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ORIGINAL ARTICLE

Patterns of Multimorbidity in Middle-Aged and Older Adults: An Analysis of the UK Biobank Data

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Abstract

Objective: To assess the prevalence, disease clusters, and patterns of multimorbidity using a novel 2-stage approach in middle-aged and older adults from the United Kingdom.

Patients and Methods: Data on 36 chronic conditions from 502,643 participants aged 40 to 69 years with baseline measurements between March 13, 2006, and October 1, 2010, from the UK Biobank were extracted. We combined cluster analysis and association rule mining to assess patterns of multimorbidity overall and by age, sex, and ethnicity. A maximum of 3 clusters and 30 disease patterns were mined. Comparisons were made using lift as the main measure of association.

Results: Ninety-five thousand seven hundred-ten participants (19%) had 2 or more chronic conditions. The first cluster included only myocardial infarction and angina (lift=13.3), indicating that the likelihood of co-occurrence of these conditions is 13 times higher than in isolation. The second cluster consisted of 26 conditions, including cardiovascular, musculoskeletal, respiratory, and neurodegenerative diseases. The strongest association was found between heart failure and atrial fibrillation (lift=23.6). Diabetes was at the center of this cluster with strong associations with heart failure, chronic kidney disease, liver failure, and stroke (lift>2). The third cluster contained 8 highly prevalent conditions, including cancer, hypertension, asthma, and depression, and the strongest association was observed between anxiety and depression (lift=5.0).

Conclusion: Conditions such as diabetes, hypertension, and asthma are the epicenter of disease clusters for multimorbidity. A more integrative multidisciplinary approach focusing on better management and prevention of these conditions may help prevent other conditions in the clusters.

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In recent years, health care systems globally are facing a challenge due to the continuous demographic transition and better diagnosis and treatment of diseases, resulting in more people living with long-term conditions. Approximately 15 million people in England are estimated to have long-term conditions; of these, 6.75 million (45%) have more than 1 long-term condition.[1] Similar prevalence estimates have been reported in other studies from Sweden, the United States, Bangladesh, Ireland, and Spain.[2-5] Multimorbidity leads to poor quality of life,[6] worse health outcomes,[7,8] and higher health care use.[9] In light of the social and health care costs associated with multimorbidity, what is needed is a multidimensional approach to studying the phenomenon, with a clear understanding of the pathogenesis, trajectories, and underlying networks of chronic conditions.

To date, a variety of studies have investigated patterns of multimorbidity,[10,11] mainly using factor analysis.[12-18] More recent studies have used latent class analysis[19,20] or cluster analysis[21] to explore patterns of multimorbidity. However, many of these studies are limited either by their small sample sizes[12,17,22,23] or by the small number of conditions used to define multimorbidity.[16,17,20,22] Furthermore, these methods investigate overall patterns but do not elucidate associations between individual conditions within the patterns well. The National Institute for Health and Care Excellence recently published guidelines on the clinical assessment and management of multimorbidity and recommend an approach that focuses on the interactions between a person's health conditions and treatments and benefits and risks of following recommendations from guidance on single health

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conditions.[24] Moreover, a systematic review assessing the effectiveness of interventions for the management of multimorbidity concluded that interventions targeted either at specific groups of conditions or at specific problems for patients with multiple conditions may be more effective than a blanket approach.[25] Therefore, it is not only important to understand the patterns of multimorbidity but also to recognize associations between conditions within these patterns, which requires new approaches to assess disease patterns in a population with multimorbidity.[10]

We used a combination of cluster analysis and data mining techniques to identify disease clusters and patterns of multimorbidity, with an emphasis on the associations between different conditions within a cluster, using a comprehensive list of chronic conditions in a large sample of adults aged 40 to 69 years from the United Kingdom. As a secondary aim, we assessed the variations in these patterns by age, sex, and ethnicity.

METHODS

Data Source and Study Design

This research was conducted using UK Biobank, a major collaborative research project that aims to improve the prevention, diagnosis, and treatment of illness. More than 500,000 participants attended 22 assessment centers throughout the United Kingdom between March 13, 2006, and October 1, 2010. The assessment included a self-completed touch screen questionnaire and a brief computer-assisted interview that collected information on sociodemographic features; family history and early life exposures; psychosocial, environmental, and lifestyle factors; medical history; and medications.[26-28] In addition, physical and functional measures were assessed, and blood, urine, and saliva samples were taken. Participants are being followed up through repeated assessment and linkages with hospital records and national mortality data.[28] The study population included 502,643 participants aged 40 to 69 years.

Defining Multimorbidity

In light of the lack of a standard definition of multimorbidity,[29] the most widely used definition of multimorbidity was considered (the coexistence of ≥2 long-term conditions in the same individual).[30]

When deciding which chronic conditions to include in the definition of multimorbidity, we used a comprehensive approach considering chronic conditions included in a previous large UK-based study (40 conditions),[29] a systematic review on multimorbidity indices (17 conditions),[31] and the quality and outcomes framework, which is a voluntary annual reward program for all primary care practices in the United Kingdom and lists chronic conditions that require more attention from the primary care practitioners.[32] Based on these 3 criteria and the data available in UK Biobank, 36 conditions were extracted from the data set for inclusion in this study to define multimorbidity (Figure 1).

Statistical Analyses

Descriptive Analysis. Data on baseline characteristics and self-reported medical conditions were extracted. Six age groups (≤45, 46-50, 51-55, 56-60, 61-64, and ≥65 years) and 5 race/ethnicity groups (white, mixed, Asian, black, and other) were created. Socioeconomic status was presented as the Townsend deprivation index, which measures area-level deprivation based on 4 indicators—unemployment, house ownership, car ownership, and overcrowding—and was derived using 2001 census data.[33,34] Positive values of the Townsend deprivation index indicate high material deprivation, whereas negative values indicate relative affluence.[35,36] Continuous covariates were summarized using mean ± SD/median (interquartile range [IQR]) as appropriate. Categorical variables were examined using frequency tables and CIs for proportions, and the χ^2 test was performed to compare these characteristics by multimorbidity. A $P<.05$ was considered statistically significant. All the descriptive statistical analyses were performed using Stata software version14 (StataCorp LLC).

Cluster Analysis and Association Rule Mining. Owing to the complex nature of the data and the inclusion of 36 chronic conditions, an overall association rule mining (ARM) analysis would be limited in yielding important associations. Therefore, we developed a 2-step approach to identifying patterns of

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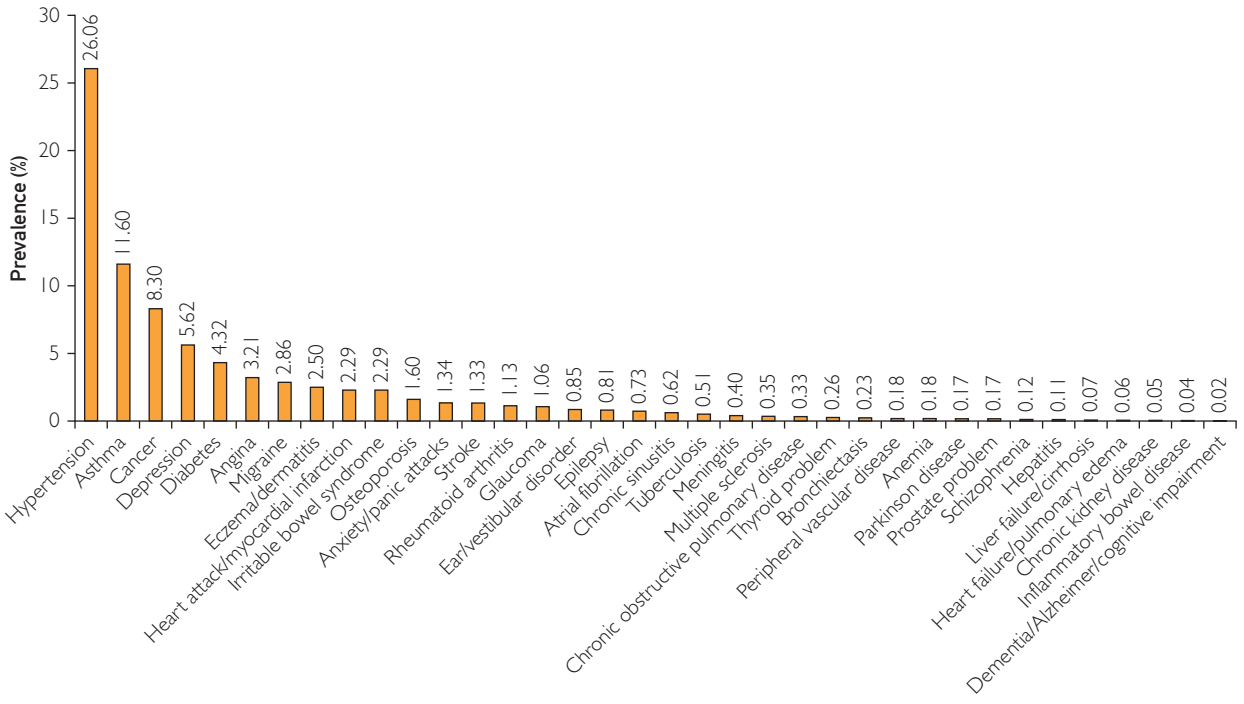

FIGURE 1. Conditions included in the multimorbidity definition by prevalence.

multimorbidity first using a cluster analysis to identify chronic conditions that cluster together and then using ARM to investigate patterns within these clusters more closely. We first used a hierarchical agglomerative clustering approach to create dendrograms that clearly displayed diseases that are associated at different levels or branches of the tree. A binary distance measure was used to produce the distance matrix resulting in more distinctive clusters compared with other proximity measures. We used the Ward method for the dendrogram analysis because this method aims to find compact clusters and minimizes the variance within clusters[37] compared with single linkage and average linkage methods, which successively chained observational into 1 cluster.[21] Possible clustering solutions were considered to determine the number of clusters to extract, and we used 3 clusters because they gave enough power for ARM analysis within each cluster.

We then conducted ARM within each cluster, restricting the maximum number of mined associations to 30 to facilitate clear visualization of the patterns because increasing the number of association rules made the visualizations too complicated but did not change the overall patterns. We made use of the 3 commonly used measurement ratios: support (how frequently the disease combinations appear in the data set), confidence (the conditional probability that a participant who has the antecedent disease will also have the consequent disease), and lift (the ratio of the observed support to that expected if the 2 events were independent). Lift measures the importance of a rule within ARM and, therefore, was considered the main measure of significance in the study. A lift of more than 1 indicates that the antecedent conditions and the consequent conditions appear more often together than expected, which can be interpreted as the antecedent having a positive effect on occurrence of the consequent. A lift of less than 1 indicates that the antecedent and consequent conditions appear less often than expected, which means that the occurrence of the antecedent has a negative effect on the occurrence of the consequent, and a lift close to 1 indicates that the antecedent

and the consequent conditions occur as often together as expected, meaning that occurrence of the antecedent has little or no effect on occurrence of the consequent conditions. Hence, the higher the lift, the higher the chance of co-occurrence of the consequent with the antecedent and the more significant the association. Results of ARM analyses are presented using summary tables of association rules and graphical visualizations showing patterns of diseases.

Subgroup Analyses. Variations of multimorbidity patterns were assessed by age, sex, and race/ethnicity. Age was recategorized into 3 subgroups (≤50, 51-60, and >60 years old) due to the complexity of the mining process required with 6 age groups. Similarly, race/ethnicity was regrouped into 2, comparing the white and nonwhite populations. All the ARM and cluster analyses in this study were performed using R software, version 3.3.1.

RESULTS

Participant Characteristics

Of the 502,643 participants, 273,467 (54.4%) were female and 472,825 (94.2%) were white. The median age was 58 years (IQR, 50 to 63 years), with approximately 40% of the participants older than 60 years (n=193,147). The median Townsend deprivation score was −2.14 (IQR, −3.63 to 0.55), indicating more representation of affluent groups in the study compared with deprived groups (Table 1).

TABLE 1. Descriptive Characteristics of the Study Population (N=502,643)

Characteristic	Participants (No. [%])
Sex	
Males	229,176 (45.6)
Females	273,467 (54.4)
Age (y)	
≤45	64,482 (12.83)
46-50	67,724 (13.47)
51-55	78,917 (15.70)
56-60	98,373 (19.57)
61-64	97,118 (19.32)
≥65	96,029 (19.10)
Race/ethnicity	
White	472,825 (94.1)
Mixed	2958 (0.6)
Asian	9882 (2.0)
Black	8066 (1.6)
Other	6134 (1.2)
Unknown	2778 (0.5)
Employment status	
Employed/self-employed	287,234 (57.1)
Retired	167,013 (33.2)
Looking after home/family	13,862 (2.8)
Unable to work due to illness/disability	16,836 (3.3)
Unemployed	8266 (1.6)
Other	8561 (1.8)
Missing	871 (0.2)
Education level	
College or university degree	161,210 (32.1)
A/As levels or equivalent	55,334 (11.0)
O levels/GCSEs or equivalent	132,117 (26.3)
Other qualifications	149,335 (29.7)
Missing	4647 (0.9)
Deprivation quintile	
1st quintile (affluent)	100,688 (20.03)
2nd quintile	100,119 (19.92)
3rd quintile	100,412 (19.98)
4th quintile	100,395 (19.97)
5th quintile (deprived)	100,402 (19.97)
Missing	627 (0.12)

Chronic Conditions and Prevalence of Multimorbidity

Hypertension, asthma, and cancer were the 3 most common conditions, with prevalences of 26.1%, 11.6%, and 8.3%, respectively (Figure 1). A total of 221,260 participants (44%) had no chronic conditions, 185,673 (37%) reported having 1 chronic condition, and 95,710 (19%) were affected by 2 or more conditions and were multimorbid. The average number of conditions and the prevalence of multimorbidity did not seem to vary by age group (P=.07). However, stratification by sex and race/ethnicity revealed slight variations (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). The prevalence of multimorbidity in the black population was found to be the lowest (16%) compared with 19% in the white, mixed, and Asian groups (P<.001). The prevalence of multimorbidity was higher in the deprived groups compared with the affluent groups (23% in quintile 5 compared with 17% in quintile 1; P<.001).

Patterns of Multimorbidity

Of the 3 clusters (Figure 2), the first cluster contained only 2 conditions: myocardial infarction (MI) and angina. These conditions

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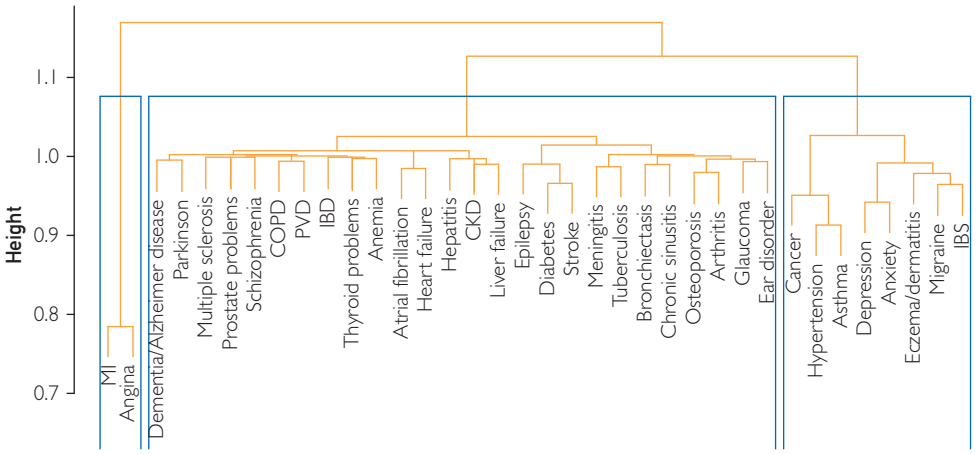

FIGURE 2. Dendrogram of cluster analysis showing 3 clusters. CKD = chronic kidney disese; COPD = chronic obstructive pulmonary disease; IBD = irritable bowel disease; IBS = irritable bowel syndrome; MI = myocardial infarction; PVD = peripheral vascular disease.

were highly associated, with a lift of 13.3, meaning that these 2 conditions are very closely linked and the probability of MI is 13 times higher in the presence of angina or vice versa. The second cluster was fairly large, consisting of 26 conditions, including cardiovascular (CV), musculoskeletal, respiratory, and neurodegenerative diseases. The ARM in this cluster resulted in 20 association rules (Table 2). Visualization of the disease patterns is shown in Figure 2, where the strongest association was found between heart failure and atrial fibrillation (lift=23.6), indicating that there is a 23 times higher likelihood of these 2 conditions occurring together than in isolation. Diabetes was found to be at the center of this cluster, with presence in 14 of the 20 association rules and with direct and indirect association with almost all the conditions in the cluster (Figure 3A). The third cluster contained 8 highly prevalent conditions: cancer, hypertension, asthma, anxiety, depression, eczema, irritable bowel syndrome, and migraine. A total of 26 association rules were extracted from the last cluster, with asthma occurring in 12 of the 26 association rules and depression and cancer appearing in 9 rules each (Figure 3B). The strongest association was observed between anxiety and depression (lift=5.0), indicating the likelihood of having depression to be 5 times higher in the presence of anxiety.

Variations of Multimorbidity Patterns by Sociodemographic Features

Cluster analysis by sex, age, and race/ethnicity resulted in similar numbers and types of conditions in each cluster, with some variations. Nevertheless, these small differences in the

TABLE 2. Association Rules Extracted From the Large Cluster (Cluster 2) in the Order of Lift

Antecedent	Consequent	Lift
Heart failure	Atrial fibrillation	23.601
Stroke, glaucoma	Diabetes	6.519
Diabetes, glaucoma	Stroke	5.349
Epilepsy	Stroke	4.711
Liver failure	Osteoporosis	4.578
Heart failure	Diabetes	4.553
Atrial fibrillation	Stroke	3.997
Chronic kidney disease	Diabetes	3.689
Bronchiectasis	Osteoporosis	3.579
Liver failure	Diabetes	3.519
Chronic obstructive pulmonary disease	Osteoporosis	3.376
Stroke	Diabetes	3.182
Schizophrenia	Diabetes	2.541
Anemia	Diabetes	2.022
Glaucoma	Diabetes	1.897
Atrial fibrillation	Diabetes	1.730
Vascular disease	Diabetes	1.514
Arthritis	Diabetes	1.496
Chronic obstructive pulmonary disease	Diabetes	1.486
Hepatitis	Diabetes	1.283

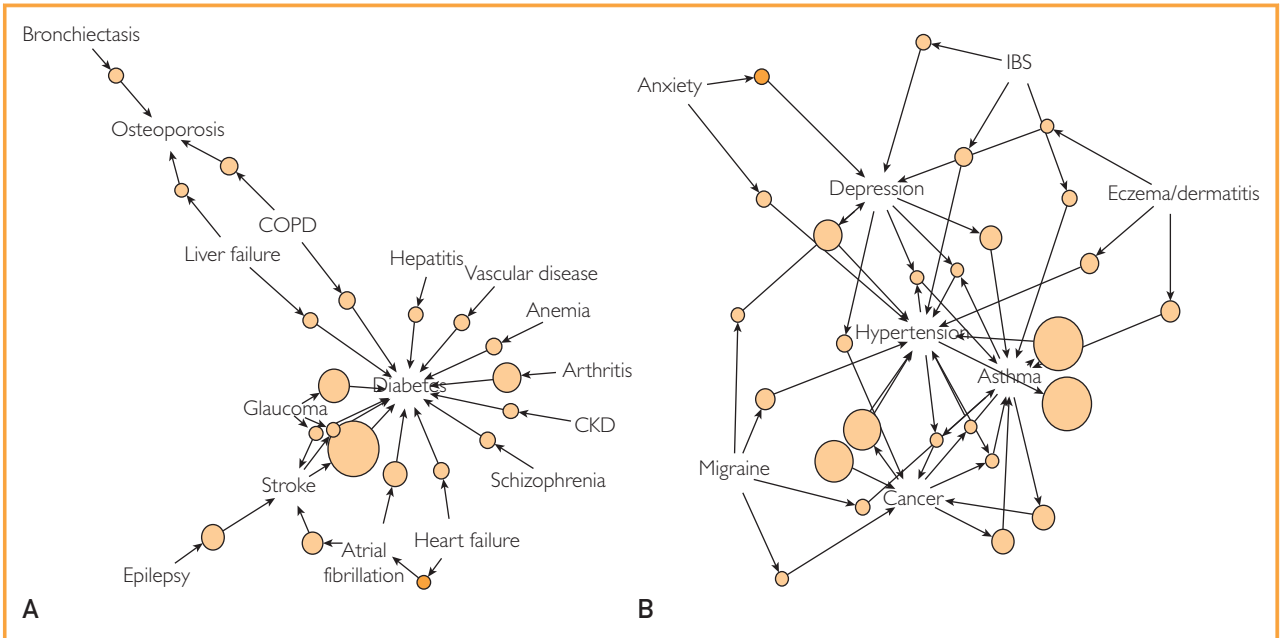

FIGURE 3. Visualization of association rules extracted from the large (cluster 2) (A) and medium (cluster 3) (B) clusters. The items grouped around a circle represent an item set, and the arrows indicate the relationship between rules. Directions of the arrows indicate antecedent and consequent items. The size of the circle represents the level of support associated with the rule and the color the level of lift (the rule with the highest lift is colored dark orange). IBS = irritable bowel syndrome.

clustering resulted in significant variations in multimorbidity patterns by sex and race/ethnicity in the large clusters. The disease patterns in the male cluster were clearly dominated by depression (Supplemental Figure 1A, 5A available online at http://www.mayoclinicproceedings.org), but the strongest association found was between heart failure and atrial fibrillation (lift=20). In the case of the female cluster, the condition that was mostly associated with other conditions was diabetes, followed by osteoporosis (Supplemental Figure 1B, 5B). A triad pattern that had diabetes and arthritis in the antecedent and stroke in the consequent showed the strongest association (lift=6.8). Similarly, the subgroup analysis by race/ethnicity showed that diabetes was the most dominant condition in the center of associations for the white population, whereas depression and cancer dominated the cluster in the nonwhite population (Supplemental Figure 2, 6 available online at http://www.mayoclinicproceedings.org). The ARM analysis by age groups resulted in largely similar multimorbidity patterns (Supplemental Figure 3, 4 available online at http://www.mayoclinicproceedings.org).

DISCUSSION

Using a large national data set from the United Kingdom, we found the prevalence of multimorbidity to be 19%. When divided into 3 clusters, the first cluster contained only MI and angina with very strong association. Diabetes was found to be at the core of the second cluster, with strong associations with heart failure, chronic kidney disease, liver failure, and stroke. In the third cluster, asthma, depression, and cancer were the epicenter.

Strength and Limitations

To our knowledge, this is the first study assessing patterns of multimorbidity in the United Kingdom, with a novel 2-step analytical approach, compared with previous studies. The study used data from more than half a million people with high sensitivity to identify participants with multimorbidity by using a comprehensive list of 36 conditions. The ARM analysis, also known as market-basket analysis, is a well-established technique in market research but is rarely applied to epidemiologic studies. To date, only 1 study has made use of ARM to examine multimorbidity patterns.[38] Due to the more complex nature of the data,

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we integrated ARM within cluster analysis to further explore the association of individual conditions within each cluster of multimorbidity. Moreover, this approach did not rely on preconceived assumptions as to how particular conditions were associated, minimizing confirmation biases because no previous hypotheses were postulated.[39] However, participation in the UK Biobank is voluntary, with higher representation from more affluent socioeconomic groups evidenced by the median Townsend deprivation index of −2.14 compared with −1.87 for the United Kingdom in the 2001 census.[35] Considering that multimorbidity is more common in deprived groups, we may have underestimated the prevalence. Nevertheless, individual estimates of chronic conditions in the present study closely mirror those from the General Lifestyle Survey in Great Britain for the same age group and period. For example, the prevalence rates of hypertension, asthma, and cancer, which were the 3 most common conditions in the present study, were 26%, 12%, and 8%, respectively, compared with 24%, 13%, and 5% in the 2009 General Lifestyle Survey in Great Britain. Therefore, we believe that the findings from the present study are largely generalizable to the UK general population.[40] To date, there is no standard way to define multimorbidity; however, we used the most common definition, with a wide range of conditions. We also used self-reported data on chronic conditions rather than medical records. However, previous research has shown good agreement between self-reported data and administrative data for chronic conditions, including diabetes, hypertension, and asthma, and moderate agreement for more acute conditions associated with chronic conditions, including stroke and MI.[41,42] In addition, due to the exploratory nature of cluster analysis, there is no set number of optimal clusters to generate, and different clustering algorithms may generate different numbers of clusters and constituents within the clusters; nevertheless, we used 3 clusters to optimize data mining within the clusters. Another important limitation of agglomerative hierarchical clustering is that each diagnosis can belong to only 1 cluster at a time. Although, the present study sample was very large, we studied only participants aged 40 to 69 years, and the clusters may vary in people 70 years and older. Last, although we found disease clusters and strength of associations between conditions within each cluster, due to the cross-sectional nature of the data, the study cannot establish any causal links between conditions; hence, a longitudinal study with a focus on trajectories of development of these conditions may shed more light on causality.

Comparison With Current Literature

The difference in populations, definitions of multimorbidity, and analysis techniques makes it difficult to compare the results of the present study with other published data. Using a similar definition of multimorbidity, a previous study using data from medical practices in Scotland found the prevalence of multimorbidity to be 23.2%,[29] which is similar to the present findings. We also found the prevalence of multimorbidity to be slightly higher in women than in men, which is consistent with previous findings.[15,43] A potential explanation for the higher prevalence in women is that women are generally more sensitized to their health and are more likely to report more conditions.[43] Previous studies have found a higher prevalence of multimorbidity in black racial/ethnic groups.[44,45] In contrast, we found the prevalence of multimorbidity to be slightly lower in black individuals. This could potentially be due to a different baseline population (more affluent participants from the United Kingdom vs population surveys from the United States) and the differences in the definition of multimorbidity between studies.

A systematic review of 14 studies on multimorbidity patterns found similarities for 3 patterns of multimorbidity, including CV and metabolic diseases, mental health problems, and musculoskeletal disorders.[10] In contrast, the present study found 3 main clusters, the first consisting of CV disorders; the second consisting of a mix of CV, musculoskeletal, respiratory, and neurodegenerative diseases; and the third dominated by mental health disorders. We found heart failure/atrial fibrillation and anxiety/depression to have the highest lifts in their respective clusters. A recent study including 1464 men older than 70 years from the Concord Health and Ageing in Men Project in Sydney, Australia, using ARM found similar results, with anxiety and heart failure having the highest lift in their population.[38] In a large epidemiologic analysis of multimorbidity in people older than 16 years from Scotland, in the most affluent

group, 10% of people with cancer also had a diagnosis of depression, and in the most deprived group, 19% of people with cancer had a diagnosis of depression.[29] In comparison, using data from all socioeconomic groups aged 40 to 69 years, we found the probability of cancer and depression co-occurring to be 6%. In the large disease cluster, most association rules seemed biologically plausible on visual examination. For example, there are etiologic associations among diabetes, heart failure, chronic kidney disease, vascular disease, glaucoma, and stroke, with an interlinked pathophysiology. However, some combinations, such as epilepsy and stroke, are less common. Nevertheless, recent data from Taiwan National Health Insurance claims data showed the incidence of stroke to be 3-fold higher in people with epilepsy compared with controls.[46] Similarly, an association between schizophrenia and diabetes, despite not being commonly known, has been demonstrated previously.[47-49]

Interestingly, although mental health disorders, including depression, are more common in women, the present results suggest that depression in males is more closely interlinked to conditions such as heart disease and systemic disorders compared with females, in whom depression is not as strongly linked to other conditions in the cluster. Previous studies on the association between depression and heart disease by sex present conflicting evidence. A prospective study investigating the effects of recent-onset depression and CV events found that men with new-onset depression were twice as likely to have a CV event compared with those who were never depressed; however, this association was not evident in women.[50] In contrast, another study assessing the association between depression and heart failure by sex found depression to be an independent risk factor for heart failure in elderly women but not in men[51]; however, this may be due to better survival in women compared with men. Nevertheless, the differences in associations between mental health disorders such as depression and heart disease by sex require further investigation. The prevalence of multimorbidity was not significantly different by age (18.9% in those aged ≤45 years compared with 19.1% in those ≥65 years; P=.06). Similarly, the patterns of multimorbidity did not vary by age group, which is in contrast to the findings of previous studies.[29,52,53] This may be due to the fact that there was not much age variation in the population because participants were aged 40 to 69 years at the baseline assessment, and if a wider age group was to be included there may be variations in the patterns. Last, we found the prevalence of multimorbidity to be the lowest in the black race/ethnic group (16.1%) and highest in the Asian group (19.6%) compared with the white group (19.1%). This is, again, in contrast with a previous study using the Rochester Epidemiology Project records-linkage data on 138,858 participants, capturing health care visits between 2005 and 2010, which found the prevalence of multimorbidity to be higher in the black race/ethnicity group than in the white group and lower in the Asian group than in the white group. However, after age 70 years, the black group was found to have the lowest prevalence of multimorbidity, followed by the Asian and white groups.[52] These differences can potentially be explained by the differences in socioeconomic inequalities and educational attainment of different race/ethnicities in the 2 regions. Nevertheless, more research is needed to comprehensively examine the patterns of multimorbidity in different race/ethnic groups.

CONCLUSION

We found that almost one-fifth of the present study population had multimorbidity. We also found that conditions such as diabetes, asthma, depression, and cancer were the central point of disease clusters and directly or indirectly related to several conditions in their respective clusters. Because the present research was based on cross-sectional data, further research should focus on longitudinal data to assess trajectories of the development of multimorbidity and their effects on health outcomes. Furthermore, a more integrative multidisciplinary approach focusing on better management and prevention of conditions such as diabetes and hypertension, which are the epicenter of disease clusters and potentially part of the trajectories of several other chronic conditions. In addition to the introduction of specific multimorbidity guidelines, guidelines on the management of individual index conditions should also be examined and potentially revised to include the co-management of a myriad of conditions that cluster around it.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ARM** = association rule mining; **CKD** = chronic kidney disese; **COPD** = chronic obstructive pulmonary disease; **CV** = cardiovascular; **IBD** = irritable bowel disease; **IBS** = irritable bowel syndrome; **IQR** = interquartile range; **MI** = myocardial infarction; **PVD** = peripheral vascular disease

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Potential Competing Interests: Professor Davies has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; has served as a speaker for Mitsubishi Tanabe Pharma Corp; and has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, and Lilly. Professor Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Servier, and Merck Sharp & Dohme; has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme; and has received funds for research, has received honoraria for speaking at meetings, and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme, and Novo Nordisk. The rest of the authors report no competing interests.

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