Association of polypharmacy with one-year trajectories of cognitive and physical function in nursing home residents: results from a multicentre European study

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Abstract

Objectives: To test the association between polypharmacy and 1-year change in physical and cognitive function among nursing home (NH) residents.

Design: Longitudinal multicentre cohort study based on data from the Services and Health for Elderly in Long TERm care (SHELTER) study.

Setting: NH in Europe (n=50) and Israel (n=7).

Participants: 3234 NH older residents.

Measurements: Participants were assessed through the interRAI long-term care facility (LTCF) instrument. Polypharmacy was defined as the concurrent use of 5-9 drugs and excessive polypharmacy as the use of ≥10 drugs. Cognitive function was assessed through the Cognitive Performance Scale (CPS). Functional status was evaluated through the Activities of Daily Living (ADL) Hierarchy scale. The change in CPS and ADL score, based on repeated assessments, was the outcome and their association with polypharmacy was modelled via linear mixed models. The interaction between polypharmacy and time was reported (beta and 95% confidence intervals [95%CI]).

Results: 1630 (50%) residents were on polypharmacy and 781 (24%) on excessive polypharmacy. After adjusting for potential confounders, residents on polypharmacy (beta 0.10; 95%CI 0.01-0.20) and those on excessive polypharmacy (beta 0.13; 95%CI 0.01-0.24) had a significantly higher decline in CPS score as compared with those using <5 drugs. No significant change according to polypharmacy status was shown for ADL score.

Conclusions: Polypharmacy is highly prevalent among older NH residents and, over one year, is associated to worsening cognitive function, but not with functional decline.

Introduction

In Western Countries, 1.5% to 8% of older adults live in nursing homes (NH) (1). This population presents with an high prevalence of multimorbidity, geriatric syndromes, frailty and disability (2). The clinical complexity of these individuals, and their management, is further complicated by the use of multiple drugs, a condition known as polypharmacy (3).

Polypharmacy is frequent in NH residents, with prevalence ranging between 13% and 93% (4), and it exposes NH residents to an increased risk of iatrogenic events, unplanned hospitalizations and geriatric syndromes (e.g. delirium) (5,6). In cross-sectional studies, a high pharmacological burden has been associated with cognitive and physical function, two of the most important health indicators in older adults (7,8).

The relationship between polypharmacy and negative health outcomes may be bidirectional. On one hand, multiple chronic conditions and syndromes call for complex pharmacological regimens (9). On the other hand, polypharmacy increases the risk of negative drug interactions and adverse drug events, leading to the development of negative health outcomes (10). Therefore, to better explore the hypothesis of a relationship between polypharmacy and negative health outcomes, longitudinal studies are needed. The aim of the present study was to investigate the association between polypharmacy and 1-year change in physical and cognitive function in NH residents.

Methods

Study population. This is a multicentre cohort study based on data from the Services and Health for Elderly in Long Term care (SHELTER) study. SHELTER includes information on 4156 NH residents from 50 European facilities (10 in Czech Republic, 9 in England, 4 in Finland, 4 in France, 9 in Germany, 10 in Italy and 4 in Netherlands) and from 7 facilities in Israel. All the NH residents admitted to the participant facilities before the beginning of the study were included. Also, those admitted within the three following months entered the study. From the initial sample, we excluded 808 participants because they had less than 2 time-point evaluations (including baseline) and 114 participants because data on drug use were missing, leaving a study population of 3234 NH residents.

All participants were evaluated through the interRAI-LTCF assessment tool at time zero and after three, six and twelve months. Participants were followed-up until either the end of the study, their drop-out from the study or death. Completeness in drafting the current short report was assessed via the STROBE checklist. The research protocol was approved by the relevant institutional review boards and written consent was obtained from all participants.

Drug use and polypharmacy. As part of the InterRAI LTCF assessment, information on all the drugs the participants had been taking in the 3 days prior to the evaluation was collected. Drug data was taken from different information sources, including physician order sheets and drug administration records. Drug information was collected according to the Anatomical Therapeutic and Chemical codes. Drugs with no ingredients that are absorbed systemically (e.g. topical treatments) and rescue drugs and assumed in the 3 days prior to the assessment were also recorded. Polypharmacy was defined as the concurrent use of 5-9 drugs and excessive polypharmacy as the use of ≥10 drugs.

Cognitive and physical function. Cognitive function was assessed through the Cognitive Performance Scale (CPS), included in the InterRAI LTCF. CPS combines information on memory impairment, level of consciousness and executive function, with scores ranging from 0 (intact) to 6 (very severe impairment) and has been shown to be highly correlated with the Mini Mental State Examination (MMSE) in a number of validation studies (11). To evaluate functional status, the seven-point MDS Activities of Daily Living (ADL) Hierarchy scale was used (12). The ADL Hierarchy scale ranges from 0 (no impairment) to 6 (total dependence). Changes in CPS and ADL Hierarchy scale scores, based on repeated assessments, were considered the outcomes of the present study.

Covariates. Information on participants' sex and age at baseline was retrieved from the InterRAI LTCF questionnaire. Information on the following chronic conditions has been also collected: heart failure, ischemic heart disease, Parkinson's disease, stroke, diabetes, cancer, and dementia. Pain was defined as any pain of moderate or severe intensity presented during the last three days. Dyspnoea was defined as the presence of shortness of breath during the last three days. Depressive symptoms were considered as present for Depression Rating Scale (DRS) scores >2 (range 0-14).

Statistical approach. The association between polypharmacy and cognitive and physical function was tested trough multilevel mixed-effect linear regression models, considering the clustering of the observations within participants and within facilities, and adjusting for potential confounders. The beta coefficients and 95% confidence intervals (95%CI) for the interaction between polypharmacy and time (factor*time) were reported. Sensitivity analyses were run excluding participants dying and dropping-out during the follow-up. Stata 14 (Stata Corp) for Windows was used for all the analyses.

Results

At baseline, the mean age of the sample was 83.4 years, with no significant difference by polypharmacy status. Overall, 1630 (50%) were taking 5-9 drugs and 781 (24%) were taking ≥10 drugs. Median follow-up period was 0.95 years [IQR 0.75-1.1]. Among participants, 493 (15%) died during the follow-up and 172 (7%) were transferred to another institution, hospitalized or discharged to home. The characteristics of participating residents according to their polypharmacy status are presented in **table 1**. At the univariate analysis, severity of cognitive impairment and functional impairment were inversely associated with polypharmacy status, with residents in the <5 drugs group having the highest level of cognitive and functional impairment. At the same time, prevalence of ischemic heart disease, heart failure, stroke, Parkinson's disease, dementia, diabetes, cancer and symptoms such as pain, dyspnoea and depressive symptoms, progressively increased with polypharmacy status. **Table 2** shows the association between polypharmacy and cognitive (CPS scale) and physical (ADL scale score) function. After adjusting for potential confounders, residents using 5-9 drugs (beta coefficient 0.10; 95%CI 0.01-0.20) and those using ≥10 drugs (beta coefficient 0.13; 95%CI 0.01-0.24) had a significantly higher decline in CPS score as compared with those using <5 drugs. No significant change according to polypharmacy status was shown in ADLs. Similar results were obtained after excluding those dying or dropping out during follow-up (data not shown).

Discussion

According to this multicentre prospective study, polypharmacy is associated with worse trajectories of cognitive decline – but not functional decline – over one year, in older NH residents. To the best of

our knowledge, this is the first study showing a longitudinal association between polypharmacy and cognitive decline in such population.

Several cross-sectional studies have investigated the association between polypharmacy and cognitive impairment, though contrasting. For example, a Japanese study involving 1152 community-dwelling participants showed that those on polypharmacy presented 80% increased likelihood to have a worse global cognitive performance, as measured through the MMSE, than those not on polypharmacy (13). On the other hand, in the SHELTER population, our group previously described an inverse cross-sectional association between polypharmacy and cognitive impairment (14). Such results do not allow any strong speculation on the nature of the association, and confounding by indication bias may explain the reported negative association.

In the present study, we found a selective, longitudinal, and dose-response association between the use of multiple drugs and cognitive impairment. Several potential mechanisms may explain our results. First, several drugs frequently prescribed in institutionalized older people present anticholinergic properties (e.g. antipsychotics, antiulcer drugs etc.).The negative impact of anticholinergics on cognitive function has been consistently demonstrated in the literature (15,16). The use of these drug classes is considered a potential modifiable risk factor for cognitive impairment and dementia in older adults. Second, use of psychotropic drugs is a well-known risk factor for cognitive decline and dementia. A terrific prevalence of psychotropic drugs has been described in older adults living in NH: as previously reported, in the SHELTER population 36% of participants were on benzodiazepines, 36% on antidepressants, 26% on antipsychotics, and 34% used analgesics that may contain opioids (14). Third, polypharmacy may be considered an indicator of clinical complexity, reflecting the high number of underlying concurrent chronic diseases and symptoms, and can be considered as a proxy of disease severity. The potential impact of somatic diseases on cognitive function has been repeatedly suggested throughout literature and the found association between polypharmacy and cognitive decline may reflect such body-mind relationship (17). In our analyses we accounted for several concurrent diseases and conditions, however, we are not able to fully discard the hypothesis of residual confounding.

Some limitations of the present study should be mentioned. First, polypharmacy was assessed based on drugs used at the baseline assessment and we did not take into consideration changes in drug regimens occurring during the study period and this may have affected the strength of the described association. Second, although the InterRAI LTCF is a standardized, comprehensive assessment instrument, the recording of drug data is not its specific focus. In particular, only drugs prescribed in the three days prior to the assessment were recorded in the present study. This could have determined an underestimation of polypharmacy as several drugs may be assumed weekly or even more rarely. Finally, as above mentioned, despite adjusting the analyses for several potential confounders, we cannot exclude that the association between cognitive decline and polypharmacy is due to residual confounding.

Conclusions

The present study shows that polypharmacy is highly prevalent among older NH residents and is associated to a worsening in cognitive performance, but not with functional decline, over one year. Further studies are needed to assess the nature of the described relationship and to identify the best strategies to optimize pharmacological treatment in frail older people.

CONTRIBUTORSHIP

Conception of the work: DLV, ERV, GO. Data analysis: DLV, GO. Results interpretation: all the co-authors. Drafting the article: DLV, ERV. Critical revision of the manuscript: all the co-authors. Final approval of the manuscript: all the co-authors. All the authors fulfil the ICMJE criteria for authorship.

DECLARATION OF INTERESTS

The authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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277 **Table 1.** Sample characteristics at baseline by polypharmacy status.

	Overall N = 3234	**<5 drugs N = 823**	**5-9 drugs N = 1630**	**≥10 drugs N =781**	**p**
Demographics					
Age (years)	83.4±9.2	83.0±10.5	83.7±8.8	83.2±8.6	0.183
Sex (F)	2388 (74)	599 (73)	1218 (75)	571 (73)	0.509
Functional assessment					
CPS scale (continuous)	2.8±2.0	3.1±2.1	2.8±2.0	2.3±1.9	<0.001
Borderline impairment (1-2)	1012 (31)	230 (28)	499 (31)	283 (36)	<0.001
Mild/moderate impairment (3-4)	1250 (39)	275 (34)	627 (39)	348 (45)	
Severe impairment (5-6)	957 (30)	309 (38)	500 (31)	148 (19)	
ADL scale (continuous)	3.3±1.9	3.5±2.0	3.3±1.9	3.1±1.9	<0.001
Mild disability (1-2)	639 (20)	159 (19)	309 (19)	171 (22)	<0.001
Moderate disability (3-4)	1384 (43)	317 (39)	703 (43)	364 (47)	
Severe disability(5-6)	1206 (37)	346 (42)	614 (38)	246 (32)	
Clinical assessment					
Ischemic heart disease	908 (28)	144 (18)	481 (30)	283 (37)	<0.001
Dementia	1729 (53)	492 (60)	894 (55)	343 (44)	<0.001
Heart failure	542 (17)	67 (8)	292 (18)	183 (24)	<0.001
Parkinson's disease	228 (7)	40 (5)	109 (7)	79 (10)	<0.001
Stroke	718 (22)	145 (18)	369 (23)	204 (26)	<0.001
Diabetes	701 (22)	120 (15)	350 (22)	231 (30)	<0.001
Cancer	326 (10)	55 (7)	172 (10)	99 (13)	<0.001
Pain	668 (21)	81 (10)	323 (20)	264 (34)	<0.001
Dyspnea	153 (5)	22 (3)	71 (4)	60 (8)	<0.001
Depressive symptoms	1035 (32)	194 (24)	517 (32)	324 (42)	<0.001

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279 Measures are reported as mean ± standard deviation or count and percentage (%)

280 CPS= cognitive performance scale; ADL=activities of daily living

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Table 2. Association between polypharmacy and cognitive (CPS scale) and physical (ADL) function.

	Model 1 Betacoeff.[¥] for factor*time (95% CI)	**Model 2 Betacoeff.[¥] for factor*time (95% CI)**
CPS change		
<5 drugs	*Ref.*	*Ref.*
5-9 drugs	0.09 (0.01; 0.20)	0.10 (0.01; 0.20)
≥10 drugs	0.13 (0.02; 0.25)	0.13 (0.01; 0.24)
ADL change		
<5 drugs	*Ref.*	*Ref.*
5-9 drugs	0.08 (-0.01; 0.17)	0.07 (-0.02; 0.16)
≥10 drugs	0.08 (-0.03; 0.18)	0.07 (-0.03; 0.18)

[¥]Beta coefficients can be interpreted as the change in the CPS and ADL scores over 1 year.

Model 1 adjusted for age, sex and facility

Model 2 adjusted for age, sex, heart failure, ischemic heart disease, Parkinson's disease, stroke, diabetes, cancer, dyspnoea, dementia, pain, depressive symptoms and facility.

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