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Original Study

Drug Burden Index and Cognitive and Physical Function in Aged Care Residents: A Longitudinal Study

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A B S T R A C T

Objectives: Anticholinergic/antimuscarinic and sedative medications (eg, benzodiazepines) have been found to be associated with poorer cognitive and physical function and mobility impairment in older age. However, previous studies were mostly conducted among community-dwelling older individuals and had often a cross-sectional design. Accordingly, our aim was to examine longitudinal associations between cumulative exposure to anticholinergic and sedative medications and cognitive and physical function among residents from aged care homes.
Design: Longitudinal study.
Setting and Participants: A total of 4624 residents of Dutch aged care homes of whom data were collected between June 2005 and April 2014.
Methods: Outcome measures were collected with the Long-Term Care Facilities assessment from the international Residential Assessment Instrument (interRAI-LTCF) and included the Cognitive Performance Scale, the Activities of Daily Living (ADL) Hierarchy scale, a timed 4-meter walk test, distance walked, hours of physical activity, and days being outside. Cumulative exposure to anticholinergic and sedative medications was calculated with the Drug Burden Index (DBI), a linear additive pharmacological dose-response model. Associations were examined with linear mixed models to take the potential dependence of observations into account (ie, data were collected at repeated assessment occasions of residents who were clustered in aged care homes). Analyses were adjusted for sex, age, dementia, comorbidity (neurological, psychiatric, cardiovascular, oncological, and pulmonary), fractures, depressive symptoms, and medications excluded from the DBI.
Results: We observed significant longitudinal associations between a higher DBI and poorer ADLs, fewer hours of physical activity, and fewer days being outside. We found no significant longitudinal association between a higher DBI and poorer cognitive function.
Conclusions and Implications: Over time, cumulative exposure to anticholinergic and sedative medications is associated with poorer physical but not cognitive function in aged care residents. Careful monitoring of aged care residents with high cumulative anticholinergic and sedative medication exposure is needed.

Medications with anticholinergic and sedative potency have been associated with increased fall risk,[1] bone and hip fractures,[2] physical function impairment in older age,[3–6] and cognitive impairment and dementia.[3,4,7–9] These medications are prescribed for various medical conditions including urinary incontinence, pain alleviation, Parkinson's disease, psychiatric disorders, cardiovascular disease,

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alimentary tract and metabolic disorders, and respiratory conditions. Given the prevalence of comorbidity, polypharmacy, or the coincident prescribing of 5 or more medications, and functional impairments among residents from aged care homes, prescribing of 1 or more anticholinergic and or sedative medications is common and residents are likely to be vulnerable to their adverse effects.

The Drug Burden Index (DBI) was previously developed and validated as a clinical risk assessment tool to estimate cumulative exposure to anticholinergic and sedative medications.[10] The DBI sums the exposure, calculated using the dose-response equation, to each medication with these effects (see Methods Polypharmacy and DBI). A growing body of evidence supports a link between a higher DBI and aggravation of physical and cognitive impairment in older persons also after adjusting for comorbidity.[10–12] So far, however, most of these studies were conducted among community-dwelling older individuals. Only a few studies have been conducted among residents from aged care homes.[13–16]

A previous finding showing that residents from aged care homes had an increased risk for potentially inappropriate medication use compared with community-dwelling individuals[17] further underlines the need to investigate anticholinergic and sedative exposure in the former group. Furthermore, as previous studies were often cross-sectional, longitudinal studies over time should be conducted. Accordingly, we aimed to examine the question of whether there were longitudinal relationships of cumulative exposure to anticholinergic and sedative medications with cognitive and physical function in aged care residents.

Methods

Study Design and Participants

Longitudinal observational data were collected from residents of Dutch aged care homes between June 2005 and April 2014. In the Netherlands, persons are eligible to live in an aged care home if they are impaired in self-care ability and when home and family care no longer suffice in offering appropriate support. Trained nursing staff routinely collected data at repeated assessment occasions for the purpose of care planning. They used the Long-Term Care Facilities assessment from the international Residential Assessment Instrument (interRAI-LTCF), a comprehensive and standardized assessment of residents' demographic characteristics, physical, cognitive, psychosocial and behavioral function, as well as diseases and medication use. Nursing staff provided registered medications in person. For the present analyses, residents were excluded if they were younger than 65 years at the first assessment occasion; if they were potential problem drinkers (ie, drinking ≥5 units of alcohol at a single occasion), as excessive alcohol consumption is likely to distort the outcomes of cognitive and physical function and mobility impairment; or when the interRAI-LTCF assessment was not performed. Furthermore, we selected assessment occasions that were separated by intervals of 60 days or longer. Residents or their legal representatives gave permission to use their interRAI-LTCF data by signing a service contract with the aged care home. Data were subsequently de-identified for research purposes. Given these conditions, no further ethical clearance by a medical research ethics committee was needed at the time of the data collection.

Polypharmacy and DBI

On each assessment occasion, the name, dose, unit, route of administration, and frequency of intake of each medication were recorded by nursing staff as well as whether a medication was prescribed "pro re nata." All medications were coded according to their standardized Anatomic Therapeutic Chemical classification (ATC) codes of the World Health Organization.[18] Both medications prescribed by a physician and over-the-counter medications were considered, but only if the medication had been taken in the 3 days before the interRAI-LTCF assessment. All doses were recalculated into total daily doses expressed in milligrams. The DBI was calculated at each assessment occasion as follows (see Equation 1):

$$\mathrm{DBI} = \sum \frac{D}{\delta + D} \tag{1}$$

where D stands for the prescribed daily dose of an individual medication and δ represents the DR_{50} or the dose that gives 50% of the maximal effect. All medications prescribed pro re nata were excluded from the DBI calculation, as pro re nata prescribing renders the estimation of their dosages difficult. In a systematic manner, we previously compiled a list of all medications with *probable* anticholinergic and/or sedative properties. Because the DR_{50} is unknown, it was estimated by substituting it with the

Table 1
Demographic and Clinical Characteristics of the Participants at Baseline

Characteristics	n	Statistic
Demographics		
n (%) Sex	4621	
Men		1236 (26.7)
Women		3385 (73.3)
M (SD) age (y)	4615	83.6 (7.0)
Medication characteristics		
M (SD) number of prescribed medications	4624	7.0 (3.7)
M (SD) number of prescribed medications excluded from DBI	4624	5.1 (3.0)
n (%) Hyperpolypharmacy (≥10 medications)	4624	1117 (24.2)
Comorbidities		
n (%) comorbidity	4624	
Dementia*		1795 (38.8)
Other neurological†		1319 (28.5)
Psychiatric‡		1057 (22.9)
Cardiovascular§		1933 (41.8)
Oncological		513 (11.1)
Pulmonary‖		593 (12.8)
n (%) Fractures in past 30 days**	4624	423 (9.1)
M (SD) Depression Rating Scale of symptoms in past 30 days (range 0–14)	4617	2.0 (2.6)
Outcomes		
M (SD) Cognitive Performance Scale (range 0–6)	4598	1.8 (1.7)
M (SD) ADL Hierarchy Scale (range 0–6)	4620	2.3 (1.8)
M (SD) Timed 4-m walk test (s)	2124	14.3 (8.6)
M (SD) Distance walked (6-point scale: 0, did not walk, 5 > 1 km) in past 3 d	3253	2.3 (1.5)
n (%) Hours of physical activity in past 3 d	3252	
None		434 (13.3)
1		1044 (32.1)
2		1027 (31.6)
3		410 (12.6)
≥4		337 (10.4)
n (%) Days being outside	3253	
None		1717 (52.8)
1		551 (16.9)
2		642 (19.7)
3		343 (10.5)

*Includes Alzheimer disease, other dementia.
†Includes paraplegia, hemiplegia, quadriplegia, Parkinson disease, and stroke.
‡Includes depression, anxiety, bipolar disorders, and schizophrenia.
§Coronary heart disease, congestive heart failure, and diabetes.
‖Chronic obstructive pulmonary disease.
**Hip and other fractures.

lowest oral dose recommended for adults by the Knowledge Base of the Royal Dutch Society of Pharmacists (in Dutch: KNMP).[19] See Appendix 1 for an example that illustrates the calculation of the DBI for one of the aged care residents.

Outcomes of Cognitive and Physical Function and Mobility Impairment

All outcomes were components of the interRAI-LTCF assessment. InterRAI is a collaborative network of researchers from more than 30 countries committed to the design and the promotion of evidence-informed clinical care for, among others, frail older people. For that goal, InterRAI collects data with validated assessment methods (http://www.interrai.org). Cognitive function was assessed with the Cognitive Performance Scale (CPS).[20] Activities of daily living (ADLs) were assessed with the ADL Hierarchy Scale (ADL-HS).[21] Both the CPS and the ADL-HS are decision trees to precisely classify a patient's cognitive and ADL impairments as rated by nursing staff. Physical function was assessed with a timed 4-m walk test, as well as ratings by nursing staff of distance walked, hours of physical activity, and days being outside, the latter being a proxy of physical function (see Appendix 2). All components of the interRAI-LTCF assessment underwent rigorous examination of reliability and validity by the interRAI collaborative network.[22,23] Previously, the CPS was found to be correlated with the Mini Mental State Examination,[20] whereas the ADL-HS was found to be predictive of staff time involved in the care for residents.[21]

Statistical Methods and Longitudinal Analysis

Descriptive statistics of baseline demographic and clinical characteristics were given for the whole sample. In addition, residents with different levels of anticholinergic and sedative exposure were compared on these characteristics by classifying the DBI into no exposure (DBI = 0) and tertiles of exposure: (1st tertile, low exposure: DBI $\leq$ 0.8, 2nd tertile, moderate exposure: DBI $>$ 0.8–1.65, and 3rd tertile, high exposure: DBI $>$1.65).

In linear mixed model analyses, we examined longitudinal relationships between cumulative exposure to anticholinergic and sedative medications (DBI) and the outcome variables of cognitive function (CPS), activities of daily living (ADL-HS), and physical function (timed 4-m walk test, distance walked, hours of physical activity, and days being outside) collected at each assessment occasion. Data were arranged in a long-format with observations from each individual resident at different assessment occasions arranged underneath each other (and likewise residents from each specific aged care home being arranged underneath each other). These models had a 3-level structure to take the potential dependence of observations into account (ie, repeated assessment occasions from residents who were clustered within aged care homes). Specifically, these models included a random intercept and slope at the participant level to account for dependence of repeated assessment occasions clustered within residents and a random intercept to account for dependence of residents clustered within aged care homes. Linear mixed model analyses also allow for a different number of repeated measures per resident and are thereby an appropriate and flexible approach to deal with missing data in the repeatedly measured outcome variables. In all analyses, we first estimated unadjusted effects. We then adjusted for sex, age, dementia (Alzheimer disease and other dementia), other neurological comorbidity (including paraplegia, hemiplegia, quadriplegia, Parkinson disease, and stroke), psychiatric comorbidity (including depression, anxiety, bipolar disorders, and schizophrenia), cardiovascular comorbidity (including coronary heart disease, congestive heart failure, and diabetes), oncological comorbidity, pulmonary comorbidity (chronic obstructive pulmonary disease), fractures (hip and other fractures), depressive symptoms as measured with the Depression Rating Scale (DRS),[24] and medications excluded from the DBI. We estimated unstandardized regression coefficients along with 95% confidence intervals (95% CIs) for all associations. Analyses were performed using SPSS Statistics for Windows, version 24 (IBM Corp., Chicago, IL) and Multilevel Analysis for Windows (MLwiN) version 2.32 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK).

Results

Of the 5141 residents from 89 aged care homes for whom data were available at baseline, 314 residents (6.1%) were excluded because they were younger than 65 years, 165 residents (3.2%) because of potential problem drinking, and 38 residents (0.7%) because the

Table 2
Baseline Characteristics of Residents With No Anticholinergic and Sedative Exposure and Low, Moderate, and High Exposure (Tertiles) of Drug Burden Index (DBI)

Characteristics	No Exposure	Low (1st Tertile DBI)	Moderate (2nd Tertile DBI)	High (3rd Tertile DBI)
	n = 1087	n = 1255	n = 1148	n = 1131
n (%) Female residents	781 (71.8)	932 (74.3)	874 (76.1)	798 (70.6)
	n = 1087	n = 1254	n = 1146	n = 1128
M (SD) Age (y)	84.6 (7.0)	83.8 (6.8)	83.8 (6.8)	82.3 (7.0)
	n = 1088	n = 1257	n = 1148	n = 1131
n (%) Comorbidity				
Dementia*	386 (35.5)	473 (37.6)	481 (41.9)	455 (40.2)
Other neurological†	282 (25.9)	384 (30.5)	315 (27.4)	338 (29.9)
Psychiatric‡	120 (11.0)	232 (18.5)	286 (24.9)	419 (37.0)
Cardiovascular§	411 (37.8)	521 (41.4)	466 (40.6)	535 (47.3)
Oncological	101 (9.3)	118 (9.4)	126 (11.0)	168 (14.9)
Pulmonary‖	83 (7.6)	128 (10.2)	161 (14.0)	221 (19.5)
n (%) Fractures**	107 (9.8)	111 (8.8)	110 (9.6)	95 (8.4)
	n = 1088	n = 1255	n = 1144	n = 1130
M (SD) Depression Rating Scale (range 0–14)	1.4 (2.1)	1.7 (2.4)	2.1 (2.6)	2.8 (3.1)
	n = 1088	n = 1257	n = 1148	n = 1131
M (SD) Number of medications excluded from DBI	4.4 (2.7)	4.9 (2.9)	5.3 (3.0)	5.9 (3.0)

*Includes Alzheimer disease, other dementia.
†Includes paraplegia, hemiplegia, quadriplegia, Parkinson disease, and stroke.
‡Includes depression, anxiety, bipolar disorders, and schizophrenia.
§Coronary heart disease, congestive heart failure, and diabetes.
‖Chronic obstructive pulmonary disease.
**Hip and other fractures.

interRAI-LTCF assessment was unavailable. A total of 4624 residents were therefore included in the present analyses. Of these, 2382 residents had data at 2 or more assessment occasions, 1631 residents at 3 or more, and 1195 residents had data at 4 or more assessment occasions. Table 1 presents the demographic and clinical characteristics of the residents at baseline. On average, residents were treated with 7 medications. Hyperpolypharmacy or the coincident prescribing of 10 or more medications was observed in approximately a quarter of the residents. Neurological and cardiovascular comorbidity were most prevalent (Table 1).

Of the 105,240 identified medication prescriptions, 28,918 (27.5%) were for an anticholinergic and/or sedative medication. These included medications for the alimentary tract and metabolism (n = 1199; 4%; ATC code A), cardiovascular conditions (n = 5278; 18%; ATC code C), psycholeptics including antipsychotics, anxiolytics, and hypnotics/sedatives (n = 10,303; 36%; ATC code N05), psychoanaleptics including antidepressants and psychostimulants (n = 5163; 18%; ATC code N06), other central nervous system active medications (n = 4504; 16%; ATC code N01-N04 and N07), respiratory medications (n = 1499; 5%; ATC code R), as well as other medications (n = 972; 3%; gynecologic medications, ATC code G02; urologicals, ATC code G04; anti-mycobacterials, ATC code J04; anti-inflammatory/antirheumatic medications, ATC code M01; and muscle relaxing medications, ATC code M03).

Comparisons between residents with no exposure (DBI = 0) and tertiles of exposure (1st tertile, low exposure: DBI ≤ 0.8, 2nd tertile, moderate exposure: DBI > 0.8–1.65, and 3rd tertile high exposure: DBI >1.65) demonstrated that those with moderate and high exposure had more depressive symptoms as indicated by higher mean DRS scores and had more often psychiatric comorbidity. Those with high exposure had also more often cardiovascular and pulmonary comorbidity (Table 2) and used on average more medications that were not included in the DBI. Moderate and minor differences were observed for percentage of female residents, mean age, and percentages of dementia, other neurological comorbidity, oncological comorbidity, and fractures.

Figure 1 depicts the longitudinal trajectories of the outcomes of cognitive and physical function for no exposure and the 3 DBI tertiles.

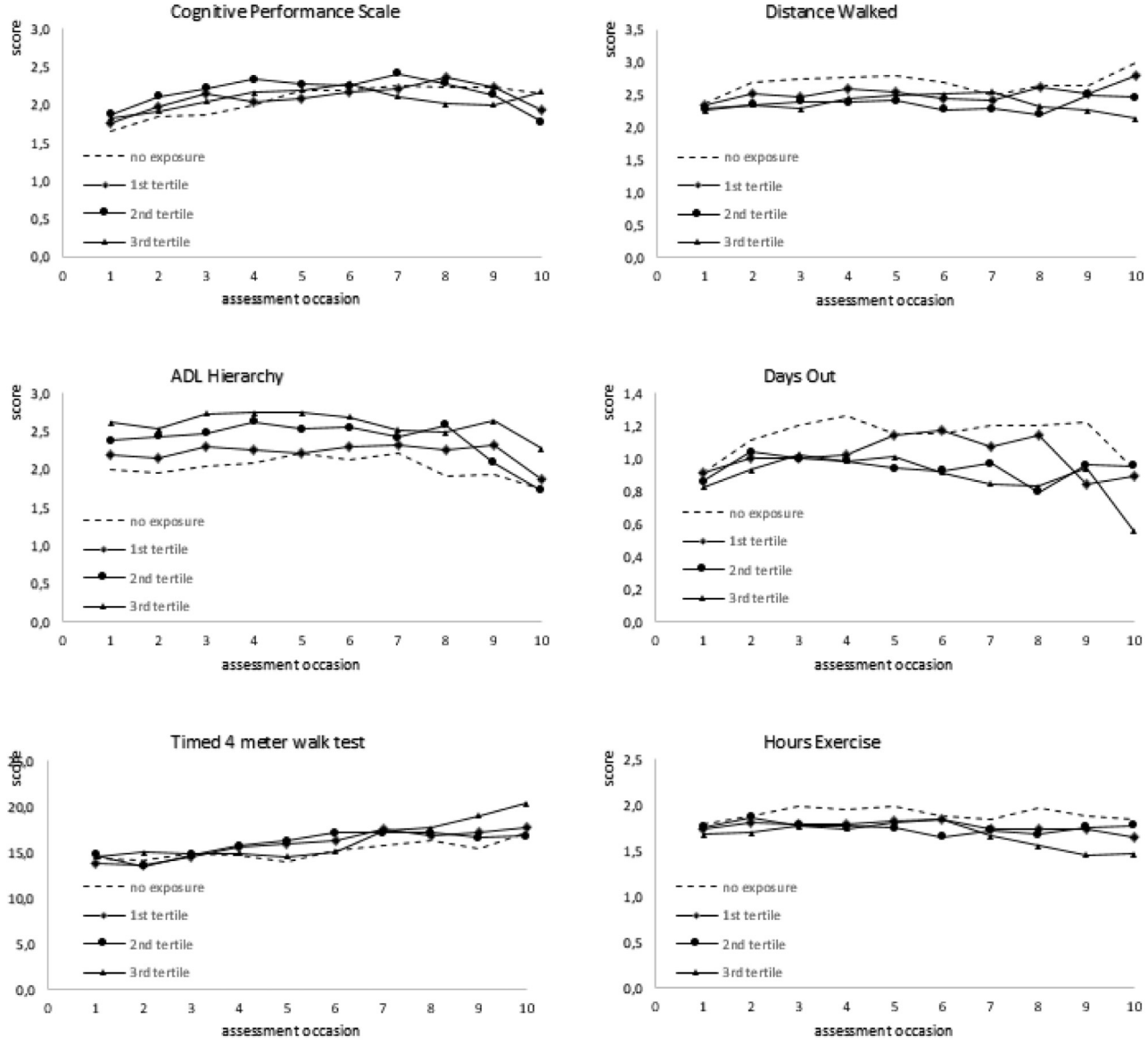

Fig. 1. Longitudinal trajectories of outcomes of cognitive and physical function for no exposure and DBI.

After adjustment for sex, age, dementia, comorbidity (neurological, psychiatric, cardiovascular, oncological, and pulmonary), fractures, depressive symptoms, and medications excluded from the DBI, associations remained significant between the 2nd and 3rd DBI tertiles and poorer ADLs, and between the 3rd DBI tertile and fewer hours of physical activity and fewer days being outside (Table 3). For comparison, the associations between the DBI and these outcomes corresponded with several years of decline in ADLs (2nd tertile DBI = 0.17 [95% CI 0.08–0.25], 3rd tertile DBI = 0.19 [95% CI 0.09–0.29] vs age = 0.04 [95% CI 0.036–0.048]), several years of decline in hours of physical activity (3rd tertile DBI = −0.10 [95% CI −0.17 to −0.03] vs age = −0.02 [95% CI −0.024 to −0.016]), and days being outside (3rd tertile DBI = −0.09 [95% CI −0.17 to −0.02] vs age = −0.02 [95% CI −0.026 to 0.018]). After controlling for the previously mentioned covariates, associations between a higher DBI and cognitive function, distance walked and time needed to complete the 4-m walk test were no longer significant.

Discussion

This longitudinal analysis of data from aged care residents demonstrated significant associations between a higher exposure to anticholinergic and sedative medications (as measured with the DBI) and poorer ADLs, fewer hours of physical activity, and fewer days being outside. These associations were adjusted for sex; age; dementia; presence of neurological, psychiatric, cardiovascular, oncological, and pulmonary comorbidity; fractures; depressive symptoms; and medications excluded from the DBI. The relevance of these findings is underlined by the observation that these associations were equal to several years of decline on these outcomes. Thus, the present findings are an important addition to previous cross-sectional analyses that were mainly conducted in samples of community-dwelling older individuals. The present findings also complement previous research showing higher exposure to anticholinergic and sedative medications to be associated with increased fall risk[13] and decreased quality of life[14] in aged care residents. The importance of these findings is further underlined by the observation in the present study that more than a quarter of the medication prescriptions were for an anticholinergic or sedative medication, which was consistent with previous research.[17,25]

It is not entirely clear why the association of cumulative anticholinergic and sedative exposure with cognitive function did not remain significant after adjusting for covariates. The CPS, as a measure of cognitive function, has been extensively validated.[26] In our sample, there was no clear evidence for a restriction of range in CPS scores. It may be possible that in aged care residents of whom many have dementia, neurodegenerative processes caused by Alzheimer's disease with concomitant cerebrovascular damage may be a stronger driver of cognitive decline than anticholinergic and sedative medication use.

This study had several strengths. In addition to the use of validated and standardized outcome measures with ample variance, a strength of the study design was that data were collected longitudinally from a large number of residents from a substantial number of different aged care homes. Also, the fact that data were routinely collected for providing health care is likely to have reduced selection or volunteer bias, which provides support for the generalizability of the findings.

Table 3
Unadjusted and Adjusted Longitudinal Associations Between Exposure to Anticholinergic and Sedative Medications (DBI) and Outcomes of Cognitive and Physical Function

Outcomes	DBI	
	Unstandardized Regression Coefficients (95% CIs)	
	Unadjusted	Adjusted*
Cognitive Performance Scale†		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	0.07 (95% CI 0 to 0.14)	0.02 (95% CI −0.04 to 0.08)
2nd Tertile (DBI > 0.8–1.65)	0.12 (95% CI 0.05 to 0.2)	0.04 (95% CI −0.03 to 0.1)
3rd Tertile (DBI > 1.65)	0.15 (95% CI 0.07 to 0.23)	−0.02 (95% CI −0.09 to 0.05)
ADL Hierarchy Scale†		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	0.13 (95% CI 0.04 to 0.22)	0.07 (95% CI −0.02 to 0.15)
2nd Tertile (DBI > 0.8–1.65)	0.27 (95% CI 0.18 to 0.36)	**0.17 (95% CI 0.08 to 0.25)**
3rd Tertile (DBI > 1.65)	0.37 (95% CI 0.27 to 0.47)	**0.19 (95% CI 0.09 to 0.29)**
Distance Walked‡		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	−0.09 (95% CI −0.18 to 0)	−0.05 (95% CI −0.14 to 0.04)
2nd Tertile (DBI > 0.8–1.65)	−0.16 (95% CI −0.24 to −0.07)	−0.07 (95% CI −0.16 to 0.02)
3rd Tertile (DBI > 1.65)	−0.25 (95% CI −0.35 to −0.15)	−0.09 (95% CI −0.19 to 0.01)
Timed 4-meter walk test†		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	0.18 (95% CI −0.39 to 0.75)	−0.03 (95% CI −0.59 to 0.53)
2nd Tertile (DBI > 0.8–1.65)	0.36 (95% CI −0.22 to 0.95)	−0.16 (95% CI −0.73 to 0.41)
3rd Tertile (DBI > 1.65)	0.75 (95% CI 0.1 to 1.4)	−0.09 (95% CI −0.76 to 0.58)
Hours of Physical Activity‡		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	−0.04 (95% CI −0.1 to 0.02)	−0.03 (95% CI −0.09 to 0.03)
2nd Tertile (DBI > 0.8–1.65)	−0.09 (95% CI −0.15 to −0.03)	−0.06 (95% CI −0.12 to 0)
3rd Tertile (DBI > 1.65)	−0.15 (95% CI −0.22 to −0.08)	**−0.10 (95% CI −0.17 to −0.03)**
Days being Outside‡		
No exposure (DBI = 0)	Reference	Reference
1st Tertile (DBI ≤ 0.8)	−0.04 (95% CI −0.1 to 0.03)	−0.03 (95% CI −0.1 to 0.04)
2nd Tertile (DBI > 0.8–1.65)	−0.08 (95% CI −0.15 to −0.02)	−0.06 (95% CI −0.13 to 0)
3rd Tertile (DBI > 1.65)	−0.12 (95% CI −0.2 to −0.05)	**−0.09 (95% CI −0.17 to −0.02)**

NOTE. Bold values are statistically significant ($P < .05$).

*Adjusted for sex, age, dementia, other neurological, psychiatric, cardiovascular, oncological comorbidity, pulmonary comorbidity, fractures, depressive symptoms, and medications not included in the DBI. Higher score indicates.

†Poorer functioning.

‡Better functioning.

Measurement of cumulative exposure to anticholinergic and sedative medications with the DBI has 3 main advantages for research. First, the DBI is feasible and noninvasive, as it is based on patients' medication prescriptions and does not require blood sampling. Second, the DBI takes the dosage of each anticholinergic and sedative medication into account, thus arriving at a more precise estimate of exposure. Third, the DBI includes a wide array of medications with anticholinergic and sedative properties. A previous systematic review supported the adequacy of the use of the DBI in longitudinal research as a measure of cumulative anticholinergic and sedative exposure.[27]

Potential limitations should be mentioned as well. As in all observational studies, we cannot rule out residual confounding. However, we attempted to minimize confounding by excluding participants with potential problem drinking behavior and by adjusting for relevant neurological, psychiatric, cardiovascular, and other comorbidities and the number of prescribed medications other than those included in the DBI. We also acknowledge that different measures of anticholinergic exposure may include different medications and weight them differently. As a result, the DBI and other scales may yield different exposure estimates and may also find different associations with functional decline.[28] Furthermore, we admit that the time interval of 60 days that separated assessment occasions was somewhat arbitrarily chosen. The main reason is that we wanted to be able to study associations over time, and hence chose 60 days. It should be noted that the vast majority of the follow-up assessments were done after 60 days. Also, in-between follow-up assessments that took place earlier than 60 days, mostly concerned a sudden acute clinical change. Thus, including these observations could have distorted longitudinal associations. Finally, although the assessment methods of the outcomes of the present study have been extensively validated, these were predominantly rating scales. With specific regard to the outcome "days being outside," this may not only have reflected physical function but also nursing staff's opportunity to walk outside with residents in a wheelchair. It may therefore be worthwhile to complement the CPS with more extensive and objective neuropsychological tests of cognitive function and the timed 4-m walk test with additional objective performance tests of physical function.

Conclusions and Implications

An important implication of the present findings for clinical practice is that aged care residents should be monitored with the DBI tool. The DBI is a feasible and noninvasive way to detect medication-induced aggravation of functional impairment, which may already be compromised owing to preexistent frailty in aged care residents. Deprescribing of potentially inappropriate medications, including anticholinergic and sedative medications, was previously found to be successful in nursing home residents.[29–31] In future research of physical function in frail aged care residents and older community-dwelling persons, the DBI may be considered as a covariate in analyses. Taken together, we conclude that there are significant and relevant longitudinal associations between elevated cumulative exposure to anticholinergic and sedative medications and measures of functional impairment but not cognitive impairment in residents from aged care homes.

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Appendix

Appendix 1 Overview of outcomes

Outcome	Description	Scoring
Cognitive Function		
Cognitive Performance Scale	A flow chart based on nursing staff's ratings of residents' cognitive impairment. In a sequence of steps, nursing staff ratings of patients' cognitive impairment are being classified from being 'intact' to being 'very severely impaired'. First, residents' decision-making capacity is classified. If this is intact and patients can subsequently make themselves understood and their memory turns out to be intact, they will be rated as having 'intact' cognitive functioning. If on the other hand, patients have problems concerning decision-making, making themselves understood and if they have memory problems, they will be rated as having a compromised cognitive function. Depending on the severity of their problems, the rating ranges from 'mild to 'very severe impairment'.	7-point scale (0, intact; 6, very severe impairment)
Activities of daily living		
ADL Hierarchy Scale	A flow chart based on nursing staff's ratings of patients' functional dependence. In a sequence of steps, patients' functional dependence is classified with regard to the following ADLs: personal hygiene, toilet use, locomotion, and eating. Ratings range from 'no impairment' to 'total dependence'. The ADL Hierarchy scale groups activities of daily living according to the stage of the disablement process in which they occur. ADL losses associated with severe impairment, eg, eating, are assigned higher scores of dependence than ADLs associated with less severe degrees of functional impairment.	Total score (0, no independent; 6 total dependence)
Physical function		
Performance Test	A timed 4-meter walk test.	Seconds (higher score indicates more disability, scores are censored to maximum of 30 seconds)
Distance Walked	Farthest distance walked at one time without sitting down in the past 3 days (with support as needed)	6-point scale (0, did not walk; 5 > 1 km)
Hours of Physical Activity	Hours of physical activity in the past 3 days	5-point scale (0, none; 4, > four hours)
Days being Outside	Number of days in the past 3 days that a resident came outside	4-point scale (0, no days out; 3, three days)

Abbreviation: ADL, Activities of Daily Living.

Appendix 2 Example to illustrate calculation of DBI

Aged Care Resident	Medications	ATC Code	Total Prescribed Daily Dose	Recommended Lowest Oral Dose	*DBI value per medication*	
342	MONOCEDOCARD	C01DA14	25	25	0.50	
342	TRAMADOL	N02AX02	100	50	0.67	
342	SEVREDOL	N02AA01	10	40	0.20	
342	TEMAZEPAM	N05CD07	10	10	0.50	+
				DBI	1.87	