The diabetes mellitus multimorbidity network in people over 50 years: An analysis of Chinese data

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Abstract

Objective: To characterize the patients in the diabetes mellitus (DM) multimorbidity network in people over 50 years and explore the association between DM and other chronic non-communicable diseases (NCDs) and the variations in age and sex subgroups.

Methods: Data on 75 NCDs were extracted from electronic medical record of 309,843 hospitalized patients older than 50-years-old who had at least one NCD. The association rules analysis was used as a novel cluster method.

Result: The four NCDs that co-occurred with DM at the highest prevalence were hypertension (Hyp) (14.19%), dyslipidemia (Dys) (7.27%), cerebrovascular disease (CVD) (7.00%) and chronic liver disease (CLD) (6.15%). The most common triads were (Hyp, CVD, DM) (5.55%); (Hyp, Dys, DM) (4.80%); and (Hyp, coronary heart disease (CHD), DM) (4.44%). A total of 12 NCDs were closely related to DM (>1.1) with (cholelithiasis (Cho), DM) as an unexpected combination. Coexistence of (Dys, DM) and (gout, DM) had the largest in male and female groups. The negative related cluster contained seven NCDs (<0.9). There were nine NCDs included in the strong association rules. In males, the strongest rule was (peripheral vascular disease (PVD), Dys, DM), while (Hyp, Dys, CLD, DM) was the strongest in females. Most combinations were different by age and sex. In patients younger than 70 years, Hyp, CLD, and Dys were the most dominant NCDs in the DM multimorbidity network. In patients 70 years or older, chronic kidney disease (CKD), CVD, CHD, and heart disease (HD) frequently co-occurred with DM. Gout was more common in females. There were differences in the findings for Dys in male and female groups.

Conclusion: Future primary healthcare policies for DM should be formulated based on age and sex. In patients younger than 70 years, more attention for hypertension, CLD, and Dyslipidemia is needed, while attention for CKD, CVD, CHD and HD is needed in patients older than 70 years. More attention should be paid to the prevention and treatment of the concurrence of gout and DM in females. Furthermore, there should be different recommendations in the guidelines for treatment of dyslipidemia in DM patients by sex.

Introduction

The global prevalence of DM in adults is on the rise. In 2017, the global prevalence of adults with DM was 8.8% and it is expected to rise to 9.9% by 2045. In addition to diagnosed DM, approximately 352.1 million people worldwide are at risk of developing DM or pre-DM, and that number is expected to rise to 531.6 million by 2045 [1]. China has one of the largest DM populations in the world. In 2017, there were 425 million adults with DM worldwide, of which 114 million (more than a quarter) were from China. The number of adults with DM in China is expected to rise to 120 million in 2045 [2]. Therefore, prevention and treatment of DM are very important. Moreover, many DM patients suffer from at least one additional disease, which is called multimorbidity. This means that two or more non-communicable diseases (NCDs) co-occur in a patient [3]. Multimorbidity affects more than half of the elderly population and

almost all hospitalized geriatric patients [4]. The coexistence of NCDs in DM patients is more than a random event. Typically, it is due to the causal relationship between some diseases and a shared pathogenic factor [5, 6]. Some studies aimed to identify the multimorbidity patterns in patients and confirmed the existence of clinically plausible multimorbidity patterns that evolve over time [7, 8]. Such beyond-chance associations among diseases may occur when one disease causes others or when diseases share common or correlated risk factors, which may be biological risk factors [9]. Unfortunately, recommended management approaches for multimorbidity in patients with DM are lacking in most practice guidelines, which is the main scientific evidence-based tool available to clinicians [10, 11].

There is a difference in the etiological analysis of patients with a single NCD and those with multimorbidity [12]. This is not efficient and often results in an increase of intervention measures, such as numerous hospital visits, polypharmacy, and repeated investigations [13, 14]. Consequently, the current healthcare systems fail to appropriately address the healthcare needs of geriatric patients with multimorbidity.

No effective interventions for multimorbidity in patients with DM have yet been addressed in most developing countries. Improving the health status and quality of life of people affected by multimorbidity requires a new integrated and innovative treatment model [15, 16]. Exploring the interrelationships and underlying networks of multimorbidity in patients with DM may help to meet this challenge and may provide new insights for interventions in people with DM and multimorbidity.

Occurrences of multimorbidity in patients with DM has been recognized and investigated in previous studies [17–22]. Several risk factors of DM include ethnicity, obesity and unhealthy diet [23–26]. Some studies have shown that the multimorbidity patterns in people with DM was different among groups stratified by sex and age [10, 17, 20, 21, 27–29].

Multimorbidity has been a recent focus in studies. Studies used cluster analysis [17, 19, 21], network analysis [18, 20, 22, 27, 30] or latent class analysis [31, 32] to explore the multimorbidity patterns in people with DM. However, many of these studies were limited either by their small sample sizes [18, 21, 27, 33, 34] or by the small number of conditions [18, 21, 31, 33, 35] used to study multimorbidity patterns. These previous studies provided limited information on the DM multimorbidity network. They investigated patterns of all included NCDs, but not further study the patterns of the associations between NCDs and DM.

In this study, we presented the DM multimorbidity network in middle-aged and older adults and we used association rules mining (ARM) to explore the relationship between 74 NCDs and DM. The ARM is a method used to examine associations between variables. Several applications of ARM in the medical domain include examining of disease co-occurrences [17, 19, 27], identifying adverse effects of drugs [36], and detecting risk factors for disease [23, 25, 26, 37, 38]. We focused on examining patterns which are present in people with DM. First, we studied whether they were associations between NCDs and DM. Second, the study explored the multimorbidity patterns in people with DM and assessed the variations in these patterns by age and sex.

Methods

Data Source and Study Design

The original data was obtained from the electronic medical record homepages of hospitalized cases in various medical institutions in Shenzhen, China between January 1, 2017, and December 31, 2018. We included data of a total of 309,892 participants aged ≥ 50 years with at least one NCD, including data on sex, age and discharge diagnosis information on NCDs.

All diagnoses were coded according to the International Classification of Disease version 10 and 75 NCDs were included. We analyzed the data using the Apriori algorithm, and applied the association rules about DM.

Defining Multimorbidity

The most widely used definition of multimorbidity was considered, which is the co-occurrence of two or more NCDs in an individual [14].

Statistical Analyses

Descriptive Analysis

Patients were categorized into four subgroups based on age (50 – 59, 60 – 69, 70 – 79, and ≥ 80 years). There were two sex groups. Continuous variables are presented as median (interquartile range; IQR). A $P < 0.05$ was considered statistically significant. All the tests showed a significant P value, which were not presented in the results. All the descriptive statistical analyses and ARM in this study were preformed using R 3.4.3.

Association Rule Mining

Association rules are used to examine associations between NCDs [18, 39]. This is a fast method to discover combinations of comorbidities that occur more frequently than expected and might provide insights into NCDs and aging mechanisms.

The three commonly used measurement ratios were used. The support (sup) is a measure of how frequently NCD A and NCD B combinations appear in the dataset. It measures the strength of a rule and is defined as: $\mathrm{sup}(\mathrm{AB}) = \mathrm{P}(\mathrm{AB})$. The confidence (con) is the conditional probability that a participant who has NCD A also has NCD B, and it defined as: $\mathrm{con}(\mathrm{AB}) = \mathrm{P}(\mathrm{B}\,|\,\mathrm{A}) = \mathrm{P}(\mathrm{AB})\,/\,\mathrm{P}(\mathrm{A})$. The lift is the ratio of the observed $\mathrm{sup}(\mathrm{AB})$ to that expected if A, B are independent. It is defined as: $\mathrm{lift}(\mathrm{AB}) = \mathrm{P}(\mathrm{AB})\,/\,(\mathrm{P}(\mathrm{A})\mathrm{P}(\mathrm{B}))$. The lift measures the strength of an association as a rule within ARM and is therefore considered the main outcome in this study. It can be used to identify rules whether the dependence between A and B is weak or strong [24]. We applied this method to examine association in a dataset of people with DM and other NCDs using a classifier based on lift. When $\mathrm{lift}(\mathrm{AB}) = \mathrm{a} > 1$, this indicates that A combined with B occurs a-fold more than expected under statistical independence. It can

be interpreted as a positive relationship between A and B. When $\mathrm{lift}(\mathrm{AB}) < 1$, this indicates that the joint set {A, B} appear less often than expected, there is a negative relationship between A and B. When $\mathrm{lift}(\mathrm{AB}) = 1$, this indicates that there is no association between A and B. Hence, a higher sup indicates a more important joint set {A, B}. A higher lift indicates a stronger association of the joint set {A, B}. S up, con, lift are related to the effect size of associations, as opposed to simple tests of statistical significance [18].

Results

Participants' Characteristics

The dataset consisted of 309,892 inpatients, of whom 149,834 (48.35%) were female and 160,058 (51.65%) were male. The median age was 63 years (IQR, 56 − 72) and that of males and females was 63 years (IQR, 55 − 71) and 64 years (IQR, 57 − 73), respectively. 21.09% (65,341/309,892) of participants had only one NCD, while 19.49% (60,399/309,892), 16.23% (50,286/309,892) and 13.27% (41,121/309,892) had two, three or four NCDs, respectively. Table 1 shows the proportion of people with DM in different age groups of males and females. The proportion of people with DM in the overall dataset was 22.89%, with a higher proportion among males (23.81%) than females (21.90%). The proportion of people with DM varied by age. The age group of 50 − 59 years and that of 70 − 79 years had the lowest (19.62%) and highest (27.58%) proportion of people with DM, respectively.

Table 1
Prevalence of DM in different age groups of males and females

Age	Female(*n*/%)	Male(*n*/%)	*P*-value
50~	8739(15.82)	15399(22.73)	< 0.001
60~	11527(23.66)	11964(24.43)	< 0.001
70~	8358(29.16)	7291(25.99)	< 0.001
80~	4159(24.17)	3464(22.69)	< 0.001

Table 2 shows the ten most common dyads, triads and quartets NCDs combination associated with DM by sex. The most common NCDs included Hyp, Dys, CVD, CLD, PVD, CHD, CKD, HD, gout, arrhythmia (Arr), anemia (Ane), and prostate disease (PD). Among the dyads NCDs combinations, the three most common combinations in males were (Hyp, DM) (14.17%), (CVD, DM) (7.40%), and (Dys, DM) (7.24%), while these were (Hyp, DM) (14.21%), (Dys, DM) (7.30%), and (CVD, DM) (6.58%) in females. The dyad (CKD, DM) combination was ranked fourth among males and seventh among females. The proportion of people with the dyad {CKD, DM} combination in males is almost 1.5 times higher than that in females. The proportion of males with triad combinations including DM was generally higher than that of females with the same combinations. For example, the proportion of males with the combination {Hyp, CKD, DM} was significantly higher than that of females (4.72% vs 3.44%). However, the proportion of females with the

combination (Hyp, Dys, DM) was higher than that of males (5.03% vs 4.59%). In addition, Dys occur 1 time in the male group and 3 times in the female group. The combination {Hyp, CVD, DM} was the most common combination among both sex groups. Among quartets of NCDs combinations, the ten most common combinations were different by sex. The most common quartet combination was (Hyp, Dys, CVD, DM) in females and (Hyp, HD, CHD, DM) in males. The quartet (Hyp, PVD, CVD, DM) combination was the second most common combination in both sexes. All combinations of NCD included Hyp due to its high prevalence.

Table 2
Prevalence of the 10 most common morbidity about DM.

Type	Order	Total		Female		Male	
		Conditions	%	Conditions	%	Conditions	%
dyads	1	Hyp	14.19	Hyp	14.21	Hyp	14.17
	2	Dys	7.27	Dys	7.30	CD	7.40
	3	CD	7.00	CD	6.58	Dys	7.24
	4	CLD	6.15	CLD	5.63	CKD	6.78
	5	PVD	5.88	PVD	5.40	CLD	6.64
	6	CHD	5.73	CHD	5.14	PVD	6.33
	7	CKD	5.72	CKD	4.59	CHD	6.29
	8	HD	3.80	HD	3.29	PD	4.53
	9	gout	3.35	gout	3.03	HD	4.27
	10	Arr	2.65	Ane	2.47	gout	3.65
triads	1	Hyp,CD	5.55	Hyp,CD	5.36	Hyp,CD	5.73
	2	Hyp,Dys	4.80	Hyp,Dys	5.03	Hyp,CKD	4.72
	3	Hyp,CHD	4.44	Hyp,CHD	4.18	Hyp,CHD	4.69
	4	Hyp,PVD	4.32	Hyp,PVD	4.14	Hyp,Dys	4.59
	5	Hyp,CKD	4.10	Hyp,CLD	3.73	Hyp,PVD	4.49
	6	Hyp,CLD	3.87	Hyp,CKD	3.44	Hyp,CLD	4.00
	7	HD,CHD	3.19	Dys,CD	2.81	HD,CHD	3.67
	8	Hyp,HD	2.98	Dys,CLD	2.78	Hyp,HD	3.24
	9	PVD,CD	2.87	Hyp,HD	2.70	PVD,CD	3.10
	10	Dys,CLD	2.83	HD,CHD	2.68	Hyp,PD	2.95
quartet	1	Hyp,HD,CHD	2.51	Hyp,Dys,CD	2.29	Hyp,HD,CHD	2.77
	2	Hyp,PVD,CD	2.37	Hyp,PVD,CD	2.24	Hyp,PVD,CD	2.50
	3	Hyp,Dys,CD	2.19	Hyp,HD,CHD	2.23	Hyp,Dys,CD	2.10
	4	Hyp,PVD,Dys	1.87	Hyp,Dys,CLD	1.88	Hyp,CKD,CD	1.91

Note: DM in the table is omitted

Type	Order	Total		Female		Male	
		Conditions	%	Conditions	%	Conditions	%
	5	Hyp,Dys,CLD	1.84	Hyp,PVD,Dys	1.87	Hyp,CHD,CD	1.89
	6	Hyp,CHD,CD	1.83	Hyp,CHD,CD	1.78	Hyp,PVD,Dys	1.87
	7	Hyp,PVD,CHD	1.66	Hyp,Dys,CHD	1.65	Hyp,Dys,CLD	1.80
	8	Hyp,Dys,CHD	1.65	Hyp,PVD,CHD	1.56	Hyp,PVD,CHD	1.76
	9	Hyp,CKD,CD	1.64	Hyp,PVD,CLD	1.50	Hyp,CKD,CHD	1.75
	10	Hyp,PVD,CLD	1.58	Hyp,CLD,CD	1.47	Hyp,CKD,PVD	1.74
Note: DM in the table is omitted							

Multimorbidity Patterns In People With Dm

The minimum sup was set as 0.005, as a small sup would result in $lift$ with a large random error. When $lift > 1.1$, the ARM showed a list of NCDs which were positively related to DM, while $lift < 0.9$ created a list of NCDs which were negatively related to DM. The remaining NCDs were weakly related or not related to DM.

After analysis, there were a total of 25 NCDs. Figure 1 and Fig. 2 show the results of the ARM by $lift$ and sup, respectively. In Fig. 2, the gray grid indicates $sup < 0.005$.

There were 12 NCDs positively related to DM, including CVD, CHD, Cho, CKD, CLD, HD, Hyp, Dys, gout, PVD, transient cerebral ischemia (Tci), and PD. The proportion of people with most of these NCDs in combination with DM increased with age. Moreover, this proportion increased more in females than in males. The proportion of people with (Dys, DM), (Tci, DM), and (Hyp, DM) was higher in males than that in females. In the group of 50–69 years, the proportion of people with (PVD, DM), (gout, DM), (CLD, DM), (HD, DM), (Cho, DM), (CHD, DM) and (CVD, DM) was higher in males than that in females, with an opposite finding in those aged 70 years and above. The proportion of people with (Tci, DM), (gout, DM) and (Cho, DM) increased slowly with increasing age, while that of (Dys, DM) and (CLD, DM decreased with increasing age in males.

The most common rule was (Hyp, DM). This combination was approximately 1.22 to 1.66-fold more present than expected by chance. The combination (PVD, DM) had the highest $lift$ in the group of 50 – 59 years. The combination was 2.01 and 1.82-fold more present in females and males, respectively, than would be expected if they were independent. The combinations (Dys, DM) and (gout, DM) had the highest lift value in people of 60 years or older in male and female group, respectively.

Ane, Arr, dizziness/vertigo (Diz), osteoarthropathy (Ost), senile cataract (SC), spondylosis (Spo) were in the weakly related or not related group.

A total of seven NCDs were negatively related to DM, which were bronchiectasis (Bro), chronic gastritis (CG), chronic obstructive pulmonary disease (COPD), disc degeneration (DD), malignant tumor (MT), osteoporosis (OP) and pulmonary heart disease (Pul PHD). In the subgroups of sex and age, DD appeared in the positively related and negatively related groups. The co-occurrence of these NCDs in DM patients were less than a random event.

The NCDs included in this study and related to DM with $\sup < 0.005$ were chronic pain, indigestion, chronic cholecystitis, spleen diseases, varicose vein of lower extremity, schizophrenia, bipolar disorder, dementia, Alzheimer's disease, bronchiectasis, glaucoma, asthma, chronic sinusitis, chronic rhinitis, chronic nasopharyngitis, chronic pharyngitis, chronic laryngitis, diverticulosis of intestine, hypothyroidism, hyperthyroidism, hearing loss, tinnitus, vision impairment or blindness, psoriasis, eczema, migraine, depressed, epilepsy, anxiety, Parkinson's disease, constipation, chronic tonsillitis, eating disorders, sleep disorders, chronic rheumatic heart disease, heart disease (not specifically), chronic renal failure, chronic gastric ulcer, chronic duodenum ulcer, chronic peptic ulcer, chronic gastrojejunal ulcer, rheumatoid arthritis, obesity, systemic connective tissue disease, edentulous, somatoform disorder, paralysis, urinary incontinence, neurological disorders, and chronic viral hepatitis. To study the relationship between these diseases and DM more samples are needed.

Variations Of Multimorbidity Patterns In People With Dm By Sex And Age

The association rules included a total of nine NCDs, which were CVD, CHD, CKD, CLD, HD, Hyp, Dys, PVD and gout. When looking at different age and sex groups, the types and order of the most common NCDs were quite different in these subgroups. Multimorbidity in patients with DM was more prominent in males and older individuals.

The multimorbidity patterns in people with DM generated by the ARM are presented in Fig. 3. Increased length of the sector indicated a larger $\sup$. Among the four age groups of males, 48, 81, 137 and 108 rules were detected, while 16, 53, 136 and 115 were found in females. The ten most common rules are shown for each group. The proportion of people with the rules was mostly higher in males than that in females, especially in the group of 50 – 59 years. The most common of all rules was Hyp, followed by Dys and CHD. The prevalence of Hyp was similar in all age and sex groups. Among males, the most common rule which included Dys was (Hyp, Dys, DM) with a large $\sup$. Among females, Dys and DM were more likely to be associated with other NCDs than that in males and the majority of rules that included Dys appeared in quartets. CHD occurred more frequently in males than in females (sixteen vs. seven) and more frequently in the group of 70 years and older than in the group of 50 – 69 years

(seventeen vs. six). In addition, there were four rules that included gout in the female group, while there were none in the male group.

The proportion of people with multimorbidity substantially increased with age, but slightly decreased in the group of 80 years and older. The rules in the groups of younger than 70 years were triads, while most of rules were quartets in the groups of 70 years and older. Hyp, CLD and Dys appeared more frequently in the association rules for the groups of younger than 70 years. The combinations (Hyp, CLD, DM), (Hyp, Dys, DM) and (CLD, Dys, DM) appeared often when ranking the most common combinations by sup in the group of 50 – 59 years. Among those in the group of 70 years and older, the DM multimorbidity network was complex. CKD, CVD, CHD and HD frequent appeared in the association rules.

When exploring the important and strong multimorbidity patterns in people with DM, the threshold for values were set as sup=0.01, lift=1.5, and con was unbounded. If a minimum con threshold was set at 0.8, all rules should have lift metrics starting at 0.8, which is close to 1 [24].

Discussion

Multimorbidity is common in DM patients older than 50 years. In this analysis of data from a large hospital, it was demonstrated that 12 NCDs were strongly related to DM. The most unexpected finding of a NCD related to DM was Cho. Furthermore, seven NCDs were negatively related to DM. Ane and Arr were weakly related to DM, while Diz, Ost, SC and Spo were not related to DM. The relationship between DD and DM depended on age. The NCDs CVD, CHD, CKD, CLD, HD, Hyp, Dys, PVD and gout were common in the DM multimorbidity network. Emphasis on these NCDs is needed for the prevention and treatment of DM. The DM multimorbidity network showed inconsistent results when looking at different ages and sexes. Multimorbidity in patients with DM was more prominent in males and older people. There were differences in the findings for some NCDs in males and females, such gout and Dys.

The results showed that the combination (Cho, DM) (lift>1.2) occurred at least 1.2 times more than expected under statistical independence. This was likely as Cho and DM had the same pathological pathways or potential risk factors. Clarifying the relationship between Cho and DM is of great significance for patients. There were associations between Hyp, CHD, PVD, gout, PD, CLD, CKD, and DM and these NCDs have an interlinked pathophysiology [19, 40], as previously described in literature. For the group of 50 – 59 years, the strongest association rule was (PVD, DM) (lift>1.8). The likelihood of occurrence of DM in people with PVD was at least 1.8 times higher than in those included in the analysis. For people older than 60 years, (Dys, DM) and (gout, DM) had the largest lift in males and females, respectively. This indicates that Dys in males and gout in females have the strongest relationship with DM. The relationship between DD and DM was dependent on age. There may be some potential negative associations between DD and DM. It is essential to note that the relationship of (DD, DM) by age needs to be further examined.

Our next step was to explore the association rules between NCDs and DM by subgroup analyses.

The DM multimorbidity network in males was more complex than that in females. The male group had more rules and a higher proportion of individuals with multimorbidity. The most common NCD associated with DM was Hyp, followed by Dys and CHD. There were significant differences in the associations (gout, DM) and (Dys, DM) for males and females. Gout was stronger related to DM in females than that in males meaning that there is a higher risk for females. The association with Dys was different in males and females. Among males, the most common rule for Dys appeared in (Hyp, Dys, DM) with a large sup. Among females, Dys was more likely to be related to other NCDs than that in males. The majority of Dys rules appeared in quartets.

Our results highlighted some important combinations with DM and showed differences in the type and order of the most common associations by sex and age. The proportion of people with multimorbidity in those with DM increased with advancing age, but it was lower in those older than 80 years compared to those of 70 to 79 years. The difference by age and sex may be explained by survival bias. For those younger than 70 years, triad was the most common type of rule. Hyp, Dys and CLD are common diseases. They play an important part in multimorbidity in patients with DM, while CKD, CVD, CHD and HD frequently co-occur in people with DM older than 70 years. It suggests that screening for additional NCDs in each age group in a targeted manner becomes more efficient.

Investigating the DM multimorbidity network remains an underexplored area of research [41]. Despite the increasing prevalence of multimorbidity in patients with DM, there are no specific recommendations for diagnosis and treatment [42].

Our results confirmed and expanded on results of previous studies on multimorbidity in patients with DM in older adults. Together they supported policies for the management of DM patients with multimorbidity in primary care and community settings. These results have the potential to consider the DM multimorbidity network as a framework for addressing the care of older adults with complex multimorbid conditions. Moreover, different strategies should be developed to prevent multimorbidity pattern in people with DM with different strategies in males and females.

When developing guidelines for the management of patients, age, sex and potential risks of diseases need to be taken into account for recommendations on the diagnosis and monitoring. Some concurrent conditions may not necessarily have a clinical impact but may complicate interpretation of symptoms.

Strength And Limitations

This is the first study assessing the DM multimorbidity network using ARM, rather than using network analysis [18, 20, 22, 27, 30] or cluster analysis [17, 19, 21]. ARM has been developed as a novel cluster method to examine associations of NCDs and provides the objective indicator lift. It does not rely on preconceived assumptions whether certain conditions are associated, thereby minimizing confirmation biases because no hypotheses were postulated [19] and is thus an objective parameter. This study used medical records of patients with chronic conditions rather than self-reported data and had a large sample

size, resulting in reliable results. The results provided evidence that contributed to previous research conclusions and provided a reference of the DM multimorbidity network for follow-up research.

Several limitations of our study need be acknowledged. First, our research data were from hospitalized patients and therefore the proportions of people with multimorbidities could not be applied to the whole population. However, this did not conflict with the main aim of this study, which was to focus on the DM multimorbidity network. Second, due to the cross-sectional nature of the data, the results did not demonstrate causal links between NCDs. The results can only be interpreted as a basis for further longitudinal or experimental studies exploring the pathogenesis of multiple NCDs.

Comparison With Studies In Literature

The results of this study showed that 12 NCDs were positively related to DM, and 7 NCDs were negatively related. The shared etiologies of most diseases and DM has been demonstrated, such as for CVD [43], CHD [44], CHD [45], CKD [46], CLD [47], HD [48], dyslipidemia [49, 50], PD [51], gout [52], PVD [53], and Tci [54]. Our results were more reliable due to a larger sample size than in previous studies, and thereby provides evidence that supports our conclusions. There is lack of clarity in understanding the co-occurrence of cholelithiasis and DM. A study showed that cholelithiasis was directly related to body weight and abdominal adiposity [55]. Obesity is related to DM, suggesting that there is a potential relationship between cholelithiasis and DM.

To our knowledge, there is no specific recommendation to screen for Diz, Ost, SC, and Spo in patients with DM, while Arr and Ane are related to DM [56, 57]. Our results showed that Arr and Ane were weakly associated with DM.

When looking at the negative associations, there are limited studies on CG, MT, OP, and Pul with regard to NCDs that complicate DM. The published studies on the co-occurrence of COPD and DM are controversial [58, 59]. A review study [60] listed seven studies on DM and DD, of which four showed that DM was a significant risk factor of DD, and the remaining three failed to find any association. Another study concluded that DM had a devastating effect on DD [61]. Our results showed a negative association between DD and DM, adding to the clinical evidence that is not consistent. There may be some potential influencing factors of COPD, DD and DM, resulting in a negative association between COPD and DM. The biological link is still unclear.

Most of the studies in literature on multimorbidity use ARM. It is difficult to compare the results of this study directly with published studies, since there is heterogeneity in definitions, populations [18, 19, 62], analytical methods, and data collection. The published studies focused on the association rules among all the included NCDs. Only several rules on DM are generated, and most of them were already well-know, such as{Hyp, DM}[7, 18, 20, 21, 27, 30, 62], {Dys, DM}[7, 18, 20, 21, 27], {CHD, DM} [19, 21, 28], {CKD, DM} [19]. These rules were also shown in our results.

Previous multimorbidity studies have not found a relationship between Cho, gout, PVD, Tci, PD and DM. The combination {Obesity, DM} ($lift$>3.0) was not found in this study ($sup = 0.0029 < 0.005$). Stoke, arthritis and cancer did not appear in studies using the ARM method. In our study, MT was found in the negative related group. This could be due to the different types of MT that are used in the definition of multimorbidity studies.

This study focused on the DM multimorbidity network, rather than the multimorbidity network of all NCDs. Our results were more detailed and comprehensive. Many combinations have not been found in previous studies.

Conclusion

Our results indicated that the DM multimorbidity network varied by age and sex. It suggested that targeted screening for DM according to age and sex would increase efficiency. Males and older people were more vulnerable to multimorbidity in those with DM, and particular multimorbidities in people with DM cluster together frequently and more often than expected by chance. Moreover, conditions such as CVD, CHD, CKD, CLD, HD, Hyp, Dys, gout, and PVD were common in the DM multimorbidity network and were directly or indirectly related to DM. Hyp, CLD, Dys were more common in people younger than 70 years, while CKD, CVD, CHD and HD were more common in people older than 70 years. The combinations (Dys, DM) and (gout, DM) had the greatest $lift$ in males and females, respectively. The relationship between Dys, gout and DM in males and females needs to be considered. The combination Cho and DM gave an unexpected multimorbidity score and represents a complex comorbid condition. A more integrated multidisciplinary approach focusing on improved management and prevention of DM may help prevent other conditions in the network. The guidelines on the management of patients with DM should be focused on recommendations based on age and sex and potentially revised to consider the co-management of conditions that cluster around DM.

Declarations

Authors' contributions: J-D.N. and C.C. conceived and designed this research, C.C. extracted the data and performed statistical analyses, M-Y.L. and Y-L.L. searched literatures and designed the list of conditions, S-M.C. and T-Y.L. provided great assistance to the whole process of research design and data analysis, X-Y.P. and L.Z. provided key ideas for paper writing, M-Y.L. and Y-L.L. organized the tables, C-C. and H-S.L. drew the figures. C.C. wrote the initial draft of the paper. J-D.N. and C.C. provided major suggestions for the revision of the paper. All authors edited and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

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Patient consent for publication: Not required.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

Informed written consent was obtained from all participants included in this study. The study was approved by the Research Ethics Committee of Guangdong Medical University (YJYS2018046).

Conflict of interest

The authors declare that they have no competing interests.

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Figures

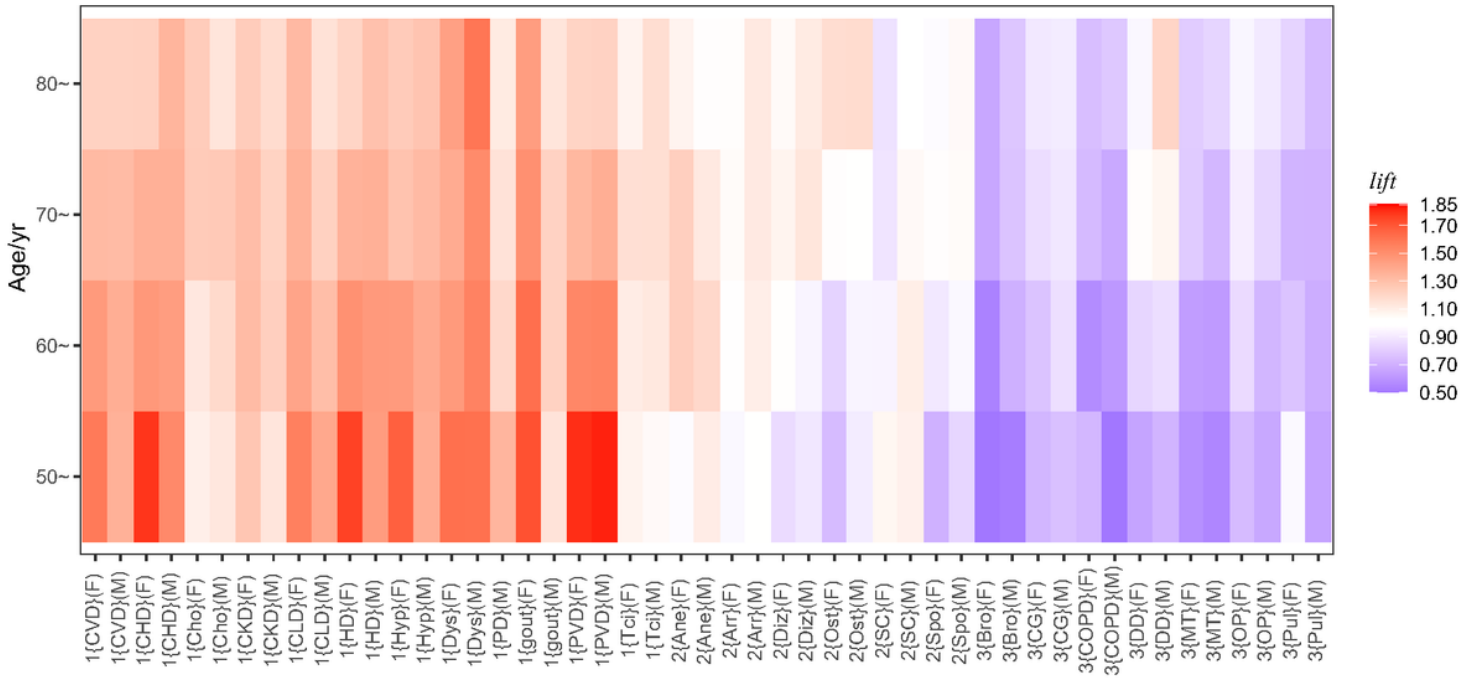

Figure 1

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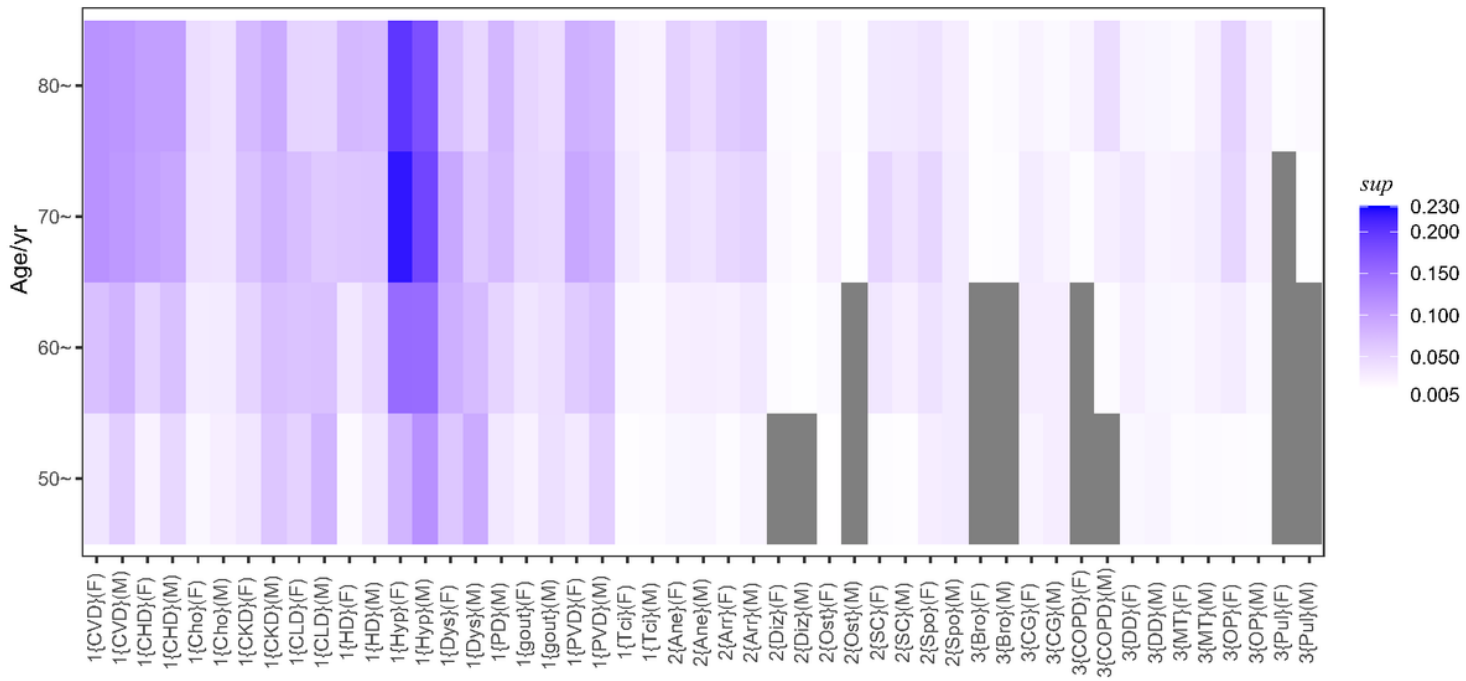

Figure 2

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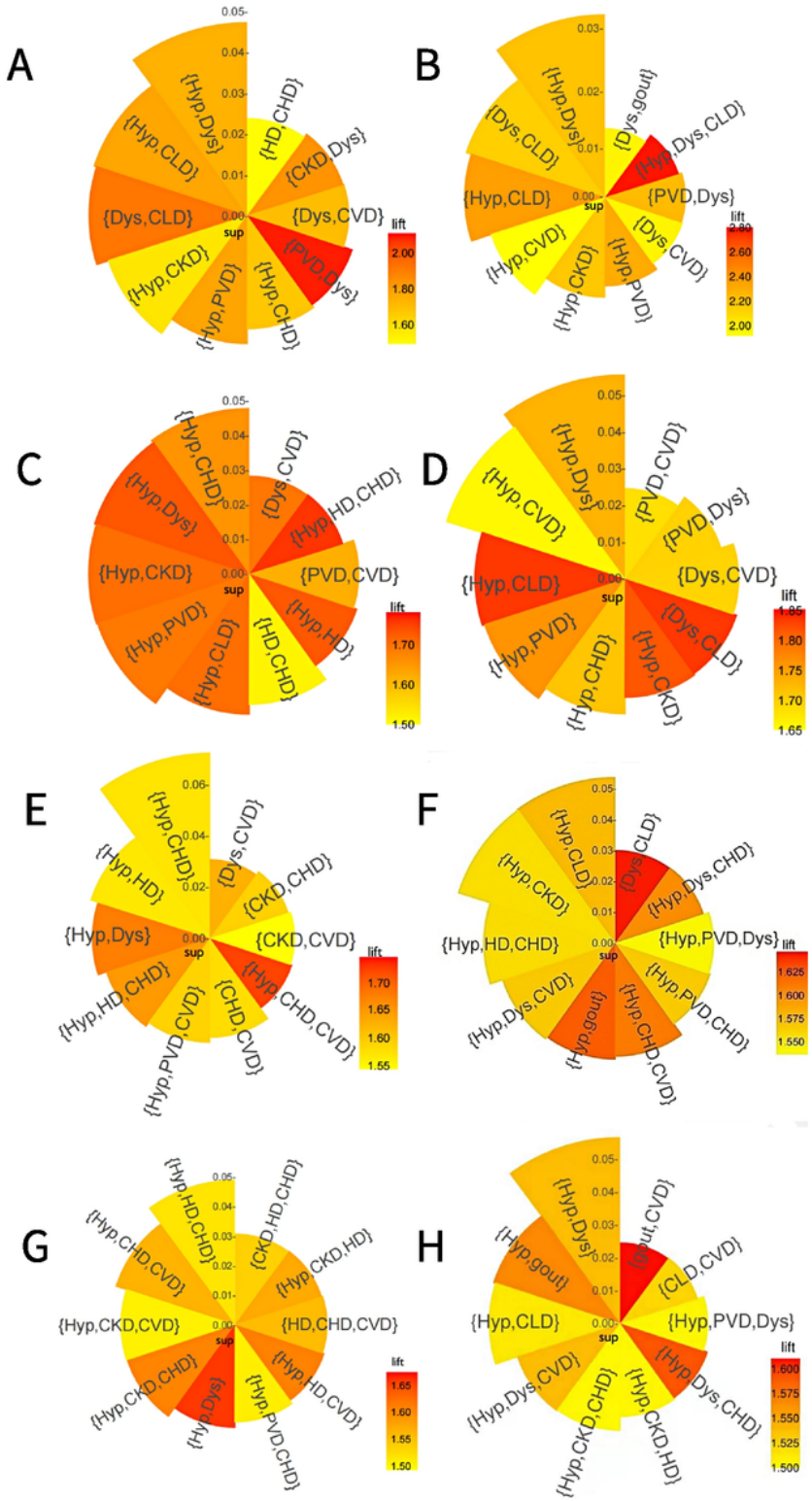

Figure 3

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