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Increases in multimorbidity with weight class in the United States

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Summary

Little is known regarding how multimorbidity combinations associated with obesity change with increase in body weight. This study employed data from the national Cerner HealthFacts Data Warehouse to identify changes in multimorbidity patterns by weight class using network analysis. Networks were generated for 154 528 middle-aged patients in the following categories: normal weight, overweight, and classes 1, 2, and 3 obesity. The results show significant differences (P -value <0.05) in prevalence by weight class for all but three of 82 diseases considered. The percentage of patients with multimorbidity (excluding obesity) increases from 55.1% in patients with normal weight, to 57.88% with overweight, 70.39% with Class 1 obesity, 73.99% with Class 2 obesity, and 71.68% in Class 3 obesity, increasing most substantially with the progression from overweight to class 1 obesity. Most prevalent disease clusters expand from only hypertension and dorsalgia in normal weight, to add joint disorders in overweight, lipidemias in class 1 obesity, diabetes in class 2 obesity, and sleep disorders and chronic kidney disease in class 3 obesity. Recognition of multimorbidity patterns associated with weight increase is essential for true precision care of obesity-associated chronic conditions and can help clinicians identify and address preclinical disease before additional complications arise.

Keywords

multimorbidity; network analysis; precision care

1 | INTRODUCTION

Multimorbidity is defined as the occurrence of two or more chronic health conditions within the same patient, and patients with obesity are at substantially higher risk of developing

multimorbidity compared to patients of normal weight.¹⁻³ Multimorbidity prevalence among the middle-aged was 32.8% in 2010,⁴ but its prevalence in the patients with obesity exceeds 60%.^{5,6} Since obesity rates are increasing worldwide, obesity is contributing to a rapidly worsening pandemic of multimorbidity. Obesity-associated multimorbidity is particularly concerning among middle-aged adults since many more are afflicted with obesity and multimorbidity than are older adults² and they will live longer lives with multimorbidity and associated complications. Research demonstrates that numerous chronic conditions develop as complications of obesity.⁷ Furthermore, the multiple chronic conditions associated with obesity are inordinately expensive to treat.^{8,9} Relative to other multimorbidity combinations, those involving obesity are associated with increased social isolation and vulnerability,¹⁰ poorer outcomes, and increased hospitalization.¹¹

These challenges necessitate precision and patient-centered care approaches that tailor clinical management of multimorbidity according to individual patient needs using evidence-based treatment paradigms explicitly designed and tested for the most prevalent multimorbidity combinations. International experts are challenging the single-disease framework for health care delivery and are calling for enhanced focus on multimorbidity and support for generalist clinician efforts to provide personalized and comprehensive care for the increasing number of people with diseases occurring in combination.¹² As Bierman and colleagues note, true precision care for multimorbidity requires careful tailoring of treatment to “an individual's profile of conditions, health and functional status, goals, and preferences” rather than according to genetic, molecular diagnostic, or pharmacogenomic profiles.¹² Thus, to support true precision care, there is a critical need to study most prevalent patterns of obesity-related multimorbidity because the impacts of multimorbid disease combinations are greater than the impacts expected for the sum total of their individual morbidities.^{3,12} Patients with multimorbidity have a higher risk of adverse outcomes and are more likely to receive ineffective care.¹³ Multimorbidity greatly exacerbates physical and cognitive decline, as diseases in common multimorbidity patterns interact to compromise compensatory mechanisms. In turn, cognitive and physical impairments increase the burden of multimorbidity.¹⁴

Patients with multimorbidity are in particular need of proactive, individualized care plans.¹⁵ Proactive care for multimorbidity is a difficult proposition, as the “timing and mechanisms of an individual's deterioration” are an understudied problem, and cannot easily be predicted.¹⁶ However, the recently developed evidence-based National Institute for Health and Care Excellence (NICE) guidelines for management of multimorbidity¹⁷ and the Ariadne principles on which they are based,¹⁸ emphasize the importance of regular re-assessment of multimorbidities in the context of comprehensive primary care. Research indicates that true precision and patient-centered primary care—explicitly designed to address multi-morbidity—is associated with positive health outcomes for patients.¹⁹ Our group has recently demonstrated the importance of access to primary care for high-risk subgroups of patients with obesity-associated multimorbidity.⁵

Furthermore, prior research demonstrates that comorbidity network analysis is a highly useful methodology for identifying genetic relationships between diseases²⁰⁻²² and patterns of multimorbidity.^{23,24} Networks can visualize intricate patterns and provide insight into

the characteristics of disease-disease relationships. Amell et al used network analysis to find age and gender-related trends in disease association.²⁵ They were also able to indicate diseases with low cumulative risk, which still inform continued disease clustering, and pleiotropy (two or more unrelated effects in the production of a single disease) influencing multimorbidity. Miles et al contend that multimorbidities occur when stressors from an individual's physical and sociocultural environment provoke maladaptive responses in more than one of the body's numerous interconnected physiological networks, thus resulting in interrelated pathologies and chronic conditions.²⁶ Similarly, Vos et al demonstrated that the progression of multimorbidity patterns suggest that disorders originating in one organ system strain or affect other systems.²⁷ However, isolating internal and external causes can be challenging. Conventional clinical methods for assessing multimorbidity rely on simple counts of individual diseases, which provide limited insight into the progression and causality of multimorbidity patterns.²⁸ Despite the strong causal connections between weight increase and comorbidity, most previous studies have only assessed static comorbidity patterns and differences in the prevalence and interactions of comorbidities by age and gender.^{23,25}

The current study is among the first to assess the increase of comorbidity prevalence and interactions by weight class. Our previous network analysis research highlighted 18 most frequently occurring disease combinations (prevalence 10% of the population with obesity) for patients with obesity.⁶ This current paper builds upon these previous findings by documenting how multimorbidity progresses with increase in weight class for all diseases with prevalence 1%. The current study's primary aims are to demonstrate the most prevalent obesity-associated multimorbidity combinations and the increase of multimorbidity by weight class for middle-aged patients in the U.S. To minimize the adverse effects of multimorbidity, patients need proactive, precision, and patient-centered care plans that explicitly address the most critical needs of patients with the most prevalent multimorbidity combinations. Researchers need better information on these most prevalent multimorbidity patterns to prioritize which combinations to study for practical treatment recommendations. By identifying the most common comorbidity clusters by weight class, this study will also provide important clues regarding the underlying mechanisms leading to disease co-occurrence in patients with obesity. Specifically, the study seeks to assess whether comorbidity networks change with weight class in terms of central nodes, cluster formation, number of comorbidities, and strength of association rules. This research will support the development of precision and patient centered care approaches by stratifying patients with obesity-associated multimorbidity into groups with similar characteristics.

2 | METHODS

2.1 | Participants and data

The study employed data for 2017 (the most recent year of available data) from the Cerner HealthFacts Data Warehouse, which includes records for over 70 million patients treated at hospitals and clinics throughout the United States between 2001 and 2017. It includes various encounter types, such as outpatient, inpatient, and emergency departments. Data from this system include medical histories, diagnoses, laboratory information, prescriptions,

patient demographics, clinic type, procedures, and surgical information. The data are de-identified and exclude the 16 identifiable variables that necessitate IRB approval for access, and this dataset is striped of those prior to our access. Because of the de-identified nature of the data, this study is not human subjects research and is considered exempt from IRB according to the policy of the National Institutes of Health office of Human Subjects Research. Participants are included who met the following inclusion criteria: (a) Age 45-64, 2), 1 outpatient encounter in 2017 with body mass index BMI 18.5 (excluding underweight patients), and 1 international classification of diseases and related health problems, 10th revision (ICD-10) diagnosis code. All inpatient encounters were excluded since HealthFacts data is incomplete for inpatient encounters. In addition, all diagnosis codes from encounters prior to 2017 were excluded. This approach was designed to provide a conservative estimate of period prevalence of diagnosed conditions for the most recent year of HealthFacts data available at the time of the study.

2.2 | Independent variables

The average BMI value in 2017 was used to assign weight class. We use the World Health Organization weight classification standard which includes three classes of obesity with each class representing an increase in disease risk.^{29,30} Study participants were considered positive for individual diseases or comorbidities if they experienced one or more ICD-10 diagnosis (eg, type II diabetes and essential hypertension) within the study year. All sub-classifications of diseases were classed with their broad disease code (eg, E11.0, Type 2 diabetes mellitus with hyperosmolarity was tagged with E11, Type 2 diabetes mellitus). There is no international consensus on the best way to define multimorbidity.³¹ For the current study, multimorbidity was defined as “the co-occurrence of multiple disease or medical conditions within 1 person”.³² All diagnoses related to injury and health status and ICD-10 sub-classifications representing overweight/obesity, disease cause, manifestation, symptoms, location, and severity were excluded. To assess our sample's representativeness, we used the two-proportion z-test using our sample before adjusting for excluded diagnoses codes and the 2017 behavioural risk factor surveillance system (BRFSS) sample of middle-aged participants.

2.3 | Prevalence of diseases by weight class

The G-test of independence was used to assess differences in prevalence of individual diseases and multimorbidity by weight class employing a *P*value <.05 to determine significance.

2.4 | Network analysis

The R tidygraph (<https://CRAN.R-project.org/package=tidygraph>) library was employed to generate separate directed networks, network measurements, and for community detection. In each weight class network, nodes represent prevalent diseases and the edges connecting nodes represent co-occurrence. Linkage weights for connections (eg, a link from disease **a** to disease **b**) are generated using an association rule that requires the percent of patients who have **a** who also have **b** above a minimum threshold of 33%. The width of the link between nodes represents the strength of association rule from disease **a** to disease **b**. We

chose a minimum support threshold to generate networks only including prevalent disease combinations. A threshold of 33% allows for a significant association, without being overly strict.

Several other network attributes were calculated for each identified network including prevalence for each node, centrality scores, local transitivity, and graph density. For each network, we only included diseases with prevalence at or above 1% for the respective weight class. We calculated a centrality score for each node using alpha centrality³³—the generalized version of eigen centrality for directed networks—to indicate how often a node appears in the shortest path between nodes, indicating its importance in the network. For each node, local transitivity was used to assess how connected its linked nodes are to each other. This score can highlight subsections of the graph in which diseases are connected in groups of three or more (possibly representing not comorbidity, but multimorbidity combinations of three or more). Finally, graph density was calculated to measure the ratio of the number of edges to the number of possible edges,³⁴ which represents overall network connectivity. A network with maximal density is one in which all nodes are connected to all other nodes in the network.

2.5 | Clustering of diseases by weight class

A community structure detection algorithm based on the leading eigenvector of the community matrix was employed to find diseases that clustered together. This algorithm “finds the densely connected subgraphs in a graph by calculating the leading non-negative eigenvector of the modularity matrix of the graph”³⁵ and identifies clusters of nodes (ie, communities) that have more edges between diseases than edges to nodes outside of the cluster. Since the analysis employs directed networks with weighted edges, this approach results in clustering of nodes representing diseases with the highest prevalence in communities with other nodes directed at them.

2.6 | Visualizations

We used several R packages to visualize the networks. We used the ggraph package (<https://CRAN.R-project.org/package=ggraph>) to visualize disease-disease relationships. In this graph, node size represents prevalence, edge weight represents association rules, and node transparency is local transitivity. We used the circlize package (<https://CRAN.R-project.org/package=circlize>) to visualize disease clusters. We used the Sankey visualization from the plot.ly package (<https://plot.ly/>) to visualize differences in community structure across weight classes.

2.7 | Evaluation

The quadratic assignment procedure (QAP)³⁶ was employed to measure associations between pairs of networks adjacent to one another in weight class progression (eg, healthy weight vs overweight, overweight vs class 1 obesity, etc.). This test measures the correlation of two network matrices and uses quadratic assignment procedures to develop standard errors to test for the significance of the associations. QAP is a resampling-based method, similar to the bootstrap, for calculating the correct standard errors. We used the R statnet package implementation of this test (<https://CRAN.R-project.org/package=statnet>).

We report the correlation coefficient and *P* values for correlation between pairs of adjacent networks. This method provides a statistical assessment of between network structural similarity. We used the nonparametric bootstrap routine developed by Epskamp et al, bootnet, to assess the accuracy and stability of each network.³⁷ Accuracy refers to how prone a network is to sampling variation, and stability refers to how similar the interpretation of the network remains with fewer observations. We report two bootnet measures: node strength (indicating the level of direct connection between a node and other nodes) and closeness (indicating the level of indirect connection between a node and other nodes). Values $> .5$ are considered significant for each bootnet measure. Additionally, we used the network comparison test (NCT), which uses permutations to test if two samples feature different underlying network structures.³⁸ We use two measures from this test: differences in global strength (sum of absolute edges values by network) and maximum differences in edge weights.

We used normalized mutual information (NMI) to measure similarity between disease clusters across weight classes.³⁹ The NMI method compares all labelled clusters in one network with all labelled clusters in another network. Each pair-wise comparison indicates how much information they share. Mutual Information:

$$I(X, Y) = \sum_x \sum_y p(x, y) \log p(x, y) / (p(x) p(y)),$$

where $p(x, y)$ is the probability of x and y $p(x)$ is the probability of x . This measure is normalized so that communities of small size do not have high mutual information scores due to size. NMI is calculated as follows:

$$NMI(X, Y) = \frac{2(I(X, Y))}{H(X) + H(Y)},$$

where $H(X)$ is the entropy of X and $H(Y)$ is the entropy of y . This modification makes this method sensitive to smaller communities and does not punish communities with a significant number of links to other communities. Normalized Mutual Information scores are between 0 and 1. We used the igraph R package (<https://igraph.org/r/>) to perform this network evaluation.

2.8 | Differences in community membership by weight class

We used the overlap coefficient⁴⁰ to identify diseases that are grouped in communities with a significantly different set of diseases across weight classes. This measure identifies the overlap between two finite sets. It is defined as the intersection between two sets divided by the size of the smaller set as follows:

$$overlap(X, Y) = \frac{|X \cap Y|}{\min(|X|, |Y|)},$$

where set X is a complete subset of Y or the reverse is true, the overlap coefficient is equal to 1.

Because the overlap is divided by the smaller size, the coefficient is representative of the most the sets could have in common even if the communities are different sizes. For instance, if E11, type II diabetes, is in a community with one set of diagnoses in the overweight network and is in a class one obesity community with only 33% of those diagnoses, E11 would have a low overlap coefficient for those two communities.

3 | RESULTS

As shown in Table A1, our proportions of patients within gender, race, and weight class distributions are differ by 1% to 6.6% from the proportions of middle-aged adults nationally. Table A2 shows the CONSORT diagram for this study. Of the 154 528 included in our study, 131 349 (85%) percent of patients are Caucasian, 13 908 (9%) are African American, 3091 (2%) unknown, and 6181 (4%) are in another category. Racial terms are those present in the HealthFacts datasets. Table A3 shows each weight class network's break down by race, gender, and age. The average age was 50 years for individuals with class 3 obesity, class 2 obesity, and normal weight; 51 years for class 1 obesity; and 54 years for overweight. Eighty-four to 86% of people in each network self-identify as Caucasian, 7 to 11% as African American, and 4 to 7% as Other/Unknown. Sixty-four percent of patients with normal weight were female; 52% with overweight, 52% with class 1 obesity, 59% with class 2 obesity, and 62% with class 3 obesity. The normal weight network represents 37 852 patients (24%). The overweight network represents 55 491 (36%). The class 1 obesity network represents 22 909 (15%). The class 2 obesity network represents 13 892 patients (9%). The class 3 obesity network represents 24 384 (16%). The average number of diseases increases from 12 in patients with normal weight, to 23 with overweight, 60 with Class 1 obesity, 70 with Class 2 obesity, and 72 in Class 3 obesity, increasing most substantially with the progression from overweight to class 1 obesity. Of the total number of 82 disease categories that met our inclusion criteria, the prevalence of all but three disease categories (C50 neoplasms, K52 gastritis, K62 other diseases of the rectum) was found to be significantly associated with weight class. The 82 diagnoses are described in Table A4. Multimorbidity (excluding obesity) is present in 54.88% of patients with normal weight, 57.88% with overweight, 70.39% with Class 1 obesity, 73.99% with Class 2 obesity, and 71.68% in Class 3 obesity. When obesity is included as a comorbidity as is most customary in studies of multimorbidity,⁴¹ multimorbidity is present in 55.1% of patients with normal weight, 57.88% with overweight, 91.70% with Class 1 obesity, 92.83% with Class 2 obesity, and 91.70% in Class 3 obesity. These differences in rates of multimorbidity among weight classes are statistically significant with P value<.05 for the g-test of independence.

Our results show large differences in graph density by weight class with the normal weight graph having a density of 0.083, the overweight graph having a density of 0.053, the class 1 obesity graph having a density of 0.029, the class 2 obesity graph having a density of 0.029, and the class 3 obesity graph with a density of 0.027. The networks with fewer diseases manifest a larger proportion of their maximum number of possible connections (comorbidities) than do the more extensive networks, and therefore, have higher density. This is predictable. As was explained previously, the maximum number of connections between nodes increases dramatically as more nodes are added to a network. Thus, a high density of comorbidities within a large network of diseases would require each of the

diseases to be comorbid with a much larger number of other diseases than would be the case for a smaller network of diseases.

3.1 | Network visualization

Figure 1 demonstrates the strong association between level of obesity and disease prevalence. As weight class increases, disease clusters expand from only hypertension and dorsalgia in normal weight, to add joint disorders in overweight, lipidemias in class 1 obesity, diabetes in class 2 obesity, and sleep disorders and chronic kidney disease in class 3 obesity. The number of comorbidities increases progressively in a dose-response fashion from normal weight through class 3 obesity. Though the normal-weight and overweight networks have higher graph densities, their graphs have nodes that are separated into 2 or 3 easily identifiable groups—unlike the class 1 to 3 obesity networks. Most edges in the network are directed at the highly prevalent diseases (dorsalgia, diabetes, hypertension, lipidemias, and other joint disorders). As weight class increases, there are new highly prevalent nodes with many edges directed at them. Hypertension and dorsalgia are highly connected nodes for normal-weight patients, lipidemias, and other joint disorders become highly connected in the overweight network. Diabetes becomes highly connected in the class 1 obesity network.

All the highly connected and prevalent nodes have low local transitivity, except diabetes (E11) in the class 1 obesity network and sleep disorders (G47) in the class 3 obesity network. Several low prevalent/high local transitivity nodes connect to both highly prevalent nodes and low prevalent nodes representing a set of diseases that likely represent multimorbidity patterns of three or more. The strongest association rules are between diseases in the M (musculoskeletal and connective tissue) category.

Figure 2 shows that the number of diseases within each clinical disease category increases with increases in weight class. Numbers of diseases for those with overweight and obesity are particularly high for the E (endocrine, nutritional, metabolic), F (mental, behavioural, neurodevelopmental), G (nervous system), I (circulatory system), J (respiratory system), K (digestive system), and M (musculoskeletal) clinical categories. The highest peaks are seen in the J, K and M categories for patients with class 2 and 3 obesity. Category H (eye and adnexa) is only present in the class 3 obesity network and category B (infectious diseases) is only present in the class 2 and class 3 obesity networks.

Figure 3 shows clusters of diseases and the edges between clusters. Most edges go from low prevalence nodes to highly prevalent nodes. The cluster labels represent the most central nodes in each cluster. As weight class increases from normal weight to the class 3 obesity, the network structure evolves to add new diagnoses that cluster around prevalent diseases also present in lower weight classes. The hypertension cluster gains nodes primarily in the E (endocrine, nutritional, metabolic), F (mental, behavioural, neurodevelopmental), J (respiratory system), K (digestive system), N (genitourinary system), and M (musculoskeletal) categories as weight class increases. The dorsalgia cluster evolves into a joint disorders cluster predominantly including M diseases with occasional G (nervous system) diagnoses. The lipidemia cluster first appears in the overweight weight class and progressively expands to add diseases in the B (infectious and parasitic), E, D (blood

and immune mechanism), F, I (circulatory system), J (respiratory system), K, L (skin and subcutaneous tissue), N, and M categories. The diabetes cluster only emerges as a central node in the class 3 obese network. It clusters with the B, D, E, F, G, H (eye and adnexa), I, K, L, and N disease categories. Similarly, the small sleep disorder and chronic kidney disease clusters only emerge in the class 3 obesity network.

The results of the bootnet network stability test indicate that all five networks are stable with global strength scores and closeness scores of 0.75 for each. Comparison of network structure across weight classes (Figure 4A) demonstrates that there are statistically significant major differences in disease prevalence across weight class networks, suggesting our network analysis findings represent real trends. Between pairs of adjacent networks (adjacent by weight class), all QAP correlations are statistically significant with $P\text{value} < .05$. Only the class 2 and class 3 obesity networks were strongly correlated when assessed using the QAP procedure. Alternatively, the normal weight and overweight networks were found to be most similar (Figure 4B) using the NMI method. Thus, the QAP and NMI tests show similarity between networks at opposite ends of the weight class spectrum. The QAP test assesses the overall network. As class 3 and 2 share the highest percentage of nodes (85%) and similar connections, those two networks have the strongest QAP correlation. The nodes in the normal weight and overweight networks are also very similar, with both sharing hypertension and dorsalgia and only adding other joint disorders in overweight. Therefore, the NMI score is the highest for those two networks. Results from the NCT test show that global strength scores are statistically different between normal weight with overweight and overweight with class 1. Comparison of adjacent networks between obese classes were not statistically significant. With the exception of the comparison between the class 2 and class 3 obese networks, all networks were statistically different in edge weights.

Figure 5 shows how the addition of new diseases across weight class impacts the way nodes are clustered. The dorsalgia cluster predominantly remains the same across three weight classes and then combines with the other joint disorders cluster as more clinically related codes are added in the final two weight classes. Many diseases switch from the hypertension cluster to the lipidemias cluster and vice versa at each weight change. The diabetes cluster emerges as a split from the lipidemias group and the addition of seven new diagnoses, which include B37 (candidiasis), and I51 (complications, and ill-defined descriptions of heart disease). The other codes are from the E and L categories. In the class 3 obesity network, the sleep disorders and CKD clusters emerge from the lipidemia cluster as independent nodes with no new diagnoses present.

The diseases that group in communities with a significantly different set of diseases across weight classes (ie, with a low overlap coefficient) are shown in Table 1. This table illustrates the changes in disease comorbidity patterns by weight class. No diseases were found to have a low overlap coefficient for the transition between healthy weight and overweight and that transition has been excluded from this result-set. D64 (other anaemia's) and E87 (other disorders of fluid, electrolyte, and acid-base balance) change at each transition to a new obesity class. For the transition from the overweight class network and the class 1 obesity network, the diseases in the D, E, I, and N clinical disease categories split, moving from the hypertension community into a hypertension community and a lipidemias community. For

the transition between the class 1 and class 2 obesity networks, the diseases in the D, E, F, J, and K clinical disease categories move from the lipidemias community to the hypertension community. M79 (nontraumatic compartment syndrome) transitions from the hypertension community to the other joint disorders' community. Diagnoses from a variety of clinical categories change communities within the transition between transitions. For the transition between the class 2 and class 3 obesity networks, many diseases in the D, E, I, F, J, L, K, G, N clinical disease categories move from the lipidemias, and hypertension communities into the lipidemias, hypertension, and new diabetes communities.

4 | DISCUSSION

The current study is among the first to document increasing prevalence and severity of multimorbidity by weight class in adults with overweight and obesity. We found that prevalence of multimorbidity generally increased with weight class and exceed 70% in all classes of obesity even when obesity itself is not considered as comorbidity. Previous researchers have shown that prevalence of multimorbidity are rapidly increasing in parallel with the obesity pandemic and that obesity is a potent risk factor for multimorbidity.^{1,3,41,42} But this study conclusively shows that obesity is highly associated with multimorbidity. Indeed, when we considered obesity itself as comorbidity as is most customary in the literature, the prevalence of multimorbidity exceeded 90% in our national population-based sample. Obesity-associated health behaviours (eg, poor diet and lack of physical activity) have now surpassed smoking as the top cause of premature death and disability.⁴³ Yet Americans remain largely unaware of the severe health outcomes associated of obesity. This research makes those associations clear. Unlike middle-aged adults of normal weight, adults with obesity are almost guaranteed to experience serious, life-threatening multimorbidity. These results should prompt an immediate national coordinated response to address the obesity pandemic.

Even more importantly, to our knowledge the current study is the first to demonstrate predictable increases in multimorbidity with weight class. We found that multimorbidity networks vary significantly by weight class—as weight class increases, disease clusters predictably expand from only including hypertension and dorsalgia in those of normal weight, to add other joint disorders in overweight, lipidemias in class 1 obesity, diabetes in class 2 obesity, and sleep disorders and CKD in class 3 obesity. Therefore, not only do chronic conditions accumulate with increase in weight class but also chronic conditions with higher severity become prevalent. Sleep disorders and CKD seen in class 3 obesity have higher overall severity, placing patients at higher risk of adverse outcomes, than the most prevalent comorbidities seen in the other weight classes. Previous studies of obesity-associated multimorbidity have either been limited in geographic scope to non-U.S. populations and/or have not examined increases of multimorbidity across weight classes.^{1,2,42} Similar to Ledenbaum et al in Canada, we found that all of the major morbidity clusters seen in the different weight classes include highly prevalent diseases across a range of clinical categories.¹ Many of these individual diseases change the most prevalent node with which they are clustered as weight class increases, indicating that the observed changes in multimorbidity patterns exceed what might be expected simply through increases in

disease prevalence. Thus, the specific multimorbidity combinations seen in various weight classes likely represent specific phenotypes with important clinical significance.

The clinical implications of the predictable increases in level of multimorbidity with weight class are profound. First, the study's demonstration of a major increase in the number of diagnosed comorbidities among individuals with class 1 obesity vs those with overweight suggests that it may be beneficial to carefully and routinely track patient weight trajectories for this potentially dangerous change in weight class. Health systems that are truly focused on population health should routinely employ tracking and early intervention at time of preclinical disease (ie, in overweight and early obesity), even if multimorbidity not yet present. Although many intervention approaches for patients with multimorbidity lack evidence of effectiveness,⁴⁴ systematic reviews and national guidelines based on strong evidence have shown that multicomponent behavioural weight loss interventions are evidence-based and effective in improving outcomes for vulnerable patients. Providers should routinely take immediate steps in patients with new onset of obesity to screen for the most common multimorbidities and initiate these evidence-based multicomponent behavioural interventions for obesity.^{44,45} The finding that the prevalence of multimorbidity crests with class 2 obesity, supports guidelines recommending most intensive efforts to reverse obesity such as obesity surgery with the onset of class 2 obesity.⁴⁶ Our study results strongly support efforts to routinely provide intensive behavioural and/or surgical obesity interventions prior to the development of serious complications of obesity-associated multimorbidity.⁴⁶⁻⁴⁸ Furthermore, many common chronic conditions remain undiagnosed for long periods of time⁴⁹ and determining for which conditions a patient should be screened is challenging. These facts are made more significant given that multimorbidity is a key mediator of reduced life expectancy.⁵⁰ The current research can be used to facilitate evidence-based screening approaches that focus on early identification of the comorbidities for which a patient is at highest risk.

Second, by identifying most prevalent multimorbidity networks for each weight class, the current study provides an important framework for expanding the delivery of precision care. This research helps fully document the highly complex care needs of patients with obesity. Previous research has demonstrated common multimorbidity patterns in patients with complex care needs,⁵¹ but this research has not evaluated changes in these patterns with weight class. Algorithms for multimorbidity treatment based on weight class developed by other authors⁷ can be refined based on the current research. Multimorbidities that are related in terms of their pathogenesis require different treatment strategies than disease combinations that are unrelated.⁵² In the case of obesity-associated multimorbidities, all treatment plans should include multicomponent behavioural interventions for obesity and/or bariatric surgery.^{46,47,53} Recent research demonstrated that use of a polypill with three antihypertensive medications and a lipid lowering medication in combination in patients with hypertension and hyperlipidemia improved adherence and major clinical outcomes.⁵² Consistent with evidence-based guidelines for treatment of multimorbidity,^{17,18} patients with obesity-associated multimorbidity need proactive, individualized, precision care plans in the context of comprehensive primary care.^{15,19} True precision and patient-centered primary care should be explicitly designed to address multi-morbidity and treatment strategies should simultaneously address multiple chronic conditions whenever possible.

Some of the particular patterns of multimorbidity seen in the various weight classes seen in the current study are noteworthy. First, hypertension is a central node in every weight class network. Research shows that the combination of obesity and hypertension is associated with declines in cognitive performance,⁵⁴ and our work shows the hypertension cluster connecting to many neurological disorders. The hypertension cluster gains primarily in five categories as weight class increases, many of which include conditions which are known to occur as a consequence of uncontrolled hypertension. Unlike most other disease clusters, hypertension primarily clusters with diseases outside its clinical disease category (diseases of the circulatory system) in the obese networks reflecting the diverse pathologies linked to hypertension and obesity. These findings highlight the central importance of intensive monitoring and treatment of hypertension in all patients at risk for obesity.

Second, the current study demonstrates that an especially high level of diversity in the lipidemias and diabetes clusters, suggesting that the adverse metabolic consequences of obesity are particularly severe. The links between obesity, cardiovascular risk, metabolic syndrome, and dyslipidemia are well known, and studies have called for a focus on lipid metabolism in patients with obesity and the need for interventions.⁵⁵ This research highlights the need to initiate behavioural and pharmaceutical treatments for the metabolic syndrome early in patients at risk for obesity, and consideration be given to employing polypill strategies⁵⁶ that include both statins and biguanides (ie, Metformin) earlier in the progression from overweight to obesity. Research into diabetes typically highlights its co-occurrence with other relevant diseases such as hypertension, lipidemias, CKD, cardiovascular disease, and overweight/obesity.⁵⁷ Our results both confirm these trends, as well as highlighting less prevalent diagnoses that cluster around diabetes.

Third, the current study demonstrates the high prevalence of musculoskeletal disorders in multimorbidity combinations because of their high prevalence, shared pathogenic processes, and shared risk factors.⁵⁸ With changes in weight class, the musculoskeletal clusters remain less diverse in terms of clinical categories than the other clusters. Co-morbidity association is also highest in this category identified by the thick edges representing their association rules. These findings are the result of most patients with advanced obesity experiencing chronic back and large joint pain (mostly knees). Patient-centered care requires that patients both are made aware of the routine consequences of weight progression on quality of life and are provided with effective evidence-based therapies for chronic musculoskeletal pain early in the course of their disease progression.⁵⁸ Since musculoskeletal disorders are prevalent even among normal weight individuals utilizing healthcare, comprehensive primary care needs to routinely include evidence-based support for daily physical activity and stretching and strengthening exercises, therapies known to be most effective for chronic musculoskeletal conditions. Our study indicates that routine availability of these essential therapies is particularly important for patients with BMIs in the overweight or obese ranges.

Lastly, our research clearly demonstrates the devastating consequences of class 3 obesity. Virtually all patients with class 3 obesity experience severe multimorbidity with high prevalence of conditions highly linked to premature death and disability. The emergence of diabetes, CKD, and sleep disorders as distinct clusters in the class 3 obesity network, reflects the high prevalence of serious complications in this population. The most interesting of these

nodes is sleep disorders, which has a low prevalence in all the obesity networks except the class 3 network, and is the center of a community in the class 3 obesity network. Its high prevalence indicates that the nodes with which it is connected (hypertension, diabetes, and extrapyramidal and movement disorders) likely co-occur together as a group. These findings suggest that combination behavioural and pharmaceutical treatment strategies that simultaneously address prevalent groupings of comorbidities are particularly appropriate in those with severe obesity.

The current study is subject to several limitations. Most importantly, since our methodological approach was designed to provide a conservative estimate of period prevalence of diagnosed conditions using the most recent data available, true disease prevalence is likely underestimated. Several factors contribute to possible underestimation of true disease prevalence. First, the study only included outpatient diagnoses, did not capture undiagnosed conditions, and is unlikely to have captured conditions of low severity. However, studies suggest that outpatient ICD-10 diagnosis codes for large healthcare delivery systems are generally accurate for assessing common major comorbidities.⁵⁹ Second, potential lost to follow-up issues could have occurred resulting in missed outpatient diagnoses made by providers not included in the database. However, since Healthfacts data generally includes all diagnoses for included providers, rates of lost to follow-up are likely to be small. Third, because our primary definition of multimorbidity did not include obesity (based on either ICD-10 diagnosis or BMI) as a comorbidity, true multimorbidity prevalence in patients with obesity was underestimated. The extensive literature on multimorbidity generally includes obesity as a comorbidity⁴¹ but in order to assess obesity's association with multimorbidity, we needed to exclude it from our set of chronic conditions. On the other hand, use of EHR data likely biased the patient population towards people who utilize the healthcare delivery system. As a result, multimorbidity prevalence may be overestimated among patients in the normal weight and overweight subgroups. A further limitation is the cross-sectional study design, as time-varying network analysis would have allowed for assessment of changes at the individual level. Additionally, while the networks were similar in terms of age and race, there was sizable variation in the percent females for the different networks. Stratifying by gender may produce significantly different results.

By using network analysis to identify critical differences in multimorbidity by weight class, the current study provides a useful framework for advancing precision and patient-centered care for people with overweight and obesity. Early recognition of emerging multimorbidity clusters associated with weight increase can help alert clinicians and patients to preclinical disease and assist their efforts to address root causes of illness before additional comorbidities develop and complications arise. Thus, knowledge of the complexity of obesity's association with multimorbidity can inform medical practice and potentially help delay or prevent disease progression. Obesity exacerbates comorbidity patterns in multiple clinical categories and this research helps fully document the highly complex care needs of patients with obesity. There is a critical need for thorough understanding of comorbidity to guide health system design at every level.⁶⁰ The worsening parallel pandemics of obesity and obesity-associated chronic conditions merit an aggressive health system response that prioritizes availability and delivery of comprehensive primary care services that routinely include multicomponent behavioural healthy eating and weight

loss interventions for all those at risk of obesity and bariatric surgery for all those with advanced obesity. All primary care facilities should have strong support infrastructure for promoting daily physical activity and stretching and strengthening to most effectively treat the common musculoskeletal consequences of obesity. And polypill treatment strategies should be developed and delivered for the most common comorbidity clusters in all weight classes given their enhanced real-world effectiveness. By bringing attention and understanding to the common patterns of overweight and obesity-associated multimorbidity in the U.S., the current study's findings can help guide the design of truly proactive, precision, and patient-centered primary care approaches that better address the real needs of patients with overweight and obesity. In future work, we plan to analyse obesity network differences by race and gender. We also plan to further investigate why the percentage of patients with multimorbidity remained relatively flat across the obese weight classes. The current network analysis provides a roadmap for deploying precision care to address the parallel pandemics of obesity and obesity-associated chronic conditions. It is time to get on the road.

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Appendix

TABLE A1

The 180 945 adults included in the analysis are similar to middle-aged adults nationally in gender, race, and weight class distributions. Two-sided two-proportions z-test analysis was used. Our statistical test shows that for all comparisons are statistically significant different in proportion. However, with a large sample size, any difference of 1% or more indicates the null hypothesis that the proportions are the same should be rejected. Reviewing the proportions, we can see that the values are within 1% to 6.6% difference for everything with the exception of the other racial category

Characteristic	Cerner healthfacts sample before excluding by diagnosis (N = 177 033)	BRFSS 2017 population middle-aged adults not underweight (N = 148 381)	p value
Percent female	101 794 (57.5%)	82 102 (55.3%)	2.2e-16
Race			
Caucasian	150 124 (84.8%)	114 823 (77.4%)	2.2e-16
African American	15 793(9.2%)	12 899 (8.7%)	.02
Other	3364 (1.9%)	20 659 (13.9%)	2.2e-16
Unknown	7258 (4.1%)	NA	
Weight class			

Characteristic	Cerner healthfacts sample before excluding by diagnosis (N = 177 033)	BRFSS 2017 population middle-aged adults not underweight (N = 148 381)	p value
Normal weight	45 125 (25.5%)	40 078 (27.0%)	2.2e-16
Overweight	64 778(35.8%)	54 648 (36.8%)	9.855e-10
Obese	67 130 (37.1%)	53 655 (36.2%)	2.667e-08

TABLE A2

CONSORT diagram detailing cohort selection process

TABLE A3

shows each network's break down by race, gender, and age

Weight Class Network	Caucasian	African American	Other/Unknown	Female	Average Age
Normal	31 827 (84%)	3566 (9%)	2459 (7%)	24 196 (64%)	50
Overweight	46 612 (84%)	5549 (10%)	3884 (7%)	28 855 (52%)	54
Class 1 Obesity	19 702 (86%)	2061 (9%)	1145 (5%)	11 913 (52%)	51
Class 2 Obesity	11 808 (85%)	1528 (11%)	556 (4%)	8196 (59%)	50
Class 3 Obesity	20 970 (86%)	1799 (7%)	1615(7%)	15 118 (62%)	50

TABLE A4

Lists the 82 diagnosis that met our inclusion criteria. The table includes ICD-10 descriptions (<https://www.cdc.gov/nchs/icd/icd10cm.htm>)

ICD-10CM Code	Description
B35	Dermatophytosis
B37	Candidiasis
C50	Malignant neoplasm of breast
D12	Benign neoplasm of colon, rectum, anus and anal canal
D50	Iron deficiency anaemia
D64	Other anaemia's
E03	Other hypothyroidism
E04	Other nontoxic goitre
E11	Type 2 diabetes mellitus
E29	Testicular dysfunction
E55	Vitamin D deficiency
E78	Disorders of lipoprotein metabolism and other lipidemias
E83	Disorders of mineral metabolism
E86	Volume depletion
E87	Other disorders of fluid, electrolyte and acid–base balance
F10	Alcohol related disorders
F17	Nicotine dependence
F31	Bipolar disorder
F32	Major depressive disorder, single episode
F33	Major depressive disorder, recurrent
F41	Other anxiety disorders
F43	Reaction to severe stress, and adjustment disorders
G25	Other extrapyramidal and movement disorders
G43	Migraine
G47	Sleep disorders
G56	Mononeuropathies of upper limb
G62	Other and unspecified polyneuropathies
G89	Pain, not elsewhere classified
H25	Age-related cataract
I10	Essential (primary) hypertension
I12	Hypertensive chronic kidney disease
I25	Chronic ischemic heart disease
I42	Cardiomyopathy
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I51	Complications and ill-defined descriptions of heart disease
I87	Other disorders of veins

ICD-10CM Code	Description
J01	Acute sinusitis
J02	Acute pharyngitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J18	Pneumonia, unspecified organism
J20	Acute bronchitis
J30	Vasomotor and allergic rhinitis
J32	Chronic sinusitis
J40	Bronchitis, not specified as acute or chronic
J44	Other chronic obstructive pulmonary disease
J45	Asthma
J98	Other respiratory disorders
K21	Gastro-oesophageal reflux disease
K29	Gastritis and duodenitis
K44	Diaphragmatic hernia
K52	Other and unspecified noninfective gastroenteritis and colitis
K57	Diverticular disease of intestine
K59	Other functional intestinal disorders
K62	Other diseases of anus and rectum
K63	Other diseases of intestine
K64	Haemorrhoids and perianal venous thrombosis
K76	Other diseases of liver
L02	Cutaneous abscess, furuncle and carbuncle
L03	Cellulitis and acute lymphangitis
L97	Non-pressure chronic ulcer of lower limb, not elsewhere classified
M06	Other rheumatoid arthritis
M10	Gout
M17	Osteoarthritis of knee
M19	Other and unspecified osteoarthritis
M25	Other joint disorder, not elsewhere classified
M47	Spondylosis
M48	Other spondylopathies
M51	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders
M54	Dorsalgia
M62	Other disorders of muscle
M75	Shoulder lesions
M77	Other enthesopathies
M79	Other and unspecified soft tissue disorders, not elsewhere classified
N18	Chronic kidney disease (CKD)
N20	Calculus of kidney and ureter
N28	Other disorders of kidney and ureter, not elsewhere classified
N39	Other disorders of urinary system
N40	Benign prostatic hyperplasia

ICD-10CM Code	Description
N52	Male erectile dysfunction
N95	Menopausal and other perimenopausal disorders

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What is already known about this subject?

- Obesity is causally linked to multiple chronic conditions and over 60% of patients with obesity have multimorbidity.
- The most prevalent obesity-related multimorbidity combinations include Type 2 diabetes, lipidemias, hypertension, coronary artery disease, gastro-esophageal reflux disease, sleep disorders, and musculoskeletal conditions.

What this study adds?

- There is a very predictable increase in level of multimorbidity with weight class.
- As weight class increases, disease clusters expand from only hypertension and dorsalgia in normal weight to add joint disorders in overweight, lipidemias in class 1 obesity, diabetes in class 2 obesity, and sleep disorders and chronic kidney disease in class 3 obesity.
- Multimorbidity (excluding obesity) is present in 55.1% of patients with normal weight, 57.9% with overweight, 70.4% with Class 1 obesity, 74.0% with Class 2 obesity, and 71.7% in Class 3 obesity.
- By highlighting key differences in patterns of multimorbidity by weight class, network analysis provides a useful framework for advancing precision care.

FIGURE 1.
 Networks of prevalent multimorbidity combinations for each weight class

FIGURE 2.
Number of diseases by clinical disease category and weight class

FIGURE 3.
Differences in cluster groupings by weight class. Labels represent the most central node in each cluster

FIGURE 4. Associations among prevalent multimorbidity clusters by weight class. A, Associations between pairs of adjacent weight class networks assessed by quadratic assignment procedure (QAP), and B, Similarity between disease clusters across weight classes assessed by normalized mutual information (NMI) scores

FIGURE 5. Evolution of multimorbidity network structure with increase in weight class. NW represents the communities the normal weight network, OW represents the overweight network, OC1 represents the class 1 obesity network, OC2 represents the class 2 obesity network, and OC3 represents the class 3 obesity network

TABLE 1

Diseases that change cluster label across weight classes (Nodes with a low overlap coefficient across weight classes). Values in the cells indicate the overlap coefficient and which community they come from and go to. Diagnoses that change together are grouped

Diagnoses	Overweight = > Class 1 Obesity*	Class 1 obesity = > Class 2 Obesity*	Class 2 obesity = > Class 3 Obesity*
D64(Other anaemias), E87(Other disorders of fluid, electrolyte and acid-base balance)	0.38 (Hypertension = > Hypertension)	0.24 (Hypertension = > Lipidemias)	0.445 (Lipidemias = > Diabetes)
I10 (Essential Hypertension)	0.38 (Hypertension = > Hypertension)		
E11 (Diabetes Mellitus), I48 (Atrial fibrillation and flutter), I44 (Other chronic obstructive pulmonary disease)	0.5 (Hypertension = > Lipidemias)		0.455(Lipidemias = > Diabetes)
N18 (Chronic kidney disease)	0.5 (Hypertension = > Lipidemias)		
M79 (Nontraumatic compartment syndrome)		0.08(Hypertension = > Other joint disorder, not elsewhere classified)	
D12(Benign neoplasm of colon, rectum, anus and anal canal), F41(Other anxiety disorders), F43 (Reaction to severe stress, and adjustment disorders), J30(Vasomotor and allergic rhinitis)		0.17 (Lipidemias = > Hypertension)	
K52(Other and unspecified non-infective gastroenteritis and colitis)		0.17 (Lipidemias = > Hypertension)	0.227 (Hypertension = > Diabetes)
K62 (Other diseases of anus and rectum)		0.24 (Hypertension = > Lipidemias)	
J18(Pneumonia, unspecified organism),		0.24 (Hypertension = > Lipidemias)	0.222 (Lipidemias = > Hypertension)
K76(Other diseases of liver), L03(Cellulitis and acute lymphangitis)		0.24 (Hypertension = > Lipidemias)	0.455 (Lipidemias = > Diabetes)
G56 (Mononeuropathies of upper limb)			0.125 (Hypertension = > Lipidemias)
E03(Other hypothyroidism), E86(Volume depletion), F32(Major depressive disorder, single episode), F33 (Major depressive disorder, recurrent), K21 (Gastro-oesophageal reflux disease)			0.222 (Lipidemias = > Hypertension)
F31(Bipolar disorder), K59(Other functional intestinal disorders), N20 (Calculus of kidney and ureter), N39(Other disorders of urinary system)			0.227 (Hypertension = > Diabetes)
G62(Other and unspecified polynuropathies), I50 (Heart failure), N28(Other disorders of kidney and ureter, not elsewhere classified)			0.455 (Lipidemias = > Diabetes)