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CLINICAL INVESTIGATION

Journal of the American Geriatrics Society

The impact of age, sex, and gender on polypharmacy and potential prescribing cascades: Lessons from five databases

Paula A. Rochon MD, MPH[1,2,3,4] | **Joyce Li MSc**[1] | **Denis O'Mahony MD, DSc**[5] | **Graziano Onder MD**[6,7] | **Mirko Petrovic MD, PhD**[8] | **Shelley A. Sternberg MD**[9] | **Jerry H. Gurwitz MD**[10] | **Rachel D. Savage PhD**[1,2,4] | **Wei Wu MSc**[1] | **Vasily Giannakeas PhD**[1,2] | **Altea Kthupi MPH**[1] | **Kieran Dalton PhD**[11] | **Lisa M. McCarthy PharmD, MSc**[12,13,14] | **Robin Mason PhD**[1] | **Amanda Giancola MSc**[1] | **Parya Borhani MPH**[1] | **Antonio Cherubini MD, PhD**[15,16]

[1]Women's Age Lab and Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada

[2]ICES, Toronto, Ontario, Canada

[3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[4]Institute of Health Policy, Management & Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[5]Department of Medicine (Geriatrics), University College Cork, Cork, Ireland

[6]Department of Geriatrics, Orthopedics and Rheumatology, Università Cattolica del Sacro Cuore, Rome, Italy

[7]Center of Aging, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy

[8]Department of Internal Medicine and Paediatrics, Ghent University, Ghent, Belgium

[9]Department of Medicine, Division of Geriatrics, Maccabi Healthcare Services, Tel Aviv, Israel

[10]Division of Geriatric Medicine, UMass Chan Medical School, Worcester, Massachusetts, USA

[11]Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland

[12]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

[13]Institute for Better Health, Trillium Health Partners, Toronto, Ontario, Canada

[14]Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada

[15]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy

[16]Geriatria, Accettazione geriatrica e Centro di Ricerca per l'invecchiamento, IRCCS INRCA, Ancona, Italy

Correspondence
Paula A. Rochon, Women's Age Lab, Women's College Hospital, University of Toronto, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada.
Email: paula.rochon@wchospital.ca

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Abstract

Background: Few studies describe how gender-related factors may contribute to polypharmacy and prescribing cascades. Describing these patterns using cross-national comparisons can improve the robustness of findings and provide lessons on the importance of considering age, sex, and gender in pharmacological research. The aim of the study was to explore the intersection of age, sex, and gender with polypharmacy and co-prescribing suggesting a potential prescribing cascade.

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Methods: In this cross-sectional descriptive study, we assessed polypharmacy and calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade in patients aged ≥65 years from five international secondary databases: population-level community and nursing home (ICES, Maccabi Healthcare Services), clinical trial (SENATOR), and patient registry (REPORT-AGE, SHELTER). The intersection of age, sex, and gender was explored.

Results: All databases provided age and sex; none included gender-identity data. Gender-related sociocultural factors, socioeconomic status (SES) measured as income and educational attainment, and marital status were not uniformly collected. Compared with males, females had lower income, has less educational attainment, and were more frequently widowed. Polypharmacy was more common in men. Co-prescribing suggesting a prescribing cascade was more frequent in females in four databases and was also more frequent in lower SES and unmarried groups (significant in ICES (community and nursing home) and Maccabi (community), with a nonsignificant trend in Maccabi (nursing home) and three remaining databases). Using two population-level databases, the prevalence of co-prescribing suggesting a prescribing cascade was highest among females 85 years and older who were also in the lower SES group (11.0% ICES and 14.6% Maccabi). Gender disparity was highest in this group (ICES Differential Prevalence = 3.0%, Maccabi Differential Prevalence = 3.8%).

Conclusion: Older adults with lower SES experienced polypharmacy or co-prescribing suggesting a prescribing cascade more frequently than those with higher SES. Within the lower SES groups, females more frequently than males had evidence of co-prescribing suggesting a prescribing cascade. Considering the role of sex and gender-related sociocultural factors may help to better understand some contributors to polypharmacy and prescribing cascades. The research applications are highlighted in our five lessons learned.

KEYWORDS

age, gender, polypharmacy, prescribing cascades, sex

INTRODUCTION

Improving drug prescribing and reducing medication-related harm by addressing polypharmacy is the focus of global efforts, including the *Medication without Harm* initiative[1,2] led by the *World Health Organization*. The initiative's lack of consideration of the impact of age, sex, and gender on polypharmacy represents a missed opportunity to optimize prescribing interventions for older adults. Age- and sex-related differences due to drug pharmacokinetics and pharmacodynamics have been well documented.[3] Females are more likely than males to experience adverse drug events (ADEs)[3–5] and their incidence increases with age.[6,7] Additionally, older females are more likely than older males to develop multiple chronic health conditions[8] that may require pharmacotherapy, making its optimization for females particularly important. Females are also more likely than males to experience potentially inappropriate prescribing contributing to problematic polypharmacy,[9–11] further increasing their ADE risk and negative health-related outcomes.[7,12,13] Yet, few studies have considered the role of gender-related sociocultural factors on polypharmacy or prescribing cascades,[14] important contributors to potentially inappropriate prescribing.[10,14] As such, descriptive epidemiology plays an important role in describing these factors.[15,16]

Biological sex and gender-related sociocultural variables are important modifiers of health and disease.[17] Although sex (typically categorized as male and female)

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is more consistently collected and considered in research, gender—a complex sociocultural construct—is less often considered. This is in part because self-reported gender has often not been collected in routine health data. Nonetheless, there are opportunities to explore gender by examining the intersection between sex, age, and gender-related sociocultural factors that may be already collected in databases and are under-utilized by researchers. This approach provides an opportunity to consider how gender may contribute to differences observed between males and females in drug prescribing. At its most simplistic, gender refers to one's sense of identity as a man, woman, or nonbinary individual. The Jhpiego framework[18] characterizes gender as a complex construct, involving dimensions beyond identity to include gender-related roles and relations, in addition to institutionalized gender.[19] Some examples include caregiving responsibilities (gender roles), marital status (gender relations), and socioeconomic status (SES) (institutionalized gender) but does not adequately consider gender variation by age. This multidimensional nature of gender makes it challenging to evaluate in research.

In this descriptive study, we aimed to assess the influence of age, sex, and gender on drug prescribing in older adults and create lessons learned about the importance of including these data, in research. We used five international secondary databases and data triangulation methodology to explore the intersection of these factors with polypharmacy and a potential prescribing cascade, both risks for potentially inappropriate prescribing.

Key points

- Gender was inconsistently measured in secondary databases; when measured, older women were of lower SES than older men.
- Older adults in lower SES groups based on income or educational attainment more frequently experienced polypharmacy or co-prescribing suggesting a prescribing cascade than those in higher SES groups.
- Within lower SES groups, females had evidence of co-prescribing suggesting a prescribing cascade more often than males.

Why does this paper matter?

Understanding the role that gender-related sociocultural factors play, in addition to age and sex, is important for research in general, and specifically research designed to optimize prescribing in older people as outlined in our five lessons learned.

METHODS

Through the international GenderNet-funded iKASCADE project,[20] in collaboration with academic geriatricians from six countries, we triangulated data by bringing together five secondary databases to explore common patterns of polypharmacy and a potential prescribing cascade, through an age, sex, and gender lens. Data triangulation is a relatively recent research approach where multiple data sources are brought together to address a common question.[21] Most frequently used in qualitative research, triangulation is also applied to quantitative data, and provides the opportunity to corroborate findings and identify patterns from different data types and sources, thereby increasing the generalizability of the study results. Each investigator conducted descriptive analyses of their data and provided summary tabular form data. This study followed the "Items That Should be Included in Reports of Descriptive Studies" modeled after the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cross-sectional studies (see Supplementary Table S1).[16]

Database description

Five secondary databases, describing older adults and their prescribed drug therapies, were provided by our iKASCADE partners from Belgium, Canada, Ireland, Israel, Italy, and the United States.[20] Two population-level databases provided separate data for the community and nursing home setting including ICES (formerly Institute for Clinical Evaluative Sciences) and the Maccabi Healthcare Services database. ICES provided population-level data on the 2,377,885 older adults in Ontario, Canada,[22] using Ontario's Registered Persons Database (RPDB). The RPDB provides basic demographic information for registrants of the province's universal, publicly funded healthcare system. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Administrative healthcare databases were linked using unique encoded identifiers and analyzed at ICES. The Maccabi Healthcare Services database provided population-level data from their 289,994 older healthcare recipients in Israel.[23] Two patient registry databases

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provided data: Report-AGE provided data from 6737 older adults with multimorbidity and polypharmacy admitted to a geriatric hospital[24] in Italy and SHELTER provided data from 3966 residents living in one of 57 nursing homes in Europe.[25] One clinical trial database from the SENATOR project[26] provided data on 1537 hospitalized older adults with multimorbidity in six European medical centers. Supplementary Table S2 describes these databases, types of data, number of included individuals, location and description, the principal investigator, the index date used, and ethics approval details. We selected the index date of January 1, 2020, for the population-level data because it precedes COVID-19. The index dates for the remaining databases were defined as the date of the respective hospital or nursing home admission.

Variables

Age and sex data were extracted. Older adults were defined as those 65 years of age and older. Age was categorized into 65–74, 75–84, and 85 years of age or older. Sex was identified as male or female only. Gender nonbinary status data were collected.

Steps were taken to ensure harmonization of the data variables. To identify gender-related sociocultural variables, we followed three steps. First, investigators discussed the possible gender-related sociocultural variables available from their respective databases. Second, a framework for the classification of the gender-related sociocultural variables was identified.[18] This framework considered gender in three ways: (1) gender-related identity (man, woman, nonbinary[27]), (2) gender roles and relations,[28,29] and (3) institutionalized gender, referring to the ways that health and social care systems and institutions perpetuate gender inequities. Third, investigators identified the gender-related sociocultural variables in their respective databases that aligned with this framework. Supplementary Table S3 summarizes the gender-related sociocultural variables, their definition, and the database where these data were found. Institutionalized gender data, measured as SES, were available from the ICES population-level database based on income, the Maccabi population-level database based on SES clusters, and the SENATOR clinical trial database based on educational attainment. In the ICES database, lower SES was identified by eligibility for a low-income subsidy from the Ontario Drug Benefit program,[30] defined as an annual income of $19,300 (Canadian) or less per individual or a combined annual income of $32,300 (Canadian) or less per couple.

In the Maccabi Healthcare Services database, SES was classified into clusters from 1 to 10, with 1 symbolizing very low and 10 very high SES status. Residences in clusters 1–3 were categorized as lower SES status. In the SENATOR database, educational attainment was classified as no school/primary only, secondary, or third level.

Gender-related roles and relations data, measured as marital status, were available in the Report-AGE and SHELTER databases. Marital status classifications were simplified as "married" (partner/cohabitant/common law, married) and "unmarried" (single, widow, separated, or divorced) for the analysis. Unmarried status can disadvantage both men and women from a social support and socioeconomic perspective, particularly women.[31]

Drug prescribing measures

Two drug prescribing measures, polypharmacy and a potential prescribing cascade,[32,33] were used. Polypharmacy was defined as five or more long-term daily drug therapies[32,33] and hyperpolypharmacy as 10 or more daily drug therapies prescribed at the index date.[32,33] These numeric measures of polypharmacy were selected as all databases included number of drug therapies.

Co-prescribing suggesting a prescribing cascade was included, as prescribing cascades are an important contributor to polypharmacy and a risk for potentially inappropriate prescribing.[11] A prescribing cascade occurs when a drug therapy is initiated, an adverse event develops (often misinterpreted as a new medical condition), and a subsequent drug therapy is prescribed to treat this adverse event. The calcium channel blocker (CCB) to diuretic prescribing cascade was selected because it is among the best characterized,[34–36] and most common, with an estimated 16.8 million people being prescribed amlodipine in the United States alone in 2020.[37] Furthermore, this prescribing cascade occurs in the community, hospital, and nursing home settings and was measurable in the smaller databases included in our study. Other prescribing cascades were explored, including the antipsychotic to antiparkinsonian medication and the overactive bladder to cholinesterase inhibitor prescribing cascades, but the numbers of these prescribing cascades were too small to report in these different settings. The CCB and diuretic medications included in each database related to this prescribing cascade are described in Supplementary Table S4. Co-prescribing suggesting a prescribing cascade was measured by the number and percentage of co-prescribing of any CCB and any diuretic at the index date to allow measuring this prescribing cascade across all databases.

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TABLE 1 Table 1: Description of the age, sex and gender-related sociocultural factors among older adults in five secondary databases.

	Community		Geriatric hospital	Nursing home			Hospital
Characteristic	**ICES**	**Maccabi Healthcare**	**Report-AGE**	**ICES**	**Maccabi Healthcare**	**SHELTER**	**SENATOR**
Number	2,302,515	283,292	6737	75,370	6702	3966	1537
Age: Mean years	74.7	73	85.9	85.1	84	84.6	78.2
Female, %	54.3%	54.1%	57.8%	69.2%	68.4%	74.2%	47.2%
Mean number of medications	3.6	6	6.0	6.0	7	7.1	9.3
Gender-related Sociocultural Factors							
Socioeconomic status (SES)							
Income %: Low	13.1%	Data unavailable		23.8%		Data unavailable	
Cluster %: Low	Data unavailable	18.6%	Data unavailable		22.2%	Data unavailable	
Educational attainment			Data unavailable				
No more than primary, %							38.9%
Secondary, %							47.4%
Third level, %							13.7%
Marital status							
Data available, *n*	Data unavailable		5699	Data unavailable		3236	Data unavailable
Unmarried, %			56.5%			80.8%	
Single, %			6.9%			12.7%	
Widowed, %			48.9%			61.3%	
Separated/ Divorced, %			0.8%			6.7%	
Married/common law, %			43.5%			19.2%	
Marital status not reported, *n*			1038			730	

Note: In the ICES database, lower socioeconomic status was identified by eligibility for a low-income subsidy from the Ontario Drug Benefit program,[30] defined as an annual income of $19,300 (Canadian) or less per individual or a combined annual income of $32,300 (Canadian) or less per couple. In the Maccabi Healthcare Services database, socioeconomic status of the older adult was classified into clusters from 1 to 10, with 1 symbolizing a very low and 10 a very high socioeconomic status. Residences in clusters 1–3 were categorized as lower socioeconomic status. In the Report-AGE and SHELTER databases, marital status was not reported by all older adults. These data were not reported for 15.3% of those in the Geriatric Hospital and 18.4% in the SHELTER database, primarily female older adults. In the SENATOR database, no more than primary education was classified as lower socioeconomic status. Third level of educational attainment was university/college level education. Data unavailable indicates that the data does not exist.

Abbreviation: *n*, number.

Analyses

Data were stratified by setting of care, starting from the most independent group (community-dwelling), to the frailest group (nursing home residents). Descriptive statistics characterized the age, sex, and gender-related sociocultural factors available from each database. Data from the gender-related sociocultural variables (gender-related identity, SES, and marital status) were collected and stratified by sex (male, female) and age groups (65–74, 75–84, 85 years of age and older).

For the continuous variables (age and number of medications), the t-test was used to compare the difference between females and males. For categorical variables, the chi-squared test was used to compare the difference between females and males and between gender-related sociocultural variables. The Cochrane-Armitage trend test was used to compare the difference among the age groups. All tests were two-tailed tests with significance level of 0.05.

We used the Differential Prevalence (DP) measure described in the United Nations *Integrating a Gender Perspective into Statistics*[38] report to measure the gender gap. This DP measure was calculated by obtaining the percentage of a gender-related sociocultural variable (e.g., educational attainment) within the female

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TABLE 2 Polypharmacy, hyperpolypharmacys and co-prescribing suggesting a prescribing cascade prevalence by setting of care, database, and sex.

Setting of care	Database	Sex (*n*)	Numeric polypharmacy measures		Calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade, *n* (%)
			Polypharmacy, *n* (%)	Hyperpolypharmacy, *n* (%)	
Community	ICES	Female (1,249,355)	380,996 (30.5)[a]	56,383 (4.5)[a]	57,448 (4.6)[a]
		Male (1,053,160)	361,752 (34.3)[a]	56,043 (5.3)[a]	46,197 (4.4)[a]
	Maccabi	Female (153,366)	71,863 (46.9)	25,455 (16.6)[a]	10,795 (7.0)[a]
		Male (129,926)	61,191 (47.1)	20,152 (15.5)[a]	8645 (6.7)[a]
Geriatric Hospital	Report-AGE	Female (3897)	2601 (66.7)	473 (12.1)	312 (8.0)
		Male (2840)	1919 (67.6)	350 (12.3)	229 (8.1)
Nursing home	ICES	Female (52,193)	31,774 (60.9)[a]	8927 (17.1)[a]	2925 (5.6)[a]
		Male (23,177)	15,047 (64.9)[a]	4930 (21.3)[a]	1017 (4.4)[a]
	Maccabi	Female (4587)	3176 (69.2)[a]	1294 (28.2)[a]	390 (8.5)[a]
		Male (2115)	1522 (72.0)[a]	671 (31.7)[a]	145 (6.9)[a]
	SHELTER	Female (2943)	2128 (72.3)	684 (23.2)	70 (2.4)
		Male (1023)	744 (72.7)	257 (25.1)	14 (1.4)
Hospital	SENATOR	Female (725)	668 (92.1)	308 (42.5)	72 (9.9)
		Male (812)	761 (93.7)	364 (44.8)	76 (9.4)

Abbreviation: *n*, number.

[a]*p*-value<0.05 with chi-square test for the comparison between females and males.

population and subtracting it from the percentage of the same measure within the male population. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

RESULTS

The five secondary databases ranged in size from 2,303,515 community-dwelling older adults in the ICES population-level database to 1537 older hospitalized patients in the SENATOR clinical trial database. All databases included age and sex details. None provided gender-identity data on whether sex assigned at birth differed from reported gender. Three databases provided SES data with ICES and Maccabi Healthcare providing income data and SENATOR providing educational attainment. Two database (Report-AGE and SHELTER) provided marital status.

Table 1 and Supplementary Table S5 describe the age and gender-related sociocultural factors available from each database stratified, overall and by sex. Four databases included more females than males, and females were, on average, older than males. Using population-level data from ICES community-dwelling older adults, 15.2% of females were in the lower SES category compared with 10.5% of males, a pattern also seen in the Maccabi population-level database. When educational attainment was examined, 46.2% of females in the SENATOR clinical trial database had no more than primary education, compared with 32.4% of males. When examining unmarried status in the Report-AGE geriatric hospital database, 75.9% of females were unmarried compared with 31.8% of males, mostly because they were widowed. Similarly, SHELTER study nursing home data showed that 87.9% of females were widowed compared with 60.1% of males. Marital status data were incomplete from both Report-AGE and SHELTER databases, with 15.4% and 18.4% not providing this information, respectively.

Table 2 describes the overall relation between sex and potentially inappropriate prescribing measures of polypharmacy, hyperpolypharmacy, and CCB and diuretic co-prescribing suggesting a prescribing cascade for each database. For polypharmacy measures, males more frequently experienced polypharmacy or hyperpolypharmacy in all but one database. Specifically, males had a greater prevalence of polypharmacy than females in the ICES community (34.3% vs. 30.5%, $p < 0.001$), ICES nursing home (64.9% vs. 60.9%, $p < 0.001$), and Maccabi nursing home (72.0% vs. 69.2%, $p = 0.024$) databases. There was also a greater prevalence of hyperpolypharmacy in males over females in these databases. In the Maccabi community-based population-level database, polypharmacy was more frequent in females. When

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TABLE 3 Prevalence of polypharmacy and potential prescribing cascade by gender-related sociocultural variables.

Socioeconomic status: Income, cluster and educational attainment based								
Income and cluster based								
	ICES (community) income based		**Maccabi (community) cluster based**		**ICES (nursing home) income based**		**Maccabi (nursing home) cluster based**	
	Higher SES (n = 2,049,492)	**Lower SES (n = 253,023)**	**Higher SES (n = 230,637)**	**Lower SES (n = 52,655)**	**Higher SES (n = 58,794)**	**Lower SES (n = 16,576)**	**Higher SES (n = 5214)**	**Lower SES (n = 1488)**
Numeric polypharmacy measures								
Polypharmacy, %	29.7[a]	53.1[a]	45.8[a]	52.3[a]	60.1[a]	69.2[a]	69.7	71.6
Hyperpolypharmacy, %	4.0[a]	12.0[a]	15.0[a]	20.8[a]	17.5[a]	21.5[a]	29.0	30.4
Calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade								
Co-prescribing, %	4.2[a]	7.0[a]	6.6[a]	8.1[a]	4.8[a]	6.8[a]	7.9	8.3
Educational attainment based								
	SENATOR (Hospital)							
	Higher education (n = 939)	**Lower education (n = 598)**						
Numeric polypharmacy measures								
Polypharmacy, %	91.8[a]	94.8[a]						
Hyperpolypharmacy, %	41.6[a]	47.0[a]						
Calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade								
Co-prescribing, %	8.5	11.4						
Marital status								
	Report-AGE (Geriatric hospital)		**SHELTER (nursing home)**					
	Married (n = 2479)	**Unmarried (n = 3220)**	**Married (n = 622)**	**Unmarried (n = 2614)**				
Numeric polypharmacy measures								
Polypharmacy, %	68.5[a]	65.2[a]	75.4	74.2				
Hyperpolypharmacy, %	12.5[a]	10.4[a]	28.5	25.6				
Calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade								
Co-prescribing, %	8.0	8.3	1.9	2.2				

Note: In the SENATOR database, no more than primary education was classified as lower educational attainment. Secondary or third level of educational attainment was classified as higher educational attainment.
Abbreviation: SES, socioeconomic status.
[a]p-value <0.05 with chi-square test for the comparison between the gender-related sociocultural variables (married vs. unmarried, higher SES vs. lower SES, higher education attainment vs. lower education attainment).

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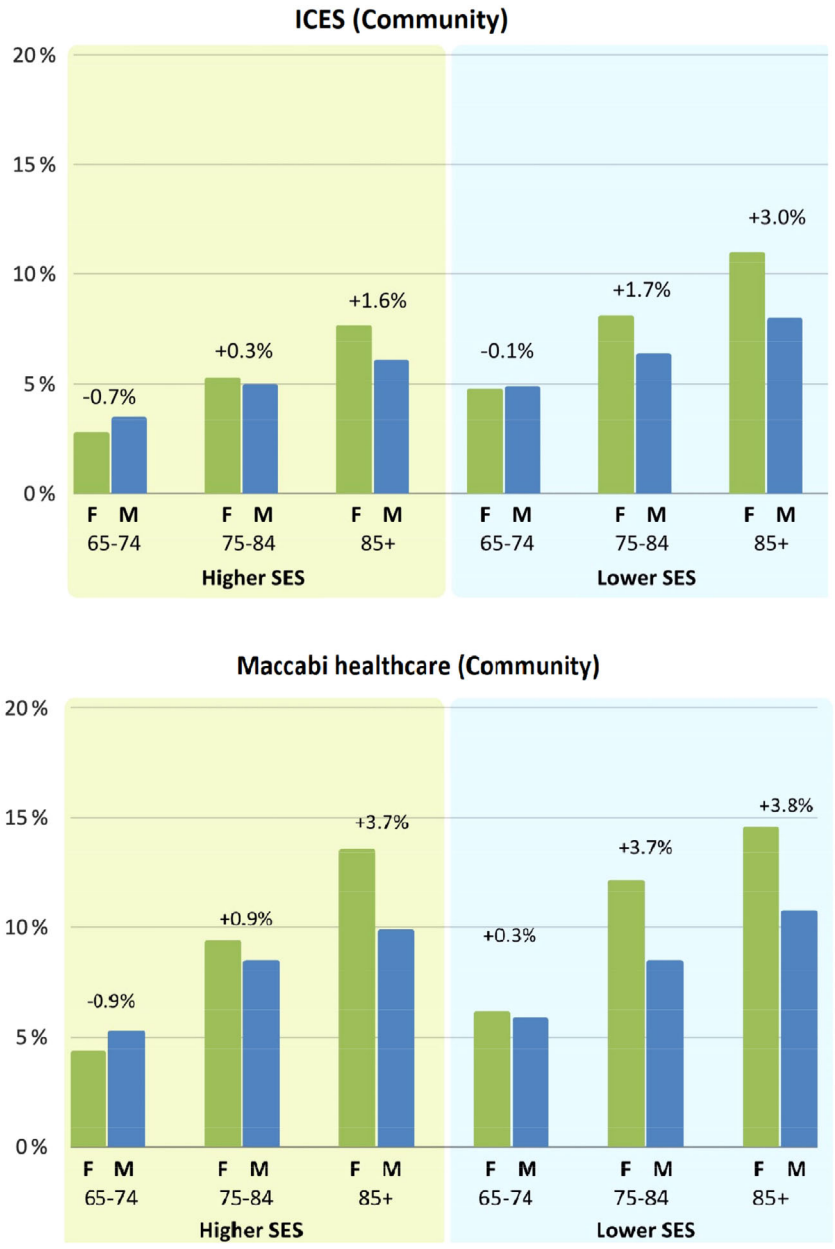


FIGURE 1 Prevalence of calcium channel blocker (CCB) to diuretic co-prescribing suggesting a prescribing cascade in older adults by sex, age, and socioeconomic status. The figure describes the calcium channel blocker to diuretic co-prescribing suggesting a prescribing cascade in older adults living in the community in Ontario, Canada and Maccabi Health System, Israel, on January 1st, 2020. This index date was selected because it precedes the presence of COVID-19. The percentage of a co-prescribing was provided by the intersection with sex (female [F] or male [M]), age (65–74 years old, 75–84 years old, or 85 years of age or older), and the gender-related sociocultural factors of socioeconomic status (SES) that was available from this population-level data. The differential prevalence[38] (the percent of the female population experiencing co-prescribing subtracting the corresponding percent within the male population) is provided between the bars representing the female and male older adults.

looking at co-prescribing suggesting a prescribing cascade, results showed consistent patterns with higher proportions of females than males having evidence of this co-prescribing in all but one database, where they were similar (Report-AGE: 8.0% females vs. 8.1% males, $p = 0.93$). Sex differences were significant in the ICES population-level community (4.6% females vs. 4.4% males, $p < 0.001$) and nursing home databases (5.6% females vs. 4.4% males, $p < 0.001$). A similar pattern was evident for the Maccabi population-level community (7.0% vs. 6.7%, $p < 0.001$) and nursing home databases (8.5% vs. 6.9%, $p = 0.021$).

Table 3 describes polypharmacy, hyperpolypharmacy, and CCB and diuretic co-prescribing suggesting a prescribing cascade by gender-related sociocultural variable available from each database. Overall, three databases provided SES data, two based on income and one on educational attainment. Those categorized as being in the lower SES groups experienced polypharmacy or hyperpolypharmacy more frequently than those in the higher SES groups. Two databases (Report-AGE and SHELTER) provided marital status data. There was more polypharmacy or hyperpolypharmacy among those who were married in the Report-AGE geriatric hospital database and a nonsignificant trend for those who were married in the SHELTER database.

Co-prescribing suggesting a prescribing cascades was more common in the lower relative to the higher SES groups in the ICES community (7.0% vs. 4.2%, $p < 0.001$), Maccabi community (8.1% vs. 6.6%, $p < 0.001$), and ICES

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nursing home databases (6.8% vs. 4.8%, $p < 0.001$), with a nonsignificant trend in the Maccabi nursing home database (8.3% vs. 7.9%, $p = 0.57$) and SENATOR hospital database (11.4% vs. 8.5%, $p = 0.06$). No differences were apparent based on marital status.

Supplementary Figure S1 describes co-prescribing suggesting the CCB to diuretic prescribing cascade by sex and its intersections with age and SES using ICES and Maccabi community-dwelling population-level databases. The overall gender difference was small (Differential Prevalence [DP] 0.2% in ICES and 0.3% in Maccabi). The prevalence of co-prescribing suggesting a prescribing cascade increased across age groups ($p < 0.001$ with a trend test). Figure 1 illustrates that the largest difference was found in those aged 85 years and older (DP 2.1% in ICES and 3.7% in Maccabi) and in the lower SES groups (DP 1.6% in ICES and 1.8% in Maccabi). Further, the gender difference was largest for those aged 85 years of age or older in the lower SES group (DP 3.0% in ICES and 3.8% in Maccabi databases).

DISCUSSION

In this novel descriptive study, we examined polypharmacy and co-prescribing suggesting a prescribing cascade, two contributors to potentially inappropriate prescribing, by triangulating data from five diverse secondary databases, including older adults from 14 countries. We found consistent patterns across the different data types and sources, providing an opportunity to corroborate findings. As reported in the literature,[39,40] our study found that older women were more frequently in the lower SES category than older men,[41] based on income, SES clusters, or educational attainment. For educational attainment, almost 14% more older females than males reported only receiving primary school education. Additionally, women were more likely than men to be unmarried, mostly because they were widowed.[42] Overall polypharmacy, hyperpolypharmacy, and co-prescribing suggesting a prescribing cascade tended to be more frequent in the lower relative to the higher SES groups, a pattern seen across all databases. Lower SES has been associated with greater use of potentially inappropriate medications, possibly related to factors including less access to health and drug information, and in some cases to receiving inferior quality of health care.[43] Furthermore, those within the lower SES group are more likely to receive suboptimal combinations of drug therapies[44,45] and it is possible that some of these combinations may represent prescribing cascades.

Second, we found similar patterns of co-prescribing suggesting a CCB to diuretic prescribing cascade across databases when analyzing by age, sex, and gender-related sociocultural factors. Our results found that females were generally more impacted by co-prescribing, suggesting a higher prevalence of a CCB to diuretic prescribing cascade than in men. Furthermore, this impact was greatest among those females with multiple intersecting factors—specifically, those in the oldest age and lower SES group. By restricting our analyses to individuals with a pattern of co-prescribing suggesting a prescribing cascade, specifically those taking a CCB and a diuretic simultaneously, we created a more homogeneous group of individuals being treated for a single condition, likely hypertension.[34] Exploring a potential prescribing cascade using a more homogeneous group could reveal patterns that would otherwise be obscured when triangulating data from these diverse databases. Our findings warrant, we contend, further exploration of the association between age, sex, and gender-related sociocultural factors and other potential prescribing cascades.

Third, although age and sex data were available from all databases, none collected gender-identity data. Data on gender-related sociocultural factors were inconsistently collected. Our study demonstrates that some gender-related sociocultural factors can be explored in secondary databases by using available SES data based on income, SES clusters, or educational attainment, as well as exploring marital status. Future studies would greatly benefit from routinely collecting and including these and other gender-related variables in research.

Our study revealed a few unexpected findings when looking at polypharmacy and hyperpolypharmacy, that warrant further investigation. First, the prevalence of polypharmacy and hyperpolypharmacy was generally higher among men. The literature on this issue is inconclusive, where some studies suggest that women are prescribed more drug therapies than men,[46] whereas other studies report polypharmacy as being more common in men.[47,48] No sex difference for polypharmacy prevalence was found in the SENATOR clinical trial secondary database. This may be due to these individuals being part of a hospital-based research study where multimorbidity was an inclusion requirement. Future research should examine sex differences by drug classes contributing to polypharmacy. Prior research suggests that women are more likely to be prescribed drug therapy for the management of conditions like depression and sleep disorders, whereas men are more likely to be prescribed medications for secondary prevention of chronic conditions.[10]

Additionally, polypharmacy and hyperpolypharmacy were more frequent among married compared with unmarried individuals. Those who are married may be more likely to be encouraged by a spouse to seek needed care. This reflects the importance of distinguishing

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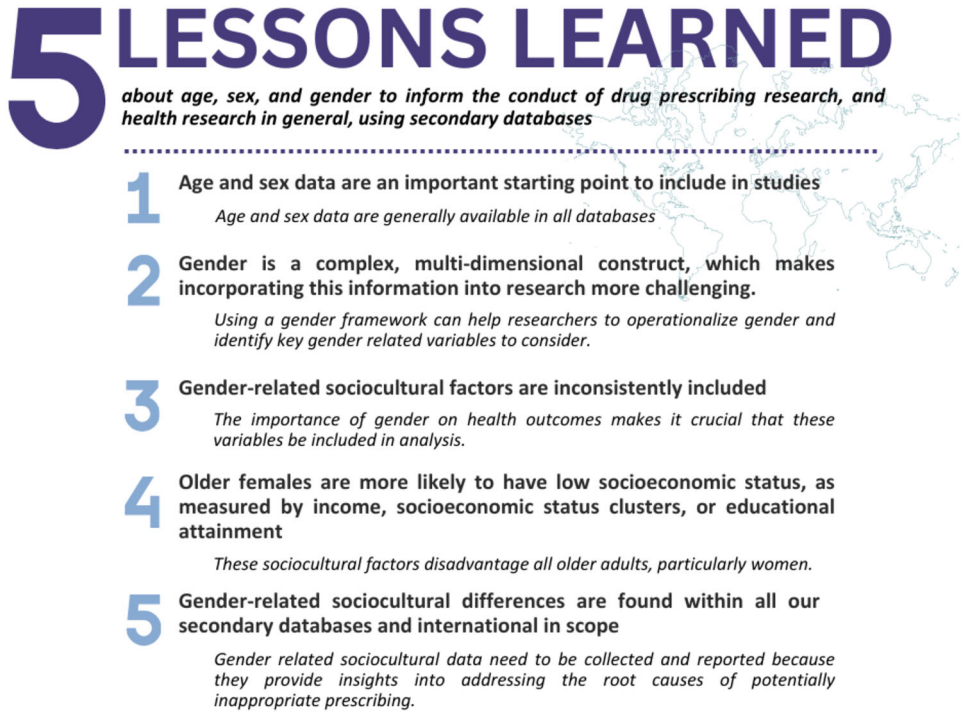


FIGURE 2 Five lessons learned about age, sex, and gender-related sociocultural variables to inform research.

appropriate polypharmacy, where individuals seek out health care and receive needed medications to manage health conditions, from problematic polypharmacy that can be harmful.[11]

LIMITATIONS

Although data triangulation provides the opportunity to corroborate findings and identify patterns from different data types and sources (thereby increasing the validity of results), there were some limitations. First, databases included were originally collected for different purposes and not designed to be compared or to explore gender-related sociocultural variables. Only a few variables were available to study the gender construct, limiting our ability to explore gender in a robust manner. The variables that we did identify have likely been routinely included in many databases, but not used within a gender framework. Nevertheless, the fact that common sex and gender-related patterns emerged from these diverse databases using these few gender-related sociocultural variables strengthens our findings. Our study highlights that even including a small subset of variables from the gender framework is helpful and underscores the importance of considering gender in more robust ways in future research. Second, observed differences could be due to overall differences in the health of females and males and their associated comorbidities. By exploring the CCB to diuretic prescribing cascade, we created a more homogeneous group of older adults likely being treated for hypertension. Although a prescribing cascade is generally characterized by sequential prescribing, determining this was not possible from the smaller databases. As such, we used co-prescribing as a crude indicator to suggest a prescribing cascade. Finally, gender-related sociocultural factors were not uniformly available. Nevertheless, the gender-related sociocultural factors of SES and marital status that were available across the databases followed a similar pattern.

We generated five lessons learned from triangulating data from these diverse databases. These lessons can inform our understanding of the genesis of polypharmacy and co-prescribing suggesting prescribing cascades, and they can assist researchers to explore age, sex, and gender in drug prescribing research and research in general (see Figure 2). First, analyzing age and sex data is an important starting point to be included in studies. As our study illustrates, age and sex data are routinely collected and therefore available in all databases. Second, gender is a complex, multidimensional construct, which makes incorporating this information into research challenging. Our study demonstrates some of these challenges. Using a gender framework, investigators can explore opportunities to include gender-related data from the outset of their study. Third, gender-related factors were inconsistently included. Given the importance of gender on health, it is crucial that investigators aim to include the appropriate variables in their research. We included SES, measured as income and educational attainment in our study, but

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there are many other variables in the gender framework that could be explored. Fourth, older females more frequently than males had low SES, as measured by income or educational attainment. Finally, these findings highlight the need to take account of gender-related sociocultural differences that were found within all secondary databases and were international in scope. These data are important because they may provide insights that are needed to address the root causes of potentially inappropriate prescribing.

CONCLUSION

By triangulating data from five diverse secondary databases using descriptive statistics, we found that older females were adversely affected by sociocultural factors more frequently than older males. Further, older adults with lower SES tended to more frequently experience polypharmacy or co-prescribing suggesting a CCB to diuretic prescribing cascade. Within these lower SES groups, females had evidence of this co-prescribing more frequently than males.

Considering the role of gender and profiling their differences provides an opportunity for more targeted approaches to optimize prescribing. Furthermore, it may help to better understand the genesis of polypharmacy and potential prescribing cascades. These findings have important research applications highlighted in our five lessons learned that can be used to optimize drug prescribing research and more generally improve the quality of health research, using secondary databases.

AUTHOR CONTRIBUTIONS

PAR, JL, DOM, GO, MP, SAS, JHG, RS, WW, VG, LMG, AC made a substantial contribution to the concept of the article. PAR, DOM, GO, SAS, AC were involved in the acquisition of data. All authors were involved in the interpretation of data. PAR drafted the manuscript. All authors critically assessed, edited, and approved the final manuscript. JL created the figures in the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PAR is the guarantor.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of financial interest that are directly relevant to the content of this study. Dr. Rochon is a Deputy Editor for the Journal of the American Geriatrics Society.

SPONSOR'S ROLE

The sponsor was not involved in the design, methods, subject recruitment, data collection, analysis, or preparation of the manuscript.

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ORCID

Paula A. Rochon https://orcid.org/0000-0002-5973-4151
Joyce Li https://orcid.org/0000-0001-8112-2701
Mirko Petrovic https://orcid.org/0000-0002-7506-8646
Rachel D. Savage https://orcid.org/0000-0002-2746-373X
Kieran Dalton https://orcid.org/0000-0003-1209-8079
Lisa M. McCarthy https://orcid.org/0000-0001-9087-1077

TWITTER

Paula A. Rochon *rochonpaula*

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. Checklist of items that should be included in reports of descriptive studies.
Table S2. Description of the secondary databases providing drug prescribing data on adults 65 years of age or older.
Table S3. Description of the gender-related sociocultural variables from each secondary database using the Canadian Institutes of Health Research Framework.
Table S4. Definition of the medication included in each database.
Table S5. Description of the age, sex and gender-related sociocultural factors among older adults in five secondary databases by sex.
Figure S1. Prevalence of calcium channel blocker to diuretic co-prescribing suggesting a prescribing cascade in older adults disaggregated by sex, age, socioeconomic status, and their intersections.

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