Neuropsychiatr Invest. 2023;61(2):42-48

Original Article
10.5152/NeuropsychiatricInvest.2023.22021

Cardiovascular Disease and Mental Disorder-Associated Temporal Hyper-morbidity in a Population: A Novel Representation of Diagnosis Frequency

Pang Hua Chai[1,2], **David Cawthorpe**[2,3,4,5,6]

[1]*University of Calgary, Faculty of Kinesiology, Calgary, Alberta, Canada*
[2]*University of Calgary Cumming School of Medicine, Faculty of Medicine, Calgary, Alberta, Canada*
[3]*Department of Psychiatry, University of Calgary Cumming, School of Medicine, Calgary, Alberta, Canada*
[4]*Department of Community Health Sciences, University of Calgary Cumming, School of Medicine, Calgary, Alberta, Canada*
[5]*Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[6]*The University of Calgary, Calgary, Alberta, Canada*

ABSTRACT

Introduction: Somatoform and psychosomatic disorders have long been associated with cardiovascular disease. We examined in a 16-year population the full range of mental, biomedical, and biophysical, temporal hyper-morbidity associated with cardiovascular system diseases. The analysis introduces a novel approach to big-data representation in terms of presenting across dependent groupings the frequency that diagnoses are made within individuals for the full range of independent diagnoses.

Methods: The study employed a 16-year population sample of, the diagnoses of 768 460 individuals (54% female), to examine the full range of international classification of disease diagnoses associated with cardiovascular disease employing odds ratios and proportions to compare within and between groups and temporal differences for the full range of international classification of disease diagnoses for each sex.

Results: Overall and temporal differences were observed across age within both the main classes and the full range of international classification of disease diagnoses for each sex. Comparing the groups with and without cardiovascular disease, the diagnosis frequency ratios of biomedical and biophysical morbidity associated with mental disorders preceding cardiovascular disease at younger ages were greater than the ratio of biomedical and biophysical morbidity without mental disorders preceding cardiovascular disease.

Conclusions: The integration into psychiatric and general education and practice of the consideration of a psychosomatic or somatoform diagnosis, especially in relation to circulatory diseases, also requires examination of the full range of associated biomedical and biophysical diagnoses, as well as the history of the temporal order of biomedical and biophysical disease manifestation within the presenting individual that references population norms.

Keywords: Mental, morbidity, psychosomatic, disease, diagnosis, cardiovascular

Corresponding author:
Pang Hua Chai

E-mail:
panghua.chai@ucalgary.ca

Received: September 26, 2022
Accepted: March 05, 2023
Publication Date: June 26, 2023

Cite this article as: Hua Chai P, Cawthorpe D. Cardiovascular disease and mental disorder-associated temporal hyper-morbidity in a population: A novel representation of diagnosis frequency. *Neuropsychiatr Invest.* 2023;61(2):42-48.

INTRODUCTION

Circulatory and cardiac diseases remain a primary concern for society as chronic diseases[1] and perioperative consequences.[2,3] True cardiac emergency visits are often obfuscated by psychosomatic presentations, such as anxiety.[1,4] Psychosomatic illness has had varying definitions over its evolution as a diagnostic category and is generally defined as a physical manifestation of psychological and emotional stress.[5-9] Psychosomatic illness is a diagnosable category within the International Classification of Disease version 9 (ICD-9) with a long-standing association with cardiac disease.[10-12] As well, the mental disorder has been identified as a predictor of circulatory and cardiac diseases.[2,4,13] Physiological malfunction arising from mental factors (ICD code 306) and includes a cardiovascular subtype (ICD code 306.2) and otherwise are identified in the Diagnostic and Statistical Manuel of Mental Disorders Fifth Edition, Text Revision (DSM-5-TR) as somatoform disorders. Psychosomatic symptom assessment has been studied in noncardiac,[14] suspected,[14] and diagnosed cardiac disease.[15] The association within the category of diagnosed cardiac disease extends to the point of examining potential biomarkers.[16] The heart is a particular focus of psychosomatic symptom manifestation.[4,17,18]

Most studies generally examine the concurrent morbidity of cardiovascular system-associated psychosomatic disorders (CVD) and tend to analyze the joint presentation of either one or the other, or both, without taking into account temporal hyper-morbidity, an emerging field of study.[19] Comorbidity and multimorbidity are well described,[4,17,18] wherein hyper-morbidity represents the occurrence of a diagnosis in a proportion greater than chance alone. Temporal hyper-morbidity considers time, specifically in this article, the full range of past, present, and future index (first) diagnoses of cardi ovascular-associated disorders within the study sample. As this article is among the first descriptions of cardiovascular-associated disorder temporal hyper-morbidity in a population, the comparative upper limits of associated disorders and diseases are not yet described. This article goes beyond a comparison of psychosomatic disorders alone or specific chronic diseases, such as diabetes, by employing a 16-year population-based sample. The results focus on the full ICD-9 range of diagnoses to describe the temporal hyper-morbidity[19] (e.g., over-represented past, present, and future disorders) associated with diseases of the circulatory system (ICD-9 codes 390-459). Additionally, the age-specific temporal hyper-morbidity associated with index mental disorders (ICD-9 codes 290-319; MD) and cardiovascular disease is described. It was hypothesized that age-specific index cardiovascular system hyper-morbidity would be greater compared to those without cardiovascular system disease. Further, mental disorder-associated cardiovascular temporal hyper-morbidity would be greater than the cardiovascular temporal hyper-morbidity of those without mental disorders.

MATERIAL AND METHODS

Ethics

The study was approved by the regional ethics board (Ethics ID: REB15-1057_REN7).

Sample

Using a 16-year population sampling frame, the records of 768 460 individuals (54% female) were selected from the regional health service registry in the Calgary health zone (Calgary, Alberta, Canada) representing physician diagnoses (84 217 057; 57% female) from the years 1993 to 2010 of any presenting concern. Each ICD-9 diagnosis was tied to patient visit dates. There were 11 629 454 visits (e.g., billings for prescriptions, laboratory tests, and procedures) without a formal ICD-9 diagnosis. The anonymous dataset included ICD-9 diagnoses, visit dates, age at visit, and sex. The sampling frame employed to develop the sample was designed to saturate the power of the available data. An initial data cube (n=~150 000) of those admitted to all regional, tertiary, inpatient, emergency, and ambulatory, publicly funded, mental health services were matched on sex and age (range 0-108 years) of the index visit. For every data point in the initial data cube, 9 matching data points were requested. Only about 7 matched records were delivered indicating saturation of power within the large dataset (physician billing data), indicating that all available help-seeking individuals from the catchment from 1993 to 2010 were included in the analyzed data. In other words, all individuals during the study period were included, except those who did not seek health services or visit a physician for whatever reason (e.g., healthy, deceased, migrated, etc.).

Process of Real-World Data Aggregation

Each patient could visit their physician multiple times; hence, the total frequency of any diagnosis could be calculated for each patient. The physician billing records included all physician billings submitted, which could be for physician office visits, visits billed to ambulatory clinics, or diagnoses made for patients visiting emergency services or admitted to the hospital. The specific ambulatory and inpatient billings were not parsed in this analysis for simplicity and to provide a complete accounting for patients' diagnoses over 16 years.

Data Grouping

The data were collapsed into 4 groups for each sex representing the dependent variables: presence (+) or absence (–) of cardiovascular disease (CD) and additionally those with (+) and without (–) an MD). The independent variables consisted of each of the ICD diagnostic groupings and the full range of ICD-associated diagnoses (~992 diagnoses, V codes, missing diagnoses, and procedures).

Analysis

The sample was described, with results presented in tables and graphs. The tables describe the age distributions and total diagnoses within groups (Table 1) for each sex and the counts of unique individuals within groups as well as the average number, mean, and

Table 1. Means and Standard Deviations of Age with Total Diagnoses Within Groups

Group	Statistic	Female	Male
–CD –MD	Mean age	26.07	23.56
	SD age	16.85	17.53
	Total diagnoses	5 531 538	4 980 324
+CD –MD	Mean age	54.94	53.39
	SD age	21.23	20.46
	Total diagnoses	4 870 958	4 037 991
–CD +MD	Mean age	31.71	28.14
	SD age	14.74	17.13
	Total diagnoses	15 987 602	7 913 308
+CD +MD	Mean age	54.08	55.56
	SD age	19.81	19.16
	Total diagnoses	35 202 896	17 321 894

CD, cardiovascular disease; MD, mental disorder; SD, standard deviation; present (+); absent (–).

Table 2. Count of Individuals, Means, Standard Deviations, and Ranges of Diagnoses Within Groups

Sex	Group	Unique Individuals	Mean	SD	Min*	Max*
Males	−CD −MD	132 278	37.65	43.47	1	977
	+CD −MD	40 986	98.52	99.96	1	2632
	−CD +MD	94 363	83.86	87.51	1	2694
	+CD +MD	84 507	204.98	190.19	2	4343
Females	−CD −MD	111 009	49.83	52.33	1	1052
	−CD +MD	126 642	126.24	106.83	1	3243
	+CD −MD	38 609	126.16	107.76	1	2432
	+CD +MD	140 066	251.33	190.86	2	3558

CD, cardiovascular disease; MD, mental disorder; SD, standard deviation; present (+); absent (−).
*Minimum/maximum range of diagnoses.

standard deviations (SD) of diagnoses for individuals within each group for both sexes (Table 2).

The dependent variable was expressed as a novel adaptation of the odds ratio (OR) in relation to the average frequency of all ICD disorders (independent variable) per individual within groups with and without the dependent variable CD and with or without the dependent variable any mental disorder (MD) stratified on age. The within-group quotients were represented in terms of the numerators (frequency of diagnoses) and denominators (count of unique individuals within each dependent group for each diagnosis):

$$\text{Quotient of diagnosis},n = \left[\frac{(\text{frequency of diagnosis},n)}{(\#\text{unique individuals within diagnosis},n)}\right],$$

where n ranged from diagnosis 1 to 992.

Groups with and without CD and with and without any MDs were compared. The ratio in each comparison was the ratio of the quotients of each diagnosis n grouping of the dependent variables. The ratio numerator for each diagnosis was the quotient of those with CD with and without any MD expressed as a proportion denominated by the corresponding quotient of those without CD and/or without any MD:

$$\text{Ratio of diagnosis},n = \left[\frac{(\text{quotient } n \text{ with CVD} \pm \text{MD})}{(\text{quotient } n \text{ without CVD or MD})}\right],$$

where n ranged from diagnosis 1 to 992.

Ratio of diagnosis, n = [(quotient n with CVD ± MD)/(quotient n without CVD or MD)], where n ranged from diagnosis 1 to 992.

Only diagnoses where respective diagnoses for each of the dependent groups were represented (e.g., >1 diagnosis within the dependent group) were depicted graphically. Of note, some diagnoses were not represented in either group (discussed in Limitations section).

Graphically depicted in Figure 1 are the calculated age-specific ratios for all ICD-9 diagnoses (independent variables) divided by the age-specific unique individual sample sizes. Overall hyper-morbidity by age was indicated when the ratio comparing groups within each diagnosis was greater than the value one.

Additionally, the temporal hyper-morbidity of ICD diagnoses arising before and after CD with MD was illustrated in Figure 2. These ratios were calculated to show the ratios of the cumulative age-specific prevalence of any biomedical/biophysical or MD arising either before or after the index diagnosis of any CD. Cases, where the diagnoses were assigned on the same day, fell into the "after" category for ease of representation.

The data were analyzed employing STATA and represented graphically using Microsoft Excel and Mathematica.

RESULTS

Table 1 shows the means and SD of age with total diagnoses for each group. Note that those without cardiovascular disease (−CD) or mental disorder (−MD) and those with a mental disorder (+MD) and no cardiovascular disease (−CD) are younger. Those with cardiovascular disease (+CD) with (+) or without (−) mental disorders (MD) are older for both males and females.

The total number of diagnoses within each group does not include either MD or CD in the tally and represents the ICD-9 diagnoses representing biomedical and biophysical diseases and disorders associated with the grouping of either MD or CD.

Table 2 shows the counts of unique individuals together with the means, SDs, and ranges of diagnoses for individuals within each group. Note that for both sexes, those in the group with both mental disorder (+MD) and cardiovascular disease (+CD) have the highest mean number of diagnoses per individual and higher ranges compared to those in the groups without any mental disorder (−MD) and cardiovascular disease (−CD) or mental disorder (+MD) without cardiovascular disease (−CD).

As in Tables 1 and 2, the total number of diagnoses within each group does not include either MD or CD in the tally and represents the ICD-9 diagnoses representing biomedical and biophysical diseases and disorders associated with the grouping of either MD or CD. On this basis, the groups are directly comparable in terms of their overall hyper-morbidity. Morbidity, that is, the presence of associated diagnoses arising among those with either mental disorder (+MD) or cardiovascular diseases (+CD), or both (+CD+MD) is higher than those without either. Hyper-morbidity is highest among those with both mental disorder (+MD) and cardiovascular diseases (+CD).

Figure 1 represents the ratio of the frequency of each diagnosis among the groups of those with and without cardiovascular disorders across all ages. All ICD-9 disorders represented in both groups are represented in the graph. In Figure 1, peaks below the value 1 indicate the diagnoses where the proportional frequency ratio of those with and without CD was less in the group with CD. Values greater than 1 indicate the diagnoses where the proportional frequency ratio of those with and without CD was greater in the group with CD. Note that the plateaus at the top of each graph peak at the value 6 wherein the frequency (intensity) of the underpinning age-specific diagnoses of each plateau were higher than the value 6.

Figure 2 shows, in comparison for males and females, the proportions of the total number of all age-specific diagnoses and age-specific MDs denominated by age-specific sample size arising before and after the index cardiovascular diagnosis within those having a CD diagnosis. The ratio within each before and after group compares

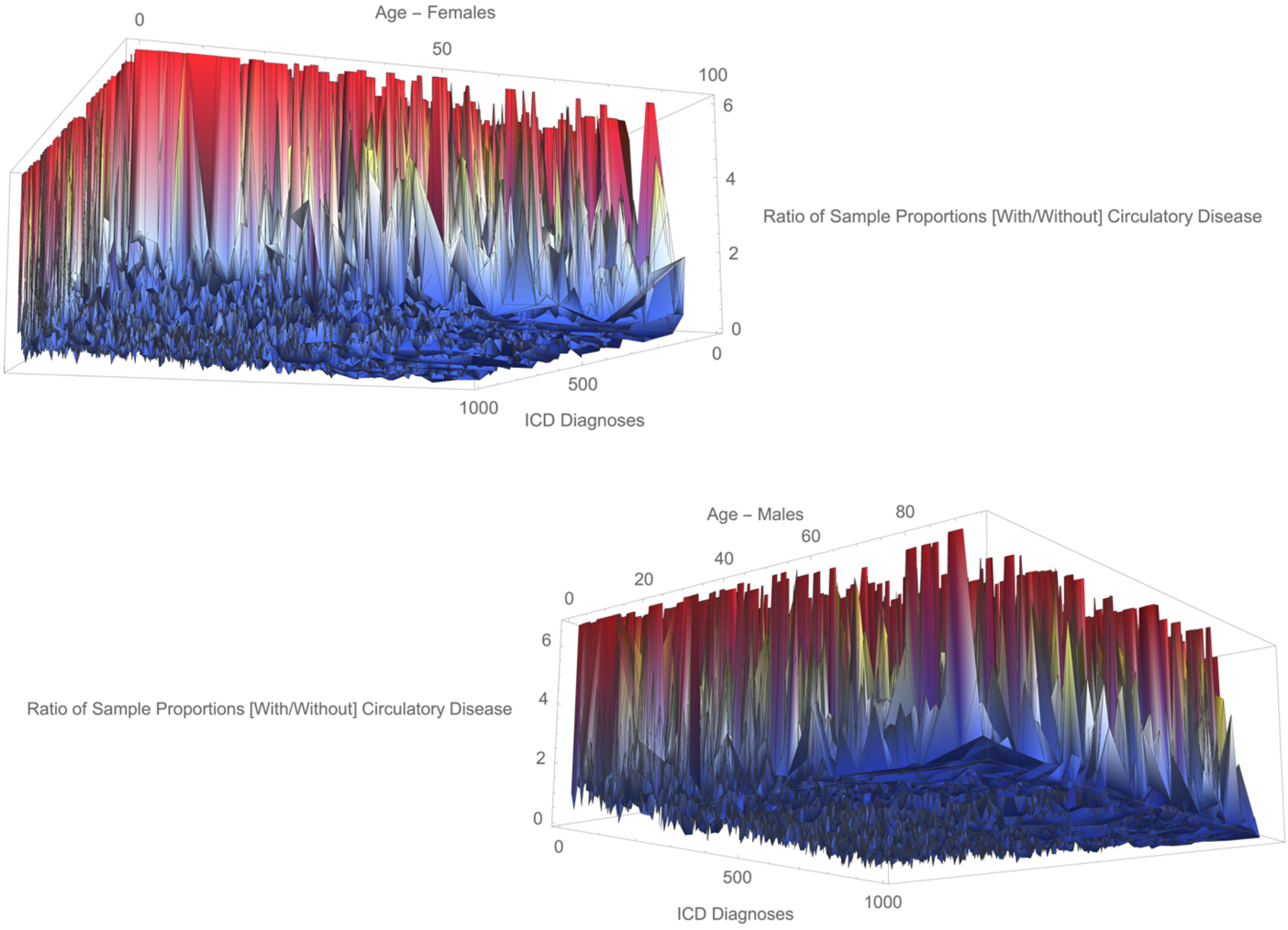

Figure 1. Ratio of the frequency of diagnoses for those with and without cardiovascular disease of each age-specific ICD diagnosis proportion (age-specific frequency denominated by age-specific sample size) for females (upper) and males (lower). ICD, International Classification of Disease.

the proportion of the total frequency of all diagnoses and the total frequency of MDs for each underlying age-specific sample under the conditions of [before/after] the index CD diagnosis. As may be seen in Figure 2, from the ratios for both males and females of the 0-50 and 51-75 groupings and most ages over 87 years in the 76- to 95-year-old group, MDs (darker traces) tend to precede the index diagnosis of any CD compared to all disorders (lighter traces). For both younger males and females, where the ratio is less than the value of 1, the CD tends to precede the index date of MD (dark traces) and the index date for all diagnoses (light traces). With increasing age, as might be expected, the reverse is the case, with the ratio increasing well beyond the value of 1 with age for both sexes.

DISCUSSION

The analysis of the temporal hyper-morbidity of mental and circulatory disease indicates that complex morbidity both before and after circulatory diseases with and without any MD in attendance is worthy of examination. The present results show that it is important to consider the frequency (intensity) with which any diagnosis is assigned with respect to the dependent groupings of interest. This analytical approach provides an index of disease severity when comparing groups, whereas the simple counts of unique individuals inherent in the traditional OR calculation do not. Further, when the cumulative frequency counts of all diagnoses are represented within ratios for groupings of the dependent variables comparing ratios calculated for groupings arising before and after cardiovascular diagnoses, it is apparent that there is a lifespan effect of MD on all CD-related multimorbidity for both sexes.

The present findings are a signpost pointing to the need to investigate the underpinning mechanisms. For example, other studies of cancers[20] and ulcerative colitis[21] employing the same dataset have pointed to the potential long-term adverse effects of neuroleptics**.** Together with the present study, this body of work illustrates the complex yet poorly understood relationships between MDs and the full range of biomedical and biophysical diseases. The associations that appear when examined in a population indicate a wide range of morbidities (ICD diseases) that extend well beyond the current concept of discrete psychosomatic or somatoform categories (Figure 1). Relating such biomedical and biophysical symptoms to a circumscribed range of mental problems in systems such as the cardiovascular system is outdated and inaccurate, given the results of this population-based study. While there are well-established causes of some forms of cardiovascular morbidity, such as smoking, substance dependence, sedentary behavior, etc., the results of

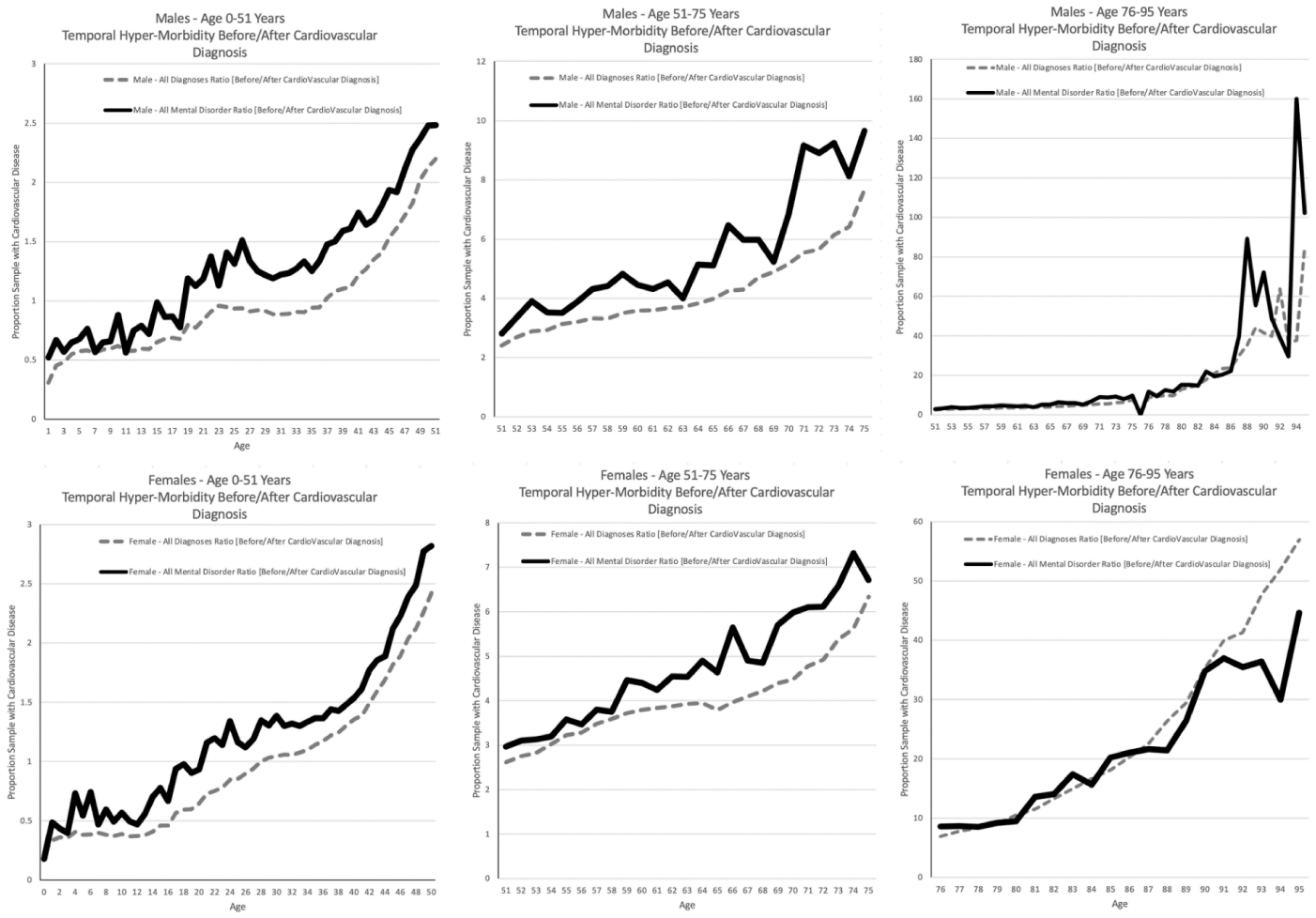

Figure 2. Temporal hyper-morbidity for males (upper) and females (lower) by 3 age groupings.

the present approach to analysis hold the potential to identify other putative pathways for deeper examination.

The challenge is medical practitioners' conceptualization of discrete categories of psychosomatic illness with respect to CD. For the majority, physician-diagnosed MD precedes the index physician diagnosis of CD. It may be that CD within vulnerable populations, like that of cancers[20] and ulcerative colitis,[21] may be related to long-term unstudied adverse effects of neuroleptics via disruption of cell-cell communication wherever a binding receptor is encountered in the body. For example, studies of ulcerative colitis support the notion that alterations in serotonin metabolism in the bowel may be linked to the use of neuroleptics, such as those commonly used to treat anxiety and depression.[22-24]

Limitations

Individuals can be in the dataset for a maximum of 16 years so they can be counted across more than one specific age. Hence, there are other ways to examine the data. However, a recent analysis comparing a prospective cohort within this dataset and the same grouping across the whole dataset[25] has shown that this potential bias does not unduly influence the observed rates of multimorbidity for each analytical approach. Furthermore, the data only includes the date on which any diagnosis was recorded in the physician billing database and did not indicate how long a patient had a disease before the date of coding.

Further, the diseases arising in one dependent group and not in another could not be represented graphically without introducing the bias inherent in substituting some value, such as one, where a zero naturally occurred. Therefore, these diagnoses were not included in the analysis or described, being a subject for an independent analysis. While conclusions may be drawn from the ratios of occurrence of any independent diagnosis in 2 dependent groups, not enough is known to warrant any discussion about the protection or risk conferred or associated with the presence or absence of any diagnosis in only one group without representation in another corresponding group (~100 diagnoses across the dependent groups). Additionally, the relatively rare forms of congenital CD were not included in the main definition of the dependent CD category.

The ICD definitions employed were based on the use of ICD-9 definitions up to 2010, the last year of the analyzed physician billing dataset. The ICD code definitions vary somewhat from edition to edition, which may limit some aspects of interpretation. In the present study, only ICD-9 diagnoses (published before 2010 and after 1993) were reported in the physician billing data and employed to derive the study results. The ICD-11 (published in May 2021) is the current standard for reporting diagnoses. Were the updated ICD-11 version have been employed as the instrument for classifying diagnoses between 1993 and 2010, the results might well be somewhat different. Nevertheless, the algorithms and methods employed to obtain the results from the 1993 to 2010 dataset could be applied to more

contemporary ICD-11 data and diagnostic population-based data from other countries to evaluate the stability, reliability, validity, and, ultimately the clinical utility of the findings. Importantly, research examining DSM-5 and ICD-11 somatoform disorders as early as 2007 concludes the following:

> "The insufficient criterion and predictive validity of the present somatoform classification underlines the need to revise the diagnostic criteria. However, an abolishment of the whole category of somatoform disorders would ignore the substantial convergent and divergent validity of the current classification and would exclude patients with somatoform symptoms from the current health care system. A careful revision of the current somatoform disorder diagnoses, based on positive criteria of psychological, biological and social features, has the potential to substantially improve the reproducibility and clinical utility of the existing classification system."[26]

CONCLUSIONS

Studies of the clinical impact of psychosomatic or somatoform mental illness and especially those focusing on circulatory diseases need to consider the full range of diagnoses and the temporal order of associated disease manifestation within the individual. Psychosomatic or somatoform presentations, as defined in the ICD-9 codes, are represented in the range of MDs (ICD-9 codes 290-319) analyzed but are not specifically highlighted. Rather, this article points to the need to examine the full range of biomedical and MDs, in addition to the narrower bandwidth of psychosomatic or somatoform presentations, when it comes to an understanding of the actual morbidity associated with CD, which goes far beyond the boundaries of diagnosed psychosomatic illness.

Once established within relevant cultures, the population-based reference estimates of the occurrence frequency of specific diseases or disorders may serve to guide clinical decision-making to determine whether an individual is above or below the norm in terms of any apparent disease manifestation. As a result, a different and perhaps more precise understanding of psychosomatic disease may emerge over time with fewer false positives or negatives.

Future research in the area of complex temporal hyper-morbidity[19] exemplified in this article will depend on the advancement of standardized algorithms underpinning the analysis of the temporal order of diseases and disorders that arise within individuals. The papers examining cancer,[20] ulcerative colitis,[21] and preventable diseases[27] illustrate the importance of physician-assigned diagnoses. Hopefully and ideally, future cardiovascular research will integrate diagnosis with genomics, transcriptomics, proteomics, and metabolomics.[28] The art of diagnosis remains a central signpost guiding treatment and a cornerstone of what will ultimately become molecular-based, person-centered medicine.

The importance of this article is illustrated by the recent actions of the World Psychiatry Association, which formed a Comorbidity Section in 2020 to address the observed degree of temporal hyper-morbidity of biomedical and biophysical morbidity[29,30] that transcends the traditional DSM and ICD conceptualization of somatoform and psychosomatic disorders. The formation of this section was, in part, a result of papers published related to the present study (e.g., same sample), which also call for a shift in the paradigms of psychiatric practice in terms of conceptualization, assessment, treatment, follow-up, and liaison with other divisions of medicine,[20,21,25,26] as well as forming the basis of population health assessment.[31]

Ethics Committee Approval: Ethics committee approval was received for this study from the University of Calgary Conjoint Health Research Ethics Board (CHREB) ethics committee (date: August 1, 2022, number: REB-15-1057_REN7).

Informed Consent: Waiver of consent granted.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.H.C., D.C.; Design – P.H.C., D.C.; Supervision – P.H.C., D.C.; Resources – P.H.C., D.C.; Materials – P.H.C., D.C.; Data Collection and/or Processing – P.H.C., D.C.; Analysis and/or Interpretation – P.H.C., D.C.; Literature Search – P.H.C., D.C.; Writing Manuscript – P.H.C., D.C.; Critical Review – P.H.C., D.C.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke Statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596. [CrossRef]
2. Tyerman Z, Mehaffey JH, Hawkins RB, et al. History of serious mental illness is a predictor of morbidity and mortality in cardiac surgery. *Ann Thorac Surg*. 2021;111(1):109-116. [CrossRef]
3. Gabriel RA, Sztain JF, A'Court AM, Hylton DJ, Waterman RS, Schmidt U. Postoperative mortality and morbidity following non-cardiac surgery in a healthy patient population. *J Anesth*. 2018;32(1):112-119. [CrossRef]
4. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. *Curr Cardiol Rep*. 2016;18(12):120. [CrossRef]
5. Nakao M, Takeuchi T, Fricchione G. Definition of psychosomatic medicine and the applicability of DSM-IV-TR to outpatients visiting a Japanese psychosomatic clinic. *Psychother Psychosom*. 2014;83(2):120-121. [CrossRef]
6. Wirsching M. Psychosomatic medicine and psychotherapy in transition. The ecological change in progress to a new definition. *Z Psychosom Med Psychoanal*. 1991;37(4):389-401.
7. Röder H. Psychosomatic medicine--a chance for integrated medicine. Position, definition, trends. *Z Gesamte Inn Med*. 1988;43(2):29-33.
8. Hobbs GE. Psychosomatic medicine: A concept in search of A definition. *Can Psychiatr Assoc J*. 1965;10:1-2. [CrossRef]
9. Osman Dick JG. Definition and transcendency of psychosomatic medicine. *Dia Med*. 1955;27(78):2563.
10. Liebermann LP, Szutrely J. Psychosomatic examination of cardiac children. *Paediatr Danub*. 1949;5(3-4):203-213.
11. Weiss E. Psychosomatic cardiac disease. *Med Clin North Am*. 1954;11:1789-1800. [CrossRef]
12. Kirketerp P. Cardiac neurosis from the psychosomatic viewpoint. *Manedsskr Prakt Laegegern*. 1951;29(8):298-308.
13. Desai R, Patel K, Dave H, et al. Nationwide frequency, sequential trends, and impact of co-morbid mental health disorders on hospitalizations, outcomes, and healthcare resource utilization in adult congenital heart disease. *Am J Cardiol*. 2020;125(8):1256-1262. [CrossRef]
14. Funakoshi S, Hosoi M, Tsuchida O. Psychosomatic medicine for non-cardiac chest pain. *Nihon Rinsho*. 2009;67(9):1796-1802.
15. Bahremand M, Shahbazirad A, Moradi G, Zokaei A. An investigation of pain intensity patterns and psychosomatic symptoms among the cardiac patients admitted to an Iranian Hospital. *Caspian J Intern Med*. 2021;12(2):167-172. [CrossRef]

16. László A, Lénárt L, Illésy L, Fekete A, Nemcsik J. The role of neurotrophins in psychopathology and cardiovascular diseases: psychosomatic connections. *J Neural Transm (Vienna)*. 2019;126(3):265-278. [CrossRef]
17. Korbmacher B, Schäfer R. Psychosomatic background of classic cardiovascular risk factors. *Dtsch Ärztebl Int*. 2012;109(43):733. [CrossRef]
18. Littman AB. Review of psychosomatic aspects of cardiovascular disease. *Psychother Psychosom*. 1993;60(3-4):148-167. [CrossRef]
19. Jakovljević M, Ostojić L. Comorbidity and multimorbidity in medicine today: challenges and opportunities for bringing separated branches of medicine closer to each other. *Psychiatr Danub*. 2013;25(suppl 1):18-28.
20. Cawthorpe D, Kerba M, Narendran A, Ghuttora H, Chartier G, Sartorius N. Temporal order of cancers and mental disorders in an adult population. *BJPsych Open*. 2018;4(3):95-105. [CrossRef]
21. Cawthorpe D, Davidson M. Temporal comorbidity of mental disorder and ulcerative colitis. *Perm J*. 2015;19(1):52-57. [CrossRef]
22. Jørandli JW, Thorsvik S, Skovdahl HK, et al. The serotonin reuptake transporter is reduced in the epithelium of active Crohn's disease and ulcerative colitis. *Am J Physiol Gastrointest Liver Physiol*. 2020;319(6):G761-G768. [CrossRef]
23. Blackwell J, Alexakis C, Saxena S, et al. Association between antidepressant medication use and steroid dependency in patients with ulcerative colitis: a population-based study. *BMJ Open Gastroenterol*. 2021;8(1). [CrossRef]
24. Han L, Zhao L, Zhou Y, et al. Altered metabolome and microbiome features provide clues in understanding irritable bowel syndrome and depression comorbidity. *ISME J*. 2022;16(4):983-996.
25. Chai PH, Chang S, Cawthorpe D. The Temporal hyper-morbidity of Asthma and attention deficit disorder: implications for Interpretation Based on Comparison of Prospective and Cross-Sectional Population Samples. *Psychiatry Investig*. 2021;18(2):166-171. [CrossRef]
26. Löwe B, Mundt C, Herzog W, et al. Validity of current somatoform disorder diagnoses: perspectives for classification in DSM-V and ICD-11. *Psychopathology*. 2008;41(1):4-9. [CrossRef] Epub 2007 Oct 18.
27. Chartier G, Cawthorpe D. From 'Big 4' to 'Big 5': a review and epidemiological study on the relationship between psychiatric disorders and World Health Organization preventable diseases. *Curr Opin Psychiatry*. 2016;29(5):316-321. [CrossRef]
28. Lim SY, Selvaraji S, Lau H, Li SFY. Application of omics beyond the central dogma in coronary heart disease research: A bibliometric study and literature review. *Comput Biol Med*. 2021;140:105069. [CrossRef]
29. Heinze G, Sartorius N, Guizar Sanchez DP, et al. Integration of mental health comorbidity in medical specialty programs in 20 countries. *Int J Psychiatry Med*. 2021;56(4):278-293. [CrossRef]
30. Fiorillo A, de Girolamo G, Simunovic IF, et al. The relationship between physical and mental health: an update from the WPA working group on managing comorbidity of mental and physical health. *World Psychiatry*. 2023;22(1):169-170. [CrossRef]
31. Cawthorpe D. A novel population-based health index for mental disorder. *Perm J*. 2013;17(2):50-54. [CrossRef]