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Exploring the associations between polypharmacy and COVID-19-related hospitalisations and deaths: a population-based cohort study among older adults in Quebec, Canada

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ABSTRACT

Objectives To study the association between polypharmacy and the risk of hospitalisation and death in cases of COVID-19 in the population over the age of 65.

Design Population-based cohort study.

Setting Quebec Integrated Chronic Disease Surveillance System, composed of five medico-administrative databases, in the province of Quebec, Canada.

Participants 32 476 COVID-19 cases aged over 65 whose diagnosis was made between 23 February 2020 and 15 March 2021, and who were covered by the public drug insurance plan (thus excluding those living in long-term care). We counted the number of different medications they claimed between 1 April 2019 and 31 March 2020.

Outcome measures Robust Poisson regression was used to calculate relative risk of hospitalisation and death associated with the use of multiple medications, adjusting for age, sex, chronic conditions, material and social deprivation and living environment.

Results Of the 32 476 COVID-19 cases included, 10 350 (32%) were hospitalised and 4146 (13%) died. Compared with 0–4 medications, polypharmacy exposure was associated with increased hospitalisations, with relative risks ranging from 1.11 (95% CI 1.04 to 1.19) for those using 5–9 medications to 1.62 (95% CI 1.51 to 1.75) for those using 20+. Similarly, the risk of death increased with the number of medications, from 1.13 (95% CI 0.99 to 1.30) for those using (5–9 medications to 1.97 (95% CI 1.70 to 2.27) (20+). Increased risk was mainly observed in younger groups.

Conclusions Polypharmacy was significantly associated with the risk of hospitalisations and deaths related to COVID-19 in this cohort of older adults. Polypharmacy may represent a marker of vulnerability, especially for younger groups of older adults.

Strengths and limitations of this study

- This is a large epidemiological study performed with population-based data, including all hospitalisations and deaths that occurred in the first two waves of the pandemic among older adults in Quebec who were not living in long-term care.
- Generalisation to other regions and subsequent waves of COVID-19 should be done with caution.
- Administrative data do not provide clinical information, such as COVID-19 disease severity and long-term sequelae, severity of chronic conditions or indications for medication use.
- Misclassification of hospitalisations and deaths attributable to COVID-19, as well as misclassification of living environment may have occurred.

INTRODUCTION

In the first two waves of COVID-19, the individuals most affected by the disease and its complications were older adults, as well as those with chronic diseases such as hypertension, diabetes, cardiovascular disease, chronic respiratory diseases or cancer.[1–3] These comorbidities often involve the use of several concomitant medications called polypharmacy.[4 5] Being exposed to many medications can be a sign of the severity of the diseases present but can also lead to an increased risk of drug–drug interactions and adverse events,[6–8] making patients potentially more vulnerable to complications in general and in the context of the COVID-19.

A limited number of studies have investigated the association between polypharmacy and COVID-19.[9–15] In a systematic review, Iloanusi *et al*[16] reported that in five out of seven studies, polypharmacy was associated with negative clinical outcomes, such as acute kidney injuries[9] or adverse drug reactions.[10] One of these studies showed that there was a dose relationship between the level of polypharmacy and having a COVID-19 positive test.[11] Mortality was increased among males with polypharmacy in a study conducted in Spain,[12] whereas two studies conducted

among patients hospitalised with COVID-19 showed no associations between polypharmacy and death.[13 14] It remains unclear if polypharmacy is independently associated with COVID-19 hospitalisation and mortality, or it is driven by the presence of other risk factors in patients with polypharmacy such as older age and chronic diseases. Also, some studies were limited to hospitalised patients and as such their results cannot be generalised to individuals from the community.[9 10 13 14] We, thus, propose to evaluate the association between the number of medications and the risk of death and hospitalisation in confirmed cases of COVID-19 in the population older than 65 years of age in Quebec, Canada, adjusting for age and chronic conditions.

METHODS

Data sources and study population

We constructed a cohort that included all individuals aged over 65 years who had a confirmed diagnosis of COVID-19 between 23 February 2020 and 15 March 2021 (a time window covering waves 1 and 2 of COVID-19). The COVID-19 diagnosis and related-death were retrieved from the information system database Trajectoire de santé publique (TSP), from the Ministère de la Santé et des Services sociaux, where records of every case of SARS-CoV-2 infection are entered by regional public health departments since February 2020. We excluded individuals who were not covered by the public drug insurance plan of the province of Québec in the study period (ie, those with private insurance or living in long term care). Hence, all individuals with a COVID-19 diagnosis who were covered by the public drug insurance plan were included and there was no lost to follow-up.

We gathered other data from the Quebec Integrated Chronic Disease Surveillance System (QICDSS), developed by the Institut national de santé publique du Québec (INSPQ). The QICDSS is composed of five administrative databases: healthcare registration plan, physician services, hospitalisation data (Med-Écho), pharmaceutical services and death registry.[17] The physician services and hospitalisation databases provide diagnostic codes using the 9th revision of the International Classification of Diseases (ICD-9) and the 10th revision (ICD-10), respectively. The pharmaceutical database includes data on each dispensation of medication, including the medication name and dose, the dispensing date and the number of days' supply. The provincial health plan covers 99% of the population, while the public drug plan covers 90% of individuals aged 65 years and over.[17] Individuals in long-term care and those covered by private insurance are not covered by the public drug plan. Demographic data in the database include age, sex and validated neighborhood-level material and social deprivation index scores.[18] The living environment was determined from data retrieved from the TSP and the QICDSS.

Variables

Polypharmacy

We defined medication use based on a count of the medications claimed in the 2019 fiscal year (1 April 2019 to 31 March 2020). We used the common denomination (chemical name) of the medication. As there is no standard definition of polypharmacy,[5] we stratified the use of medications into frequency categories (0–4, 5–9, etc). As the most common threshold for polypharmacy is set at five medications,[4 5] we used the 0–4 category as the reference group in our analyses.

Outcomes: hospitalisations and deaths

For each individual, we documented the presence of a hospitalisation and/or of a death attributable to COVID-19. A COVID-19 hospitalisation was defined as a hospital stay of at least 1 day for which a COVID-19 diagnosis code (ICD-10-CA U07.1)[19] was recorded in the Med-Écho database. Hospital stays that were primarily related to psychiatry, rehabilitation, accommodation or long-term care were excluded. A death was defined as COVID-19 related if the disease contributed directly or indirectly to the death, according to the evaluation of the public health department. The date of death and the contribution of COVID-19 were reported by regional public health departments (Direction de santé publique) as part of epidemiological investigations and validated with the forms filled in by the physicians after death. Individuals who had both a COVID-19 hospitalisation and death were included in both the hospitalisation and death analyses.

Covariates

Covariates included sex, age, material and social deprivation index, living environments and number of chronic conditions. Sex was dichotomised as male and female, as the variable available in the database does not provide other options, and gender is not documented. Age was calculated as the difference between the date of COVID-19 diagnosis and the date of birth and categorised into four groups: (66–69, 70–74, 75–79 and 80+ years). Material and social deprivation were measured in quintiles, according to the index used in the QICDSS. The index is an ecological substitute based on postal code which estimates material deprivation (according to employment, educational attainment and income of the area) and social deprivation (proportion of single-parent families and individuals living alone).[18] The living environments were grouped into three categories: home, private seniors' residence (*résidence privée pour aînés, RPA*), and intermediate facility (resource intermédiaire, RI). We measured the number of chronic conditions using count of 21 groups of conditions of the Combined Comorbidity Index, previously validated in the QICDSS.[20] The conditions included chronic diseases (and their risk factors, associated conditions or symptoms), that were potential risk factors for complications with COVID-19[3] or other respiratory infections such as influenza.[21] At least one diagnostic code (primary or secondary) had to be recorded in Med-Écho or at least two diagnostic codes had to be recorded in the fee-for-service medical services file within 2 years, with at least 30 days between each

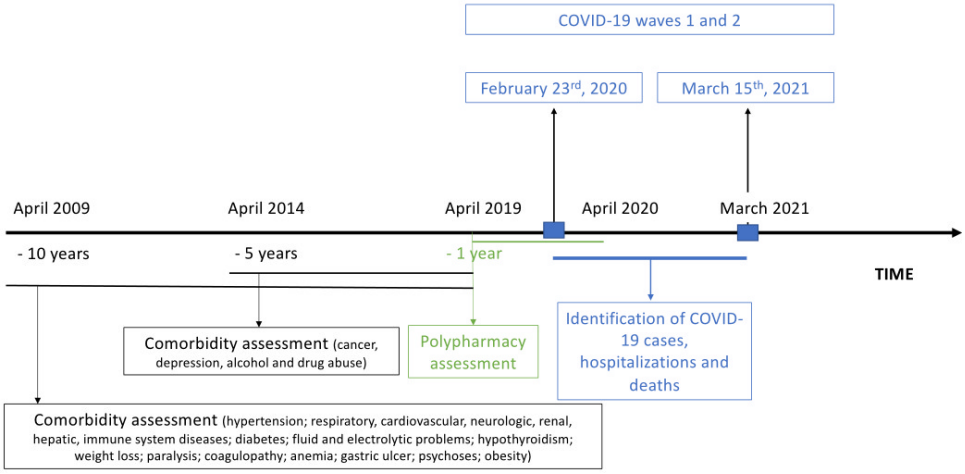

Figure 1 Graphical depiction of study design. To be considered as a condition, at least one diagnostic code (primary or secondary) had to be recorded in Med-Écho or at least two diagnostic codes had to recorded in the fee-for-service medical services file within 2 years, with at least 30 days between each diagnostic code. Polypharmacy was assessed using the count of the different medications claimed in the period between April 2019 and March 2020.

diagnostic code.[20 22] We looked for diagnoses in the previous 10 years (between 1 April 2009 and 31 March 2019) for 17 conditions: hypertension, respiratory diseases, cardiovascular diseases, diabetes, neurologic diseases, renal diseases, hepatic diseases, immune system diseases, fluid and electrolytic problems, hypothyroidism, weight loss, paralysis, coagulopathy, anaemia, gastric ulcer, psychoses and obesity. For the other four conditions, that is, cancer (with or without metastasis), depression, alcohol abuse, and drug abuse, the search for diagnosis codes was carried out with data from the previous 5 years (from April 2014 to 31 March 2019). Figure 1 illustrates the time frame of the study and periods where the variables were collected.

Statistical analysis

We calculated descriptive statistics for the study population according to the outcomes of COVID-19 infection (hospitalisation and death). We used robust Poisson regression to explore the association between the use of medications and hospitalisation and death and provided the respective relative risks with their 95% CIs. We incorporated and retained all covariates in the model. Furthermore, since we suspected the impact of polypharmacy may be modified by age, we performed stratified analyses according to age groups. Finally, as a sensitivity analysis, we conducted the analyses adding the individuals who died before March 2020 (and therefore did not have a complete year of medication insurance coverage to calculate their polypharmacy exposure). We also performed the analysis using the total number of medications used as a continuous variable.

Patients and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

Between 23 February 2020 and 15 March 2021, 51 682 cases of COVID-19 infections were reported among adults older than 65 years in Québec. After excluding individuals living in long-term care (n=15 707) and those not covered by the public drug plan for the entire year (n=3499), a total of 32 476 cases were included in the analyses. Their mean (median) age was 79.6 (79.0) years and 57.7% were women (table 1). Among the studied population, only 17.0% (n=5523) were not exposed to polypharmacy, that is, the individuals used between 0 and 4 medications in the year before the COVID-19 diagnosis. A total of 10 350 (31.9%) cases were hospitalised and 4146 (12.8%) died.

An increased number of medications used in the previous year was associated with a higher risk of complications from COVID-19 (table 2). Compared with people using 0–4 medications, the risk of hospitalisation increased steadily with polypharmacy exposure, from an adjusted RR (aRR) of 1.11 (95% CI 1.04 to 1.19) for those using 5–9 medications to an aRR of 1.62 (95% CI 1.51 to 1.75) for those using 20 medications and more. Similarly, the aRR of death increased from 1.13 (95% CI 0.99 to 1.30) for those using 5–9 medications to 1.97 (95% CI 1.70 to 2.27) for those using 20 medications and more.

Increased age and larger number of chronic diseases were associated with increased risk of both hospitalisation and mortality (table 2). The risk of both events was also increased for men compared with women, whereas the hospitalisation risk was decreased among those living in private senior residencies (0.82; 95% CI 0.79 to 0.85) and intermediate facilities (0.80; 95% CI 0.75 to 0.85) as compared with those living at home.

The stratification by age revealed that the increase in risk with polypharmacy was mainly observed in groups of younger individuals (figure 2, online supplemental table 1). In the 66–69 years group, for example, the aRR of death for those using 5–9 medications was 1.91 (95%

Table 1 Characteristics of cases of COVID-19 according to their outcomes, in older adults in Quebec, Canada, during the first and second waves (23 February 2020 to 15 March 2021)

Characteristics	All cases (N=32 476)	Outcomes of COVID-19 infection*		
		Cases not hospitalised, not dead (N=20 973)	Cases hospitalised (N=10 350)	Cases dead (N=4146)
Age (year) mean±SD	79.59±8.87	78.31±8.81	81.38±8.40	84.73±8.18
Age group (year)—no (%)				
66–69	5207 (16.03)	4199 (20.02)	974 (9.41)	171 (4.12)
70–74	6096 (18.77)	4478 (21.35)	1562 (15.09)	395 (9.53)
75–59	5470 (16.84)	3493 (16.65)	1870 (18.07)	556 (13.41)
80+	15 703 (48.35)	8803 (41.97)	5944 (57.43)	3024 (72.94)
Sex—no (%)				
Male	13 738 (42.30)	8205 (39.12)	5050 (48.79)	2095 (50.53)
Female	18 738 (57.70)	12 768 (60.88)	5300 (51.21)	2051 (49.47)
No conditions, mean±SD	3.34±2.61	2.82±2.37	4.25±2.75	4.87±2.73
No conditions—no (%)				
0	3584 (11.04)	3008 (14.34)	551 (5.32)	126 (3.04)
1	5928 (18.25)	4556 (21.72)	1275 (12.32)	347 (8.37)
2	5438 (16.74)	3896 (18.58)	1409 (13.61)	461 (11.12)
3	4283 (13.19)	2788 (13.29)	1366 (13.20)	479 (11.55)
≥4	13 243 (40.78)	6725 (32.07)	5749 (55.55)	2733 (65.92)
Material deprivation—no (%)				
1 (least deprived)	4431 (13.64)	2888 (13.77)	1410 (13.62)	526 (12.69)
2	4369 (13.45)	2883 (13.75)	1339 (12.94)	517 (12.47)
3	4811 (14.81)	3125 (14.90)	1543 (14.91)	580 (13.99)
4	5555 (17.10)	3708 (17.68)	1698 (16.41)	610 (14.71)
5 (Most deprived)	6038 (18.59)	3910 (18.64)	1985 (19.18)	667 (16.09)
Missing data	7272 (22.39)	4459 (21.26)	2375 (22.95)	1246 (30.05)
Social deprivation—no (%)				
1 (least deprived)	3834 (11.81)	2649 (12.63)	1070 (10.34)	395 (9.53)
2	4296 (13.23)	2967 (14.15)	1201 (11.60)	454 (10.95)
3	4732 (14.57)	3176 (15.14)	1441 (13.92)	509 (12.28)
4	5730 (17.64)	3622 (17.27)	1968 (19.01)	690 (16.64)
5 (most deprived)	6612 (20.36)	4100 (19.55)	2295 (22.17)	852 (20.55)
Missing data	7272 (22.39)	4459 (21.26)	2375 (22.95)	1246 (30.05)
Living environments—no (%)				
Home	18 422 (56.72)	12 544 (59.81)	5587 (53.98)	1618 (39.03)
Private senior residency	11 591 (35.69)	6953 (33.15)	3970 (38.36)	2073 (50.00)
Intermediate facility	2463 (7.58)	1476 (7.04)	793 (7.66)	455 (10.97)
No. medications used in past year—no (%)				
0–4	5523 (17.01)	4388 (20.92)	1064 (10.28)	276 (6.66)
5–9	9579 (29.50)	6796 (32.40)	2545 (24.59)	853 (20.57)
10–14	8619 (26.54)	5477 (26.11)	2813 (27.18)	1173 (28.29)
15–19	5009 (15.42)	2686 (12.81)	2037 (19.68)	942 (22.72)
20+	3746 (11.53)	1626 (7.75)	1891 (18.27)	902 (21.76)

*Some individuals had both outcomes (hospitalisation and death), which explains why the total of 'cases not hospitalised, not dead +cases hospitalised +cases dead' does not equal the total number of cases. From the 4146 deaths, 2993 occurred among hospitalised cases. From the 1153 other deaths, 668 were in private senior residences, 194 in intermediate facilities and 291 at home.

Table 2 Adjusted relative risks of COVID-19-related hospitalisations and death according to the number of medications used among older adults in Quebec, Canada

	Hospitalisations	Deaths
	aRR (95% CI)	aRR (95% CI)
No of medications used in past year		
0–4	Ref	Ref
5–9	1.11 (1.04 to 1.19)	1.13 (0.99 to 1.30)
10–14	1.19 (1.11 to 1.27)	1.30 (1.13 to 1.50)
15–19	1.36 (1.27 to 1.46)	1.57 (1.36 to 1.82)
20+	1.62 (1.51 to 1.75)	1.97 (1.70 to 2.27)
Age group (year)		
66–69	Ref	Ref
70–74	1.28 (1.19 to 1.37)	1.73 (1.46 to 2.06)
75–59	1.59 (1.48 to 1.70)	2.28 (1.93 to 2.70)
80+	1.80 (1.69 to 1.92)	3.94 (3.36 to 4.63)
Sex		
Female	Ref	Ref
Male	1.36 (1.32 to 1.40)	1.68 (1.59 to 1.78)
No of conditions		
0	Ref	Ref
1	1.27 (1.16 to 1.40)	1.30 (1.07 to 1.59)
2	1.43 (1.30 to 1.57)	1.56 (1.28 to 1.91)
3	1.66 (1.51 to 1.83)	1.77 (1.44 to 2.17)
≥4	2.02 (1.85 to 2.21)	2.52 (2.08 to 3.06)
Material deprivation		
1 (least deprived)	Ref	Ref
2	0.96 (0.90 to 1.02)	0.98 (0.88 to 1.10)
3	0.99 (0.94 to 1.05)	0.99 (0.89 to 1.10)
4	0.95 (0.89 to 1.00)	0.92 (0.83 to 1.02)
5 (most deprived)	1.00 (0.95 to 1.06)	0.94 (0.85 to 1.04)
Social deprivation		
1 (least deprived)	Ref	Ref
2	0.98 (0.91 to 1.04)	0.95 (0.84 to 1.07)
3	1.05 (0.99 to 1.12)	0.95 (0.85 to 1.08)
4	1.16 (1.09 to 1.23)	1.02 (0.91 to 1.14)
5 (most deprived)	1.16 (1.10 to 1.23)	1.04 (0.93 to 1.16)
Living environments		
Home	Ref	Ref
Private senior residency	0.82 (0.79 to 0.85)	1.12 (1.05 to 1.20)
Intermediate facility	0.80 (0.75 to 0.85)	1.29 (1.17 to 1.42)

aRR, adjusted RR.

CI 1.07 to 3.39) but reached 8.80 (95% CI 5.09 to 15.22) for those using 20 medications and more. On the other hand, among the 80+ year group, the aRRs remained non-statistically and clinically significant until medication exposure reached highest levels (15–19 medications: 1.24 (95% CI 1.06 to 1.46); 20+ medications: 1.38 (95% CI 1.17 to 1.63)). Similar observations were noted for the hospitalisation risk, although the point estimates were not as elevated.

The results from the sensitivity analysis including the 23 individuals who died before the end of the polypharmacy exposure period were similar to the main analyses (online supplemental table 2). The analysis using the number of medications as a continuous variable revealed that for each additional medication, the adjusted risk of hospitalisation increased by 2.2% and by 3.2% for death (online supplemental table 3). As in the main analysis, the risk associated with the number of medications decreased with increasing age (online supplemental table 3).

DISCUSSION

Our results suggest that polypharmacy was associated with increased risk of COVID-19 complications among older adults in Quebec during the first two waves of the pandemic, even after adjustment for major risks factors such as age and chronic diseases.

Two main hypotheses may explain why polypharmacy may be associated with a grimmer prognosis. First, polypharmacy may be a marker of frailty and of disease severity. Polypharmacy is intimately intricated with frailty, both as a cause and a consequence,[23] suggesting that the individuals may present a distinct vulnerability when they are exposed to polypharmacy. Similarly, the individuals using higher level of polypharmacy may suffer from more severe conditions and/or have conditions that were not included in the set of variables we studied, or that were not captured in our database. Recent studies have shown that multimorbidity[24 25] and polypharmacy[9 10 12] may both be associated with negative outcomes from COVID-19. Our study suggests that both multimorbidity and polypharmacy should be taken into account when estimating the risk of severe outcomes of COVID-19, as both factors were associated with increased risks. The second hypothesis that may explain the increased risk associated with polypharmacy is the fact that using many medications may create iatrogenic risks that lead to unfavourable consequences. Indeed, the presence of side effects and drug-drug interactions may increase the individuals' vulnerability to outcomes of COVID-19. Of note, we could not study medications that were dispensed in the hospital, but it is possible that those medications interacted with the usual polypharmacy.[26] For example, Cantudo-Cuenca *et al* have described many potent interactions, such as those involving QT prolongation, that may threaten life.[26] There is thus a genuine concern that polypharmacy may favour a potential ground for medication-related harms. Interestingly though, the fact that the impact of polypharmacy was weaker in the groups of older adults in our study may favour the first hypothesis, that is, frailty and/or severity of diseases could play a larger role in the observed impact of polypharmacy. Indeed, since older adults are in general more susceptible than the younger ones to side effects and drug-drug interactions, one could expect that the risk associated with polypharmacy would be higher in the older groups if the iatrogenic risk was at stake.

Further research is needed to disentangle the effects of medications from the ones of conditions affecting the individuals using polypharmacy. Apart from the number, the

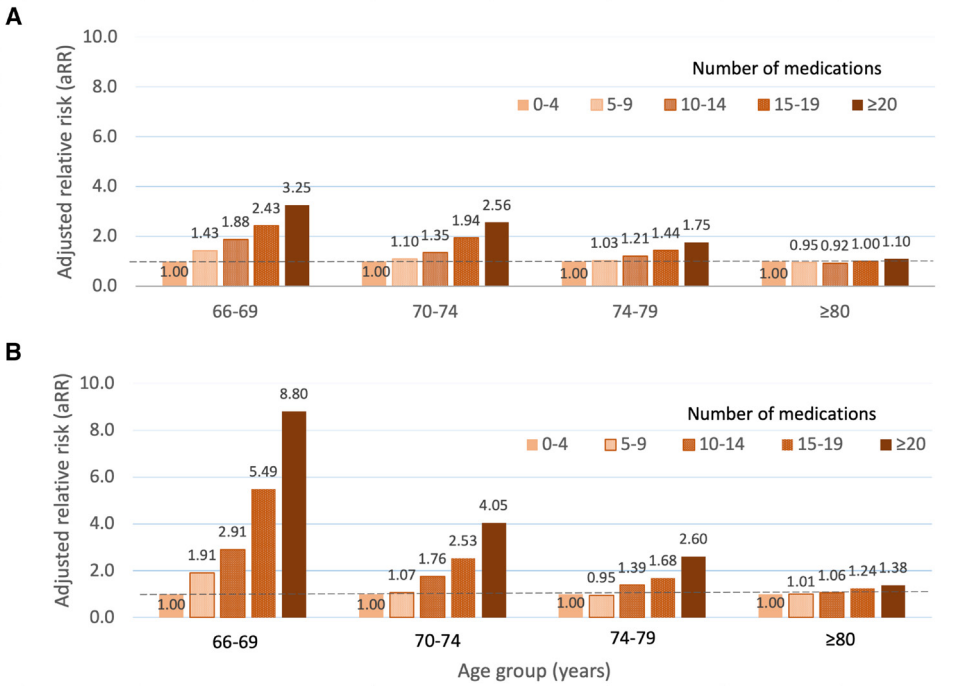

Figure 2 Stratified analyses by age group. The figure presents aRR of hospitalisation (A) and death (B) according to the number of medications used in the year preceding COVID-19 pandemic. The results are presented according to age groups, and are adjusted for sex, living environments, material and social deprivation index and number of chronic conditions. The dotted line represents the null value (aRR=1). Complete results with CIs are presented in online supplemental table 1.

type of medications (and the respective conditions that are treated) could be further explored, to help determine the role of those potential contributors to the negative impacts that were observed. Also, considering that age plays a modifier role in the relation between polypharmacy and hospitalisations and deaths, it would be relevant to study more in depth the role of age, particularly for the individuals under the age of 65. There is also an interest to explore whether polypharmacy may be associated with other sequalae, such as consequences of long COVID-19.

Considering the vulnerability of people residing in private senior residencies and intermediate facilities, the reduced hospitalisation risk observed among them may seem intriguing. The counterintuitive protective effect is most likely artificial: the limited knowledge of the clinical picture of a new disease with rapid deterioration in older adults, as well as government policy of restrictions of transfers to acute-care hospitals may have prevented timely transfers, especially during first COVID-19 wave.

The study was performed with population-based data, including all hospitalisations and deaths that occurred in the first two waves of the pandemic among older adults in Quebec who were not living in long-term care. With a high number of cases, we were notably able to perform subgroup analyses with adequate power. However, there are limitations. First, we did not have access to clinical data, which precluded us to study the severity of COVID-19 disease, the severity of chronic conditions, the health state (eg, frailty, sarcopenia, malnutrition), and the indications for medication use. Similarly, we did not assess the specific pharmacological regimen and potential drug–drug interactions. Since we studied medications from the year before COVID-19 pandemic, there may have been changes in the therapy during the studied year, and some of the medications may no longer have been used, or other added. Limitations due to the use of administrative data also comprise the possible misclassification of hospitalisations and deaths attributable to COVID-19, as well as misclassification of living environment. Nevertheless, the misclassification is likely to be non-differential and therefore would underestimate the associations. For most of the period included in this study, COVID-19 vaccines were not available in the province of Quebec. Vaccination in private seniors' residences and intermediate facilities started in January 2021. By the end of the study (15 March 2021), 86% of residents were vaccinated, while vaccination of people over 60 years in the community was in the early phases of deployment (https://www.inspq.qc.ca/COVID-19/donnees/vaccination). During most of the study period, the ancestral SARS-CoV-2 variant circulated, with an onset of detection of the alpha variant during last 2 months (February–March 2021, https://www.inspq.qc.ca/COVID-19/donnees/variants#evo). However, we do not believe that our conclusion is invalidated by these factors because polypharmacy is not expected to be associated with COVID-19 vaccination or with a specific variant. Nonetheless, generalisation to other regions and subsequent waves of COVID-19 should be done with caution.

CONCLUSION

Polypharmacy was associated with an increased risk of hospitalisation and mortality in older adults who contracted COVID-19 in the first two waves of the pandemic, even after

adjusting for age and the presence of chronic diseases. Polypharmacy, thus, appears to be an important vulnerability marker. Future research is needed to explore which part of the associations results from the consequence of the severity of the diseases that have conditioned the use of several medications, and which part is the result of iatrogenic risks specific to the medications used.

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Contributors CS and MS designed the study. VB performed the statistical analysis. CS drafted the manuscript. CS, VB, MS, YC, RG and MS interpreted the results, critically reviewed and edited the manuscript, approved the final version and agreed to be accountable for all aspects of the work. CS is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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