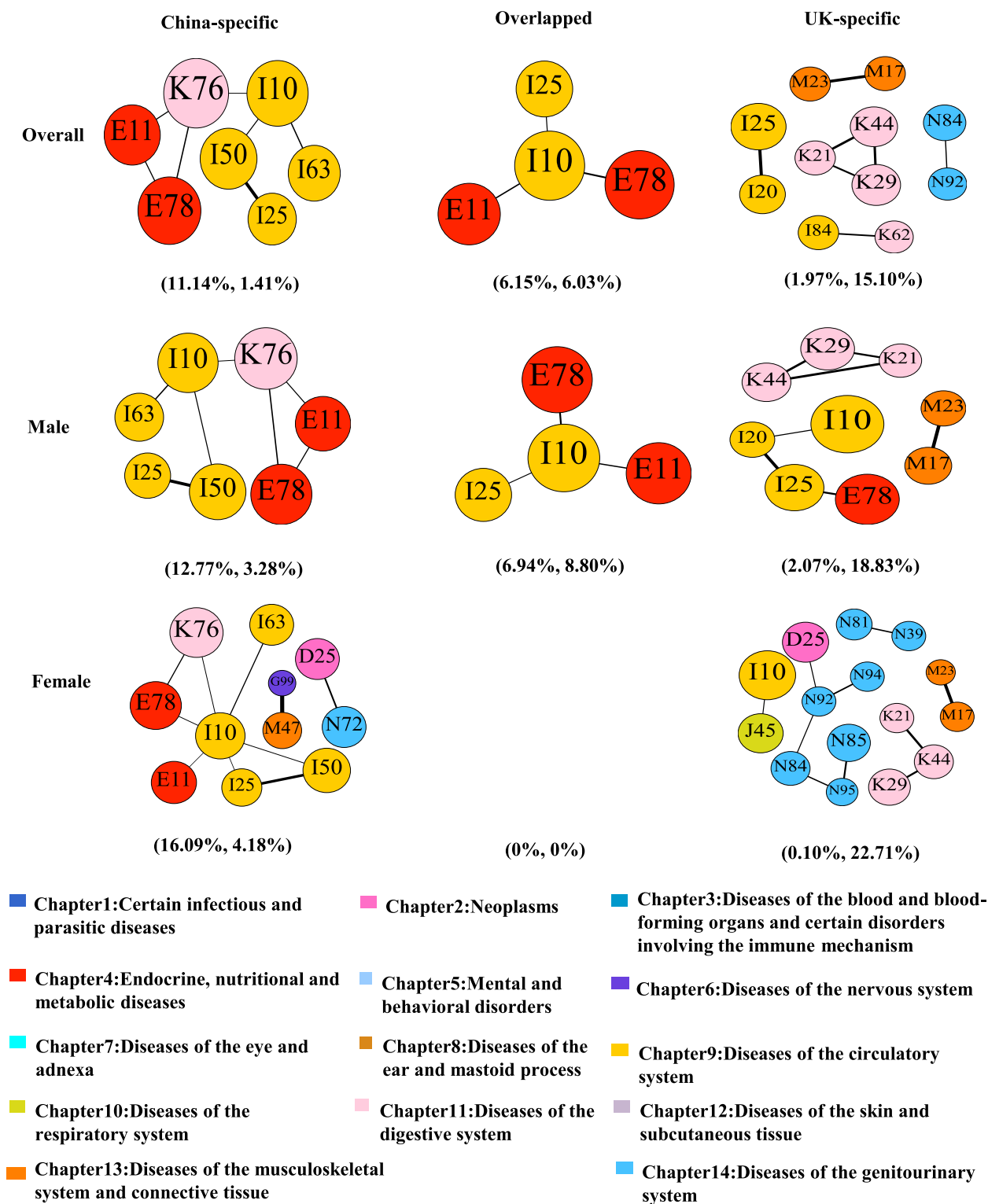


Fig. 4 (See legend on previous page.)

cerebral infarction, I63; chronic ischemic heart disease, I25; type 2 diabetes mellitus, E11; liver diseases, K76; dyslipidemia, E78). In contrast, UK-specific comorbidities were mostly associated with diseases of the genitourinary system. Diaphragmatic hernia (K44)-related comorbidities (with gastritis and duodenitis, K29; gastroesophageal reflux disease, K21) were also specific in UK female inpatients (Fig. 4, Additional File 1: Table S7).

For hub diseases, dyslipidemia (E78), essential hypertension (I10), gastritis and duodenitis (K29), and leiomyoma of the uterus (D25) overlapped between Chinese and UK female inpatients. In Chinese female inpatients, disorders of fluid, electrolyte and acid–base balance (E87), type 2 diabetes mellitus (E11), liver diseases (K76), heart failure (I50), atherosclerosis (I70), and cerebral infarction (I63) were specific hub diseases (Additional File 1: Table S8). Comorbidities covered by its *hub diseases' associated network* represented 35.05% (347/990) of unique comorbidity patterns and 65.00% (64,403/99,086) of frequency of comorbidities in the complete network. In UK female inpatients, obesity (E66), asthma (J45), genitourinary diseases including endometriosis (N80), polyp of the female genital tract (N84), noninflammatory disorders of cervix uteri (N85), and uterus, except cervix (N88), were specific hub diseases. Comorbidities covered by its *hub diseases' associated network* represented 37.40% (141/377) of unique comorbidity patterns and 55.02% (14,034/25,508) of frequency of comorbidities in the complete network (Fig. 3c, Table 1, Additional File 1: Table S4).

The metrics distribution of nodes in Chinese and UK inpatients

The hub diseases metrics were found to be ranked at the forefront of all node-related metrics in both Chinese and UK inpatients, suggesting that hub diseases are more likely to appear in inpatients with multimorbidity. Additional File 2: Figure S8 revealed a wider metric distribution among nodes in China, indicating greater complexity in multimorbidity networks compared to the UK (Additional File 3).

Discussion

This study is the first to compare comorbidity patterns in Chinese and UK inpatients using multimorbidity networks. We observed higher per-capita disease counts and a greater proportion of multimorbidity among aging Chinese inpatients compared to their UK counterparts. Chinese inpatients consistently exhibit more complex multimorbidity networks. Comorbidities involving essential hypertension (I10), dyslipidemia (E78), type 2 diabetes mellitus (E11), and gastritis and duodenitis (K29) are most common in both populations. However, Chinese

inpatients consistently demonstrate a higher frequency of comorbidities in circulatory diseases and endocrine/nutritional/metabolic diseases. In the UK, digestive diseases-related and genitourinary diseases-related comorbidities are also common, particularly the latter among female inpatients.

Our investigation reveals that Chinese inpatients exhibit a higher proportion of multimorbidity and a more intricate multimorbidity network compared to their UK counterparts. Notably, the lower socio-economic status of China, coupled with environmental and early life stressors associated with poverty and inadequate social infrastructure, may lead to the earlier onset of diseases, consequently resulting in a higher frequency of multimorbidity [1]. Besides, lower health literacy in China leads to delayed diagnosis and treatment of chronic diseases and comorbidities [1, 27, 28]. Lifestyle factors, such as tobacco use, unhealthy diets, and physical inactivity, are also more common in China [28, 29]. Furthermore, limited healthcare access and the absence of state-driven multimorbidity prevention programs in China result in greater disease burden and complexity [1]. Conversely, the UK has implemented comprehensive type 2 diabetes mellitus-related complication surveillance to manage multimorbidity in diabetic individuals [30]. The National Institute for Health and Care Excellence provides key healthcare services for adults with multimorbidity [31], a key resource currently lacking in China.

Our study confirms previous findings that circulatory and endocrine/nutritional/metabolic diseases-related comorbidities are prevalent in China [17, 32]. These patterns were echoed by a recent systematic review by Prados-Torres et al., where similar findings have been reported in 10 of the 14 multimorbidity studies [32]. The heightened prevalence of these comorbidities in China may be linked to the swift transformation of dietary patterns in the population. Western-style diets, increasingly popular in developed Chinese regions, have led to greater red and processed meat consumption [1, 33, 34]. Additionally, our data from Shaanxi Province may also indicate a common “starchy” dietary pattern, characterized by rice, noodles, and flour products in this Chinese region [35]. This dietary pattern may contribute to overweight and obesity, resulting in abnormal adipocytokine secretion and elevated risk of related comorbidities [36, 37]. Other lifestyle issues, including tobacco use, sedentary behavior, abnormal sleep duration, and low social participation, have also been identified as contributing risk factors to circulatory and endocrine/nutritional/metabolic diseases-related comorbidities in China [29, 34, 38, 39].

In the UK, there are multiple underlying reasons for the notable comorbidities related to digestive and

genitourinary diseases. First, UK inpatients exhibit higher awareness of and greater access to clinics for diagnostic testing due to good public health literacy. UK clinicians also place greater emphasis on managing genitourinary and digestive diseases, resulting in more frequent diagnoses of these comorbidities. Second, the population-wide average of standard drinks consumed per day is higher in the UK than in China [40], with excessive alcohol consumption contributing to alterations in the gut microbiome and gut epithelial integrity that increase the likelihood of digestive disorders and their associated comorbidities [41–43]. Excessive alcohol consumption may also cause urinary system diseases such as chronic kidney disease [44, 45]. It may also contribute to risky sexual behavior and increased risk of sexually transmitted infections, leading to the development of genitourinary diseases and associated comorbidities [46]. Female UK inpatients have a high prevalence of genitourinary disease-related comorbidities, likely attributed to their older age. The older age means a higher likelihood of experiencing menopause, which is associated with a decrease in estrogen stimulation and the development of genitourinary disorders such as vaginitis, bladder dysfunction, and urethral dysfunction [47, 48]. Other potential contributing factors include tobacco use, a higher number of sexual partners, and higher fertility rates in the UK [29, 46, 48–51].

We discovered that prevalent diseases often serve as hub diseases in multimorbidity networks. We found that comorbidities covered by the hub diseases' associated network account for over 68% and 55% frequency of comorbidities in the complete network for China and the UK, respectively. This finding highlights the potential importance of identifying hub diseases as a means of recognizing potential risk factors and underlying biological mechanisms for multimorbidity. Targeted surveillance and prevention of hub diseases could reduce the onset of associated comorbidities, improve healthcare utilization, and enable healthcare professionals to provide appropriate treatment plans [1]. This approach to care would shift from a single-condition treatment measurement to a patient-centered approach, allowing for comprehensive care and reducing the burden of polypharmacy. Policymakers can use these findings to establish more effective multimorbidity treatment guidelines, while patients can receive cost-effective treatment, and healthcare providers can enhance treatment efficiency and save medical resources [52, 53].

The main strength of our study is the important comparison of multimorbidity patterns in 14 ICD-10 disease chapters among middle-aged inpatients in China and the UK. However, several limitations still existed. First, we used undirected graphs based on baseline inpatient

records, rather than directed graphs derived from inpatient cohort data. Our primary objective was to compare comorbidity patterns between two regions. However, conducting direct comparisons of temporal multimorbidity patterns between these regions posed challenges due to different observation periods. Second, our study, exclusively examining inpatients, may introduce sampling bias, limiting our understanding of multimorbidity. This hinders generalizability to outpatients with different patterns and factors. Third, the initial absolute number of diagnoses in different datasets which is related to the accessibility of different healthcare systems will affect the complexity of the multimorbidity network. Fourth, half of Chinese inpatients being blood donors may lead to underestimating disease prevalence due to the healthy donor effect, introducing sampling bias, and compromising the study's representativeness for the general population, affecting its external validity. Fifth, the high prevalence of misdiagnosis and missed diagnosis in China may have underestimated comorbidity complexity. Sixth, the UK-Biobank population, being healthier and more health-literate than the general UK population, may underestimate disease prevalence and miss common comorbidity patterns, making it less representative of the broader population. Nevertheless, our conclusion remains that multimorbidity networks are more complex in Chinese inpatients than in those in the UK.

Conclusions

In conclusion, we identified higher multimorbidity prevalence and more diverse comorbidity patterns and complex multimorbidity networks in Chinese inpatients, compared to the UK inpatients. While circulatory diseases and endocrine/nutritional/metabolic disease-related comorbidities are common in both Chinese and UK inpatients, digestive and genitourinary diseases-related comorbidities are more specific in UK inpatients. Hub diseases' associated network accounts for the majority of comorbidity counts in the complete network in both China and the UK. Identifying common comorbidity patterns and hub diseases can inform prevention strategies, thus enhancing patient-centered care, reducing healthcare burden, and providing valuable insights for policymakers, patients, and treatment guidelines in different regions.

Abbreviations

UK	United Kingdom
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
CHMRs	Centralized Hospital Medical Records
HES	Hospital Episode Statistics
ORs	Odds ratios
MCC	Maximal clique centrality

Clo_Cen Closeness centrality
 Clu_Coe Clustering coefficient
 Bet_Cen Betweenness centrality

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-023-03204-y>.

Additional file 1: Additional Text: The explanation of network metrics. **Table S1.** ICD-10 chapters and corresponding content categories. **Table S2.** The number of different datasets. **Table S3.** The per-capita disease diagnoses from 1-14 ICD-10 chapters in overall, male and female inpatients among China and the UK. **Table S4.** Number of nodes and edges in the overall, male and female networks among Chinese and UK inpatients. **Table S5.** The odds ratios (ORs) and frequency of the statistically significant (*P* value, Bonferroni correction) and common (prevalence >1/10000) comorbidity patterns included in the complete multimorbidity network in Chinese overall inpatients (1367 patterns). **Table S6.** The odds ratios (ORs) and frequency of the statistically significant (*P* value, Bonferroni correction) and common (prevalence >1/10000) comorbidity patterns included in the complete multimorbidity network in the UK overall inpatients (467 patterns). **Table S7.** The most common comorbidity patterns in the overall, male and female inpatients among Chinese and UK inpatients (27 patterns). **Table S8.** The hub diseases in the overall, male and female inpatients among Chinese and UK inpatients (24 diseases). **Table S9.** The most common diseases (top10) in the overall, male and female inpatients among Chinese and UK inpatients (24 diseases).

Additional file 2: **Figure S1.** The records selection flowchart of the Shaanxi, China dataset. **Figure S2.** The records selection flowchart of the UK-Biobank dataset. **Figure S3.** The selection flowchart of the multimorbidity networks for the overall inpatients among Chinese inpatients. **Figure S4.** The selection flowchart of the multimorbidity networks for male and female among Chinese inpatients. **Figure S5.** The selection flowchart of the multimorbidity networks for the overall among UK inpatients. **Figure S6.** The selection flowchart of the multimorbidity networks for male and female among UK inpatients. **Figure S7.1.** The number of unique comorbidity patterns related to each chapter (ICD-10, 1–14 chapters) in overall, male and female inpatients in China and the United-Kingdom (UK). **Figure S7.2.** The total frequency of comorbidities related to each chapter (ICD-10, 1–14 chapters) in overall, male and female inpatients in China and the United-Kingdom (UK). **Figure S8.** Property distribution for all nodes and hub nodes of the overall, male and female inpatients among China and UK. **Figure S9.** The proportion trend of ICD-10 1–14 chapters by age.

Additional file 3. The initial diseases included and the detailed information of nodes and edges among each multimorbidity networks.

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Authors’ contributions

LZ, YB, and JY conceived the study. JY, AS, XG, TM, and SS contributed to the acquisition and interpretation of data from Shaanxi, China. YB, PL, and MW did the data cleaning. YB did the statistical analysis and model building with the assistance from LZ, XZ, LW, and YZ. YB and LZ drafted the manuscript. All authors contributed to the interpretation of the results and revision of the manuscript and approved the final version of the manuscript. CKF, XS, LW, XZ, ZZ, JY, and MH provided epidemiological, technical, or material support. LZ,

YB, JY, AS, XG, TM, SS, PL, and MW had full access to the data from Shaanxi, China, and LZ, YB, PL, MW, ZL, and HL had full access to the data from UK-Biobank. LZ, YB, PL, and MW take responsibility for the integrity of the data and the accuracy of the data analysis. LZ is the guarantor for the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials

The data from Shaanxi, China, needs to be obtained by sending a data request application to the corresponding author’s email and requires approval from Shaanxi Provincial People’s Hospital. The data of UK Biobank are available in a public, open access repository. This research has been conducted using the UK Biobank Resource under application number 79244. The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/accessed on 17 August 2022).

Declarations

Ethics approval and consent to participate

Ethical approval for our study related to the Shaanxi, China, was obtained from the institutional review board of the People’s Hospital of Shaanxi Province (No:2020-R002). It was pre-registered at China National Medical Research Register and Chinese Clinical Trial Registry; the registration number is ChiCTR2200055983 and MR-61–21-01-1750, respectively. The UK Biobank was approved by the North West Research Ethics Committee (06/MRE08/65), and all participants signed an informed consent document.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8(1):48. <https://doi.org/10.1038/s41572-022-00376-4>.
2. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinical-Medicine*. 2023;57:101860. <https://doi.org/10.1016/j.eclinm.2023.101860>.
3. Kingston A, Robinson L, Booth H, Knapp M, Jagger C. Projections of multimorbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing*. 2018;47(3):374–80. <https://doi.org/10.1093/ageing/afx201>.
4. Laires PA, Perelman J. The current and projected burden of multimorbidity: a cross-sectional study in a Southern Europe population. *Eur J Ageing*. 2019;16(2):181–92. <https://doi.org/10.1007/s10433-018-0485-0>.
5. He L, Biddle SJH, Lee JT, Duolikun N, Zhang L, Wang Z, et al. The prevalence of multimorbidity and its association with physical activity and sleep duration in middle aged and elderly adults: a longitudinal analysis from China. *Int J Behav Nutr Phys Act*. 2021;18(1):77. <https://doi.org/10.1186/s12966-021-01150-7>.
6. Salisbury C, Man MS, Bower P, Guthrie B, Chaplin K, Gaunt DM, et al. Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet (London, England)*. 2018;392(10141):41–50. [https://doi.org/10.1016/s0140-6736\(18\)31308-4](https://doi.org/10.1016/s0140-6736(18)31308-4).
7. Organization WH. Multimorbidity: technical series on safer primary care. <https://www.who.int/publications/i/item/9789241511650>. Accessed 03 May 2023.
8. Sim SZ, Koh HL, Lee SPS, Young DY, Lee ES. How does multimorbidity affect middle-aged adults? A cross-sectional survey in the Singapore primary healthcare setting. *BMC Fam Pract*. 2020;21(1):190. <https://doi.org/10.1186/s12875-020-01262-2>.
9. Infurna FJ, Gerstorf D, Lachman ME. Midlife in the 2020s: opportunities and challenges. *Am Psychol*. 2020;75(4):470–85. <https://doi.org/10.1037/amp0000591>.
10. Dong G, Feng J, Sun F, Chen J, Zhao XM. A global overview of genetically interpretable multimorbidities among common diseases in the UK Biobank. *Genome medicine*. 2021;13(1):110. <https://doi.org/10.1186/s13073-021-00927-6>.
11. Siggaard T, Reguant R, Jørgensen IF, Haue AD, Lademann M, Aguayo-Orozco A, et al. Disease trajectory browser for exploring temporal, population-wide disease progression patterns in 7.2 million Danish patients. *Nat Commun*. 2020;11(1):4952. <https://doi.org/10.1038/s41467-020-18682-4>.
12. Hidalgo CA, Blumm N, Barabási AL, Christakis NA. A dynamic network approach for the study of human phenotypes. *PLoS Comput Biol*. 2009;5(4):e1000353. <https://doi.org/10.1371/journal.pcbi.1000353>.
13. Strauss MJ, Niederkrötenhaler T, Thurner S, Kautzky-Willer A, Klimek P. Data-driven identification of complex disease phenotypes. *J R Soc Interface*. 2021;18(180):20201040. <https://doi.org/10.1098/rsif.2020.1040>.
14. Ofori-Asenso R, Chin KL, Curtis AJ, Zomer E, Zoungas S, Liew D. Recent patterns of multimorbidity among older adults in high-income countries. *Popul Health Manag*. 2019;22(2):127–37. <https://doi.org/10.1089/pop.2018.0069>.
15. Yao SS, Cao GY, Han L, Chen ZS, Huang ZT, Gong P, et al. Prevalence and patterns of multimorbidity in a nationally representative sample of older Chinese: results from the China Health and Retirement Longitudinal Study. *J Gerontol A Biol Sci Med Sci*. 2020;75(10):1974–80. <https://doi.org/10.1093/gerona/glz185>.
16. Khan MR, Malik MA, Akhtar SN, Yadav S, Patel R. Multimorbidity and its associated risk factors among older adults in India. *BMC Public Health*. 2022;22(1):746. <https://doi.org/10.1186/s12889-022-13181-1>.
17. Wang L, Qiu H, Luo L, Zhou L. Age- and sex-specific differences in multimorbidity patterns and temporal trends on assessing hospital discharge records in Southwest China: network-based study. *J Med Internet Res*. 2022;24(2):e27146. <https://doi.org/10.2196/27146>.
18. Hucklenbroich P. “Disease entity” as the key theoretical concept of medicine. *J Med Philos*. 2014;39(6):609–33. <https://doi.org/10.1093/jmp/jhu040>.
19. Organization WH. ICD-10 International Statistical Classification of Diseases and Related Health Problems. <https://icd.who.int/browse10/2016/en/#/>. Accessed 03 May 2022.
20. Zhang L, Li H, Su S, Wood EM, Ma T, Sun Y, et al. Cohort Profile: The Shaanxi Blood Donor Cohort in China. *Front Cardiovasc Med*. 2022;9:841253. <https://doi.org/10.3389/fcvm.2022.841253>.
21. Davis KAS, Bashford O, Jewell A, Shetty H, Stewart RJ, Sudlow CLM, et al. Using data linkage to electronic patient records to assess the validity of selected mental health diagnoses in English Hospital Episode Statistics (HES). *PLoS ONE*. 2018;13(3):e0195002. <https://doi.org/10.1371/journal.pone.0195002>.
22. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. <https://doi.org/10.1371/journal.pmed.1001779>.
23. Curtin F, Schulz P. Multiple correlations and Bonferroni’s correction. *Biol Psychiat*. 1998;44(8):775–7. [https://doi.org/10.1016/s0006-3223\(98\)00043-2](https://doi.org/10.1016/s0006-3223(98)00043-2).
24. Pavlopoulos GA, Secrier M, Moschopoulos CN, Soldatos TG, Kossida S, Aerts J, et al. Using graph theory to analyze biological networks. *BioData mining*. 2011;4:10. <https://doi.org/10.1186/1756-0381-4-10>.
25. Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC Syst Biol*. 2014;8 Suppl 4(Suppl 4):S11. <https://doi.org/10.1186/1752-0509-8-s4-s11>.
26. Yao L, Wei T, Zeng A, Fan Y, Di Z. Ranking scientific publications: the effect of nonlinearity. *Sci Rep*. 2014;4(1):6663. <https://doi.org/10.1038/srep06663>.
27. Hagger MS, Hardcastle SJ, Hu M, Kwok S, Lin J, Nawawi HM, et al. Health literacy in familial hypercholesterolemia: a cross-national study. *Eur J Prev Cardiol*. 2018;25(9):936–43. <https://doi.org/10.1177/2047487318766954>.
28. Agrawal S, Agrawal PK. Association between body mass index and prevalence of multimorbidity in low- and middle-income countries: a cross-sectional study. *Int J Med Public Health*. 2016;6(2):73–83. <https://doi.org/10.5530/ijmedph.2016.2.5>.
29. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet (London, England)*. 2021;397(10292):2337–60. [https://doi.org/10.1016/s0140-6736\(21\)01169-7](https://doi.org/10.1016/s0140-6736(21)01169-7).
30. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. <https://www.nice.org.uk/guidance/ng28>. Accessed May 03 2023.
31. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. <https://www.nice.org.uk/guidance/ng56>. Accessed May 05 2022.
32. Prados-Torres A, Calderón-Larrañaga A, Hanco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. *J Clin Epidemiol*. 2014;67(3):254–66. <https://doi.org/10.1016/j.jclinepi.2013.09.021>.
33. Liu J, Bai R, Chai Z, Cooper ME, Zimmet PZ, Zhang L. Low- and middle-income countries demonstrate rapid growth of type 2 diabetes: an analysis based on Global Burden of Disease 1990–2019 data. *Diabetologia*. 2022;65(8):1339–52. <https://doi.org/10.1007/s00125-022-05713-6>.
34. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol*. 2021;9(6):373–92. [https://doi.org/10.1016/s2213-8587\(21\)00045-0](https://doi.org/10.1016/s2213-8587(21)00045-0).
35. Huang L, Shang L, Yang W, Li D, Qi C, Xin J, et al. High starchy food intake may increase the risk of adverse pregnancy outcomes: a nested case-control study in the Shaanxi province of Northwestern China. *BMC Pregnancy Childbirth*. 2019;19(1):362. <https://doi.org/10.1186/s12884-019-2524-z>.
36. Salliet AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Investig*. 2017;127(1):1–4. <https://doi.org/10.1172/jci92035>.
37. Matsuzawa Y. Adipocytokines: emerging therapeutic targets. *Curr Atheroscler Rep*. 2005;7(1):58–62. <https://doi.org/10.1007/s11883-005-0076-3>.
38. Ding D, Rogers K, van der Ploeg H, Stamatakis E, Bauman AE. Traditional and emerging lifestyle risk behaviors and all-cause mortality in middle-aged and older adults: evidence from a large population-based Australian cohort. *PLoS Med*. 2015;12(12):e1001917. <https://doi.org/10.1371/journal.pmed.1001917>.
39. Zhang N, Du SM, Ma GS. Current lifestyle factors that increase risk of T2DM in China. *Eur J Clin Nutr*. 2017;71(7):832–8. <https://doi.org/10.1038/ejcn.2017.41>.

40. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* (London, England). 2018;392(10152):1015–35. [https://doi.org/10.1016/s0140-6736\(18\)31310-2](https://doi.org/10.1016/s0140-6736(18)31310-2).
41. Pohl K, Moodley P, Dhanda AD. Alcohol's impact on the gut and liver. *Nutrients*. 2021;13(9). <https://doi.org/10.3390/nu13093170>.
42. Park SH, Kim DJ. Global and regional impacts of alcohol use on public health: emphasis on alcohol policies. *Clin Mol Hepatol*. 2020;26(4):652–61. <https://doi.org/10.3350/cmh.2020.0160>.
43. Grønbaek M. The positive and negative health effects of alcohol- and the public health implications. *J Intern Med*. 2009;265(4):407–20. <https://doi.org/10.1111/j.1365-2796.2009.02082.x>.
44. Shankar A, Klein R, Klein BE. The association among smoking, heavy drinking, and chronic kidney disease. *Am J Epidemiol*. 2006;164(3):263–71. <https://doi.org/10.1093/aje/kwj173>.
45. Bundy JD, Bazzano LA, Xie D, Cohan J, Dolata J, Fink JC, et al. Self-reported tobacco, alcohol, and illicit drug use and progression of chronic kidney disease. *Clin J Am Soc Nephrol*. 2018;13(7):993–1001. <https://doi.org/10.2215/cjn.11121017>.
46. Sullivan C, Martin N, White C, Newbury-Birch D. Assessing the delivery of alcohol screening and brief intervention in sexual health clinics in the north east of England. *BMC Public Health*. 2017;17(1):884. <https://doi.org/10.1186/s12889-017-4878-3>.
47. Flores SA, Hall CA. Atrophic Vaginitis. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Carrie Hall declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
48. Ruan X, Zhang L, Cui Y, Gu M, Mueck AO. Genitourinary syndrome of menopause in Chinese perimenopausal and postmenopausal women. *Climacteric*. 2021;24(3):297–304. <https://doi.org/10.1080/13697137.2021.1889498>.
49. Unemo M, Bradshaw CS, Hocking JS, de Vries HJC, Francis SC, Mabey D, et al. Sexually transmitted infections: challenges ahead. *Lancet Infect Dis*. 2017;17(8):e235–79. [https://doi.org/10.1016/s1473-3099\(17\)30310-9](https://doi.org/10.1016/s1473-3099(17)30310-9).
50. The World Bank. Fertility rate, total (births per woman). <https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=CN-GB>. Accessed May 06 2022.
51. deVries CR. A global view of pediatric urology. *J Pediatr Urol*. 2022;18(3):271–9. <https://doi.org/10.1016/j.jpuro.2022.02.002>.
52. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* (London, England). 2012;380(9836):37–43. [https://doi.org/10.1016/s0140-6736\(12\)60240-2](https://doi.org/10.1016/s0140-6736(12)60240-2).
53. Boyd CM, Darer J, Boulton C, Fried LP, Boulton L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716–24. <https://doi.org/10.1001/jama.294.6.716>.

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