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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Adverse drug reactions and cognitive function among hospitalized older adults

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Abstract *Objective*: To explore the relationship between cognitive function and the detection of adverse drug reactions (ADRs) and to evaluate whether cognitive function could influence the association between age and ADRs.
Methods: A total of 16,926 patients admitted to 81 hospitals throughout Italy between 1991 and 1997 were included in the study. ADRs detected the during hospital stay were recorded by a study physician. Patients with a Hodkinson Abbreviated Mental Test (AMT) score <7 at hospital admission were considered cognitively impaired.
Results: A total of 1,444 ADRs were diagnosed in 976 patients (5.8% of the total sample). Overall, gastrointestinal complications (18.0% of all ADRs) were the most frequent ADRs, followed by cardiovascular (12.3%) and dermatological/allergic complications (12.3%). An ADR was recorded in 232/4,883 (4.8%) patients with cognitive impairment and in 744/12,043 (6.2%) patients cognitively intact. After adjusting for potential confounders, cognitive impairment was associated with a reduced risk of ADRs (OR 0.70; 95% CI: 0.60–0.83). This result was not consistent for all types of ADRs, since the risk of neuropsychiatric complications was significantly increased among patients with cognitive impairment (OR 2.23; 95% CI 1.40–3.54). The overall rate of ADRs was 5.2% in patients younger than 65, 6.1% in patients between 65 and 79, and 5.8% in those 80 or older. When adjusting for potential confounders, not including the AMT score, age was not found to be significantly associated with ADRs. However, when the variable for the AMT score was introduced into the model, the risk for ADRs significantly increased with increasing age.
Conclusion: Cognitive impairment is associated with a lower detection rate of ADRs, and it represents a confounder of the association between age and ADRs.

Keywords Adverse drug reactions · Cognitive status · Age · In-hospital patients · Elderly

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Introduction

In Western countries, adverse drug reactions (ADRs) are an important medical problem, resulting in 3–5% of all hospital admissions [1, 2], accounting for 5–10% of in-hospital costs [3,4] and associated with a substantial increase in morbidity and mortality [5]. Older patients are particularly vulnerable to ADRs because they are usually on multiple drug regimens and because age is associated with changes in pharmacokinetics and pharmacodynamics [6, 7]. Nonetheless, there is no conclusive evidence suggesting that age per se can be regarded as a risk factor for ADRs. In fact, depending on the study, ADRs were more [8] or less common among older patients [9] or were found to be completely unrelated to age [10, 11, 12]. These differences can be explained by the fact that studies conducted among older adults have often been inadequate. On the one hand, the issue has been approached through clinically accurate, although small, and thus

intrinsically heterogeneous studies [13]. On the other, large, retrospective databases have often been used, providing inconclusive evidence. Moreover, these studies employed different methods of ADR detection, and in most cases they were not considering all the relevant factors potentially associated with the onset of ADRs.

In particular, the impact of cognitive function on ADRs has rarely been examined in previous studies. Cognitive impairment afflicts approximately 15% of persons over 65 years, and 35–50% of those aged 85 years or above [14, 15], and it has been associated with reduced medication adherence [16] and increased sensitivity to drugs with anticholinergic properties [17]. Moreover, subjects with cognitive impairment present a different drug use pattern compared with cognitively intact persons [18, 19, 20].

Thus, the aims of the present study were (a) to explore the relationship between cognitive function and the detection of ADRs and (b) to evaluate whether cognitive function influences the association between age and ADRs. To this end, we used data from the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA), a study specifically designed to collect data about ADRs. Nationwide, continuous data acquisition since 1988 has led to the creation of a database containing information on a large and representative population of elderly patients admitted to acute-care hospitals in Italy.

Methods

GIFA database

The GIFA is a group of investigators operating in community and university-based hospitals throughout Italy. The GIFA periodically surveys drug use, occurrence of adverse drug reactions, and quality of hospital care.

The methods of the GIFA study have been described in detail elsewhere [11, 21]. Briefly, all patients admitted to 81 geriatric and internal medicine wards participating in the study were enrolled and followed until discharge. The study periods were the following: 1 May to 30 June and 1 September to 31 December 1988; 15 May to 15 June 1991; and 1 May to 30 June and 1 September to 31 October in 1993, 1995, and 1997. The study was approved by the Institutional Review Board of the Catholic University of the Sacred Heart in Rome.

For each participant, a questionnaire was completed at admission and updated daily by a study physician who received specific training. Data recorded included sociodemographic characteristics, indicators of physical function and cognitive status, clinical diagnoses on admission and at discharge, medications taken prior to admission, during hospital stay, and those prescribed at discharge.

Cognitive performance was assessed at hospital admission using the Hodkinson Abbreviated Mental Test (AMT) [22] in 1991, 1993, 1995, and 1997 surveys. This test has proven to be reliable for detecting both mild cognitive impairment and dementia in older populations [23]; it has been validated for the detection of cognitive impairment in Italian population [24]. Thus, according to these studies we defined as cognitively impaired those patients with an AMT score below 7.

Drugs were coded according to the Anatomical Therapeutic and Chemical codes [25]. Diagnoses were coded according to the International Classification of Diseases, Ninth Edition, Clinical Modification codes [26]. Comorbidity was quantified using the Charlson comorbidity index by adding scores assigned to specific discharge diagnoses, as illustrated in the original publication [27]. ADL disability was defined as need of assistance to perform ≥1 of the following tasks: eating, dressing, bathing, transferring, and using the toilet.

Adverse drug reactions

An ADR was defined according to the World Health Organization definition, which refers to any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), and drug abuse. Also, this definition does not include ADRs owing to errors in drug administration and noncompliance [28]. A study physician investigated the occurrence of any possible ADR during hospital stay, gathering information from the patients, nurses and attending physician, and reviewing charts and records. For each suspected ADR, the study physician coded clinical description, severity, and eventual evolution. In addition, he collected detailed information about the drug(s) identified as the potential culprit. The causality of the relation between drug use and ADR was assessed based upon the scores of the Naranjo algorithm [29]. ADR were classified as: definite (score, 9–12), probable (score, 5–8), possible (score 1–4), or doubtful (score, 0 or below). Only definite and probable ADRs owing to medical therapy prescribed while in-hospital were considered for this study. ADRs detected at admission and caused by drugs prescribed before admission were excluded from the present analysis.

Data analysis

From an initial sample of 28,411 patients, we excluded patients admitted in the 1988 survey, in which AMT was not collected ($n = 10{,}885$), and those with missing data for AMT ($n = 600$). In order to establish whether cognitive impairment was a risk factor for developing any ADR and single types of ADRs, logistic regression models were performed in the resulting sample of 16,926 patients. Models were adjusted for age, gender, alcohol consumption before hospital admission, Charlson Comorbidity Index, number of drugs consumed during hospital stay, type of ward, length of hospital stay, and year of survey. In previous analyses conducted in this population, these variables showed to be independent predictors of ADRs [2, 11, 30]. In additional logistic regression models we explored the risk of ADRs across four levels of cognitive function computed on the basis of the number of correct answers at the AMT: 0–2 correct answers ($n = 1{,}921$), 3–5 correct answers ($n = 1{,}798$), 6–8 correct answers ($n = 4{,}886$), 9–10 correct answers ($n = 8{,}321$).

To address whether the relation between age and ADRs could be influenced by cognitive status, we performed different logistic regression models after stratification for age groups. Odds ratios (OR) and 95% confidence intervals (CI) for ADR across age groups were calculated with and without the AMT variable in the model. These models were adjusted for gender, alcohol consumption before hospital admission, Charlson Comorbidity Index, number of drugs consumed during hospital stay, type of ward, length of hospital stay, and year of survey.

A p value below 0.05 was considered statistically significant. All analyses were performed using SPSS for Windows version 10.0.

Results

Patient characteristics

In the 1991–1997 period, a total of 16,926 patients were enrolled in the study. The principal characteristics of the population are illustrated in Table 1. Mean age was 71.1 ± 15.5 years (women: 73.3 ± 15.0 years; men:

Table 1. Characteristics of the study population (*SD* standard deviation, *IQR* interquartile range, *AMT* Abbreviated Mental Test)

	Study population ($n = 16,926$) %
Age	
< 65 years	26.0
65–79 years	41.3
≥80 years	32.7
Gender (female)	49.8
ADL disability[a]	35.7
Cognitive impairment (AMT < 7)	28.8
Alcohol consumption before hospital admission	55.2
Smokers	15.4
Education, years	
Mean (SD)	6.0 (3.6)
Median (IQR)	5 (3–8)
Charlson comorbidity index score	
0–1	62.0
2 or more	38.0
Conditions:	
Hypertension	27.3
Coronary heart disease	21.1
Diabetes	15.8
Cerebrovascular disease	14.0
COPD	12.7
Congestive heart failure	11.0
Neoplasm	11.0
Liver disease	6.1
Pneumonia	3.5
No. of drugs consumed during hospital stay	
Mean (SD)	6.7 (5.3)
Median (IQR)	6 (3–9)
Drugs consumed during hospital stay:	
Antibiotics	35.2
Diuretics	35.1
Digoxin	27.0
Calcium channel blockers	26.2
Ace inhibitors	23.3
Nitrates	20.7
Anticoagulants	20.6
ASA and antiplatelet drugs	19.8
Benzodiazepines	18.5
NSAIDs	16.0
Corticosteroids	14.8
Oral antidiabetics	9.1
Insulin	8.4
Antipsychotics	6.1
Length of hospital stay	
Mean (SD)	14.4 (10.9)
Median (IQR)	12 (7–18)
Type of ward	
Geriatric	61.1
Internal medicine	34.1
Other	4.8

[a]Needing help in one or more daily living activities

68.9 ± 15.7 years, $p < 0.001$); males and females were equally represented. At hospital admission, 4,883 (28.8%) patients presented cognitive impairment, and the mean number of correct answers at the AMT was 7.4 ± 3.1. Compared with other participants, patients with cognitive impairment were older (79.2 ± 10.7 vs 67.8 ± 15.9, $p < 0.001$), more likely female (58.6% vs 46.3%, $p < 0.001$), presented a higher Charlson comorbidity index (2.0 ± 1.9 vs 1.4 ± 1.8 $p < 0.001$), and consumed a higher number of drugs during their hospital stay (7.1 ± 5.3 vs 6.6 ± 5.4, $p < 0.001$). In particular, cognitive impairment was associated with a significantly higher rate of congestive heart failure (13.3% vs 10.1%, $p < 0.001$), cerebrovascular disease (23.8% vs 10.0%, $p < 0.001$), and with a lower rate of hypertension (23.3% vs 29.0%, $p < 0.001$) and hepatic diseases (4.6% vs 7.5%, $p < 0.001$). Moreover, patients with cognitive impairment received more frequently ASA and antiplatelet drugs (24.3% vs 19.1%, $p < 0.001$), antipsychotics (13.4% vs 3.1%, $p < 0.001$), digoxin (35.2% vs 23.6%, $p < 0.001$) and diuretics (36.8% vs 34.3%, $p = 0.002$). In contrast, Ace inhibitors (20.1% vs 24.4%, $p < 0.001$), calcium channel blockers (24.0% vs 27.1%, $p < 0.001$), NSAIDs (12.6% vs 17.4%, $p < 0.001$), and nitrates (21.5% vs 23.2%, $p = 0.018$) were prescribed less commonly than in cognitively intact patients.

Cognitive function and ADRs

During hospital stay a total of 1,444 probable or definite ADRs were detected in 976 cases (5.8% of the total sample). Overall, gastrointestinal complications (18.0% of all ADRs) were the most frequent ADR, followed by cardiovascular (12.3%) and dermatological/allergic complications (12.3%). An ADR was recorded in 232/4,883 (4.8%) patients with cognitive impairment and in 744/12,043 (6.2%) patients cognitively intact. After adjusting for potential confounders, cognitive impairment was associated with a reduced risk of ADRs (OR 0.70; 95% CI: 0.60–0.83). As shown in Table 2, cognitive impairment was associated with a significantly reduced risk of gastrointestinal (OR 0.40; 95% CI 0.27–0.61), cardiovascular complications (OR 0.60; 95% CI 0.37–0.95), and headache (OR 0.55; 95% CI 0.31–0.97). On the other hand, patients with cognitive impairment presented a two-fold increased risk of neuropsychiatric complications (OR 2.23; 95% CI 1.40–3.54), while no significant difference by cognitive status was observed for other ADRs.

Table 3 presents the most frequent drug classes that contributed to ADRs in the study sample. The most common culprit drugs were nitrates, calcium channel blockers, and diuretics among cognitively intact patients and digoxin, calcium channel blockers, and nitrates among cognitively impaired participants.

Figure 1 shows the OR and 95% CI for ADRs across different levels of cognitive function: the risk of ADRs progressively and significantly declines with the reduction in correct answers on the AMT (i.e., more severe dysfunction). Compared with patients presenting a score 9–10 on the AMT, those with a score of 6–8 had a 12% reduction in risk of experiencing an ADR, those with a score of 3–5 a 31% reduction and those with a score of 0–2 a 49% reduction (p for linear trend < 0.001).

Table 2. Types of ADRs according to cognitive status. Odds ratios are adjusted for age, gender, alcohol consumption before hospital admission, Charlson Comorbidity Index, number of drugs consumed during hospital stay, type of ward, length of hospital stay and year of survey

Type of ADR	ADRs in cognitively unimpaired ($n = 12,043$) Number (% of population)	ADRs in cognitively impaired ($n = 4,883$) Number (% of population)	Odds ratio (95% CI)
Any	744 (6.2)	232 (4.8)	0.70 (0.60–0.93)
Gastrointestinal[a]	221 (1.8)	39 (0.8)	0.40 (0.27–0.61)
Cardiovascular (non arrhythmic)	147 (1.2)	30 (0.6)	0.60 (0.37–0.95)
Dermatological/allergic	138 (1.1)	39 (0.8)	0.85 (0.55–1.35)
Headache	107 (0.9)	17 (0.3)	0.55 (0.31–0.97)
Arrhythmic	100 (0.8)	33 (0.7)	1.10 (0.70–1.76)
Metabolic/endocrine	78 (0.6)	19 (0.4)	0.65 (0.27–1.58)
Electrolytic	63 (0.5)	18 (0.4)	0.73 (0.45–1.18)
Hemorrhagic	59 (0.5)	23 (0.5)	1.00 (0.57–1.74)
Neuropsychiatric	45 (0.4)	32 (0.7)	2.23 (1.40–3.54)
Muscoloskeletal	36 (0.3)	3 (0.1)	0.33 (0.04–2.85)
Renal and genitourinary	31 (0.3)	5 (0.1)	0.33 (0.09–1.18)
Neurological	27 (0.2)	9 (0.2)	1.35 (0.58–3.15)
Hepatic	23 (0.2)	3 (0.1)	0.63 (0.12–3.21)
Hematological	17 (0.1)	8 (0.2)	0.81 (0.20–3.29)
Respiratory	14 (0.1)	3 (0.1)	1.37 (0.31–6.09)
Others	49 (0.4)	8 (0.2)	0.55 (0.22–1.35)

[a]Not including gastrointestinal bleeding

Table 3. Number of adverse drug reactions by drug class according to cognitive status

	All		Cognitively unimpaired		Cognitively impaired	
	No. of users	No. of ADRs (% of users)	No. of Users	No. of ADRs (% of users)	No. of Users	No. of ADRs (% of users)
Antibiotics	5926	69 (1.2)	3664	51 (1.4)	2298	18 (0.8)
Diuretics	5933	107 (1.8)	4136	88 (2.1)	1797	19 (1.1)
Digoxin	4568	74 (1.6)	2847	48 (1.7)	1721	26 (1.5)
Calcium channel blockers	4438	110 (2.5)	3264	90 (2.8)	1174	20 (1.7)
Ace inhibitors	3924	77 (2.0)	2942	59 (2.0)	982	18 (1.8)
Nitrates	3829	138 (3.6)	2790	118 (4.2)	1049	20 (1.9)
Anticoagulants	3492	55 (1.6)	2305	39 (1.7)	1187	16 (1.3)
ASA and antiplatelet drugs	3346	48 (1.4)	2466	35 (1.4)	880	13 (1.5)
Benzodiazepines	3127	29 (0.9)	2423	18 (0.7)	704	11 (1.6)
NSAIDs	2710	64 (2.4)	2097	55 (2.6)	613	9 (1.5)
Corticosteroids	2497	26 (1.0)	1639	22 (1.3)	858	4 (0.5)
Oral antidiabetics	1543	25 (1.6)	1131	20 (1.8)	412	5 (1.2)
Insulin	1427	38 (2.7)	946	27 (2.9)	481	11 (2.3)
Antipsychotics	1033	22 (2.1)	377	5 (1.3)	656	17 (2.6)

ADRs and age

The rate of ADRs was 5.2% in patients younger than 65, 6.1% in patients between 65 and 79, and 5.8% in those 80 or older (p for linear trend = 0.323). After adjusting for gender, alcohol consumption before hospital admission, Charlson Comorbidity Index, number of drugs consumed during hospital stay, type of ward, length of hospital stay, and year of survey, age groups were not significantly associated with ADRs (65–79 years vs <65 years OR 1.06, 95% CI 0.89–1.27; ≥ 80 years vs <65 years OR 1.00, 95% CI 0.82–1.21; p for liner trend = 0.273). However, when the variable for AMT was introduced in the model, the risk of ADRs was positively associated with increasing age. Considering participants younger than 65 years as the reference group, patients aged 65–79 and 80 or older had respectively 12% (OR 1.12, 95% CI 0.94–1.35) and 19% (OR 1.19, 95% CI 0.97–1.46) increased risk of experiencing an ADR (p for trend = 0.005).

Discussion

The present study shows that cognitive impairment is associated with a reduced overall risk of ADRs among in-hospital patients. This result is generally consistent, but not unequivocal. In fact, neuropsychiatric complications were significantly more common among patients with cognitive impairment. Moreover, this study shows that cognitive impairment is a confounder of the association between age and ADRs.

The incidence of ADRs detected during hospital stay was lower in our study than in others [5]. We think that the use of the Naranjo algorithm in the present study limited the number of events. In fact, we applied a

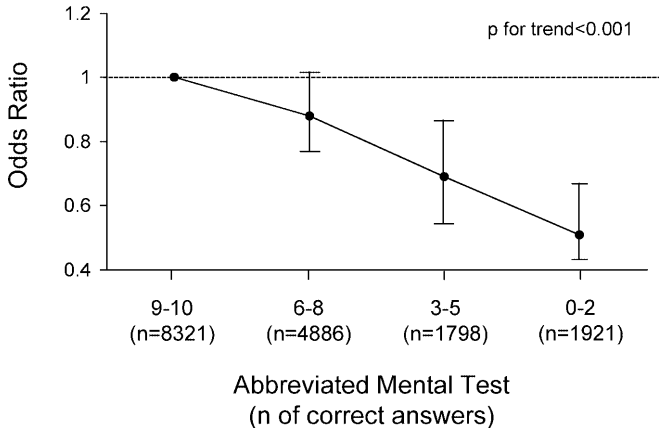

Fig. 1. Probability of adverse drug reactions according to Abbreviated Mental Test groups. Analysis was adjusted for age, gender, alcohol consumption before hospital admission, Charlson Comorbidity Index, number of drugs consumed during hospital stay, type of ward, length of hospital stay, and year of survey

cut-off score, which allowed for the exclusion of all ADRs with an unlikely or possible causal relation with drug exposure [29].

In our sample cognitive impairment was associated with a higher comorbidity compared with patients with normal cognitive function. These findings are in line with other studies conducted in different settings [31, 32]. In particular, a higher prevalence of congestive heart failure (CHF) and cerebrovascular disease and a lower rate of hypertension in cognitively impaired patients have already been reported by other authors [33, 34]. The drug-prescription pattern reflects the distribution of diseases, as shown by the fact that cognitively impaired patients received more medications than other participants. In this context the higher prescription of digoxin and diuretics and the lower use of calcium antagonists are consequences of the different prevalence of CHF and hypertension, respectively, among patients with different cognitive function. On the other hand, the greater use of antipsychotic drugs that we observed among demented patients reflects the need to treat behavioral and psychiatric complications associated with cognitive impairment.

The main result of our study was that cognitive impairment is inversely related to onset of ADRs. Possible explanations of this relationship remain speculative. This phenomenon may reflect objective limitations or cultural bias. On the one hand, physician may tend to underdiagnose ADRs because patients with cognitive impairment might be unable to verbalize or recall specific complains and/or to collaborate during the diagnostic workshop. In line with this hypothesis, McCormick et al. showed that patients with dementia tend to underreport common symptoms not suggestive of cognitive impairment (e.g., gastrointestinal discomfort, joint pain, vision problems) compared with non-demented subjects, even though comorbidity was similar in both groups [35]. This hypothesis is also consistent with earlier studies in elderly patients evaluated for dementia, in which previously unrecognised illnesses were found in nearly half of subjects [36, 37]. Hence, elderly cognitively impaired patients may be at special risk for occult medical illnesses and ADRs, perhaps as a result of difficulty in giving an accurate medical history during physician visits. On the other hand, subjects with cognitive impairment may be evaluated less carefully by physicians, leading to an underestimation of adverse drug events in this population [34]. In this context, it has recently been shown that cognitive impairment is associated with fewer diagnostic and blood tests, and with reduced visitation time by physicians [38, 39].

Alternatively, the higher prevalence of specific conditions among cognitively impaired subjects could have misled physicians in detecting ADRs related to those conditions. For example, despite a higher prevalence of cardiovascular disease, there are fewer cardiovascular adverse reactions among cognitively impaired subjects than with other participants. Indeed, it is possible that progression or exacerbation of a pre-existing cardiovascular condition is difficult to distinguish from the effects of cardiovascular ADRs, which can therefore be underreported.

The inverse association of ADRs and cognitive impairment has already been demonstrated among patients discharged from the hospital [40]. However, this finding seems in contrast with a recent paper by Gray et al., conducted among 157 in hospital patients, showing an inverse correlation between the Mini Mental Status Examination score and the ADRs rate [10]. This discrepancy can be explained by the different pattern of ADRs: in fact in Gray's study neuropsychiatric and arrhythmic complications, which are directly associated with cognitive impairment in our population, accounted for about 50% of all ADRs.

The relationship between neuropsychiatric ADRs and cognitive function is intriguing. The most probable explanation for this finding appears to be the increased anticholinergic sensitivity in patients with dementia. Dementia, particularly the Alzheimer type, has been associated with pathologic involvement of the cholinergic system, which plays an important role in central nervous system neurotransmission, memory function, and mood [41]. Thus, these patients have a reduced threshold to the effect of central cholinergic blockade and therefore have increased sensitivity to anticholinergic activity of certain drugs, resulting in increased agitation, confusion, hallucinations, and other behavioral effects [17]. In this context, we observed, among cognitively impaired patients, a higher prescription rate of agents with a well-known anticholinergic spectrum of activity, such as antipsychotics [42], which could further explain the different rate of ADRs potentially related to a reduced cholinergic activity.

Overall, after adjusting for cognitive function, we found that age per se can be regarded as a risk factor for ADRs. Cognitive function represents an important confounder for the association between age and ADRs.

Noticeably in this same population, we found that when the adverse reaction was represented by symptoms, age was either not associated [2] or was a protective factor [11]. This probably reflects a reduced report rate as a consequence of cognitive impairment related to increasing age.

Advancing age is associated with an increased incidence of diseases and with polypharmacy and, as a result, older patients are more prone to the appearance of ADR. Moreover, age-related changes in pharmacokinetics may make plasma concentration less predictable, and similar changes in pharmacodynamics may cause a narrower therapeutic window for many drugs. In addition, if we consider that few older patients are included in the pharmacological trials, which attest to the efficacy and safety of a drug, it can be concluded that the relationship between age and ADR is complex and probably not unequivocal.

The present study has some strengths. First, the relationship between cognitive function and ADRs has been studied through a large and dedicated database. Second, the hospital is an ideal setting to study this association, since pharmacological non-compliance is reduced and the daily evaluation of patients by the study physician, as well as the constant review of charts and medical records, guarantee careful reporting of all suspected ADRs. Finally, to describe the causal relationship of ADR with drug exposure, we used an algorithm that is associated with 85% interobserver agreement [29]. Nonetheless, an important limitation of the study is related to the fact that we are unable to distinguish between different types of dementia, since the diagnosis of Alzheimer disease is widely underreported in our sample. Moreover, our findings are based on an elderly hospitalized population and therefore can not be generalized to younger subjects living in the community.

In conclusion, our study shows that cognitive impairment is associated with a lower detection rate of ADRs and that, after adjusting for cognitive function, age becomes an independent risk factor for ADRs. Future studies about adverse drug events in the elderly should clarify this association.

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