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The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based Study

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Abstract

Objectives: To estimate the attributable costs of multimorbidity and assessed whether the association between the level of multimorbidity and health system costs varies by socio-demographic factors in young (<65) and older (≥65) adults living in Ontario, Canada.

Design: a population-based, cross-sectional study

Setting: the province of Ontario, Canada

Participants: 6,639,089 Ontarians who were diagnosed with at least one of 16 selected chronic conditions on April 1, 2009.

Main outcome measures: From the perspective of the publicly funded healthcare system, total annual healthcare costs were derived from linked provincial health administrative databases using a person-level costing method. We used the generalized linear models to examine the association between the level of multimorbidity and healthcare costs and the extent to which sociodemographic variables modified this association.

Results: Attributable total costs of multimorbidity ranged from $377 to $2,073 for young individuals and $1,026 to $3,831 for older adults. The association between the degree of multimorbidity and healthcare costs was significantly modified by age ($p<0.001$), sex ($p<0.001$) and neighborhood income ($p<0.001$) in both age groups. The rate of increase in healthcare costs with greater number of chronic conditions was more gradual in women than men aged 65 years or younger. For those older than 65 years, the rate of increase was less pronounced among women living with fewer than 3 chronic conditions but significantly greater among those experiencing 3+ chronic conditions compared to men. We also observed that the positive association between the level of multimorbidity and health care costs was significantly accelerated by greater levels of marginalization.

Conclusion: Socio-demographic factors are important effect modifiers of the relationship between multimorbidity and healthcare costs; they should be considered in any discussion on the implementation of healthcare policies and the organization of healthcare services aimed at controlling healthcare costs associated with multimorbidity.

KEYWORDS: multimorbidity, health system costs, socio-demographic factors, population-based study, publicly funded healthcare system

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Strengths and limitations of this study

- This population-based study was based on a large sample size and used the robust costing and generalized linear model regression techniques.
- The availability of linked and patient-level health administrative databases allows us to estimate the total health system costs associated with multimorbidity from all healthcare sectors.
- The use of health administrative databases can also minimize potential recall and non-response biases that are commonly found in survey data.
- The total healthcare costs reported in this study may be underestimated because they were derived based on selected 16 chronic conditions. Moreover, it was not possible to measure some costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated with caregiving) with our data.
- The study did not take into account the clusters of chronic conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the type and patterns of comorbid chronic conditions.

BACKGROUND

Multimorbidity, the presence of the two or more co-existing conditions within a single person, is increasingly prevalent due to advances in life-extending medical treatments and increases in life expectancy. (1, 2) Internationally, the prevalence of multimorbidity has been shown to range from 17% in young adults (3) to 82% in older adults living in nursing homes.(4) In Canada, the prevalence of multimorbidity based on 16 selected conditions in Ontario rose from 17.4% in 2003 to 24.3% in 2009, and this increase was evident across all age groups.(5)

Higher levels of multimorbidity are associated with impaired physical functioning (6), poorer quality of life (7), more frequent use of health services, and higher risk of death. (8) In addition, individuals with multimorbidity may experience faster disease progression and require complex medical care services. (9) These individuals may be at a higher risk of receiving sub-optimal care (10), inappropriate prescriptions (11) and experience potentially preventable hospitalizations. (12) These adverse health outcomes can impose substantial burden on patients, family caregivers and the healthcare system.

The relationship between multimorbidity and healthcare costs is well-documented and has been shown to be curvilinear or exponential across jurisdictions. The average Medicare payments in the US ranged from $1,154 among Part A and Part B beneficiaries with one chronic condition to $13,973 among beneficiaries with at least four chronic conditions (a 12-fold difference). (12) Similarly, the mean total health system cost among older adults with multimorbidity in Switzerland was nearly six times higher than the those without multimorbidity. (13)

Despite an abundance of research describing the relationship between multimorbidity and healthcare costs, existing studies have some important limitations. Some previous multimorbidity studies failed to account for a positively skewed distribution of cost data leading to several violations of modeling assumptions which could result in biased conclusions about the significance of the effects. (14) Multimorbidity studies that did transform cost data to the logarithmic scale may still be subject to a positive or negative bias of the predicted costs because the exponentiation of the predicted values from a log-transformed regression model provides the prediction of a median instead of arithmetic mean. (15) More importantly, the role of sociodemographic characteristics as effect modifiers in the relationship between multimorbidity and healthcare costs remains under-described, although previous research has shown that the specific types of disease clusters vary by age and sex (2, 16) and that multimorbidity is more prominent in selected visible minority and low-socioeconomic status populations. (17)

The objectives of this study were therefore to estimate the health system costs attributable to multimorbidity and assess the extent to which the relationship between the level of multimorbidity and health system costs varies according to sociodemographic characteristics.

METHODS

Study design and sample

This population-based, cross-sectional study included all residents who lived in the province of Ontario between April 1, 2009 and March 31, 2010, were enrolled in Ontario Health Insurance Plan (OHIP), and were diagnosed with at least one of the following selected 16 chronic conditions: acute myocardial infarction (AMI), arthritis, asthma, cancer, cardiac arrhythmia,

chronic coronary syndrome, chronic obstructive pulmonary disorder (COPD), congestive heart failure, dementia, depression, diabetes, hypertension, osteoporosis, renal failure , rheumatoid arthritis and stroke. These conditions were selected because previous research and clinical experts agreed that they were highly prevalent and imposed substantial care and economic burden to Canada's healthcare system. (5, 18) Each condition was identified from multiple provincial health administrative databases using diagnostic algorithms and consultation codes that have been validated or used in previous studies. (19-21) The administrative databases were linked anonymously using unique identifiers. They were housed and secured at the Institute for Clinical Evaluative Sciences (ICES) under data security and privacy policies and procedures approved by the Information and Privacy Commissioner of Ontario. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

We defined six conditions (AMI, asthma, chronic heart failure, COPD, diabetes, and hypertension) based on validated population derived registries held at ICES. (22-28) These conditions were all defined based on one diagnosis recorded in acute care or two diagnoses recorded in ambulatory care (physician) records within a two-year period, except for AMI which was defined using acute care records over a one-year period. A similar approach was adopted to define the remaining chronic conditions including arthritis, cancer, cardiac arrhythmia, chronic coronary syndrome, dementia, depression, osteoporosis, renal failure, rheumatoid arthritis and stroke.

Measures

Healthcare costs

Healthcare costs were estimated from a perspective of the publicly funded healthcare system; accordingly, only direct costs borne to the Ontario Ministry of Health and Long-Term Care were considered. In Ontario, medically necessary hospital and physician services are paid for by the publicly-financed health insurance plan. Public coverage for prescription drugs is primarily limited to residents aged 65 years and over, social assistance recipients as well as those with high prescription drug costs compared to their net household income.

We identified, measured and valued direct healthcare costs by applying a person-level costing technique that was developed and validated based on the Ontario health administrative data. (29) We calculated the costs of inpatient hospitalizations, emergency department visits, same day surgeries, and inpatient rehabilitation by multiplying the weighted volume of services by the average provincial costs per weighted case. We obtained the costs of fee-for-service physician and outpatient diagnostic or laboratory services through OHIP fee approved as outlined in the Ontario Health Insurance Schedule of Benefits and Fees. (30) We calculated non-fee-for-service physician payments by applying applicable capitation payments or the median amount reimbursed for the same service code for the specific fiscal year. (29) Costs for high-cost medical device equipment were estimated from amount reimbursed to patients recorded in the Assistive Devices Program database. Complex continuing care and inpatient psychiatric costs were based on case mix, number of days in care, and Resource Utilization Groups. (31) Patient costs for long-term care and home care were estimated using average cost per hour. We used pharmacy payments recorded in the Ontario Drug Benefit database to capture prescription medication costs for individuals eligible for public coverage. Annual total direct healthcare costs were the sum of

costs across healthcare sectors for each patient for a one-year period, i.e. from April 2009 to March 2010.

We categorized healthcare costs into five components: physician, hospital, drug, continuing care and other health care delivery costs. Physician costs included professional fees paid by the provincial insurance plan directly to physicians in private practice. Hospital costs included amounts paid to healthcare institutions, including those providing acute care, extended and chronic care, rehabilitation and convalescent care, psychiatric care, as well as drugs dispensed in hospitals. Drug costs consist of the costs for prescriptions dispensed at outpatient pharmacies to individuals eligible for provincial coverage, while continuing care costs included expenditure on home care and residential long-term (nursing-home) care. The other healthcare delivery costs category represented expenditures on an assistive device program that subsidizes high-cost equipment, such as wheel chairs, walkers, continuous positive airway pressure devices and insulin pumps, for patients with physical disabilities. All costs were expressed in 2009 Canadian Dollars.

Independent variables

Multimorbidity was defined as the occurrence of two or more chronic diseases among the 16 selected conditions within a single individual and was categorized into five groups. A categorical variable was created to capture those with no multimorbidity (single disease only), two, three, four and five or more multimorbid conditions. Socio-demographic variables consisted of age, sex, income and level of marginalization. As prescription drug costs among Ontarians aged less than 65 years are primarily covered by private drug plans, we ran separate regressions for

younger (<65 years) and older (65+ years) cohorts. We also included a continuous variable of age in the models. Income level was categorized to five quintiles, with the lowest quintile reflecting the lower income level. We used the Ontario Marginalization Index, a validated census- and geographically-based index, as a proxy for individual-level sociodemographic factors. (32) The index consisted of four dimensions of marginalization: material deprivation; residential instability; ethnic concentration; and dependency. Lower scores on each dimension represent areas that are the least marginalized and higher scores represent areas that are the most marginalized. This index has been shown to be associated with several health outcomes. (33)

We also controlled for other factors that might confound the impact of multimorbidity on healthcare costs. Selection of such factors was guided by previous healthcare costs studies (12, 34, 35) and was subject to their availability in Ontario administrative databases. This confounding factor included the type of primary care model and geographic location. The primary care model was categorized into three groups: group-based teams with capitation/salary and team-based payment (family health teams/other group models); capitation or blended payment models (family health networks/family health organizations); or primarily fee for service (family health groups and non-rostered patients). We assigned a geographic location to each individual using the Rurality Index for Ontario (36), whereby a value greater than 40 was considered to be a designated rural area.

Analysis

Annual health care costs per capita were described by health service sector, age group (<65 vs. ≥65 years), the degree of multimorbidity and each of the independent factors, such as sex, age

groups, and the level of marginalization. Multivariate regression analyses were used to assess the incremental costs of interest in this study. To identify the regression model that fits best with the cost data, we followed the steps suggested by Manning and Mullahy. (37) We first ran ordinary least-squares regressions (OLS) of the logarithmic transformation of cost data on the number of chronic conditions and other confounding factors. However, the OLS regression was deemed inappropriate because the residuals were not normally distributed. The generalized linear model (GLM) with a log-link function and a gamma distribution was chosen because a modified Park test suggested that the variance was proportional to the conditional mean. The GLM allows us to estimate mean healthcare costs without the need for retransformation.

Attributable costs due to multimorbidity were estimated by subtracting the mean predicted cost of one chronic condition from two conditions, two from three conditions, three from four conditions, and four from at least five conditions, respectively. To investigate whether the relationship between the level of multimorbidity and healthcare costs was moderated by sociodemographic factors, we added an interaction term between the level of multimorbidity and each sociodemographic factor at a time; for example, the level of multimorbidity*sex or the level of multimorbidity*income level, to the adjusted model. The significance of each interaction term was assessed by comparing the likelihood ratio of the full model with interaction terms to the model without interaction terms using the likelihood ratio test.

The model performance, including goodness of fit and specifications, was examined by checking the scaled deviance, Pearson's chi-square statistics and residual plots, respectively. All analyses

were performed using SAS statistical software for UNIX (version 9.3; SAS Institute, Cary, North Carolina).

RESULTS

We identified a cohort of 6,639,089 individuals living with at least one of the selected 16 chronic conditions in Ontario in 2009 (see Appendix 1 for baseline characteristics). Our cohort represents about 50% of the total population in the province of Ontario in 2009. Close to half of the study cohort (48%) had at least two selected chronic conditions, and this prevalence was found to increase with age. The majority of the study cohort was female (53%) and was younger than 65 years of age (75%). Nearly all individuals (91%) resided in non-rural areas, and about one-third (33%) lived in neighborhoods with a high proportion of diverse ethnic groups.

The total annual healthcare cost estimated for the study cohort was $26.5 billion. As shown in Figure 1, individuals living with at least two selected chronic conditions represented 23.7% of total population but accounted for approximately two-third (67.9%) of total allocatable healthcare costs. By contrast, individuals without multimorbidity who accounted for 76% of the total population were responsible for only 32.1% of total allocatable healthcare costs. On average, annual total costs per capita amounted to $2,217 in individuals younger than 65 years and $9,398 in those aged 65 years or older.

[Figure 1]

Table 1 shows the annual total costs per capita by baseline characteristics for young and older adults. For both age groups, per capita total healthcare costs were higher in women than men. The average healthcare costs increased with older age. The greater levels of marginalization

were associated with higher healthcare costs in both age groups. Mean total healthcare costs were the highest among individuals living in the most deprived and most unstable areas as well as those who were highly dependent. However, mean total costs decreased with higher income level.

Table 1. Annual per capita healthcare costs by baseline characteristics and age group, April 1, 2009 to March 31, 2010

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
All cohort	5,004,699	2,217 (9630)	502 (193-1317)	1,634,390	9,398 (19,796)	2,982 (1,448-7,178)
Sex						
Female	2,618,591	2,311 (9,044)	624 (248– 1,546)	923,053	9,526.96 (19,245)	2,991.97 (1,461-7,344)
Male	2,386,108	2,113 (10,233)	378.67 (132– 1,058)	711,337	9,230.31 (20,488)	2,968.13 (1,431-6,982)
Age group (years)						
<20	809,782	997 (6,420)	257 (103-600)			
20 - 44	1,784,314	1,835 (7,997)	440 (155-1,171)			
45 – 64	3,247,243	2,910 (11,414)	684 (291-1,725)			
65 - 74				1,219,877	6,424 (16,464)	2,363 (1,173-4,757)
75+				797,750	12,517 (22,351)	3,964 (1,884-12,277)
Income quintile						
Lowest	935,048	2,822 (11,333)	580 (206-1699)	314,616	10,646 (21,501)	3,325 (1,596-8,667)
Middle-low	970,797	2,360 (10,276)	521 (199-1,380)	336,928	9,529 (20,218)	3,053 (1,501-7,296)
Middle	999,087	2,107 (9,146)	498 (195-1,268)	318,557	9,319 (19,552)	2,992 (1,470-7,114)
Middle-high	1,042,284	2,008 (8,899)	487 (195-1,226)	322,798	9,120 (19,279)	2,916 (1,426-6,873)
Highest	1,009,89	1,903 (8,391)	475	331,022	8,549	2,747

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
	0		(192-1,180)		(18,309)	(1,351-6,352)
Rurality index						
Non-rural	4,579,691	2,206 (9,605)	509 (197-1,320)	1,459,014	9,448 (19,998)	3,005 (1,470-7,161)
Rural	356,361	2,522 (10,112)	501 (197-1,441)	157,864	9,333 (18,303)	2,918 (1,400-7,798)
Deprivation quintile						
Least deprived	1,282,898	1,894.17 (8,596.59)	476 (193-1,170)	371,547	9,167 (19,628)	2,823 (1,380-6,709)
Less deprived	1,136,731	2,015 (8,810)	489 (196-1,231)	368,124	8,935 (18,928)	2,898 (1,423-6,759)
Somewhat deprived	982,133	2,193 (9,240)	504 (196-1,311)	346,326	9,165 (19,300)	2,978 (1,463-7,030)
Very deprived	808,152	2,438 (10,281)	511 (200-1,443)	293,434	9,541 (19,951)	3,100 (1,520-7,467)
Most deprived	705,593	2,941 (11,861)	600 (210-1,79)	228,501	10,517 (21,250)	3,326 (1,599-8,570)
Instability quintile						
Least dependent	1,211,734	2,007 (8,674)	489 (188-1,250)	188,787	8,149 (19,413)	2,713 (1,307-5,882)
Less dependent	1,179,936	2,078 (9,134)	500 (195-1,275)	276,819	8,359 (18,652)	2,777 (1,353-6,167)
Somewhat dependent	976,538	2,230 (9,793)	506 (198-1,320)	303,853	8,717 (19,018)	2,849 (1,401-6,548)
Very dependent	808,196	2,349 (9,954)	515 (201-1,375)	326,662	9,068 (19,195)	2,944 (1,458-6,958)
Most dependent	739,103	2,650 (10,947)	550 (213-1,507)	511,811	10,961 (20,953)	3,381 (1,636-9,336)
Ethnic concentration quintile						
Lowest	564,476	2,398 (9,766)	500 (200-1,370)	283,980	9,309 (18,529)	2,983 (1,463-7,533)
Middle-low	756,120	2,288 (9,552)	491 (196-1,317)	304,526	9,170 (18,773)	2,969 (1,458-7,283)
Middle	854,573	2,280 (9,780)	497 (196-1,317)	305,524	9,540 (19,678)	3,011 (1,478-7,419)
Middle-high	1,028,876	2,190 (9,565)	502 (195-1,309)	294,164	9,600 (20,240)	3,012 (1,473-7,266)
Highest	1,711,462	2,124 (9,468)	528 (199-1,331)	419,738	9,288 (20,751)	2,981 (1,441-6,694)

Note: SD, standard deviation; IQR, interquartile range

Figure 2 illustrates the distribution of total cost per capita by type of services. Among individuals younger than 65 years of age, hospitalization was the primary cost driver and responsible for 47% of total healthcare costs, followed by physician costs (32%), drug costs (10%), and continuing care costs (6%). For older adults, hospital costs remained the largest cost component (41%), followed by continuing care costs (23%), drug costs (19%) and physician costs (15%). Figure 2 also reveals that unadjusted mean total costs increased at an increasing rate with additional numbers of chronic conditions, ranging from $1,352 in individuals younger than 65 years of age without multimorbidity to $13,105 in those living with five or more chronic conditions, corresponding to a 10-fold increase. On the other hand, while $4,185 was spent on older adults without multimorbidity, spending increased by about 5-fold to $19,196 in those living with five or more chronic conditions.

[Figure 2]

Table 2 shows adjusted attributable costs of multimorbidity after controlling for other factors. Among individuals younger than 65 years, the attributable total cost was $377 in those living with two chronic conditions and $2,073 in those living with at least 5 chronic conditions, corresponding to a six times higher attributable cost. Similarly, attributable total costs in older adults also rose with increasing number of chronic conditions, ranging from $1,026 in those with two chronic conditions to $3,831 in those with five or more. The magnitude of an incremental cost depended on a reference category. Specifically, one additional chronic condition to young adults without multimorbidity led to an attributable cost of $377, while for young adults who already had three chronic conditions, one more health condition incurred additional $798. These incremental costs were even greater in older adults, whereby an incremental cost rose from

$1,026 (1 vs. 2 conditions) to $1,652 (3 vs. 4 conditions). Similar patterns were observed for subdivided health care costs, which varied across age groups [Table 2]. An additional chronic condition caused 1- to 3-fold increase in the costs of each health sector except for hospital whereby incremental costs increased steady from $185 to $802 in the younger cohort and from $232 to $1,060 in the older adult cohort.

Table 2. Adjusted incremental total healthcare costs by the degree of multimorbidity and age group*, April 1, 2009 to March 31, 2010

conditions	< 65 years (N=5,004,699)						≥ 65 years (N=1,634,390)					
	total	physician	hospital	drug	continuing care	others	total	physician	hospital	drug	continuing care	others
2 vs. 1	376.50	200.26	185.12	232.37	288.71	23.96	1,025.76	166.48	231.60	350.29	254.14	23.54
3 vs. 2	534.34	238.28	207.22	252.84	207.83	23.81	1,279.96	201.20	247.76	403.56	314.91	28.51
4 vs. 3	798.03	286.29	264.75	316.43	234.58	24.67	1,651.92	227.04	353.60	429.01	367.45	33.17
≥5 vs. 4	2,072.57	515.80	801.64	666.13	486.58	37.64	3,831.40	400.57	1060.00	673.89	732.19	63.76

*adjusted for sex, age, income quintile, primary care model, rurality index, deprivation quintile, instability quintile, dependency quintile, and ethnic concentration quintile

We also found that the association between number of chronic conditions and health care cost was significantly modified by age and sex for both young and older adults [Table 3]. Older age was associated with a reduced rate of increase in health care cost with increasing levels of multimorbidity for individuals aged 65 years or younger but accelerated the rate of increase in those aged 65 years or older. In addition, the rate of increase in health care costs was more gradual in women aged 65 years or younger than their male counterparts. For those aged 65 years or older, the health care cost associated with more chronic conditions rose more rapidly than for men.

For both age groups, the rise in health care cost with greater level of multimorbidity was less pronounced among individuals with high income level. The association between the level of multimorbidity and health care cost was significantly modified by the level of deprivation, instability, dependency and ethnic concentration. The positive association between the level of multimorbidity and health care costs was stronger among individuals living in more deprived, unstable, dependent or diverse ethnic groups than those living in less deprived, stable, dependent or diverse ethnic concentration areas. We did not observe a significant interaction between the number of chronic conditions and the level of dependency in the older adult cohort.

Table 3. Generalized linear models results for total healthcare costs^

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
Intercept	1.6844***	0.0007	1.6049***	0.0034
Age	0.0023***	0.0001	0.0053***	0.0001
Sex				
Male	reference		reference	
Female	0.0628***	0.0002	-0.0023***	0.0006
Number of chronic conditions				
1 condition	reference		reference	

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
2 conditions	0.1092***	0.0017	0.1068***	0.0044
3 conditions	0.2189***	0.0027	0.1860***	0.0045
4 conditions	0.3312***	0.0050	0.2563***	0.0049
≥5 conditions	0.4203***	0.0080	0.3772***	0.0048
Income quintile				
Lowest	reference		reference	
Middle-low	-0.0043***	0.0005	-0.0019*	0.0010
Middle	-0.0045***	0.0005	0.00014	0.0012
Middle-high	-0.0044***	0.0006	0.0001	0.0012
Highest	-0.0080***	0.0006	-0.0045***	0.0013
Deprivation quintile				
Least deprived	reference		reference	
Less deprived	-0.0006*	0.0004	-0.0014***	0.0008
Somewhat deprived	-0.0008*	0.0004	-0.0020**	0.0009
Very deprived	0.0022***	0.0005	-0.0009	0.0011
Most deprived	0.0135***	0.0006	0.0044***	0.0013
Instability quintile				
Least unstable	reference		reference	
Less unstable	0.0039***	0.0005	-0.0019**	0.0009
Somewhat unstable	0.0073***	0.0005	-0.0008	0.0009
Very unstable	0.0122***	0.0005	0.0031***	0.0009
Most unstable	0.0247***	0.0005	0.0087***	0.0010
Ethnic concentration quintile				
Lowest	reference		reference	
Middle-low	0.0002	0.0004	-0.0005	0.0009
Middle	0.0018***	0.0004	0.0022	0.0009
Middle-high	0.0047***	0.0004	-0.0007	0.0010
Highest	0.0066***	0.0004	-0.0043***	0.0009
Dependency quintile				
Least dependent	reference		reference	
Less dependent	0.0004	0.0004	0.0012**	0.0005
Somewhat dependent	0.0001	0.0004	0.0027***	0.0005
Very dependent	0.0009**	0.0004	0.0030***	0.0005
Most dependent	0.0020***	0.0005	0.0100***	0.0005
Number of chronic conditions * sex				
1 condition* Male	reference		reference	
2 conditions * Female	-0.0171***	0.0016	-0.0029***	0.0007
3 conditions * Female	-0.0396***	0.0011	-0.0022***	0.0008
4 conditions * Female	-0.0549***	0.0007	0.0001	0.0008
≥5 conditions * Female	-0.0659***	0.0005	0.0030***	0.0008
Number of chronic conditions * age				
1 condition * age	reference		reference	

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
2 conditions * age	-0.0171***	0.0016	-0.0006***	0.0001
3 conditions * age	-0.0396***	0.0011	-0.0010***	0.0001
4 conditions * age	-0.0549***	0.0007	-0.0014***	0.0001
≥5 conditions * age	-0.0659***	0.0005	-0.0023***	0.0001
Number of chronic conditions * income quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0016*	0.0009	-0.0025*	0.0013
3 conditions * middle-low	-0.0011	0.0013	-0.0037**	0.0014
4 conditions* middle-low	-0.0043**	0.0020	-0.0043**	0.0015
≥5 conditions* middle-low	-0.0031	0.0027	-0.0046**	0.0014
2 conditions*middle	-0.0020**	0.0010	-0.0032**	0.0015
3 conditions * middle	-0.0030**	0.0014	-0.0051**	0.0015
4 conditions* middle	-0.0053**	0.0023	-0.0055**	0.0017
≥5 conditions* middle	-0.0028	0.0031	-0.0072***	0.0016
2 conditions*middle-high	-0.0024**	0.0011	-0.0031*	0.0016
3 conditions * middle-high	-0.0032**	0.0016	-0.0052**	0.0016
4 conditions* middle-high	-0.0067**	0.0025	-0.0081***	0.0018
≥5 conditions* middle-high	-0.0093**	0.0034	-0.0070***	0.0018
2 conditions*highest	-0.0015	0.0011	-0.0036**	0.0017
3 conditions *highest	-0.0031*	0.0017	-0.0063***	0.0018
4 conditions* highest	-0.0096***	0.0027	-0.0088***	0.0019
5 conditions* highest	-0.0099**	0.0038	-0.0095***	0.0019
Number of chronic conditions * deprivation quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0024***	0.0007	-0.0001	0.0011
3 conditions * middle-low	0.0038 ***	0.0010	-0.0015	0.0011
4 conditions* middle-low	0.0027	0.0017	-0.0016	0.0013
≥5 conditions* middle-low	0.0060**	0.0026	-0.0029**	0.0012
2 conditions*middle	0.0047***	0.0007	-0.0002	0.0012
3 conditions * middle	0.0067***	0.0010	-0.0018	0.0013
4 conditions* middle	0.0062***	0.0017	-0.0045**	0.0014
≥5 conditions* middle	0.0109***	0.0026	-0.0042**	0.0014
2 conditions*middle-high	0.0057***	0.0009	-0.0012	0.0014
3 conditions * middle-high	0.0071***	0.0014	-0.0031**	0.0015
4 conditions* middle-high	0.0074***	0.0022	-0.0051**	0.0016
≥5 conditions* middle-high	0.0111***	0.0032	-0.0079***	0.0016
2 conditions*highest	0.0073***	0.0011	-0.0028	0.0017
3 conditions *highest	0.0108***	0.0016	-0.0052**	0.0018
4 conditions* highest	0.0114***	0.0026	-0.0089***	0.0019
≥5 conditions* highest	0.0119***	0.0036	-0.0098***	0.0019
Number of chronic conditions * instability				
1 condition* lowest	reference		reference	

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
2 conditions*middle-low	-0.0012**	0.0007	0.0009	0.0011
3 conditions * middle-low	-0.0007	0.0010	0.0020	0.0012
4 conditions* middle-low	-0.0016	0.0017	0.0010	0.0013
≥5 conditions* middle-low	-0.0013	0.0026	0.0022	0.0014
2 conditions*middle	-0.0017**	0.0008	0.0037**	0.0014
3 conditions * middle	-0.0012	0.0012	0.0010	0.0013
4 conditions* middle	-0.0002	0.0019	0.0022	0.0014
≥5 conditions* middle	0.0025	0.0027	0.0037**	0.0014
2 conditions*middle-high	-0.0003	0.0009	0.0022*	0.0012
3 conditions * middle-high	0.0006	0.0012	0.0019	0.0013
4 conditions* middle-high	0.0011	0.0019	0.0033**	0.0014
≥5 conditions* middle-high	0.0075***	0.0027	0.0048***	0.0014
2 conditions*highest	0.0037***	0.0012	-0.0027**	0.0013
3 conditions *highest	0.0095***	0.0012	-0.0026**	0.0013
4 conditions* highest	0.0113***	0.0020	-0.0035**	0.0014
≥5 conditions* highest	0.0206***	0.0028	-0.0019	0.0014
Number of chronic conditions * ethnic concentration				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0006	0.0009	0.0011	0.0012
3 conditions * middle-low	-0.0007	0.0013	0.0022*	0.0012
Number of chronic conditions * ethnic concentration				
4 conditions* middle-low	-0.0020	0.0021	0.0012	0.0014
≥5 conditions* middle-low	0.0018	0.0029	0.0012	0.0013
2 conditions*middle	0.0004	0.0009	0.0006	0.0012
3 conditions * middle	-0.0006	0.0013	0.0003	0.0012
4 conditions* middle	-0.0034	0.0021	-0.0012	0.0014
≥5 conditions* middle	0.0016	0.0030	0.0004	0.0013
2 conditions*middle-high	0.0002	0.0009	0.0015	0.0012
3 conditions * middle-high	-0.0013	0.0014	0.0021*	0.0013
4 conditions* middle-high	-0.0056**	0.0022	0.0006	0.0014
≥5 conditions* middle-high	-0.0056*	0.0030	0.0035**	0.0014
2 conditions*highest	-0.0008	0.0012	0.0043***	0.0012
3 conditions *highest	-0.0021	0.0013	0.0047***	0.0013
4 conditions* highest	-0.0081***	0.0021	0.0044***	0.0013
≥5 conditions* highest	-0.0070**	0.0030	0.0093***	0.0013
Number of chronic conditions * dependency quintile[#]				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0016**	0.0007		
3 conditions * middle-low	0.0018**	0.0010		
4 conditions* middle-low	0.0004	0.0017		
≥5 conditions* middle-low	-0.0028	0.0026		
2 conditions*middle	0.0015**	0.0001		

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
3 conditions * middle	0.0030***	0.0011		
4 conditions* middle	0.0036**	0.0018		
≥5 conditions* middle	0.0008	0.0025		
2 conditions*middle-high	0.0017**	0.0008		
3 conditions * middle-high	0.0029**	0.0012		
4 conditions* middle-high	0.0028	0.0019		
≥5 conditions* middle-high	0.0014	0.0027		
2 conditions*highest	0.0018**	0.0009		
3 conditions *highest	0.0032**	0.0013		
4 conditions* highest	0.0041**	0.0020		
≥5 conditions* highest	0.0038	0.0028		
AIC	15,672,974		5,058,276	
BIC	15,674,535		5,059,515	

^ adjusted for primary care models and rurality index; *** P <0.001, ** P< 0.05, * p<0.10; se indicates standard error; # interaction between the number of chronic conditions and dependency quintile was not statistically significant and therefore excluded from a final model.

DISCUSSION

Individuals living multimorbidity accounted for 79% of total healthcare costs incurred by our study cohort and 68% of total allocatable healthcare costs in Ontario in 2009. Although there is a growing body of literature documenting the economic burden of multimorbidity in other jurisdictions (12, 13, 38), the current study lends further evidence that small portion of the multimorbid population was responsible for a disproportionately high percentage of total healthcare costs. We observed this disproportionate relationship in both young (<65) and (65+) older cohorts, suggesting that any approaches to containing healthcare costs of multimorbidity should be implemented across all age groups.

Our study demonstrated that healthcare costs increased significantly with higher levels of multimorbidity. This positive association exists even after the adjustment for confounding factors and a skewed distribution of cost data using the generalized linear model with a log link function

and a gamma distribution. The exponential relationship between multimorbidity and incremental healthcare costs shown in this study suggests that the financial burden of multimorbidity to the healthcare system is not simply equal to the sum of costs incurred by each individual condition. This non-linearity reflects the complex association of the degree of multimorbidity, the type of disease clusters and healthcare costs. It is likely that patients with multimorbidity might experience worse health outcomes and require more complex clinical management. (9) They are also vulnerable to receiving redundant diagnostic tests (12), suboptimal transition of care and inappropriate prescriptions. (11) This explanation is plausible as current treatment guidelines are mainly focused on individual disease management. (10) Thus, as the number of healthcare providers involved in the patient's care increases, information sharing and coordinating care across health care providers may pose a challenge. (39) Moreover, an increasing number of comorbid conditions may compromise patients' ability to self-manage their diseases. (40) The high healthcare spending on multimorbidity found in our study underscores the need for ensuring continuity and coordination of care in this population.

More importantly, our study contributes to the understanding of the association between the degree of multimorbidity and healthcare costs. We observed that each unit increase in age slowed the rise in health care costs with increasing number of chronic conditions in the young cohort but accelerated the rise in health care costs in the older cohort. This highlighted that multimorbidity had much larger impact on the youngest and oldest individuals. This age difference might reflect the distribution of healthcare costs that are typically skewed to the first year and the end of life. (41) Additionally, we found that healthcare costs in men increased faster and surpassed the level in women as the number of chronic conditions increased in individuals

younger than 65 years. This sex difference might relate to different disease clusters whereby men within this age group often experience life-threatening and more serious illnesses than women. (42, 43) For those older than 65 years, the rate of increase in healthcare costs with the greater level of multimorbidity were significantly higher in women than men. This sex difference could be partially explained by longer life expectancy and greater risk of multimorbidity in older women than men (17, 44), which may cause older women to be more dependent on formal (paid) healthcare services and other informal (unpaid) caregivers.

Our results revealed that the association between the number of chronic conditions and healthcare costs depended on neighborhood-level socioeconomic characteristics. Living in lower income and marginalized area, i.e. greater levels of instability, dependency or ethnic concentration, accelerated the rate of increase in health system costs with the greater level of multimorbidity. This might reflect a higher risk of experiencing more complex multimorbid conditions among individuals living in disadvantaged neighborhood (45) which led to greater demand and utilization of healthcare. Another possible reason is that individuals living in more deprived area may face barriers in accessing health services (46) and have delayed access to preventive healthcare interventions or treatments (47), thereby having a higher risk of worse health outcomes and high healthcare costs. As the neighborhood socioeconomic characteristics were used in this study, the effect of these characteristics on the association between the number of chronic conditions and healthcare costs should not be inferred to each individual.

Strengths and limitations

This population-based study was based on a large sample size and used the robust costing and generalized linear model regression techniques. The availability of linked and patient-level health administrative databases allows us to estimate the total health system costs associated with multimorbidity from all healthcare sectors. The use of health administrative databases can also minimize potential recall and non-response biases that are commonly found in survey data.

However, the results of this study should be interpreted in light of the following limitations. First, we estimated healthcare costs based on selected 16 chronic conditions. The selection of a limited number of chronic conditions is likely to underestimate the overall healthcare costs of multimorbidity. However, total cost estimates reported in our study were comprehensive because they amounted to 86% of total allocatable government expenditures in Ontario in 2009.(48) Second, due to a paucity of data, some costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated with caregiving) were excluded from the analysis. In addition, this study could not capture the costs of medications covered by private sectors, including private insurers and out of pocket expenses which represent the largest component of total prescription drug costs of Canadians who are younger than 65 years of age. (49) For this reason, findings from this study may not be generalizable to other jurisdictions with different healthcare systems.

Third, this study did not take into account the clusters of chronic conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the type and patterns of comorbid chronic conditions. However, previous research has shown that there were

no common clustering diseases among individuals living with multimorbidity (5) and that the number chronic conditions had a stronger link to healthcare costs than the combination of specific conditions. (50) Finally, due to the cross-sectional nature, our study may be subject to simultaneity bias or endogeneity problem, and the estimated coefficient of multimorbidity on healthcare costs may be biased and inconsistent. It is possible that having a greater number of chronic conditions increases healthcare utilization and costs. At the same time, individuals who had frequent contacts with the healthcare system might be more likely to be diagnosed with a disease(s). Future longitudinal studies are required to attest a causal association between the degree of multimorbidity and healthcare costs.

CONCLUSION

This cross-sectional, population-based study highlights the amount by which health system costs increased significantly with increasing levels of multimorbidity in a publicly financed healthcare system. The average and incremental healthcare costs reported in this study could serve as the foundation for future health economic evaluation of interventions for preventing and managing multimorbidity. As the relationship between multimorbidity and healthcare costs varies according to socio-demographic factors, interventions addressing disparities in healthcare in individuals living with multimorbidity may have a potential to reduce total health system costs.

LIST OF ABBREVIATIONS

AMI acute myocardial infarction

COPD chronic obstructive pulmonary disorder

GLM generalized linear model

ICES Institute for Clinical Evaluative Sciences

OHIP Ontario Health Insurance Plan

OLS ordinary least-squares regressions

DECLARATIONS

Ethic approval:

The study has been approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

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Competing interests: None

Authors contributions: WPW was the lead for the conception and creation of the cohort. YB has created the cohorts through data linkages and helped with data analysis and methods. KT interpreted the results and drafted the manuscript. CM, AG, SB, AK, YB, YP and WPW revised the manuscript for important intellectual content and formatting. All authors read and approved the final manuscript.

Data sharing statement: No additional data are available.

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Figure 1. Distribution of total number of population and total health system costs in Ontario from April 1, 2009 to March 31, 2010

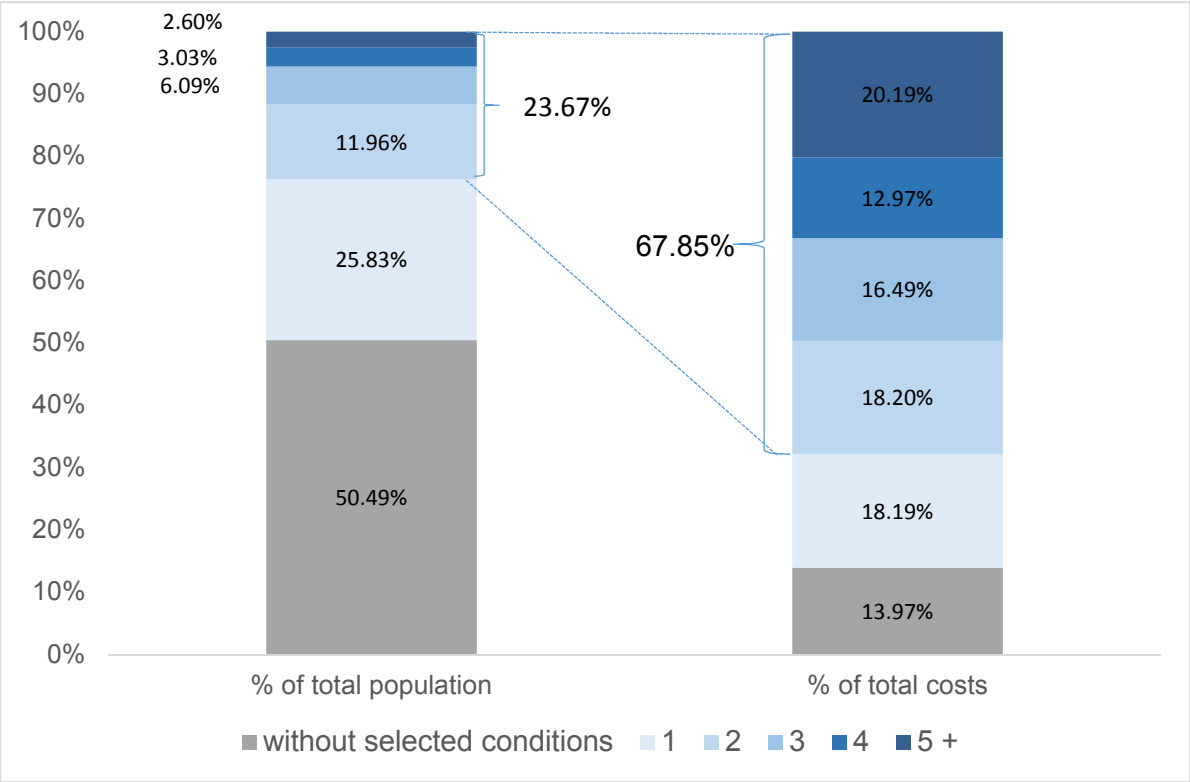
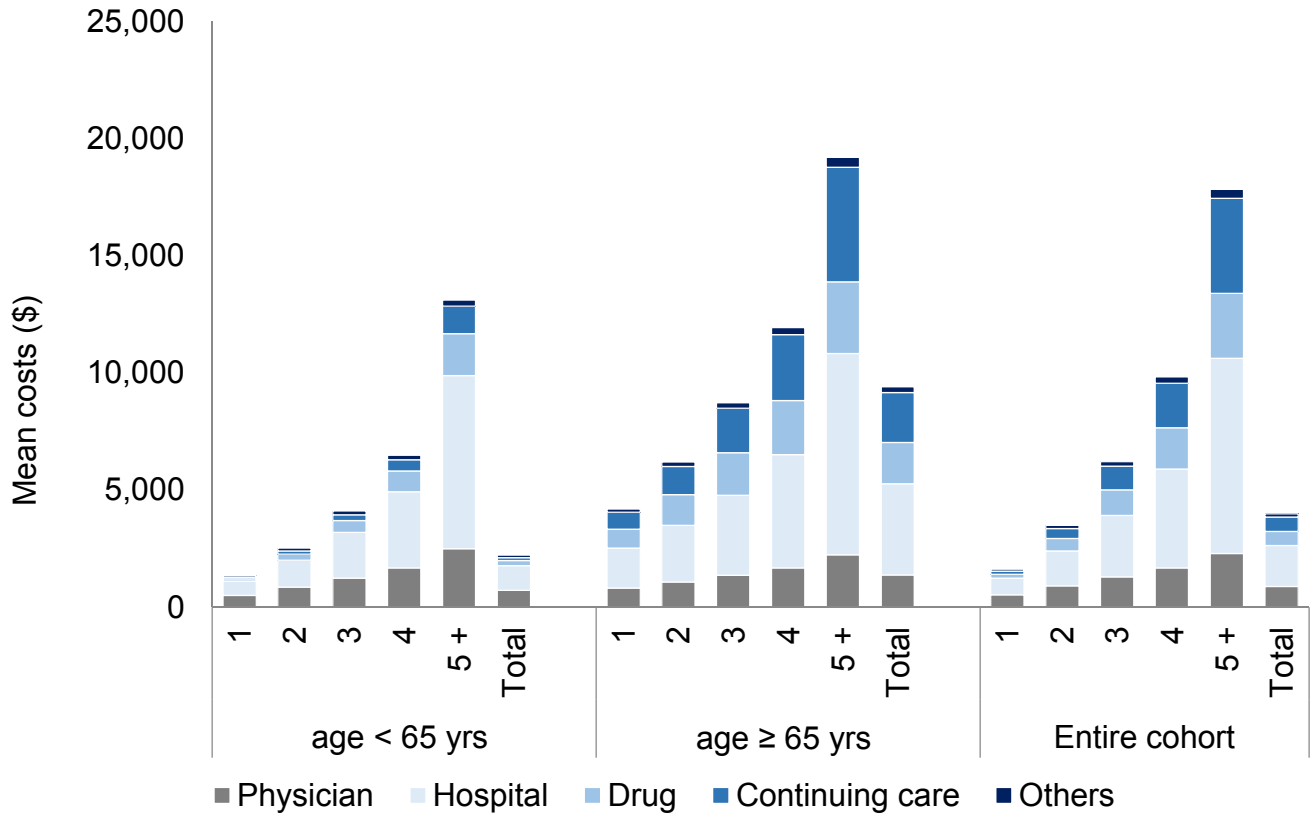


Figure 2. Unadjusted mean total healthcare cost per capita for Ontario adults, by service type, number of conditions and age group from April 1, 2009 to March 31, 2010



Appendix 1. Proportions and mean number of chronic conditions by baseline characteristics, April 1, 2009 to March 31, 2010

	N	Number of chronic conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
All cohort	6,639,089	52.2	24.2	12.3	6.1	5.2	1.88 (1.16)
Sex							
Female	3,541,644	49.2	25.3	13.4	6.6	5.5	1.94 (1.18)
Male	3,097,445	55.6	22.8	11.1	5.5	5.0	1.81 (1.14)
Age (years)							
0-19	809,782	89.8	9.3	0.8	0.1	0.01	1.11 (0.35)
20-34	908,634	77.2	18.8	3.4	0.5	0.1	1.27 (0.55)
35-44	875,680	66.5	24.4	7.0	1.7	0.5	1.45 (0.74)
45-64	2,410,603	47.0	29.9	14.4	5.7	3.0	1.88 (1.05)
65-74	836,640	25.3	29.3	22.3	12.7	10.4	2.53 (1.28)
70-74	383,237	21.8	28.2	23.2	14.2	12.6	2.68 (1.30)
75+	797,750	13.6	22.4	23.2	17.8	23.0	3.14 (1.36)
Income quintile							
Lowest	1,249,664	50.3	23.8	12.8	6.8	6.3	1.95 (1.21)
Middle-low	1,307,725	50.8	24.3	12.8	6.5	5.7	1.92 (1.18)
Middle	1,317,644	52.4	24.2	12.2	6.1	5.1	1.87 (1.15)
Middle-high	1,365,082	53.2	24.3	12.0	5.8	4.8	1.85 (1.13)
Highest	1,340,912	53.5	24.5	11.9	5.7	4.5	1.83 (1.12)
Rurality index							
Non-rural (< 40)	6,038,705	52.3	24.1	12.3	6.1	5.2	1.88 (1.56)
Rural (≥40)	514,225	48.9	25.0	13.3	6.8	5.9	1.96 (1.19)
Deprivation quintile							
Least deprived	1,654,445	55.0	24.0	11.4	5.3	4.3	1.80 (1.11)
Less deprived	1,504,855	52.6	24.4	12.2	5.9	4.9	1.86 (1.14)
Somewhat deprived	1,328,459	51.1	24.4	12.7	6.4	5.5	1.91 (1.17)
Very deprived	1,101,586	50.0	24.3	13.0	6.7	6.0	1.94 (1.20)
Most deprived	934,094	50.0	23.8	12.9	6.8	6.4	1.96 (1.21)

Supplementary Table 1. (Cont'd)

	N	Number of medical conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
Instability quintile							
Least unstable	1,715,922	56.6	24.0	11.0	4.9	3.5	1.75 (1.06)
Less unstable	1,365,580	53.2	24.4	12.1	5.8	4.6	1.84 (1.13)
Somewhat unstable	1,077,375	50.5	24.6	12.9	6.5	5.5	1.91 (1.17)
Very unstable	1,195,108	50.4	24.2	12.8	6.6	6.0	1.94 (1.20)
Most unstable	1,169,454	47.3	23.9	13.6	7.6	7.6	2.04 (1.26)
Dependency quintile							
Least dependent	1,400,521	59.3	23.3	10.0	4.3	3.1	1.69 (1.02)
Less dependent	1,456,755	55.5	24.1	11.3	5.2	4.0	1.78 (1.09)
Somewhat dependent	1,280,391	52.4	24.5	12.3	5.9	4.9	1.86 (1.14)
Very dependent	1,134,858	49.3	24.7	13.3	6.8	5.9	1.95 (1.19)
Most dependent	1,250,914	42.2	24.6	15.3	8.9	9.0	2.18 (1.31)
Ethnic concentration quintile							
Lowest	848,456	47.2	25.1	13.9	7.3	6.5	2.01 (1.22)
Middle-low	1,060,646	49.8	24.8	13.0	6.6	5.7	1.91 (1.19)
Middle	1,160,097	51.0	24.5	12.6	6.3	5.5	1.91 (1.17)
Middle-high	1,323,040	53.4	24.0	11.8	5.8	5.0	1.84 (1.14)
Highest	2,131,200	54.9	23.5	11.5	5.5	4.6	1.81 (1.12)
Primary care model							
Family health teams/ other primary care models	1,109,443	51.0	24.9	12.6	6.3	5.2	1.94 (1.28)
Family health networks /family health organizations	1,054,714	49.6	25.3	13.1	6.5	5.5	1.97 (1.30)
Community health centres/family health groups/non-rostered patients	4,474,932	53.1	23.7	12.0	6.0	5.2	1.90 (1.29)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-11
Bias	9	Describe any efforts to address potential sources of bias	*11-13*
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-13
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	Not report
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	Not report
		(c) Consider use of a flow diagram	Not report
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	Not report
Outcome data	15*	Report numbers of outcome events or summary measures	13-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16-23
		(*b*) Report category boundaries when continuous variables were categorized	16-23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19-23
Discussion			
Key results	18	Summarise key results with reference to study objectives	23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	26-27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23-25
Generalisability	21	Discuss the generalisability (external validity) of the study results	26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based Study

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Keywords:	multimorbidity, health system cost, socio-demographic factors, population-based study, publicly funded healthcare system

The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based Study

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Abstract

Objectives: To estimate the attributable costs of multimorbidity and assess whether the association between the level of multimorbidity and health system costs varies by socio-demographic factors in young (<65) and older (≥65) adults living in Ontario, Canada.

Design: a population-based, retrospective cohort study

Setting: the province of Ontario, Canada

Participants: 6,639,089 Ontarians who were diagnosed with at least one of 16 selected medical conditions on April 1, 2009.

Main outcome measures: From the perspective of the publicly funded healthcare system, total annual healthcare costs were derived from linked provincial health administrative databases using a person-level costing method. We used generalized linear models to examine the association between the level of multimorbidity and healthcare costs and the extent to which socio-demographic variables modified this association.

Results: Attributable total costs of multimorbidity ranged from $377 to $2,073 for young individuals and $1,026 to $3,831 for older adults. The association between the degree of multimorbidity and healthcare costs was significantly modified by age ($p<0.001$), sex ($p<0.001$) and neighborhood income ($p<0.001$) in both age groups. The positive association between healthcare costs and levels of multimorbidity was statistically stronger for older than younger adults. For individuals aged 65 years or younger, the increase in healthcare costs was more gradual in women than their male counterparts. For those aged 65 years or older, the increase in healthcare costs in women was significantly greater than for men. We also observed that the positive association between the level of multimorbidity and healthcare costs was significantly greater at higher levels of marginalization.

Conclusion: Socio-demographic factors are important effect modifiers of the relationship between multimorbidity and healthcare costs; they should be considered in any discussion on the implementation of healthcare policies and the organization of healthcare services aimed at controlling healthcare costs associated with multimorbidity.

KEYWORDS: multimorbidity, health system costs, socio-demographic factors, population-based study, publicly funded healthcare system

Word Counts: 295 (abstract), 4,000 (main text)

Strengths and limitations of this study

- This population-based study was based on a large sample size and used the robust costing and generalized linear model regression techniques.
- The availability of linked and patient-level health administrative databases allows us to estimate the total health system costs associated with multimorbidity from all healthcare sectors.
- The use of health administrative databases can also minimize potential recall and non-response biases that are commonly found in survey data.
- The total healthcare costs reported in this study may be underestimated because they were derived based on selected 16 medical conditions. Moreover, it was not possible to measure some costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated with caregiving) with our data.
- The study did not take into account particular clusters of medical conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the type and patterns of comorbid medical conditions.

BACKGROUND

Multimorbidity, the presence of the two or more co-existing conditions within a single person, is increasingly prevalent due to advances in life-extending medical treatments and increases in life expectancy. (1, 2) Internationally, the prevalence of multimorbidity has been shown to range from 17% in young adults (3) to 82% in older adults living in nursing homes. (4) In Canada, the prevalence of multimorbidity based on 16 selected conditions in Ontario rose from 17.4% in 2003 to 24.3% in 2009, and this increase was evident across all age groups.(5)

Higher levels of multimorbidity are associated with impaired physical functioning (6), poorer quality of life (7), more frequent use of health services, and higher risk of death. (8) In addition, individuals with multimorbidity may experience faster disease progression and require complex medical care services.(9) These individuals may be at a higher risk of receiving sub-optimal care (10), inappropriate prescriptions (11) and experiencing potentially preventable hospitalizations. (12)These adverse health outcomes can impose substantial burden on patients, family caregivers and the healthcare system.

The relationship between multimorbidity and healthcare costs is well-documented and has been shown to be curvilinear or exponential across jurisdictions. The average Medicare payments in the US ranged from $1,154 among Part A and Part B beneficiaries with one chronic condition to $13,973 among beneficiaries with at least four chronic conditions (a 12-fold difference). (12) Similarly, the mean total health system costs among older adults with multimorbidity in Switzerland was nearly six times higher than the those without multimorbidity. (13)

Despite an abundance of research describing the relationship between multimorbidity and healthcare costs, existing studies have some important methodological and conceptual limitations. Some previous studies (14, 15) used Ordinary Least Squares (OLS) regression despite the fact that the positively skewed distribution of cost data often violates the normality assumption of OLS. (16) Others attempted to overcome this problem by transforming cost data to the logarithmic scale (13, 17); however, this transformation may still result in interpretation problem as regression on transformed costs provides the prediction of a median instead of arithmetic mean costs. (18) Importantly, the role of sociodemographic characteristics as effect modifiers of the relationship between multimorbidity and healthcare costs remains poorly described, although previous research has shown that the specific types of disease clusters vary by age and sex (2, 19) and that multimorbidity is more prominent in selected visible minority and low-socioeconomic status populations. (20)

The objectives of this study were therefore to estimate the health system costs attributable to multimorbidity using more rigorous and appropriate approach and assess the extent to which the relationship between the level of multimorbidity and health system costs varies according to sociodemographic characteristics.

METHODS

Study design and sample

This population-based, retrospective cohort study included all residents who lived in the province of Ontario between April 1, 2001 and March 31, 2010, were enrolled in Ontario Health Insurance Plan (OHIP), and were diagnosed with at least one of the following selected 16

medical conditions: acute myocardial infarction (AMI), arthritis, asthma, cancer, cardiac arrhythmia, chronic coronary syndrome, chronic obstructive pulmonary disorder (COPD), congestive heart failure, dementia, depression, diabetes, hypertension, osteoporosis, renal failure, rheumatoid arthritis and stroke. These conditions were selected because previous research and clinical experts agreed that they were highly prevalent and imposed substantial care and economic burden to Canada's healthcare system.(5, 21) We excluded people if they fell under the following criteria: had an invalid health card number, were older than 105 years old, died before the index date, or had no contact with the healthcare system in the last five years before the index date (excepting infants). We also excluded people with no contact with the healthcare system within the past five years as they might have left the province or experienced an unreported death.

Data Sources

We linked multiple provincial health administrative databases anonymously using unique encrypted identifiers. The Discharge Abstract Database provides data for all hospital discharges in Ontario, and the Ontario Health Insurance Plan (OHIP) claims database includes billing claims for all physician encounters. We used the Registered Persons Database to identify Ontarians who were eligible for health insurance coverage and derive age. The linked database was housed and secured at the Institute for Clinical Evaluative Sciences (ICES) under data security and privacy policies and procedures approved by the Information and Privacy Commissioner of Ontario. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Each medical condition was defined using diagnostic algorithms and consultation codes that have been validated or used in previous studies. We defined six conditions (AMI, asthma, chronic heart failure, COPD, diabetes, and hypertension) based on validated population derived registries held at ICES. (22-28) These conditions were all defined based on one diagnosis recorded in acute care or two diagnoses recorded in ambulatory care (physician) records within a two-year period (i.e. between 2007/8 and 2008/09), except for AMI which was defined using acute care records in 2008/09. A similar approach was adopted to define the remaining medical conditions including arthritis, cancer, cardiac arrhythmia, chronic coronary syndrome, dementia, depression, osteoporosis, renal failure, rheumatoid arthritis and stroke. List of diagnostic codes used to define medical conditions are shown in Appendix 1.

Measures

Healthcare costs

Healthcare costs were estimated from a perspective of the publicly funded healthcare system; accordingly, only direct costs borne to the Ontario Ministry of Health and Long-Term Care were considered. In Ontario, medically necessary hospital and physician services are paid for by the publicly-financed health insurance plan. Public coverage for prescription drugs is primarily limited to residents aged 65 years and over, social assistance recipients as well as those with high prescription drug costs compared to their net household income.

We identified, measured and valued direct healthcare costs by applying a person-level costing technique that was developed and validated based on the Ontario health administrative data. (29) We calculated the costs of inpatient hospitalizations, emergency department visits, same day

surgeries, and inpatient rehabilitation by multiplying the weighted volume of services by the average provincial costs per weighted case. We obtained the costs of fee-for-service physician and outpatient diagnostic or laboratory services through OHIP fee approved as outlined in the Ontario Health Insurance Schedule of Benefits and Fees. (30) We calculated non-fee-for-service physician payments by applying applicable capitation payments or the median amount reimbursed for the same service code for the specific fiscal year. (29) Costs for high-cost medical device equipment were estimated from the amount reimbursed to patients recorded in the Assistive Devices Program database. Complex continuing care and inpatient psychiatric costs were based on case mix, number of days in care, and Resource Utilization Groups. (31) Patient costs for long-term care were estimated based on a fixed per diem based on prevailing government payment rates, and costs for home care were estimated using average cost per hour. We used pharmacy payments recorded in the Ontario Drug Benefit database to capture prescription medication costs for individuals eligible for public coverage. Annual total direct healthcare costs were the sum of costs across healthcare sectors for each patient for a one-year period, i.e. from April 2009 to March 2010.

We categorized healthcare costs into five components: physician, hospital, drug, continuing care and other healthcare delivery costs. Physician costs included professional fees paid by the provincial insurance plan directly to physicians in private practice. Hospital costs included amounts paid to healthcare institutions, including those providing acute care, extended and chronic care, rehabilitation and convalescent care, psychiatric care, as well as drugs dispensed in hospitals. Drug costs consist of the costs for prescriptions dispensed at outpatient pharmacies to individuals eligible for provincial coverage, while continuing care costs included expenditure on

home care and residential long-term (nursing-home) care. The other healthcare delivery costs category represented expenditures on an assistive device program that subsidizes high-cost equipment, such as wheel chairs, walkers, continuous positive airway pressure devices and insulin pumps, for patients with physical disabilities. All costs were expressed in 2009 Canadian Dollars.

Independent variables

Multimorbidity was defined as the occurrence of two or more chronic diseases among the 16 selected conditions within a single individual and was categorized into five groups. A categorical variable was created to capture those with no multimorbidity (single disease only), two, three, four and five or more multimorbid conditions. Socio-demographic variables consisted of age, sex, income and level of marginalization. As prescription drug costs among Ontarians aged less than 65 years are primarily covered by private drug plans, we ran separate regressions for younger (<65 years) and older (65+ years) cohorts. We also included a continuous variable of age in the models. Income level was categorized to five quintiles, with the lowest quintile reflecting the lower income level. We used the Ontario Marginalization Index, a validated census- and geographically-based index, as a proxy for individual-level sociodemographic factors. (32) The index consisted of four dimensions of marginalization: material deprivation; residential instability; ethnic concentration; and dependency. Lower scores on each dimension represent areas that are the least marginalized and higher scores represent areas that are the most marginalized. This index has been shown to be associated with several health outcomes. (33)

We also controlled for other factors, such as type of primary care model and geographic location, that might confound the impact of multimorbidity on healthcare costs. Selection of such factors was guided by previous healthcare costs studies (12, 34, 35) and was subject to their availability in Ontario administrative databases. The primary care model was categorized into three groups: group-based teams with capitation/salary and team-based payment (family health teams/other group models); capitation or blended payment models (family health networks/family health organizations); or primarily fee for service (family health groups and non-rostered patients). We assigned a geographic location to each individual using the Rurality Index for Ontario (36), whereby a value greater than 40 was considered to be a designated rural area.

Analysis

Annual healthcare costs per capita were described by health service sector, age group (<65 vs. ≥65 years), the degree of multimorbidity and each of the independent factors, such as sex, age group, and level of marginalization. Multivariate regression analyses were used to assess the incremental costs of interest in this study. To identify the regression model that fits best with the cost data, we followed the steps suggested by Manning and Mullahy. (37) We first ran ordinary least-squares regressions (OLS) of the logarithmic transformation of cost data on the number of medical conditions and other confounding factors. However, the OLS regression was deemed inappropriate because the residuals were not normally distributed. The generalized linear model (GLM) with a log-link function and a gamma distribution was chosen because a modified Park test suggested that the variance was proportional to the conditional mean. The GLM allows us to estimate mean healthcare costs without the need for retransformation.

Attributable costs due to multimorbidity were estimated by subtracting the mean predicted cost of one medical condition from two conditions, two from three conditions, three from four conditions, and four from at least five conditions, respectively. To investigate whether the relationship between the level of multimorbidity and healthcare costs was moderated by socio-demographic factors, we added two-way interaction terms between the level of multimorbidity and each sociodemographic factor, including sex, age, income level, deprivation quintile, instability quintile, dependency quintile and ethnic concentration quintile. The significance of interaction terms was assessed by comparing the likelihood ratio of the full model with all interaction terms to the model without interaction terms using the likelihood ratio test.

The model performance, including goodness of fit and specifications, was examined by checking the scaled deviance, Pearson's chi-square statistics and residual plots, respectively. All analyses were performed using SAS statistical software for UNIX (version 9.3; SAS Institute, Cary, North Carolina).

RESULTS

We identified a cohort of 6,639,089 individuals living with at least one of the selected 16 medical conditions in Ontario in 2009 (see Appendix 2 for baseline characteristics). Our cohort represents about 50% of the total population in the province of Ontario in 2009. Close to half of the study cohort (48%) had at least two selected medical conditions, and this prevalence was found to increase with age. The majority of the study cohort was younger than 65 years of age (75%) and just over half was female (53%). Nearly all individuals (91%) resided in non-rural

areas, and about one-third (33%) lived in neighborhoods with a high proportion of diverse ethnic groups.

The total annual healthcare cost estimated for the study cohort was $26.5 billion. As shown in Figure 1, individuals living with at least two selected medical conditions represented 24.4% of total population of Ontario (~13 million) but accounted for approximately two-thirds (67.9%) of total allocatable healthcare costs in 2009/10. By contrast, individuals without multimorbidity who accounted for 76% of the total population were responsible for only 32.1% of total allocatable healthcare costs. On average, annual total costs per capita amounted to $2,217 in individuals younger than 65 years and $9,398 in those aged 65 years or older.

[Figure 1]

Table 1 shows the annual total costs per capita by baseline characteristics for young and older adults. For both age groups, per capita total healthcare costs were higher in women than men. The average healthcare costs increased with older age. The greater levels of marginalization were associated with higher healthcare costs in both age groups. Mean total healthcare costs were the highest among individuals living in the most deprived and most unstable areas as well as those who were highly dependent. However, mean total costs decreased with higher income level.

Table 1. Annual per capita healthcare costs by baseline characteristics and age group, April 1, 2009 to March 31, 2010

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
All cohort	5,004,699	2,217 (9630)	502 (193-1317)	1,634,390	9,398 (19,796)	2,982 (1,448-7,178)
Sex						
Female	2,618,591	2,311 (9,044)	624 (248– 1,546)	923,053	9,526.96 (19,245)	2,991.97 (1,461-7,344)
Male	2,386,108	2,113 (10,233)	378.67 (132– 1,058)	711,337	9,230.31 (20,488)	2,968.13 (1,431-6,982)
Age group (years)						
<20	809,782	997 (6,420)	257 (103-600)			
20 - 44	1,784,314	1,835 (7,997)	440 (155-1,171)			
45 – 64	3,247,243	2,910 (11,414)	684 (291-1,725)			
65 - 74				1,219,877	6,424 (16,464)	2,363 (1,173-4,757)
75+				797,750	12,517 (22,351)	3,964 (1,884-12,277)
Income quintile						
Lowest	935,048	2,822 (11,333)	580 (206-1699)	314,616	10,646 (21,501)	3,325 (1,596-8,667)
Middle-low	970,797	2,360 (10,276)	521 (199-1,380)	336,928	9,529 (20,218)	3,053 (1,501-7,296)
Middle	999,087	2,107 (9,146)	498 (195-1,268)	318,557	9,319 (19,552)	2,992 (1,470-7,114)
Middle-high	1,042,284	2,008 (8,899)	487 (195-1,226)	322,798	9,120 (19,279)	2,916 (1,426-6,873)
Highest	1,009,890	1,903 (8,391)	475 (192-1,180)	331,022	8,549 (18,309)	2,747 (1,351-6,352)
Rurality index						
Non-rural	4,579,691	2,206 (9,605)	509 (197-1,320)	1,459,014	9,448 (19,998)	3,005 (1,470-7,161)
Rural	356,361	2,522 (10,112)	501 (197-1,441)	157,864	9,333 (18,303)	2,918 (1,400-7,798)
Deprivation quintile						

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
Least deprived	1,282,898	1,894.17 (8,596.59)	476 (193-1,170)	371,547	9,167 (19,628)	2,823 (1,380-6,709)
Less deprived	1,136,731	2,015 (8,810)	489 (196-1,231)	368,124	8,935 (18,928)	2,898 (1,423-6,759)
Somewhat deprived	982,133	2,193 (9,240)	504 (196-1,311)	346,326	9,165 (19,300)	2,978 (1,463-7,030)
Very deprived	808,152	2,438 (10,281)	511 (200-1,443)	293,434	9,541 (19,951)	3,100 (1,520-7,467)
Most deprived	705,593	2,941 (11,861)	600 (210-1,79)	228,501	10,517 (21,250)	3,326 (1,599-8,570)
Instability quintile						
Least dependent	1,211,734	2,007 (8,674)	489 (188-1,250)	188,787	8,149 (19,413)	2,713 (1,307-5,882)
Less dependent	1,179,936	2,078 (9,134)	500 (195-1,275)	276,819	8,359 (18,652)	2,777 (1,353-6,167)
Somewhat dependent	976,538	2,230 (9,793)	506 (198-1,320)	303,853	8,717 (19,018)	2,849 (1,401-6,548)
Very dependent	808,196	2,349 (9,954)	515 (201-1,375)	326,662	9,068 (19,195)	2,944 (1,458-6,958)
Most dependent	739,103	2,650 (10,947)	550 (213-1,507)	511,811	10,961 (20,953)	3,381 (1,636-9,336)
Ethnic concentration quintile						
Lowest	564,476	2,398 (9,766)	500 (200-1,370)	283,980	9,309 (18,529)	2,983 (1,463-7,533)
Middle-low	756,120	2,288 (9,552)	491 (196-1,317)	304,526	9,170 (18,773)	2,969 (1,458-7,283)
Middle	854,573	2,280 (9,780)	497 (196-1,317)	305,524	9,540 (19,678)	3,011 (1,478-7,419)
Middle-high	1,028,876	2,190 (9,565)	502 (195-1,309)	294,164	9,600 (20,240)	3,012 (1,473-7,266)
Highest	1,711,462	2,124 (9,468)	528 (199-1,331)	419,738	9,288 (20,751)	2,981 (1,441-6,694)

Note: SD, standard deviation; IQR, interquartile range

Figure 2 illustrates the distribution of total cost per capita by type of services. Among individuals younger than 65 years of age, hospitalization was the primary cost driver and responsible for 47% of total healthcare costs, followed by physician costs (32%), drug costs (10%), and

continuing care costs (6%). For older adults, hospital costs remained the largest cost component (41%), followed by continuing care costs (23%), drug costs (19%) and physician costs (15%). Figure 2 also reveals that unadjusted mean total costs increased with additional numbers of medical conditions, ranging from $1,352 in individuals younger than 65 years of age without multimorbidity to $13,105 in those living with five or more medical conditions, corresponding to a 10-fold increase. On the other hand, while $4,185 was spent on older adults without multimorbidity, spending increased by about 5-fold to $19,196 in those living with five or more medical conditions.

[Figure 2]

Table 2 shows adjusted attributable costs of multimorbidity after controlling for other factors. Among individuals younger than 65 years, the attributable total cost was $377 in those living with two medical conditions and $2,073 in those living with at least 5 medical conditions, corresponding to a six times higher attributable cost. Similarly, attributable total costs in older adults also rose with increasing number of medical conditions, ranging from $1,026 in those with two medical conditions to $3,831 in those with five or more. The magnitude of an incremental cost depended on a reference category. Specifically, one additional medical condition to young adults without multimorbidity led to an attributable cost of $377, while for young adults who already had three medical conditions, one more health condition incurred additional $798. These incremental costs were even greater in older adults, whereby an incremental cost rose from $1,026 (1 vs. 2 conditions) to $1,652 (3 vs. 4 conditions). Similar patterns were observed for subdivided healthcare costs, which varied across age groups [Table 2]. An additional medical condition caused 1- to 3-fold increase in the costs of each health sector except for hospital

whereby incremental costs increased steady from $185 to $802 in the younger cohort and from $232 to $1,060 in the older adult cohort.

Table 2. Adjusted incremental total healthcare costs by the degree of multimorbidity and age group*, April 1, 2009 to March 31, 2010

conditions	< 65 years (N=5,004,699)						≥ 65 years (N=1,634,390)					
	total ($)	physician ($)	hospital ($)	drug ($)	continuing care ($)	Others ($)	total ($)	physician ($)	hospital ($)	drug ($)	continuing care ($)	others ($)
2 vs. 1	376.50	200.26	185.12	232.37	288.71	23.96	1,025.76	166.48	231.60	350.29	254.14	23.54
3 vs. 2	534.34	238.28	207.22	252.84	207.83	23.81	1,279.96	201.20	247.76	403.56	314.91	28.51
4 vs. 3	798.03	286.29	264.75	316.43	234.58	24.67	1,651.92	227.04	353.60	429.01	367.45	33.17
≥5 vs. 4	2,072.57	515.80	801.64	666.13	486.58	37.64	3,831.40	400.57	1060.00	673.89	732.19	63.76

*adjusted for sex, age, income quintile, primary care model, rurality index, deprivation quintile, instability quintile, dependency quintile, and ethnic concentration quintile

We also found that the association between number of medical conditions and healthcare costs was significantly modified by age and sex for both young and older adults [Table 3]. The positive association between healthcare costs and levels of multimorbidity was significantly stronger for older than younger adults. For individuals aged 65 years or younger, the increase in healthcare costs was more gradual in women than their male counterparts. For those aged 65 years or older, the increase in healthcare costs in women was significantly greater than for men.

For both age groups, we observed small interaction effects between the number of medical conditions and other socio-demographic factors. The rise in healthcare costs with greater level of multimorbidity was less pronounced among individuals with high income level. The association between the level of multimorbidity and healthcare costs was significantly modified by the level of deprivation, instability, dependency and ethnic concentration. The positive association between the level of multimorbidity and healthcare costs was stronger among individuals living in more deprived, unstable, dependent or diverse ethnic groups than those living in less deprived, stable, dependent or diverse ethnic concentration areas. We did not observe a significant interaction between the number of medical conditions and the level of dependency in the older adult cohort.

Table 3. Generalized linear models results for total healthcare costs^

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
Intercept	1.6844***	0.0007	1.6049***	0.0034
Age	0.0023***	0.0001	0.0053***	0.0001
Sex				
Male	reference		reference	
Female	0.0628***	0.0002	-0.0023***	0.0006
Number of medical conditions				
1 condition	reference		reference	
2 conditions	0.1092***	0.0017	0.1068***	0.0044
3 conditions	0.2189***	0.0027	0.1860***	0.0045
4 conditions	0.3312***	0.0050	0.2563***	0.0049
≥5 conditions	0.4203***	0.0080	0.3772***	0.0048
Income quintile				
Lowest	reference		reference	
Middle-low	-0.0043***	0.0005	-0.0019*	0.0010
Middle	-0.0045***	0.0005	0.00014	0.0012
Middle-high	-0.0044***	0.0006	0.0001	0.0012
Highest	-0.0080***	0.0006	-0.0045***	0.0013
Deprivation quintile				
Least deprived	reference		reference	
Less deprived	-0.0006*	0.0004	-0.0014***	0.0008
Somewhat deprived	-0.0008*	0.0004	-0.0020**	0.0009
Very deprived	0.0022***	0.0005	-0.0009	0.0011
Most deprived	0.0135***	0.0006	0.0044***	0.0013
Instability quintile				
Least unstable	reference		reference	
Less unstable	0.0039***	0.0005	-0.0019**	0.0009
Somewhat unstable	0.0073***	0.0005	-0.0008	0.0009
Very unstable	0.0122***	0.0005	0.0031***	0.0009
Most unstable	0.0247***	0.0005	0.0087***	0.0010
Ethnic concentration quintile				
Lowest	reference		reference	
Middle-low	0.0002	0.0004	-0.0005	0.0009
Middle	0.0018***	0.0004	0.0022	0.0009
Middle-high	0.0047***	0.0004	-0.0007	0.0010
Highest	0.0066***	0.0004	-0.0043***	0.0009
Dependency quintile				
Least dependent	reference		reference	
Less dependent	0.0004	0.0004	0.0012**	0.0005
Somewhat dependent	0.0001	0.0004	0.0027***	0.0005
Very dependent	0.0009**	0.0004	0.0030***	0.0005

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
Most dependent	0.0020***	0.0005	0.0100***	0.0005
Number of medical conditions * sex				
1 condition* Male	reference		reference	
2 conditions * Female	-0.0171***	0.0016	-0.0029***	0.0007
3 conditions * Female	-0.0396***	0.0011	-0.0022***	0.0008
4 conditions * Female	-0.0549***	0.0007	0.0001	0.0008
≥5 conditions * Female	-0.0659***	0.0005	0.0030***	0.0008
Number of medical conditions * age				
1 condition * age	reference		reference	
2 conditions * age	-0.0007***	0.0016	-0.0006***	0.0001
3 conditions * age	-0.0014***	0.0011	-0.0010***	0.0001
4 conditions * age	-0.0022***	0.0007	-0.0014***	0.0001
≥5 conditions * age	-0.0023***	0.0005	-0.0023***	0.0001
Number of medical conditions * income quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0016*	0.0009	-0.0025*	0.0013
3 conditions * middle-low	-0.0011	0.0013	-0.0037**	0.0014
4 conditions* middle-low	-0.0043**	0.0020	-0.0043**	0.0015
≥5 conditions* middle-low	-0.0031	0.0027	-0.0046**	0.0014
2 conditions*middle	-0.0020**	0.0010	-0.0032**	0.0015
3 conditions * middle	-0.0030**	0.0014	-0.0051**	0.0015
4 conditions* middle	-0.0053**	0.0023	-0.0055**	0.0017
≥5 conditions* middle	-0.0028	0.0031	-0.0072***	0.0016
2 conditions*middle-high	-0.0024**	0.0011	-0.0031*	0.0016
3 conditions * middle-high	-0.0032**	0.0016	-0.0052**	0.0016
4 conditions* middle-high	-0.0067**	0.0025	-0.0081***	0.0018
≥5 conditions* middle-high	-0.0093**	0.0034	-0.0070***	0.0018
2 conditions*highest	-0.0015	0.0011	-0.0036**	0.0017
3 conditions *highest	-0.0031*	0.0017	-0.0063***	0.0018
4 conditions* highest	-0.0096***	0.0027	-0.0088***	0.0019
5 conditions* highest	-0.0099**	0.0038	-0.0095***	0.0019
Number of medical conditions * deprivation quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0024***	0.0007	-0.0001	0.0011
3 conditions * middle-low	0.0038 ***	0.0010	-0.0015	0.0011
4 conditions* middle-low	0.0027	0.0017	-0.0016	0.0013
≥5 conditions* middle-low	0.0060**	0.0026	-0.0029**	0.0012
2 conditions*middle	0.0047***	0.0007	-0.0002	0.0012
3 conditions * middle	0.0067***	0.0010	-0.0018	0.0013
4 conditions* middle	0.0062***	0.0017	-0.0045**	0.0014
≥5 conditions* middle	0.0109***	0.0026	-0.0042**	0.0014
2 conditions*middle-high	0.0057***	0.0009	-0.0012	0.0014

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
3 conditions * middle-high	0.0071***	0.0014	-0.0031**	0.0015
4 conditions* middle-high	0.0074***	0.0022	-0.0051**	0.0016
≥5 conditions* middle-high	0.0111***	0.0032	-0.0079***	0.0016
2 conditions*highest	0.0073***	0.0011	-0.0028	0.0017
3 conditions *highest	0.0108***	0.0016	-0.0052**	0.0018
4 conditions* highest	0.0114***	0.0026	-0.0089***	0.0019
≥5 conditions* highest	0.0119***	0.0036	-0.0098***	0.0019
Number of medical conditions * instability				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0012**	0.0007	0.0009	0.0011
3 conditions * middle-low	-0.0007	0.0010	0.0020	0.0012
4 conditions* middle-low	-0.0016	0.0017	0.0010	0.0013
≥5 conditions* middle-low	-0.0013	0.0026	0.0022	0.0014
2 conditions*middle	-0.0017**	0.0008	0.0037**	0.0014
3 conditions * middle	-0.0012	0.0012	0.0010	0.0013
4 conditions* middle	-0.0002	0.0019	0.0022	0.0014
≥5 conditions* middle	0.0025	0.0027	0.0037**	0.0014
2 conditions*middle-high	-0.0003	0.0009	0.0022*	0.0012
3 conditions * middle-high	0.0006	0.0012	0.0019	0.0013
4 conditions* middle-high	0.0011	0.0019	0.0033**	0.0014
≥5 conditions* middle-high	0.0075***	0.0027	0.0048***	0.0014
2 conditions*highest	0.0037***	0.0012	-0.0027**	0.0013
3 conditions *highest	0.0095***	0.0012	-0.0026**	0.0013
4 conditions* highest	0.0113***	0.0020	-0.0035**	0.0014
≥5 conditions* highest	0.0206***	0.0028	-0.0019	0.0014
Number of medical conditions * ethnic concentration				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0006	0.0009	0.0011	0.0012
3 conditions * middle-low	-0.0007	0.0013	0.0022*	0.0012
Number of medical conditions * ethnic concentration				
4 conditions* middle-low	-0.0020	0.0021	0.0012	0.0014
≥5 conditions* middle-low	0.0018	0.0029	0.0012	0.0013
2 conditions*middle	0.0004	0.0009	0.0006	0.0012
3 conditions * middle	-0.0006	0.0013	0.0003	0.0012
4 conditions* middle	-0.0034	0.0021	-0.0012	0.0014
≥5 conditions* middle	0.0016	0.0030	0.0004	0.0013
2 conditions*middle-high	0.0002	0.0009	0.0015	0.0012
3 conditions * middle-high	-0.0013	0.0014	0.0021*	0.0013
4 conditions* middle-high	-0.0056**	0.0022	0.0006	0.0014
≥5 conditions* middle-high	-0.0056*	0.0030	0.0035**	0.0014
2 conditions*highest	-0.0008	0.0012	0.0043***	0.0012
3 conditions *highest	-0.0021	0.0013	0.0047***	0.0013

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
4 conditions* highest	-0.0081***	0.0021	0.0044***	0.0013
≥5 conditions* highest	-0.0070**	0.0030	0.0093***	0.0013
Number of medical conditions * dependency quintile[#]				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0016**	0.0007		
3 conditions * middle-low	0.0018**	0.0010		
4 conditions* middle-low	0.0004	0.0017		
≥5 conditions* middle-low	-0.0028	0.0026		
2 conditions*middle	0.0015**	0.0001		
3 conditions * middle	0.0030***	0.0011		
4 conditions* middle	0.0036**	0.0018		
≥5 conditions* middle	0.0008	0.0025		
2 conditions*middle-high	0.0017**	0.0008		
3 conditions * middle-high	0.0029**	0.0012		
4 conditions* middle-high	0.0028	0.0019		
≥5 conditions* middle-high	0.0014	0.0027		
2 conditions*highest	0.0018**	0.0009		
3 conditions *highest	0.0032**	0.0013		
4 conditions* highest	0.0041**	0.0020		
≥5 conditions* highest	0.0038	0.0028		
AIC	15,672,974		5,058,276	
BIC	15,674,535		5,059,515	

^ adjusted for primary care models and rurality index; *** P <0.001, ** P< 0.05, * p<0.10; se indicates standard error; # interaction between the number of medical conditions and dependency quintile was not statistically significant and therefore excluded from a final model.

DISCUSSION

Individuals living with multimorbidity accounted for 79% of total healthcare costs incurred by our study cohort and 68% of total allocatable healthcare costs in Ontario in 2009. Although there is a growing body of literature documenting the economic burden of multimorbidity in other jurisdictions (12, 13, 38), the current study lends further evidence that a relatively small portion of the multimorbid population was responsible for a disproportionately high percentage of total healthcare costs. We observed this disproportionate relationship in both young (<65) and (65+)

older cohorts, suggesting that any approaches to containing healthcare costs of multimorbidity should be implemented across all age groups.

Our study demonstrated that healthcare costs increased significantly with higher levels of multimorbidity. This positive association exists even after the adjustment for confounding factors and a skewed distribution of cost data using the generalized linear model with a log link function and a gamma distribution. The exponential relationship between multimorbidity and incremental healthcare costs shown in this study suggests that the financial burden of multimorbidity to the healthcare system is not simply equal to the sum of costs incurred by each individual condition. This non-linearity reflects the complex association of the degree of multimorbidity, the type of disease clusters and healthcare costs. It is likely that patients with multimorbidity might experience worse health outcomes and require more complex clinical management.(9) They are also vulnerable to receiving redundant diagnostic tests (12), suboptimal transition of care and inappropriate prescriptions. (11) This explanation is plausible as current treatment guidelines are mainly focused on individual disease management.(10) Thus, as the number of healthcare providers involved in the patient's care increases, information sharing and coordinating care across healthcare providers may pose a challenge. (39) Moreover, an increasing number of comorbid conditions may compromise patients' ability to self-manage their diseases.(40) The high healthcare spending on multimorbidity found in our study underscores the need for ensuring continuity and coordination of care in this population.

More importantly, our study contributes to the understanding of the association between the degree of multimorbidity and healthcare costs. We observed that each unit increase in age

amplified the rise in healthcare costs associated with an increasing number of medical conditions. The observed interaction effect may partly due to patterns in the healthcare use among an older population. There is generally a pattern of poly-pharmacy and use of continuing care services that are very costly. Additionally, we found that the positive association between healthcare costs and levels of multimorbidity was stronger in men than women among individuals younger than 65 years. This sex difference might relate to different disease clusters whereby men within this age group often experience life-threatening and more serious illnesses than women.(41, 42) For those older than 65 years, the increase in healthcare costs with the greater level of multimorbidity were significantly higher in women than men. This sex difference could be partially explained by longer life expectancy and greater risk of multimorbidity in older women than men (20, 43), which may cause older women to be more dependent on formal (paid) healthcare services and other informal (unpaid) caregivers.

We observed small interaction effects of neighborhood-level socioeconomic characteristics on the association between the number of medical conditions and healthcare costs. Living in lower income and marginalized area, i.e. greater levels of instability, dependency or ethnic concentration, accelerated the increase in health system costs with the greater level of multimorbidity. This might reflect a higher risk of experiencing more complex multimorbid conditions among individuals living in disadvantaged neighborhood (44) which led to greater demand and utilization of healthcare. Another possible reason is that individuals living in more deprived area may face barriers in accessing health services (45) and have delayed access to preventive healthcare interventions or treatments (46), thereby having a higher risk of worse health outcomes and high healthcare costs. The effects of socioeconomic factors reported in this

study should be interpreted with caution as they were derived based on neighborhood. Although the interaction terms between socioeconomic factors and levels of multimorbidity were statistically significant, most of estimated effect sizes were very small and might be a result of a large sample size used in this study.

Strengths and limitations

This population-based study was based on a large sample size and used the robust costing and generalized linear model regression techniques. The availability of linked and patient-level health administrative databases allows us to estimate the total health system costs associated with multimorbidity from all healthcare sectors. The use of health administrative databases can also minimize potential recall and non-response biases that are commonly found in survey data.

However, the results of this study should be interpreted in light of the following limitations. First, we estimated healthcare costs based on selected 16 medical conditions. The selection of a limited number of medical conditions is likely to underestimate the overall healthcare costs of multimorbidity. However, total cost estimates reported in our study were comprehensive because they amounted to 86% of total allocatable government expenditures in Ontario in 2009.(47) Second, due to a paucity of data, some costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated with caregiving) were excluded from the analysis. In addition, this study could not capture the costs of medications covered by private sectors, including private insurers and out of pocket expenses which represent the largest component of total prescription drug costs of Canadians

who are younger than 65 years of age. (48) For this reason, findings from this study may not be generalizable to other jurisdictions with different healthcare systems.

Third, this study did not take into account the clusters of medical conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the type and patterns of comorbid medical conditions. We chose to use disease counts because there is no standard or guidance on how to measure and define multimorbidity and the choice of measure would be subject to data availability and the outcome of interest. (49, 50) A previous study conducted by our team (5) has shown that there were no common clustering of diseases among individuals living with multimorbidity. The number of disease clusters required to include 80% of the study population increased from 14 (among individuals with two conditions) to 2744 clusters of conditions (among individuals with 5 or more conditions). Moreover, a previous systematic review showed that 132 multimorbid definitions with 1,631 criteria were used to define multimorbidity in the published literature. (51) Our decision to use disease counts is also supported by a study by Islam et al (52) indicating that the total number of chronic conditions were more predictive for out-of-pocket healthcare costs and high cost users than the clusters, dominant groups or dominant pairs.

CONCLUSION

This cross-sectional, population-based study highlights the amount by which health system costs increased significantly with increasing levels of multimorbidity in a publicly financed healthcare system. The average and incremental healthcare costs reported in this study could serve as the foundation for future health economic evaluation of interventions for preventing and managing

multimorbidity. As the relationship between multimorbidity and healthcare costs varies according to socio-demographic factors, interventions addressing disparities in healthcare in individuals living with multimorbidity may have a potential to reduce total health system costs.

LIST OF ABBREVIATIONS

AMI acute myocardial infarction

COPD chronic obstructive pulmonary disorder

GLM generalized linear model

ICES Institute for Clinical Evaluative Sciences

OHIP Ontario Health Insurance Plan

OLS ordinary least-squares regressions

DECLARATIONS

Ethic approval:

The study has been approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

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Competing interests: None

Authors contributions: WPW was the lead for the conception and creation of the cohort. YB has created the cohorts through data linkages and helped with data analysis and methods. KT interpreted the results and drafted the manuscript. CM, AG, SB, AK, YB, YP and WPW revised the manuscript for important intellectual content and formatting. All authors read and approved the final manuscript.

Data sharing statement: No additional data are available.

Figure legends:

Figure 1. Distribution of total number of population and total health system costs in Ontario from April 1, 2009 to March 31, 2010

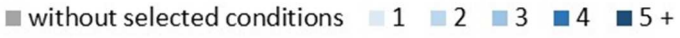
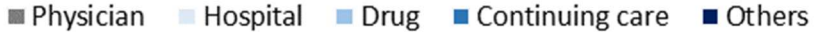


Figure 2. Unadjusted mean total healthcare cost per capita for Ontario adults, by service type, number of conditions and age group from April 1, 2009 to March 31, 2010



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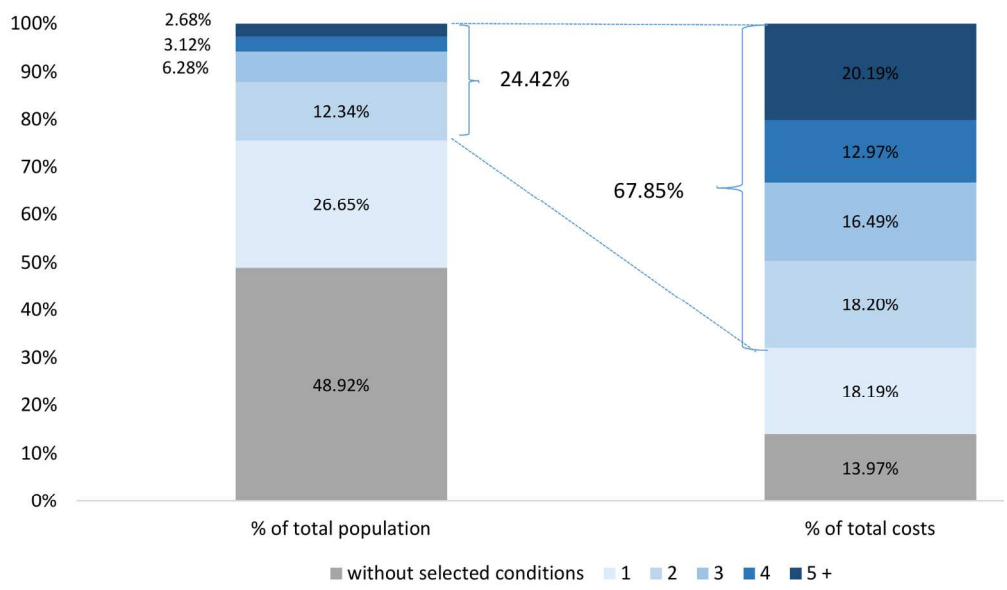

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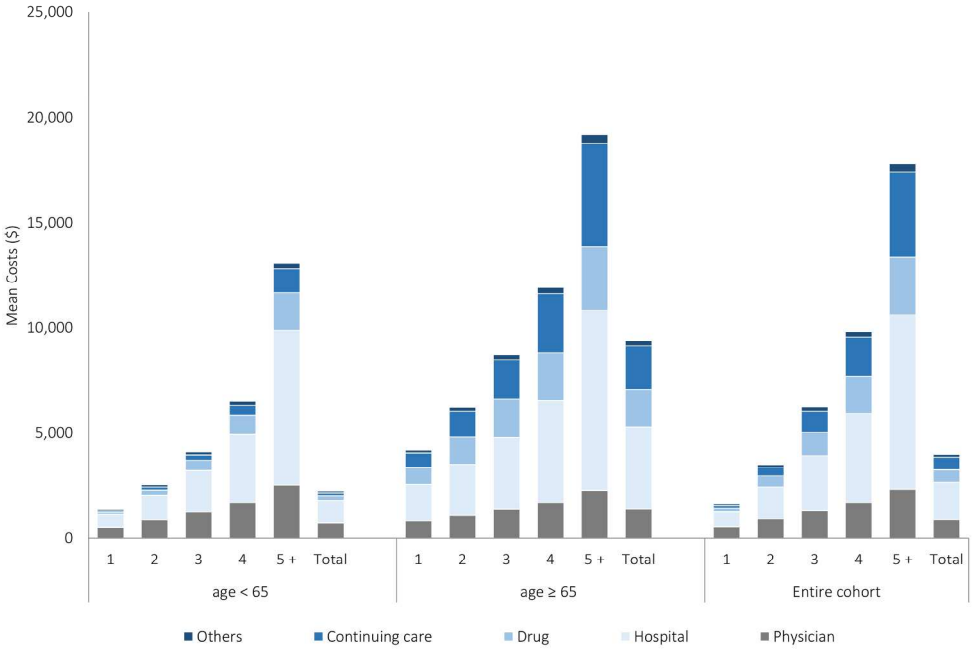

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Appendix 1. List of diagnosis codes used to define the 16 selected medical conditions

Condition	ICD 9 / OHIP fee codes	ICD 10
AMI*	410	I21, I22
Arthritis - Osteoarthritis	715	M15-M19
Arthritis - Other Arthritis (Synovitis, Fibrositis, Connective tissue disorders, Ankylosing spondylitis, Gout Traumatic arthritis, pyogenic arthritis, Joint derangement, Dupuytren's contracture, Other MSK disorders)	727, 729, 710, 720, 274, 716, 711, 718, 728, 739	M00-M03, M07, M10, M11-M14, M20-M25, M30-M36, M65-M79
Arthritis - Rheumatoid arthritis	714	M05-M06
Asthma*	493	J45
Cancer	140-239	C00-C26, C30-C44, C45-C97,
Cardiac Arrythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1
CHF*	428	I500, I501, I509
COPD*	491, 492, 496	J41, J43, J44
Dementia	290, 331, 797 (OHIP) / 290.0, 290.1, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 294.9, 331.0, 331.1, 331.2, 797 (DAD)	F000, F001, F002, F009, F010, F011, F012, F013, F018, F019, F020, F021, F022, F023, F024, F028, F03, F051, F065, F066, F068, F069, F09, G300, G301, G308, G309, G310, G311, R54
Depression	311, 300, 296	F32, F33, F412, F480
Diabetes*	250	E08 - E13
Hypertension*	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Osteoporosis	733	M81 M82
Renal failure	403, 404, 584, 585, 586, v451	N17, N18, N19, T82.4, Z49.2, Z99.2
Stroke	430, 431, 432, 434, 436	I60-I64
Coronary syndrome (excluding MI)	411-414	I20, I22-I25

Note: * validated diagnosis codes; OHIP, Ontario Health Insurance Plan; AMI, Acute Myocardial Infarction, MSK, musculoskeletal; DAD, Discharge Abstract Database; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; MI, Myocardial infarction

Appendix 2. Proportions and mean number of medical conditions by baseline characteristics, April 1, 2009 to March 31, 2010

	N	Number of medical conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
All cohort	6,639,089	52.2	24.2	12.3	6.1	5.2	1.88 (1.16)
Sex							
Female	3,541,644	49.2	25.3	13.4	6.6	5.5	1.94 (1.18)
Male	3,097,445	55.6	22.8	11.1	5.5	5.0	1.81 (1.14)
Age (years)							
0-19	809,782	89.8	9.3	0.8	0.1	0.01	1.11 (0.35)
20-34	908,634	77.2	18.8	3.4	0.5	0.1	1.27 (0.55)
35-44	875,680	66.5	24.4	7.0	1.7	0.5	1.45 (0.74)
45-64	2,410,603	47.0	29.9	14.4	5.7	3.0	1.88 (1.05)
65-74	836,640	25.3	29.3	22.3	12.7	10.4	2.53 (1.28)
70-74	383,237	21.8	28.2	23.2	14.2	12.6	2.68 (1.30)
75+	797,750	13.6	22.4	23.2	17.8	23.0	3.14 (1.36)
Income quintile							
Lowest	1,249,664	50.3	23.8	12.8	6.8	6.3	1.95 (1.21)
Middle-low	1,307,725	50.8	24.3	12.8	6.5	5.7	1.92 (1.18)
Middle	1,317,644	52.4	24.2	12.2	6.1	5.1	1.87 (1.15)
Middle-high	1,365,082	53.2	24.3	12.0	5.8	4.8	1.85 (1.13)
Highest	1,340,912	53.5	24.5	11.9	5.7	4.5	1.83 (1.12)
Rurality index							
Non-rural (< 40)	6,038,705	52.3	24.1	12.3	6.1	5.2	1.88 (1.56)
Rural (≥40)	514,225	48.9	25.0	13.3	6.8	5.9	1.96 (1.19)
Deprivation quintile							
Least deprived	1,654,445	55.0	24.0	11.4	5.3	4.3	1.80 (1.11)
Less deprived	1,504,855	52.6	24.4	12.2	5.9	4.9	1.86 (1.14)
Somewhat deprived	1,328,459	51.1	24.4	12.7	6.4	5.5	1.91 (1.17)
Very deprived	1,101,586	50.0	24.3	13.0	6.7	6.0	1.94 (1.20)
Most deprived	934,094	50.0	23.8	12.9	6.8	6.4	1.96 (1.21)

Appendix 2. (Cont'd)

	N	Number of medical conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
Instability quintile							
Least unstable	1,715,922	56.6	24.0	11.0	4.9	3.5	1.75 (1.06)
Less unstable	1,365,580	53.2	24.4	12.1	5.8	4.6	1.84 (1.13)
Somewhat unstable	1,077,375	50.5	24.6	12.9	6.5	5.5	1.91 (1.17)
Very unstable	1,195,108	50.4	24.2	12.8	6.6	6.0	1.94 (1.20)
Most unstable	1,169,454	47.3	23.9	13.6	7.6	7.6	2.04 (1.26)
Dependency quintile							
Least dependent	1,400,521	59.3	23.3	10.0	4.3	3.1	1.69 (1.02)
Less dependent	1,456,755	55.5	24.1	11.3	5.2	4.0	1.78 (1.09)
Somewhat dependent	1,280,391	52.4	24.5	12.3	5.9	4.9	1.86 (1.14)
Very dependent	1,134,858	49.3	24.7	13.3	6.8	5.9	1.95 (1.19)
Most dependent	1,250,914	42.2	24.6	15.3	8.9	9.0	2.18 (1.31)
Ethnic concentration quintile							
Lowest	848,456	47.2	25.1	13.9	7.3	6.5	2.01 (1.22)
Middle-low	1,060,646	49.8	24.8	13.0	6.6	5.7	1.91 (1.19)
Middle	1,160,097	51.0	24.5	12.6	6.3	5.5	1.91 (1.17)
Middle-high	1,323,040	53.4	24.0	11.8	5.8	5.0	1.84 (1.14)
Highest	2,131,200	54.9	23.5	11.5	5.5	4.6	1.81 (1.12)
Primary care model							
Family health teams/ other primary care models	1,109,443	51.0	24.9	12.6	6.3	5.2	1.94 (1.28)
Family health networks /family health organizations	1,054,714	49.6	25.3	13.1	6.5	5.5	1.97 (1.30)
Community health centres/family health groups/non-rostered patients	4,474,932	53.1	23.7	12.0	6.0	5.2	1.90 (1.29)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-12*
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	Not report
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not report

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	Not report
		(c) Consider use of a flow diagram	Not report
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-15
		(b) Indicate number of participants with missing data for each variable of interest	Not report
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not report
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	14-17
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16-17
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	24-27
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	27
Generalisability	21	Discuss the generalisability (external validity) of the study results	28
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29-30

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based, Retrospective Cohort Study

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The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based, Retrospective Cohort Study

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Abstract

Objectives: To estimate the attributable costs of multimorbidity and assess whether the association between the level of multimorbidity and health system costs varies by socio-demographic factors in young (<65) and older (≥65) adults living in Ontario, Canada.

Design: a population-based, retrospective cohort study

Setting: the province of Ontario, Canada

Participants: 6,639,089 Ontarians who were diagnosed with at least one of 16 selected medical conditions on April 1, 2009.

Main outcome measures: From the perspective of the publicly funded healthcare system, total annual healthcare costs were derived from linked provincial health administrative databases using a person-level costing method. We used generalized linear models to examine the association between the level of multimorbidity and healthcare costs and the extent to which socio-demographic variables modified this association.

Results: Attributable total costs of multimorbidity ranged from $377 to $2,073 for young individuals and $1,026 to $3,831 for older adults. The association between the degree of multimorbidity and healthcare costs was significantly modified by age ($p<0.001$), sex ($p<0.001$) and neighborhood income ($p<0.001$) in both age groups, and the positive association between healthcare costs and levels of multimorbidity was statistically stronger for older than younger adults. For individuals aged 65 years or younger, the increase in healthcare costs was more gradual in women than in their male counterparts, however, for those aged 65 years or older, the increase in healthcare costs was significantly greater among women than men. Lastly, we also observed that the positive association between the level of multimorbidity and healthcare costs was significantly greater at higher levels of marginalization.

Conclusion: Socio-demographic factors are important effect modifiers of the relationship between multimorbidity and healthcare costs and should therefore be considered in any discussion of the implementation of healthcare policies and the organization of healthcare services aimed at controlling healthcare costs associated with multimorbidity.

KEYWORDS: multimorbidity, health system costs, socio-demographic factors, population-based study, publicly funded healthcare system

Word Counts: 299 (abstract), 4,000 (main text)

Strengths and limitations of this study

- This population-based study was based on a large sample size and used robust costing and generalized linear model regression techniques.
- The availability of linked and patient-level health administrative databases allows the estimation of the total health system costs associated with multimorbidity from all healthcare sectors.
- The use of health administrative databases can also minimize potential recall and non-response biases that are commonly found in survey data.
- The total healthcare costs reported in this study may be underestimated because they were derived based on 16 selected medical conditions. Moreover, it was not possible to measure certain costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated with caregiving) with our data.
- The study did not take into account particular clusters of medical conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the types and patterns of comorbid medical conditions.

BACKGROUND

Multimorbidity, the presence of two or more co-existing conditions within a single person, is increasingly prevalent due to advances in life-extending medical treatments and increases in life expectancy. (1, 2) Internationally, the prevalence of multimorbidity has been shown to range from 17% in young adults (3) to 82% in older adults living in nursing homes. (4) In the province of Ontario, Canada, the prevalence of multimorbidity based on 16 selected conditions rose from 17.4% in 2003 to 24.3% in 2009, and this increase was evident across all age groups. (5)

Higher levels of multimorbidity are associated with impaired physical functioning (6), poorer quality of life (7), more frequent use of health services, and higher risk of death. (8) In addition, individuals with multimorbidity may experience faster disease progression and require more complex medical care. (9) Consequently, these individuals may be at a higher risk of receiving sub-optimal care (10), inappropriate prescriptions (11) and experiencing potentially preventable hospitalizations. (12) These adverse health outcomes can impose a substantial burden on patients, family caregivers, and the healthcare system.

The relationship between multimorbidity and healthcare costs is well-documented and has been shown to be curvilinear or exponential across jurisdictions. The average Medicare payments in the US ranged from $1,154 among Part A and Part B beneficiaries with one chronic condition to $13,973 among beneficiaries with at least four chronic conditions (a 12-fold difference). (12) Similarly, the mean total health system costs among older adults with multimorbidity in Switzerland were nearly six times higher than among those without multimorbidity. (13)

Despite an abundance of research describing the relationship between multimorbidity and healthcare costs, existing studies have some important methodological and conceptual limitations. Some previous studies (14, 15) used Ordinary Least Squares (OLS) regression despite the fact that the positively skewed distribution of cost data often violates the normality assumption of OLS. (16) Others attempted to overcome this problem by transforming cost data to the logarithmic scale (13, 17); however, this transformation may still result in interpretation problems, as regression on transformed costs provides the prediction of a median instead of the arithmetic mean costs. (18) Importantly, the role of socio-demographic characteristics as effect modifiers of the relationship between multimorbidity and healthcare costs remains poorly described, although previous research has shown that the specific types of disease clusters vary by age and sex (2, 19) and that multimorbidity is more prominent in selected visible minority and low-socioeconomic status populations. (20)

The objectives of this study were, therefore, to estimate the health system costs attributable to multimorbidity using a more rigorous and appropriate approach, and to assess the extent to which the relationship between the level of multimorbidity and health system costs varies according to socio-demographic characteristics.

METHODS

Study design and sample

This population-based, retrospective cohort study included all residents of the province of Ontario between April 1, 2001 and March 31, 2010, who were enrolled in the Ontario Health Insurance Plan (OHIP), and were diagnosed with at least one of the following selected 16

medical conditions between April 1, 2001 and March 31, 2009 (study index date): acute myocardial infarction (AMI), arthritis, asthma, cancer, cardiac arrhythmia, chronic coronary syndrome, chronic obstructive pulmonary disorder (COPD), congestive heart failure, dementia, depression, diabetes, hypertension, osteoporosis, renal failure, rheumatoid arthritis and stroke. These conditions were selected because previous research and clinical experts agreed that they were highly prevalent and represented a substantial care and economic burden for Canada's healthcare system.(5, 21) We excluded individuals if they met the following criteria: had an invalid health card number, were older than 105 years, died or moved out of the province prior to the index date. Individuals with no contact with the healthcare system within the past five years prior to the index date were also excluded (excepting infants), as they may have left the province or experienced an unreported death.

Data Sources

We linked multiple provincial health administrative databases anonymously using unique encrypted identifiers. The Discharge Abstract Database provides data for all hospital discharges in Ontario, and the Ontario Health Insurance Plan (OHIP) claims database includes billing claims for all physician encounters. We used the Registered Persons Database to identify Ontarians who were eligible for health insurance coverage and derive their age. The linked database was housed and secured at the Institute for Clinical Evaluative Sciences (ICES) under data security and privacy policies and procedures approved by the Information and Privacy Commissioner of Ontario. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Each medical condition was defined using diagnostic algorithms and consultation codes that have been validated or used in previous studies. We defined six conditions (AMI, asthma, chronic heart failure, COPD, diabetes, and hypertension) based on validated population-derived registries held at ICES. (22-28) These conditions were all defined based on one diagnosis recorded in acute care or two diagnoses recorded in ambulatory care (physician) records within a two-year period (i.e. between 2007/8 and 2008/09), except for AMI, which was defined using acute care records in 2008/09. A similar approach was adopted to define the remaining medical conditions including arthritis, cancer, cardiac arrhythmia, chronic coronary syndrome, dementia, depression, osteoporosis, renal failure, rheumatoid arthritis, and stroke. A list of diagnostic codes used to define these medical conditions are shown in Appendix 1.

Measures

Healthcare costs

Healthcare costs were estimated from the perspective of the publicly funded healthcare system; accordingly, only direct costs borne to the Ontario Ministry of Health and Long-Term Care were considered. In Ontario, medically necessary hospital and physician services are paid for by the publicly-financed health insurance plan, however, public coverage for prescription drugs is primarily limited to residents aged 65 years and over, social assistance recipients as well as those with high prescription drug costs compared to their net household income.

We identified, measured and valued direct healthcare costs by applying a person-level costing technique that was developed and validated based on the Ontario health administrative data. (29) We calculated the costs of inpatient hospitalizations, emergency department visits, same day

surgeries, and inpatient rehabilitation by multiplying the weighted volume of services by the average provincial costs per weighted case. We obtained the costs of fee-for-service physician and outpatient diagnostic or laboratory services through OHIP fee approved as outlined in the Ontario Health Insurance Schedule of Benefits and Fees. (30) Non-fee-for-service physician payments were calculated by applying applicable capitation payments or the median amount reimbursed for the same service code for the specific fiscal year. (29) Costs for high-cost medical device equipment were estimated from the amount reimbursed to patients recorded in the Assistive Devices Program database. Complex continuing care and inpatient psychiatric costs were based on case mix, number of days in care, and Resource Utilization Groups. (31) Patient costs for long-term care were estimated based on a fixed per diem according to prevailing government payment rates, and costs for home care were estimated using the average cost per hour. We used pharmacy payments recorded in the Ontario Drug Benefit database to capture prescription medication costs for individuals eligible for public coverage. Annual total direct healthcare costs were the sum of costs across healthcare sectors for each patient for a one-year period after the study index date, i.e. from April 2009 to March 2010.

We categorized healthcare costs into five components: physician, hospital, drug, continuing care and other healthcare delivery costs. Physician costs included professional fees paid by the provincial insurance plan directly to physicians in private practice. Hospital costs included amounts paid to healthcare institutions, including those providing acute care, extended and chronic care, rehabilitation and convalescent care, psychiatric care, as well as drugs dispensed in hospitals. Drug costs consisted of the costs of prescriptions dispensed at outpatient pharmacies to individuals eligible for provincial coverage while continuing care costs included expenditure on

home care and residential long-term (nursing-home) care. The other healthcare delivery costs category represented expenditures on an assistive device program that subsidizes high-cost equipment, such as wheel chairs, walkers, continuous positive airway pressure devices and insulin pumps, for patients with physical disabilities. All costs were expressed in 2009 Canadian Dollars.

Independent variables

Multimorbidity was defined as the occurrence of two or more chronic diseases among the 16 selected conditions within a single individual and was categorized into five groups. A categorical variable was created to capture those with no multimorbidity (single disease only), two, three, four and five or more multimorbid conditions. Socio-demographic variables included age, sex, income, and level of marginalization. As prescription drug costs among Ontarians aged less than 65 years were primarily covered by private drug plans, we ran separate regressions for younger (<65 years) and older (65+ years) cohorts, and also included a continuous variable for age in the models. Income level was categorized into five quintiles, with the lowest quintile reflecting the lowest income level. We used the Ontario Marginalization Index, a validated census- and geographically-based index, as a proxy for individual-level socio-demographic factors. (32) The index consisted of four dimensions of marginalization: material deprivation; residential instability; ethnic concentration; and dependency. Lower scores on each dimension represent areas that are the least marginalized and higher scores represent areas that are the most marginalized. This index has been shown to be associated with several health outcomes. (33)

We also controlled for other factors that may confound the impact of multimorbidity on healthcare costs, such as the type of primary care model and geographic location. Selection of such factors was guided by previous healthcare cost studies (12, 34, 35) and was subject to the availability of data on these factors in Ontario administrative databases. The payment scheme of primary care services was categorized into three groups: group-based teams with capitation/salary and team-based payment (family health teams/other group models); capitation or blended payment models (family health networks/family health organizations); or primarily fee for service (family health groups and non-rostered patients). Lastly, we assigned a geographic location to each individual using the Rurality Index for Ontario (36), whereby a value greater than 40 was considered to be a designated rural area.

Analysis

Annual healthcare costs per capita were described by health service sector, age group (<65 vs. ≥65 years), the degree of multimorbidity and each of the independent factors, such as sex, age group, and level of marginalization. Multivariate regression analyses were used to assess the incremental costs of interest in this study. To identify the regression model that best fits the cost data, we followed the steps suggested by Manning and Mullahy. (37) We first ran OLS of the logarithmic transformation of cost data on the number of medical conditions and other confounding factors, however, the OLS regression was deemed inappropriate because the residuals were not normally distributed. Therefore, the generalized linear model (GLM) with a log-link function and a gamma distribution was chosen because a modified Park test suggested that the variance was proportional to the conditional mean. The GLM allows us to estimate mean healthcare costs without the need for retransformation.

Attributable costs due to multimorbidity were estimated by subtracting the mean predicted cost of one medical condition from the mean predicted cost of two conditions, two from three conditions, three from four conditions, and four from at least five conditions, respectively. To investigate whether the relationship between the level of multimorbidity and healthcare costs was moderated by socio-demographic factors, we added two-way interaction terms between the level of multimorbidity and each sociodemographic factor, including sex, age, income level, deprivation quintile, instability quintile, dependency quintile and ethnic concentration quintile. The significance of interaction terms was assessed by comparing the likelihood ratio of the full model with all interaction terms to the model without interaction terms using the likelihood ratio test.

The model performance, including goodness of fit and specifications, was examined by checking the scaled deviance, Pearson's chi-square statistics and residual plots, respectively. All analyses were performed using SAS statistical software for UNIX (version 9.3; SAS Institute, Cary, North Carolina).

RESULTS

We identified a cohort of 6,639,089 individuals living with at least one of the selected 16 medical conditions in Ontario in 2009 (see Appendix 2 for baseline characteristics). Our cohort represents about 50% of the total population in the province of Ontario in 2009. Close to half of the study cohort (48%) had at least two selected medical conditions, and this prevalence was found to increase with age. The majority of the study cohort was younger than 65 years of age

(75%) and just over half was female (53%). Nearly all individuals (91%) resided in non-rural areas, and about one-third (33%) lived in neighborhoods with a high proportion of diverse ethnic groups.

The total annual healthcare cost estimated for the study cohort was $26.5 billion. As shown in Figure 1, individuals living with at least two selected medical conditions represented 24.4% of the total population of Ontario (~13 million) but accounted for approximately two-thirds (67.9%) of total allocatable healthcare costs in 2009/10. By contrast, individuals without multimorbidity who accounted for 76% of the total population were responsible for only 32.1% of total allocatable healthcare costs. On average, annual total costs per capita amounted to $2,217 in individuals younger than 65 years and $9,398 in those aged 65 years or older.

[Figure 1]

Table 1 shows the annual total costs per capita by baseline characteristics for young and older adults. For both age groups, per capita total healthcare costs were higher in women than in men. The average healthcare costs increased with older age, and greater levels of marginalization were associated with higher healthcare costs in both age groups. Mean total healthcare costs were the highest among individuals living in the most deprived and most unstable areas as well as those who were highly dependent, however, mean total costs decreased as income level increased.

Table 1. Annual per capita healthcare costs by baseline characteristics and age group, April 1, 2009 to March 31, 2010

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
All cohort	5,004,699	2,217 (9630)	502 (193-1317)	1,634,390	9,398 (19,796)	2,982 (1,448-7,178)
Sex						
Female	2,618,591	2,311 (9,044)	624 (248– 1,546)	923,053	9,526.96 (19,245)	2,991.97 (1,461-7,344)
Male	2,386,108	2,113 (10,233)	378.67 (132– 1,058)	711,337	9,230.31 (20,488)	2,968.13 (1,431-6,982)
Age group (years)						
<20	809,782	997 (6,420)	257 (103-600)			
20 - 44	1,784,314	1,835 (7,997)	440 (155-1,171)			
45 – 64	3,247,243	2,910 (11,414)	684 (291-1,725)			
65 - 74				1,219,877	6,424 (16,464)	2,363 (1,173-4,757)
75+				797,750	12,517 (22,351)	3,964 (1,884-12,277)
Income quintile						
Lowest	935,048	2,822 (11,333)	580 (206-1699)	314,616	10,646 (21,501)	3,325 (1,596-8,667)
Middle-low	970,797	2,360 (10,276)	521 (199-1,380)	336,928	9,529 (20,218)	3,053 (1,501-7,296)
Middle	999,087	2,107 (9,146)	498 (195-1,268)	318,557	9,319 (19,552)	2,992 (1,470-7,114)
Middle-high	1,042,284	2,008 (8,899)	487 (195-1,226)	322,798	9,120 (19,279)	2,916 (1,426-6,873)
Highest	1,009,890	1,903 (8,391)	475 (192-1,180)	331,022	8,549 (18,309)	2,747 (1,351-6,352)
Rurality index						
Non-rural	4,579,691	2,206 (9,605)	509 (197-1,320)	1,459,014	9,448 (19,998)	3,005 (1,470-7,161)
Rural	356,361	2,522 (10,112)	501 (197-1,441)	157,864	9,333 (18,303)	2,918 (1,400-7,798)
Deprivation quintile						

	< 65 years (N=5,004,699)			≥ 65 years (N= 1,634,390)		
	N	Per capita healthcare cost ($)		N	Per capita healthcare cost ($)	
		mean (SD)	median (IQR)		mean (SD)	median (IQR)
Least deprived	1,282,898	1,894.17 (8,596.59)	476 (193-1,170)	371,547	9,167 (19,628)	2,823 (1,380-6,709)
Less deprived	1,136,731	2,015 (8,810)	489 (196-1,231)	368,124	8,935 (18,928)	2,898 (1,423-6,759)
Somewhat deprived	982,133	2,193 (9,240)	504 (196-1,311)	346,326	9,165 (19,300)	2,978 (1,463-7,030)
Very deprived	808,152	2,438 (10,281)	511 (200-1,443)	293,434	9,541 (19,951)	3,100 (1,520-7,467)
Most deprived	705,593	2,941 (11,861)	600 (210-1,79)	228,501	10,517 (21,250)	3,326 (1,599-8,570)
Instability quintile						
Least dependent	1,211,734	2,007 (8,674)	489 (188-1,250)	188,787	8,149 (19,413)	2,713 (1,307-5,882)
Less dependent	1,179,936	2,078 (9,134)	500 (195-1,275)	276,819	8,359 (18,652)	2,777 (1,353-6,167)
Somewhat dependent	976,538	2,230 (9,793)	506 (198-1,320)	303,853	8,717 (19,018)	2,849 (1,401-6,548)
Very dependent	808,196	2,349 (9,954)	515 (201-1,375)	326,662	9,068 (19,195)	2,944 (1,458-6,958)
Most dependent	739,103	2,650 (10,947)	550 (213-1,507)	511,811	10,961 (20,953)	3,381 (1,636-9,336)
Ethnic concentration quintile						
Lowest	564,476	2,398 (9,766)	500 (200-1,370)	283,980	9,309 (18,529)	2,983 (1,463-7,533)
Middle-low	756,120	2,288 (9,552)	491 (196-1,317)	304,526	9,170 (18,773)	2,969 (1,458-7,283)
Middle	854,573	2,280 (9,780)	497 (196-1,317)	305,524	9,540 (19,678)	3,011 (1,478-7,419)
Middle-high	1,028,876	2,190 (9,565)	502 (195-1,309)	294,164	9,600 (20,240)	3,012 (1,473-7,266)
Highest	1,711,462	2,124 (9,468)	528 (199-1,331)	419,738	9,288 (20,751)	2,981 (1,441-6,694)

Note: SD, standard deviation; IQR, interquartile range

Figure 2 illustrates the distribution of total cost per capita by type of services. Among individuals younger than 65 years of age, hospitalization was the primary cost driver and responsible for 47% of total healthcare costs, followed by physician costs (32%), drug costs (10%), and

continuing care costs (6%). For older adults, hospital costs remained the largest cost component (41%), followed by continuing care costs (23%), drug costs (19%) and physician costs (15%). Figure 2 also reveals that unadjusted mean total costs increased with additional numbers of medical conditions, ranging from $1,352 in individuals younger than 65 years of age without multimorbidity to $13,105 in those living with five or more medical conditions, corresponding to a 10-fold increase. On the other hand, while $4,185 was spent on older adults without multimorbidity, spending increased by about 5-fold to $19,196 in those living with five or more medical conditions.

[Figure 2]

Table 2 shows adjusted attributable costs of multimorbidity after controlling for other factors. Among individuals younger than 65 years, the attributable total cost was $377 in those living with two medical conditions and $2,073 in those living with at least 5 medical conditions, corresponding to a six-fold increase in attributable cost. Similarly, attributable total costs in older adults also rose with increasing number of medical conditions, ranging from $1,026 in those with two medical conditions to $3,831 in those with five or more. The magnitude of an incremental cost, however, depended on the reference category. Specifically, one additional medical condition in young adults without multimorbidity led to an attributable cost of $377, while for young adults who already had three medical conditions, one additional health condition resulted in a total cost of $798. These incremental costs were even greater in older adults, among whom the incremental cost rose from $1,026 (1 vs. 2 conditions) to $1,652 (3 vs. 4 conditions). Similar patterns were observed for subdivided healthcare costs, which varied across age groups [Table 2]. An additional medical condition caused a 1- to 3-fold increase in the costs of each

health sector except for hospital care, for which incremental costs increased steadily from $185 to $802 in the younger cohort and $232 to $1,060 in the older adult cohort.

Table 2. Adjusted incremental total healthcare costs by the degree of multimorbidity and age group*, April 1, 2009 to March 31, 2010

conditions	< 65 years (N=5,004,699)						≥ 65 years (N=1,634,390)					
	total ($)	physician ($)	hospital ($)	drug ($)	continuing care ($)	Others ($)	total ($)	physician ($)	hospital ($)	drug ($)	continuing care ($)	others ($)
2 vs. 1	376.50	200.26	185.12	232.37	288.71	23.96	1,025.76	166.48	231.60	350.29	254.14	23.54
3 vs. 2	534.34	238.28	207.22	252.84	207.83	23.81	1,279.96	201.20	247.76	403.56	314.91	28.51
4 vs. 3	798.03	286.29	264.75	316.43	234.58	24.67	1,651.92	227.04	353.60	429.01	367.45	33.17
≥5 vs. 4	2,072.57	515.80	801.64	666.13	486.58	37.64	3,831.40	400.57	1060.00	673.89	732.19	63.76

*adjusted for sex, age, income quintile, primary care model, rurality index, deprivation quintile, instability quintile, dependency quintile, and ethnic concentration quintile

We also found that the association between the number of medical conditions (i.e. the degree of multimorbidity) and healthcare costs was significantly modified by age and sex for both young and older adults [Table 3], and the positive association between healthcare costs and levels of multimorbidity was significantly stronger for older than younger adults. For individuals aged 65 years or younger, the increase in healthcare costs was more gradual in women than in their male counterparts, however, among those aged 65 years or older, the increase in healthcare costs in women was significantly greater than in men.

For both age groups, we observed small interaction effects between the number of medical conditions and other socio-demographic factors. The rise in healthcare costs with as the level of multimorbidity increased was less pronounced among high-income individuals than low-income individuals, and the association between the level of multimorbidity and healthcare costs was significantly modified by the level of deprivation, instability, dependency and ethnic concentration. The positive association between the level of multimorbidity and healthcare costs was stronger among individuals living in more deprived, unstable, dependent or diverse ethnic groups than those living in less deprived, stable, dependent or high concentration of ethnic diversity areas. We did not observe a significant interaction between the number of medical conditions and the level of dependency in the older adult cohort.

Table 3. Generalized linear models results for total healthcare costs^

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
Intercept	1.6844***	0.0007	1.6049***	0.0034
Age	0.0023***	0.0001	0.0053***	0.0001
Sex				
Male	reference		reference	
Female	0.0628***	0.0002	-0.0023***	0.0006
Number of medical conditions				
1 condition	reference		reference	
2 conditions	0.1092***	0.0017	0.1068***	0.0044
3 conditions	0.2189***	0.0027	0.1860***	0.0045
4 conditions	0.3312***	0.0050	0.2563***	0.0049
≥5 conditions	0.4203***	0.0080	0.3772***	0.0048
Income quintile				
Lowest	reference		reference	
Middle-low	-0.0043***	0.0005	-0.0019*	0.0010
Middle	-0.0045***	0.0005	0.00014	0.0012
Middle-high	-0.0044***	0.0006	0.0001	0.0012
Highest	-0.0080***	0.0006	-0.0045***	0.0013
Deprivation quintile				
Least deprived	reference		reference	
Less deprived	-0.0006*	0.0004	-0.0014***	0.0008
Somewhat deprived	-0.0008*	0.0004	-0.0020**	0.0009
Very deprived	0.0022***	0.0005	-0.0009	0.0011
Most deprived	0.0135***	0.0006	0.0044***	0.0013
Instability quintile				
Least unstable	reference		reference	
Less unstable	0.0039***	0.0005	-0.0019**	0.0009
Somewhat unstable	0.0073***	0.0005	-0.0008	0.0009
Very unstable	0.0122***	0.0005	0.0031***	0.0009
Most unstable	0.0247***	0.0005	0.0087***	0.0010
Ethnic concentration quintile				
Lowest	reference		reference	
Middle-low	0.0002	0.0004	-0.0005	0.0009
Middle	0.0018***	0.0004	0.0022	0.0009
Middle-high	0.0047***	0.0004	-0.0007	0.0010
Highest	0.0066***	0.0004	-0.0043***	0.0009
Dependency quintile				
Least dependent	reference		reference	
Less dependent	0.0004	0.0004	0.0012**	0.0005
Somewhat dependent	0.0001	0.0004	0.0027***	0.0005
Very dependent	0.0009**	0.0004	0.0030***	0.0005

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
Most dependent	0.0020***	0.0005	0.0100***	0.0005
Number of medical conditions * sex				
1 condition* Male	reference		reference	
2 conditions * Female	-0.0171***	0.0016	-0.0029***	0.0007
3 conditions * Female	-0.0396***	0.0011	-0.0022***	0.0008
4 conditions * Female	-0.0549***	0.0007	0.0001	0.0008
≥5 conditions * Female	-0.0659***	0.0005	0.0030***	0.0008
Number of medical conditions * age				
1 condition * age	reference		reference	
2 conditions * age	-0.0007***	0.0016	-0.0006***	0.0001
3 conditions * age	-0.0014***	0.0011	-0.0010***	0.0001
4 conditions * age	-0.0022***	0.0007	-0.0014***	0.0001
≥5 conditions * age	-0.0023***	0.0005	-0.0023***	0.0001
Number of medical conditions * income quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0016*	0.0009	-0.0025*	0.0013
3 conditions * middle-low	-0.0011	0.0013	-0.0037**	0.0014
4 conditions* middle-low	-0.0043**	0.0020	-0.0043**	0.0015
≥5 conditions* middle-low	-0.0031	0.0027	-0.0046**	0.0014
2 conditions*middle	-0.0020**	0.0010	-0.0032**	0.0015
3 conditions * middle	-0.0030**	0.0014	-0.0051**	0.0015
4 conditions* middle	-0.0053**	0.0023	-0.0055**	0.0017
≥5 conditions* middle	-0.0028	0.0031	-0.0072***	0.0016
2 conditions*middle-high	-0.0024**	0.0011	-0.0031*	0.0016
3 conditions * middle-high	-0.0032**	0.0016	-0.0052**	0.0016
4 conditions* middle-high	-0.0067**	0.0025	-0.0081***	0.0018
≥5 conditions* middle-high	-0.0093**	0.0034	-0.0070***	0.0018
2 conditions*highest	-0.0015	0.0011	-0.0036**	0.0017
3 conditions *highest	-0.0031*	0.0017	-0.0063***	0.0018
4 conditions* highest	-0.0096***	0.0027	-0.0088***	0.0019
5 conditions* highest	-0.0099**	0.0038	-0.0095***	0.0019
Number of medical conditions * deprivation quintile				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0024***	0.0007	-0.0001	0.0011
3 conditions * middle-low	0.0038 ***	0.0010	-0.0015	0.0011
4 conditions* middle-low	0.0027	0.0017	-0.0016	0.0013
≥5 conditions* middle-low	0.0060**	0.0026	-0.0029**	0.0012
2 conditions*middle	0.0047***	0.0007	-0.0002	0.0012
3 conditions * middle	0.0067***	0.0010	-0.0018	0.0013
4 conditions* middle	0.0062***	0.0017	-0.0045**	0.0014
≥5 conditions* middle	0.0109***	0.0026	-0.0042**	0.0014
2 conditions*middle-high	0.0057***	0.0009	-0.0012	0.0014

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
3 conditions * middle-high	0.0071***	0.0014	-0.0031**	0.0015
4 conditions* middle-high	0.0074***	0.0022	-0.0051**	0.0016
≥5 conditions* middle-high	0.0111***	0.0032	-0.0079***	0.0016
2 conditions*highest	0.0073***	0.0011	-0.0028	0.0017
3 conditions *highest	0.0108***	0.0016	-0.0052**	0.0018
4 conditions* highest	0.0114***	0.0026	-0.0089***	0.0019
≥5 conditions* highest	0.0119***	0.0036	-0.0098***	0.0019
Number of medical conditions * instability				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0012**	0.0007	0.0009	0.0011
3 conditions * middle-low	-0.0007	0.0010	0.0020	0.0012
4 conditions* middle-low	-0.0016	0.0017	0.0010	0.0013
≥5 conditions* middle-low	-0.0013	0.0026	0.0022	0.0014
2 conditions*middle	-0.0017**	0.0008	0.0037**	0.0014
3 conditions * middle	-0.0012	0.0012	0.0010	0.0013
4 conditions* middle	-0.0002	0.0019	0.0022	0.0014
≥5 conditions* middle	0.0025	0.0027	0.0037**	0.0014
2 conditions*middle-high	-0.0003	0.0009	0.0022*	0.0012
3 conditions * middle-high	0.0006	0.0012	0.0019	0.0013
4 conditions* middle-high	0.0011	0.0019	0.0033**	0.0014
≥5 conditions* middle-high	0.0075***	0.0027	0.0048***	0.0014
2 conditions*highest	0.0037***	0.0012	-0.0027**	0.0013
3 conditions *highest	0.0095***	0.0012	-0.0026**	0.0013
4 conditions* highest	0.0113***	0.0020	-0.0035**	0.0014
≥5 conditions* highest	0.0206***	0.0028	-0.0019	0.0014
Number of medical conditions * ethnic concentration				
1 condition* lowest	reference		reference	
2 conditions*middle-low	-0.0006	0.0009	0.0011	0.0012
3 conditions * middle-low	-0.0007	0.0013	0.0022*	0.0012
Number of medical conditions * ethnic concentration				
4 conditions* middle-low	-0.0020	0.0021	0.0012	0.0014
≥5 conditions* middle-low	0.0018	0.0029	0.0012	0.0013
2 conditions*middle	0.0004	0.0009	0.0006	0.0012
3 conditions * middle	-0.0006	0.0013	0.0003	0.0012
4 conditions* middle	-0.0034	0.0021	-0.0012	0.0014
≥5 conditions* middle	0.0016	0.0030	0.0004	0.0013
2 conditions*middle-high	0.0002	0.0009	0.0015	0.0012
3 conditions * middle-high	-0.0013	0.0014	0.0021*	0.0013
4 conditions* middle-high	-0.0056**	0.0022	0.0006	0.0014
≥5 conditions* middle-high	-0.0056*	0.0030	0.0035**	0.0014
2 conditions*highest	-0.0008	0.0012	0.0043***	0.0012
3 conditions *highest	-0.0021	0.0013	0.0047***	0.0013

	< 65 years (N=5,004,699)		≥ 65 years (N=1,634,390)	
	coefficient	se	coefficient	se
4 conditions* highest	-0.0081***	0.0021	0.0044***	0.0013
≥5 conditions* highest	-0.0070**	0.0030	0.0093***	0.0013
Number of medical conditions * dependency quintile[#]				
1 condition* lowest	reference		reference	
2 conditions*middle-low	0.0016**	0.0007		
3 conditions * middle-low	0.0018**	0.0010		
4 conditions* middle-low	0.0004	0.0017		
≥5 conditions* middle-low	-0.0028	0.0026		
2 conditions*middle	0.0015**	0.0001		
3 conditions * middle	0.0030***	0.0011		
4 conditions* middle	0.0036**	0.0018		
≥5 conditions* middle	0.0008	0.0025		
2 conditions*middle-high	0.0017**	0.0008		
3 conditions * middle-high	0.0029**	0.0012		
4 conditions* middle-high	0.0028	0.0019		
≥5 conditions* middle-high	0.0014	0.0027		
2 conditions*highest	0.0018**	0.0009		
3 conditions *highest	0.0032**	0.0013		
4 conditions* highest	0.0041**	0.0020		
≥5 conditions* highest	0.0038	0.0028		
AIC	15,672,974		5,058,276	
BIC	15,674,535		5,059,515	

^ adjusted for primary care models and rurality index; *** P <0.001, ** P< 0.05, * p<0.10; se indicates standard error; # interaction between the number of medical conditions and dependency quintile was not statistically significant and therefore excluded from a final model.

DISCUSSION

Individuals living with multimorbidity accounted for 79% of total healthcare costs incurred by our study cohort and 68% of total allocatable healthcare costs in Ontario in 2009. Although there is a growing body of literature documenting the economic burden of multimorbidity in other jurisdictions (12, 13, 38), the current study provides further evidence that the relatively small proportion of the population with multimorbid conditions is responsible for a disproportionately high percentage of total healthcare costs. Moreover, we observed this disproportionate

relationship in both young (<65) and (65+) older cohorts, suggesting that any approaches to containing the healthcare costs of multimorbidity should be implemented across all age groups.

Our study demonstrated that healthcare costs increased significantly with higher levels of multimorbidity, and that this positive association exists even after the adjustment for confounding factors and a skewed distribution of cost data using the generalized linear model with a log link function and a gamma distribution. The exponential relationship between multimorbidity and incremental healthcare costs shown in this study suggests that the financial burden of multimorbidity to the healthcare system is not simply equal to the sum of costs incurred by each individual condition. This non-linearity reflects the complex association of the degree of multimorbidity, the type of disease clusters and healthcare costs. It is likely that patients with multimorbidity might experience worse health outcomes and require more complex clinical management.(9) They are also vulnerable to receiving redundant diagnostic tests (12), a suboptimal level of continuity of care, and inappropriate prescriptions, (11) as current treatment guidelines are mainly focused on individual disease management. (10) Thus, as the number of healthcare providers involved in the patient's care increases, information sharing and coordinating care across healthcare providers may become increasingly challenging. (39) Moreover, an increasing number of comorbid conditions may compromise patients' ability to self-manage their diseases. (40) Therefore, the high healthcare spending on multimorbidity found in our study underscores the need for ensuring continuity and coordination of care in this population.

More importantly, our study contributes to the understanding of the association between the degree of multimorbidity and healthcare costs. We observed that each unit increase in age amplified the rise in healthcare costs associated with an increasing number of medical conditions. The observed interaction effect may partly be due to patterns in healthcare use among the older population, which is often characterized by poly-pharmacy and the use of continuing care services that are very costly. Additionally, we found that the positive association between healthcare costs and levels of multimorbidity was stronger in men than in women among individuals younger than 65 years. This sex difference might relate to the prevalence of different disease clusters in men and women, as men within this age group often experience life-threatening and more serious illnesses than women. (41, 42) For those older than 65 years, the increase in healthcare costs observed with the increase in the level of multimorbidity was significantly higher in women than men. This sex difference could be partially explained by longer life expectancy and greater risk of multimorbidity in older women than men (20, 43), which may cause older women to be more dependent on formal (paid) healthcare services and other informal (unpaid) caregivers.

We observed small interaction effects of neighborhood-level socioeconomic characteristics on the association between the number of medical conditions and healthcare costs. Living in lower income and marginalized areas, i.e. areas with greater levels of instability, dependency or ethnic concentration, accelerated the increase in health system costs with increased multimorbidity. This may reflect a higher risk of experiencing more complex multimorbid conditions among individuals living in disadvantaged neighborhoods, (44) in turn leading to greater demand for and utilization of healthcare. Another plausible explanation for this phenomenon is that

individuals living in more deprived areas may face barriers to accessing health services (45) and therefore have delayed access to preventive healthcare interventions or treatments (46), consequently being at greater risk of developing poorer health outcomes and incurring higher healthcare costs. The effects of socioeconomic factors reported in this study should however be interpreted with caution, as they were derived based on neighborhood. Although the interaction terms between socioeconomic factors and levels of multimorbidity were statistically significant, most of the estimated effect sizes were very small and may be a result of the large sample size used in this study.

Strengths and limitations

This population-based study was based on a large sample size and used robust costing and generalized linear model regression techniques. The availability of linked and patient-level health administrative databases allowed the estimation of the total health system costs associated with multimorbidity from all healthcare sectors, and the use of health administrative databases minimized potential recall and non-response biases that are commonly found in survey data.

Nonetheless, the results of this study should be interpreted in light of the following limitations. First, we estimated healthcare costs based on 16 selected medical conditions, and this selection of a limited number of medical conditions is likely to underestimate the overall healthcare costs of multimorbidity. However, total cost estimates reported in our study were comprehensive, as they amounted to 86% of total allocatable government expenditures in Ontario in 2009.(47) Secondly, due to a paucity of data, certain costs (e.g., deductibles and co-payments borne by supplemental health insurance, out-of-pocket beneficiary payments and indirect costs associated

with caregiving) were excluded from the analysis. In addition, this study could not capture the costs of medications covered by private sectors, including private insurers and out of pocket expenses, which at the time of the study represented the largest component of total prescription drug costs of Canadians who are younger than 65 years of age. (48) For this reason, findings from this study may not be generalizable to other jurisdictions with different healthcare systems.

Third, this study did not take into account clusters of medical conditions. It is possible that the relationship between multimorbidity and healthcare costs may vary according to the type and patterns of comorbid medical conditions; which should be investigated in future studies. We chose to use disease counts in the present study, as there are no standards or guidelines for the definition or measurement of multimorbidity, and the choice of the measure would be subject to data availability and the outcome of interest. (49, 50) A previous study conducted by our team (5) has shown, however, that there was no common clustering of diseases among individuals living with multimorbidity, as the number of disease clusters required to include 80% of the study population increased from 14 (among individuals with two conditions) to 2,744 clusters of conditions (among individuals with 5 or more conditions), thus supporting the use of disease counts rather than clusters. Moreover, a previous systematic review showed that 132 definitions of multimorbidity with 1,631 criteria were used in the published literature. (51) Our decision to use disease counts is also supported by a study by Islam et al. (52) indicating that the total number of chronic conditions were more predictive of out-of-pocket healthcare costs and high-cost users than disease clusters, dominant groups or dominant pairs.

CONCLUSION

This population-based, retrospective cohort study highlights the amount by which health system costs increased significantly with increasing levels of multimorbidity in a publicly-financed healthcare system. The average and incremental healthcare costs reported in this study could serve as the foundation for future health economic evaluation of interventions for preventing and managing multimorbidity. As the relationship between multimorbidity and healthcare costs varies according to socio-demographic factors, interventions addressing disparities in healthcare in individuals living with multimorbidity may have the potential to reduce total health system costs.

LIST OF ABBREVIATIONS

AMI acute myocardial infarction

COPD chronic obstructive pulmonary disorder

GLM generalized linear model

ICES Institute for Clinical Evaluative Sciences

OHIP Ontario Health Insurance Plan

OLS ordinary least-squares regressions

DECLARATIONS

Ethics approval:

The study has been approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

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Competing interests: None

Authors contributions: WPW was the lead for the conception and creation of the cohort. YB created the cohorts through data linkages and helped with data analysis and methods. KT and WW drafted the manuscript. KT, CM, AG, SB, AK, YB, YP, and WPW interpreted the results and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data sharing statement: No additional data are available.

Figure legends:

Figure 1. Distribution of total number of population and total health system costs in Ontario from April 1, 2009 to March 31, 2010

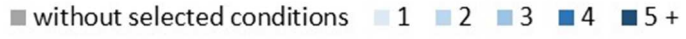
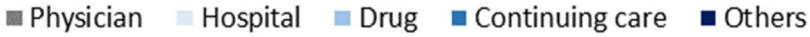


Figure 2. Unadjusted mean total healthcare cost per capita for Ontario adults, by service type, number of conditions and age group from April 1, 2009 to March 31, 2010



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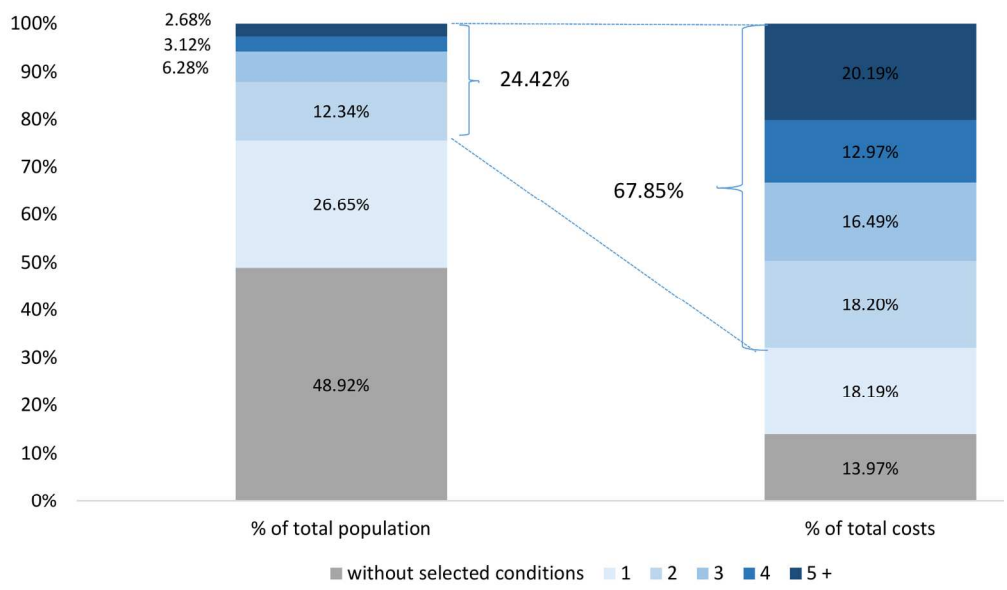

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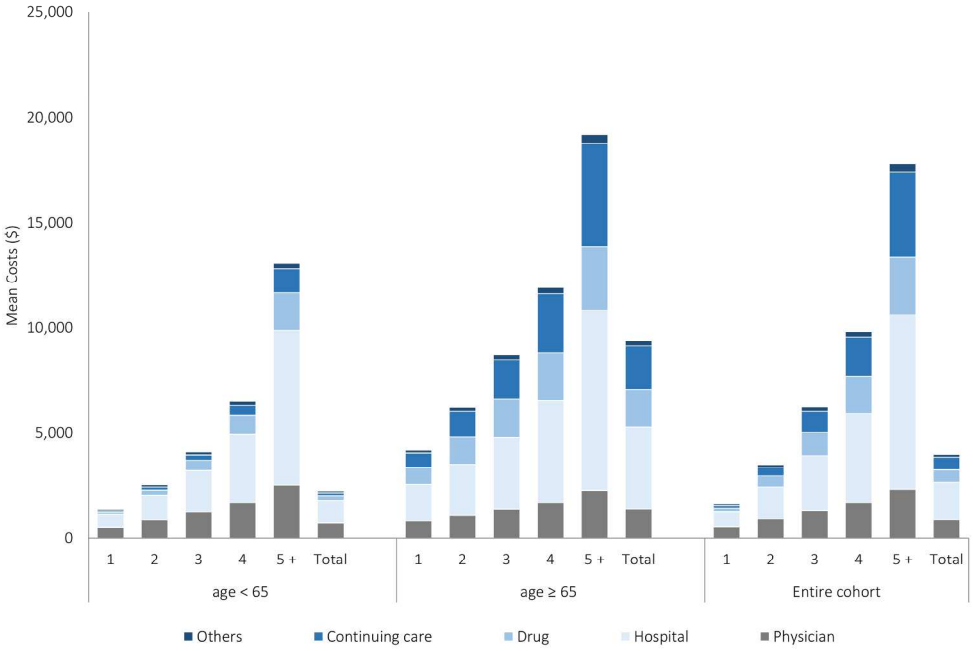

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Appendix 1. List of diagnosis codes used to define the 16 selected medical conditions

Condition	ICD 9 / OHIP fee codes	ICD 10
AMI*	410	I21, I22
Arthritis - Osteoarthritis	715	M15-M19
Arthritis - Other Arthritis (Synovitis, Fibrositis, Connective tissue disorders, Ankylosing spondylitis, Gout Traumatic arthritis, pyogenic arthritis, Joint derangement, Dupuytren's contracture, Other MSK disorders)	727, 729, 710, 720, 274, 716, 711, 718, 728, 739	M00-M03, M07, M10, M11-M14, M20-M25, M30-M36, M65-M79
Arthritis - Rheumatoid arthritis	714	M05-M06
Asthma*	493	J45
Cancer	140-239	C00-C26, C30-C44, C45-C97,
Cardiac Arrythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1
CHF*	428	I500, I501, I509
COPD*	491, 492, 496	J41, J43, J44
Dementia	290, 331, 797 (OHIP) / 290.0, 290.1, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 294.9, 331.0, 331.1, 331.2, 797 (DAD)	F000, F001, F002, F009, F010, F011, F012, F013, F018, F019, F020, F021, F022, F023, F024, F028, F03, F051, F065, F066, F068, F069, F09, G300, G301, G308, G309, G310, G311, R54
Depression	311, 300, 296	F32, F33, F412, F480
Diabetes*	250	E08 - E13
Hypertension*	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Osteoporosis	733	M81 M82
Renal failure	403, 404, 584, 585, 586, v451	N17, N18, N19, T82.4, Z49.2, Z99.2
Stroke	430, 431, 432, 434, 436	I60-I64
Coronary syndrome (excluding MI)	411-414	I20, I22-I25

Note: * validated diagnosis codes; OHIP, Ontario Health Insurance Plan; AMI, Acute Myocardial Infarction, MSK, musculoskeletal; DAD, Discharge Abstract Database; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; MI, Myocardial infarction

Appendix 2. Proportions and mean number of medical conditions by baseline characteristics, April 1, 2009 to March 31, 2010

	N	Number of medical conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
All cohort	6,639,089	52.2	24.2	12.3	6.1	5.2	1.88 (1.16)
Sex							
Female	3,541,644	49.2	25.3	13.4	6.6	5.5	1.94 (1.18)
Male	3,097,445	55.6	22.8	11.1	5.5	5.0	1.81 (1.14)
Age (years)							
0-19	809,782	89.8	9.3	0.8	0.1	0.01	1.11 (0.35)
20-34	908,634	77.2	18.8	3.4	0.5	0.1	1.27 (0.55)
35-44	875,680	66.5	24.4	7.0	1.7	0.5	1.45 (0.74)
45-64	2,410,603	47.0	29.9	14.4	5.7	3.0	1.88 (1.05)
65-74	836,640	25.3	29.3	22.3	12.7	10.4	2.53 (1.28)
70-74	383,237	21.8	28.2	23.2	14.2	12.6	2.68 (1.30)
75+	797,750	13.6	22.4	23.2	17.8	23.0	3.14 (1.36)
Income quintile							
Lowest	1,249,664	50.3	23.8	12.8	6.8	6.3	1.95 (1.21)
Middle-low	1,307,725	50.8	24.3	12.8	6.5	5.7	1.92 (1.18)
Middle	1,317,644	52.4	24.2	12.2	6.1	5.1	1.87 (1.15)
Middle-high	1,365,082	53.2	24.3	12.0	5.8	4.8	1.85 (1.13)
Highest	1,340,912	53.5	24.5	11.9	5.7	4.5	1.83 (1.12)
Rurality index							
Non-rural (< 40)	6,038,705	52.3	24.1	12.3	6.1	5.2	1.88 (1.56)
Rural (≥40)	514,225	48.9	25.0	13.3	6.8	5.9	1.96 (1.19)
Deprivation quintile							
Least deprived	1,654,445	55.0	24.0	11.4	5.3	4.3	1.80 (1.11)
Less deprived	1,504,855	52.6	24.4	12.2	5.9	4.9	1.86 (1.14)
Somewhat deprived	1,328,459	51.1	24.4	12.7	6.4	5.5	1.91 (1.17)
Very deprived	1,101,586	50.0	24.3	13.0	6.7	6.0	1.94 (1.20)
Most deprived	934,094	50.0	23.8	12.9	6.8	6.4	1.96 (1.21)

Appendix 2. (Cont'd)

	N	Number of medical conditions					
		1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)	Mean (SD)
Instability quintile							
Least unstable	1,715,922	56.6	24.0	11.0	4.9	3.5	1.75 (1.06)
Less unstable	1,365,580	53.2	24.4	12.1	5.8	4.6	1.84 (1.13)
Somewhat unstable	1,077,375	50.5	24.6	12.9	6.5	5.5	1.91 (1.17)
Very unstable	1,195,108	50.4	24.2	12.8	6.6	6.0	1.94 (1.20)
Most unstable	1,169,454	47.3	23.9	13.6	7.6	7.6	2.04 (1.26)
Dependency quintile							
Least dependent	1,400,521	59.3	23.3	10.0	4.3	3.1	1.69 (1.02)
Less dependent	1,456,755	55.5	24.1	11.3	5.2	4.0	1.78 (1.09)
Somewhat dependent	1,280,391	52.4	24.5	12.3	5.9	4.9	1.86 (1.14)
Very dependent	1,134,858	49.3	24.7	13.3	6.8	5.9	1.95 (1.19)
Most dependent	1,250,914	42.2	24.6	15.3	8.9	9.0	2.18 (1.31)
Ethnic concentration quintile							
Lowest	848,456	47.2	25.1	13.9	7.3	6.5	2.01 (1.22)
Middle-low	1,060,646	49.8	24.8	13.0	6.6	5.7	1.91 (1.19)
Middle	1,160,097	51.0	24.5	12.6	6.3	5.5	1.91 (1.17)
Middle-high	1,323,040	53.4	24.0	11.8	5.8	5.0	1.84 (1.14)
Highest	2,131,200	54.9	23.5	11.5	5.5	4.6	1.81 (1.12)
Primary care model							
Family health teams/ other primary care models	1,109,443	51.0	24.9	12.6	6.3	5.2	1.94 (1.28)
Family health networks /family health organizations	1,054,714	49.6	25.3	13.1	6.5	5.5	1.97 (1.30)
Community health centres/family health groups/non-rostered patients	4,474,932	53.1	23.7	12.0	6.0	5.2	1.90 (1.29)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8-12*
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	Not report
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not report

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	Not report
		(c) Consider use of a flow diagram	Not report
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-15
		(b) Indicate number of participants with missing data for each variable of interest	Not report
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not report
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	14-17
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17, 19
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	24-27
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	27
Generalisability	21	Discuss the generalisability (external validity) of the study results	28
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	30

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.