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Research Article

# Long-Term Exposure to Anticholinergic and Sedative Medications and Cognitive and Physical Function in Later Life

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## Abstract

**Background:** Anticholinergic and sedative medications are frequently prescribed to older individuals. These medications are associated with short-term cognitive and physical impairment, but less is known about long-term associations. We therefore examined whether over 20 years cumulative exposure to these medications was related to poorer cognitive and physical functioning.

**Methods:** Older adult participants of the Longitudinal Aging Study Amsterdam (LASA) were followed from 1992 to 2012. On seven measurement occasions, cumulative exposure to anticholinergic and sedative medications was quantified with the drug burden index (DBI), a linear additive pharmacological dose–response model. Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE), Alphabet Coding Task (ACT, three trials), Auditory Verbal Learning Test (AVLT, learning and retention condition), and Raven Colored Progressive Matrices (RCPM, two trials). Physical functioning was assessed with the Walking Test (WT), Cardigan Test (CT), Chair Stands Test (CST), Balance Test (BT), and self-reported Functional Independence (FI). Data were analyzed with linear mixed models adjusted for age, education, sex, living with a partner, BMI, depressive symptoms, comorbidities (cardiovascular disease, diabetes, cancer, COPD, osteoarthritis, CNS diseases), and prescribed medications.

**Results:** Longitudinal associations were found of the DBI with poorer cognitive functioning (less items correct on the three ACT trials, AVLT learning condition, and the two RCPM trials) and with poorer physical functioning (longer completion time on the CT, CST, and lower self-reported FI).

**Conclusions:** This longitudinal analysis of data collected over 20 years, showed that higher long-term cumulative exposure to anticholinergic and sedative medications was associated with poorer cognitive and physical functioning.

**Keywords:** Neuropsychology, Mobility impairment, Polypharmacy, Anti-muscarinics; Benzodiazepines

Polypharmacy (ie, the prescribing of ≥5 medications) is a prevalent condition in older people (1,2) that increases the risk of adverse drug effects and consequences. Particularly harmful are medications with anticholinergic and sedative properties, which are prescribed to up to a quarter of older persons (3,4). These medications have been associated with poorer cognitive functioning (5–9), poorer physical functioning (5,9,10), and increased risk of hip fractures (11). Anticholinergic medications exert central antagonistic effects on muscarinic receptors thereby inhibiting acetylcholine transmission within hippocampal, fusiform, inferior prefrontal cortical, and striatal areas (12–14). Sedative medications from the group of benzodiazepines increase the inhibitory effects of GABAergic neurons (15). Anticholinergic and sedative medications exert peripheral antagonistic effects as well. Anticholinergic medications inhibit acetylcholine-mediated muscle contractions and glandular secretion, leading to constipation and dry mouth (12). Sedative medications are known to impair neuromuscular processing important for maintaining balance (16) and to impair muscle strength (17). Various medications including those for the alimentary and respiratory tracts, as well as psychotropic, cardiovascular and pain medications have anticholinergic and/or sedative properties.

Given the prevalence of cognitive and physical impairment as well as polypharmacy and the frequent prescribing of anticholinergic and sedative medications in older people, it is important to assess the associations of prolonged cumulative exposure to anticholinergic and sedative medications with cognitive and physical functioning. However, the majority of studies that examined these associations had a short to medium follow-up duration (6,18–20) while relatively few studies had a longer follow-up duration (21,22).

Less is therefore known about prolonged exposure to anticholinergic and sedative medications. Extrapolations of short- to medium-term findings to the long term are not necessarily valid. Although anticholinergic exposure was indeed found to exert potentially irreversible brain atrophy (23), tolerance to these medications is also known to occur and could actually reduce adverse effects over time (13).

In the present study, we therefore examined older individuals' cumulative exposure to anticholinergic and sedative medications over up to 20 years. Exposure was quantified with the drug burden index (DBI) (24), which is a linear additive pharmacological dose–response model. The DBI summates the standardized doses of anticholinergic and sedative medications into an overall value of exposure (see Cumulative Exposure to Anticholinergic and Sedative Medications section). The DBI is based on patients' medication prescriptions and does not require blood withdrawal. It is therefore noninvasive and feasible for large-scale routine use.

Accordingly, we examined whether prolonged cumulative exposure to anticholinergic and sedative medications over up to 20 years was associated with poorer cognitive and physical functioning in older community-dwelling individuals.

## Methods

### Participants and Study Design

The Longitudinal Aging Study Amsterdam (LASA study) is a Dutch nationally representative prospective cohort study of community-dwelling older adults. Participants were aged 55–85 years at baseline in 1992/1993. The primary aims of the LASA study have been to investigate the determinants, trajectories, and consequences of physical, cognitive, emotional, and social functioning in older adults (25). The sample was recruited from registries of 11 municipalities in three geographic regions in The Netherlands. Older people and men were oversampled to anticipate differential attrition with regard to age and sex. Data have been collected since the baseline measurement at follow-up measurement occasions separated by 3-year intervals. For the present analyses, we used the data from 20 years collected at 7 measurement occasions until 2011/2012 (25). Data were collected by trained interviewers in participants' homes through a main interview lasting on average 1 hour and 45 minutes, a self-report questionnaire, and an additional medical interview. All participants gave informed consent and the medical ethical committee of the VU Medical Center approved the study. For the present analyses, we excluded participants with potential drinking problems in the past and present (ie, ≥6 glasses of alcohol at least once a week or 21 days per month drinking ≥4 glasses), and those who reported to have severe hearing and vision problems. This was done, because excessive alcohol consumption and sensory deficits are likely to bias performance on tests of cognitive and physical functioning (see Outcomes section).

### Cumulative Exposure to Anticholinergic and Sedative Medications

As part of the medical interview conducted at each measurement occasion, participants were asked to show their medication containers. The name, dose, frequency of intake, and duration of use of every medication was recorded on a standardized form. All medications were recoded into the codes of the Anatomical Therapeutic Chemical (ATC) classification system (26). Missing doses were imputed by mean doses in the study population. At each measurement occasion, we calculated cumulative exposure to anticholinergic and sedative medications using the DBI formula (24):

$$\mathbf{DBI} = \sum \frac{D}{\delta + D}$$

where D stands for the prescribed daily dose of an individual medication and δ represents the minimum daily oral dose according to Dutch prescribing guidelines (24). In a systematic manner, we previously compiled a list of medications with anticholinergic and/or sedative potency (27). Only medications for which a dose could be determined were considered. Therefore, only medications that were prescribed regularly by a physician at the time of the examination were included, while medications taken "pro re nata" were excluded from the DBI calculation.

### Outcomes

In conjunction with measuring global cognitive functioning with the Mini-Mental State Examination (28) (max. 30 points), cognitive functioning in the following specific domains (neuropsychological tests) were collected: selective and sustained attention [Alphabet Coding Task, number of correct responses on three trials of 1 minute (29)], learning [Auditory Verbal Learning Test, three learning trials (30)], episodic memory [Auditory Verbal Learning Test, retention condition (30)] and fluid intelligence [Raven Colored Progressive Matrices, subset A and B, 24 items (31)]. Outcomes of physical functioning were time (in seconds) to perform validated objective function tests (32) of lower extremities (Chair Stands Test, Walking Test, Balance Test) and upper extremities (Cardigan Test). In addition, participants rated their functional independence in daily life on a self-reported measure (Functional Independence Scale, 6 items on a 4-point scale). Outcomes were assessed on all measurement

occasions except for the Raven Colored Progressive Matrices which were not assessed at the seventh measurement occasion (2011–2012), and the Balance Test and the Functional Independence Scale which were not assessed at the first measurement occasion (1992–1993). See Supplementary Appendix 1 for a further description of these outcomes.

### Covariates

We assessed time independent and time dependent covariates. Time independent covariates included sex and education (years). Time dependent covariates included age, living with a partner (no/yes), BMI, depressive symptoms, number of comorbidities, and prescribed medications. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression (CES-D) scale. The CES-D scale consists of 20 items with 4-point scales ranging from 0 "rarely or never" to 3 "mostly or always." Its score ranges from 0 to 60, with higher scores indicating more depressive symptoms (33). Comorbidities included the most prevalent comorbidities in the Netherlands in people aged 55 years and older. These were heart disease (myocardial infarction, angina pectoris, coronary artery disease, congestive heart failure, and arrhythmias), diabetes, peripheral vascular disease, stroke, cancer, chronic obstructive pulmonary disease and asthma, osteoarthritis, and nervous system diseases (including Parkinson's disease).

### Statistical Analysis

Participants' background characteristics were summarized with descriptive statistics. In line with previous studies, we compared participants who had no anticholinergic and sedative exposure (DBI = 0) with those who had medium exposure (0 < DBI < 1), and high exposure (DBI ≥ 1) on baseline characteristics. We also examined Spearman's rank correlations between measures of cognitive and physical functioning with participants' characteristics. Differential attrition was examined by studying if participants' baseline characteristics predicted their completion of the final follow-up measurement occasion using multivariable logistic regression analysis.

Outliers or values >99th percentile on the outcome variables of cognitive and physical functioning were replaced by the value of the 99th percentile of each variable. Owing to skewed distributions, the Walking Test, Cardigan Test, the MMSE and the Raven Colored Progressive Matrices variables were log-transformed, while the Balance Test was dichotomized. Missing values were imputed. For the DBI and number of comorbidities, missing values were assumed to reflect absence and coded as zero. Multiple imputation was performed for missing values of education (years), CES-D, and BMI. Imputed values were obtained in three rounds and missing values were then replaced by the mean value of these three imputations. Missing values on outcomes of cognitive and physical functioning were not imputed.

In multivariable linear mixed models, we examined longitudinal relationships between cumulative anticholinergic and sedative exposure measured with the DBI (independent variable) and outcomes of cognitive and physical functioning (dependent variables). To account for dependence of repeated measurements within participants, these models included a random intercept and random slope at the participant level. Thereby, these models allow time-series to vary between individuals. Linear mixed models also allow for a different number of repeated measures per participant and are appropriate for dealing with missing data in the repeatedly measured outcome variables. The DBI categories of no, medium, and high exposure were represented by dummy variables. Analyses were adjusted for sex, education (years), age, living with a partner, BMI, depressive symptoms, number of comorbidities, and prescribed medications. However, to anticipate collinearity, adjustment was not made for the total number of medications but rather for the number of medications excluded from the DBI calculation.

In a sensitivity analysis, we calculated a DBI for anticholinergic and sedative medications that had been prescribed for at least ≥1 year(s) before each measurement occasion and we repeated the main analyses. For all parameters, we calculated 95% confidence intervals (95% CIs) and *p* values. Data transformation and imputation of missing values, descriptive analyses, and differential attrition analyses were done with SPSS Statistics for Windows, version 24.0 (IBM). Linear mixed models were conducted with MLwiN, version 2.32 (Centre for Multilevel Modelling, University of Bristol, UK).

## Results

Of the 3,107 individuals who consented to participate, 291 were excluded because they had no medication use reported and 189 were excluded for other reasons, leaving 2,627 participants eligible at baseline. A total of 2,252 participants completed the first follow-up and 726 completed the final sixth follow-up 20 years later (Figure 1). Baseline demographic and clinical characteristics are presented in Table 1. Of the eligible participants, 52% (*N* = 1,378) were women and 64% (*N* = 1,686) were living with a partner. On average, they were 70.3 (±8.7) years, had received 8.8 (±3.3) years of education, 24% (*N* = 627) reported to have ≥2 comorbidities, and 31% (*N* = 815) were prescribed ≥3 medications.

Of the eligible participants, 75% (*N* = 1,974) had no exposure, 19% (*N* = 493) had medium exposure and 6% (*N* = 160) had high cumulative exposure to anticholinergic and sedative medications as measured with the DBI at baseline. On subsequent follow-up measurement occasions, percentages of participants with no exposure ranged from 68% to 78%, with medium exposure from 15% to 22% and with high cumulative exposure from 6% to 12%.

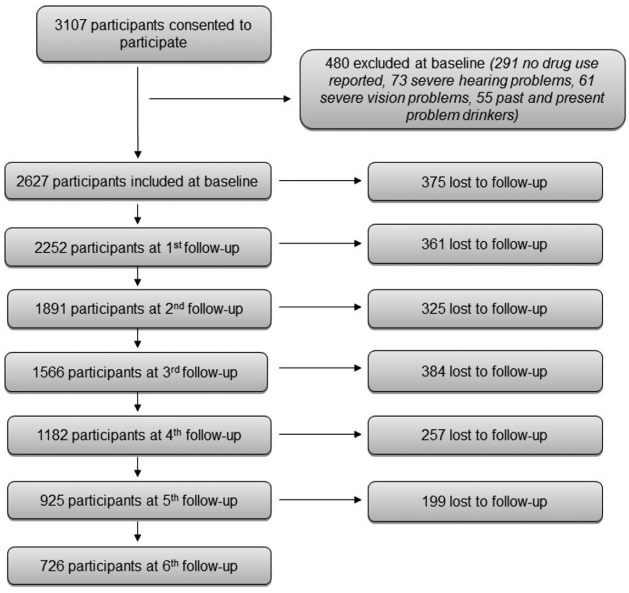


**Figure 1.** Flowchart of inclusion of participants.

**Table 1.** Characteristics of Study Participants

| | All Participants | | Participation at Final Measurement Occasion | | | |
|---|---|---|---|---|---|---|
| | | | Yes | | No | |
| Characteristics | *N* | Statistic | *N* | Statistic | *N* | Statistic |
| *Demographic/lifestyle* | | | | | | |
| *N* (%) sex | 2,627 | | 726 | | 1,901 | |
| Men | | 1,249 (48) | | 280 (39) | | 969 (51) |
| Women | | 1,378 (52) | | 446 (61) | | 932 (49) |
| *M* (*SD*) age (years) | 2,627 | 70.3 (8.7) | 726 | 63.5 (6.0) | 1,901 | 72.9 (8.1) |
| *M* (*SD*) education (years) | 2,620 | 8.8 (3.3) | 726 | 9.4 (3.3) | 1,901 | 8.6 (3.3) |
| *N* (%) living with partner | 2,627 | | 726 | | 1,901 | |
| No | | 941 (36) | | 175 (24) | | 766 (40) |
| Yes | | 1,686 (64) | | 551 (76) | | 1135 (60) |
| *M* (*SD*) baseline BMI | 2,383 | 26.8 (4.1) | 726 | 26.6 (3.7) | 1,901 | 27.0 (4.0) |
| Median (IQR) depressive symptoms[a] | 2,598 | 6 (2–11) | 726 | 6.5 (7.0) | 1,901 | 8.2 (7.8) |
| *Comorbidities* | | | | | | |
| *N* (%) comorbidities | 2,627 | | 726 | | 1,901 | |
| 0 | | 1,058 (40) | | 380 (52) | | 678 (36) |
| 1 | | 942 (36) | | 243 (34) | | 699 (37) |
| ≥2 | | 627 (24) | | 103 (14) | | 524 (28) |
| *N* (%) prescribed medications | 2,627 | | 726 | | 1,901 | |
| 0 | | 896 (34) | | 340 (47) | | 556 (29) |
| 1 | | 524 (20) | | 164 (23) | | 360 (19) |
| 2 | | 392 (15) | | 84 (12) | | 308 (16) |
| ≥3 | | 815 (31) | | 138 (19) | | 677 (36) |
| *N* (%) number prescribed non-DBI medications | 2627 | | 726 | | 1901 | |
| 0 | | 1,341 (51) | | 464 (64) | | 877 (46) |
| 1 | | 605 (23) | | 151 (21) | | 454 (24) |
| 2 | | 405 (15) | | 76 (11) | | 329 (17) |
| ≥3 | | 276 (11) | | 35 (5) | | 241 (13) |
| *N (%)* DBI | 2,627 | | 726 | | 1,901 | |
| None (0) | | 1,974 (75) | | 613 (84) | | 1,361(72) |
| Medium (0–1) | | 493 (19) | | 99 (14) | | 394 (21) |
| High (≥1) | | 160 (6) | | 14 (2) | | 146 (8) |
| *Cognitive functioning* | | | | | | |
| Median (IQR) MMSE score[b,§] | 2,616 | 28 (26–29) | 724 | 28 (27–29) | 1,892 | 27 (25–29) |
| *M* (*SD*) Alphabet Coding Task[c,§] | | | | | | |
| Trial 1 | 2,400 | 22.3 (7.7) | 678 | 26.3 (6.6) | 1,722 | 20.7 (7.5) |
| Trial 2 | 2,392 | 24.4 (7.8) | 677 | 28.4 (6.6) | 1,715 | 22.8 (7.7) |
| Trial 3 | 2,387 | 25.4 (7.8) | 676 | 29.6 (6.4) | 1,711 | 23.8 (7.7) |
| *M* (*SD*) AVLT | | | | | | |
| Word learning[d,§] | 2,425 | 7.9 (2.5) | 682 | 9.1 (2.3) | 1,743 | 7.4 (2.5) |
| Retention[e,§] | 2,425 | 61.1 (26.1) | 682 | 68.4 (20.4) | 1,743 | 58.2 (27.5) |
| *M* (*SD*) Raven Colored Progressive Matrices[§] | | | | | | |
| Set A | 2,464 | 10.1 (1.8) | 710 | 10.6 (1.4) | 1,754 | 9.9 (1.9) |
| Set B | 2,446 | 7.8 (2.8) | 710 | 9.1 (2.4) | 1,736 | 7.3 (2.8) |
| *Physical functioning* | | | | | | |
| *M* (*SD*) Walking Test[f,†] | 2,440 | 8.2 (3.7) | 707 | 6.9 (2.3) | 1,733 | 8.8 (4.0) |
| *M* (*SD*) Cardigan Test[f,†] | 2,566 | 13.4 (6.9) | 721 | 10.9 (4.2) | 1,845 | 14.4 (7.5) |
| Median (IQR) Chair Stands Test[f,†] | 2,619 | 12 (10–15) | 723 | 11 (9–13) | 1,896 | 13 (11–15) |

*Note:* Higher score indicates †: poorer functioning §: better functioning. BMI = body mass index; IQR = interquartile range; DBI = Drug Burden Index; MMSE = Mini-Mental State Examination; AVLT = Auditory Verbal Learning Test.

[a]As measured with the Center for Epidemiologic Studies Depression (CES-D) scale.

[b]Max. 30 points.

[c]Each trial lasting 1 min.

[d]Maximum score achieved on three trials.

[e]Number of retained words/maximum score and expressed as a percentage.

[f]Number of seconds needed for task.

Multivariable logistic regression analysis demonstrated that the baseline characteristics age (odds ratio [OR]: 1.16, 95% CI: 1.15–1.18), depressive symptoms (OR: 1.02, 95% CI: 1.00–1.03), and number of comorbidities (OR: 1.21, 95% CI: 1.07–1.37) were associated with an increased risk of being lost to follow-up at the final measurement occasion, whereas the characteristics female sex (OR:

**Table 2.** Baseline Characteristics of Participants in Different DBI Categories

| Characteristics | None (DBI = 0) (*N* = 1,974) | Medium (0 < DBI < 1) (*N* = 493) | High (DBI ≥ 1) (*N* = 160) |
|---|---|---|---|
| *N* (%) female participants | 1,017 (52) | 275 (56) | 86 (54) |
| *M* (*SD*) age (years) | 69.3 (8.6) | 72.6 (8.3) | 75.2 (7.3) |
| *M* (*SD*) education (years) | 8.9 (3.3) | 8.6 (3.2) | 8.1 (3.2) |
| *N* (%) living with a partner | 1,323 (67) | 272 (55) | 91 (57) |
| *M* (*SD*) BMI | 26.8 (3.8) | 27.0 (4.3) | 27.2 (4.7) |
| *M* (*SD*) depressive symptoms[a] | 6.8 (6.7) | 9.9 (8.9) | 11.9 (9.9) |
| *N* (%) with ≥2 comorbidities[b] | 358 (18) | 178 (36) | 91 (57) |
| *N* (%) with ≥3 non-DBI medications prescribed | 130 (7) | 106 (22) | 40 (25) |

BMI = body mass index; DBI = drug burden index.

[a]As measured with the Center for Epidemiologic Studies Depression (CES-D) scale.

[b]Includes chronic obstructive pulmonary disease and asthma, heart disease, diabetes, peripheral arterial disease, incontinence, rheumatoid arthritis, and cancer.

0.45, 95% CI: 0.36–0.56), years of education (OR: 0.96, 95% CI: 0.93–0.99), and living with partner (OR: 0.77, 95% CI: 0.61–0.98) were associated with a decreased risk of being lost to follow-up at the final measurement occasion. BMI (OR: 1.03, 95% CI: 0.99–1.05), number of medications (OR: 1.00, 95% CI: 0.99–1.00), and medium versus no exposure (OR: 1.07, 95% CI: 0.80–1.42) and high versus no exposure (OR: 1.80, 95% CI: 0.97–3.36) to anticholinergic and sedative medications as measured with the DBI were not associated with being lost to follow-up at the final measurement occasion.

Of the 29,091 identified medication prescriptions, doses were imputed for 1,032 prescriptions (3.5%). A total of 5,443 (19%) prescriptions were for an anticholinergic or sedative medication including cardiovascular medications (32%), psycholeptic (29%) and psychoanaleptic medications (8%), other medications for the nervous system (10%), drugs for the respiratory tract (9%), for the alimentary tract (7%), and for the musculo-skeletal system (3%).

At baseline, participants with medium or high cumulative exposure to anticholinergic and sedative medications were slightly older, less often living with a partner, had more depressive symptoms, had more often ≥2 comorbidities and more often ≥3 non-DBI medications prescribed than those with no exposure (Table 2). Small to moderate associations were observed for sex, age, educational level, marital status, BMI, depressive symptoms, number of comorbidities, and non-DBI medications with measures of cognitive and physical functioning (Supplementary Appendix 2).

Multivariable linear mixed model analyses of data collected over up to 20 years demonstrated that, after adjusting for covariates, cumulative anticholinergic and sedative exposure was associated with poorer outcomes of cognitive functioning. Participants with medium and high exposure had poorer performance on the three trials of the Alphabet Coding Task, and the learning condition of the Auditory Verbal Learning Test. Moreover, those with high exposure had also poorer performance on the two trials of the Raven Colored Progressive Matrices. For the Alphabet Coding Task, the strengths of these associations (βs ranging from −0.84 to −0.94) were weaker than the associations between sex and these tests (βs ranging from 1.52 to 1.92). For the Raven Colored Progressive Matrices, the strengths of these associations (βs ranging from 0.07 to 0.08, log-transformed) were comparable to the associations of sex and these tests (βs ranging from 0.05 to −0.07, log-transformed). No associations were found with global cognitive functioning as measured with the MMSE and retention on the Auditory Verbal Learning Test.

Associations were also found between the DBI and poorer physical functioning. Participants with medium and high exposure had poorer performance on the Chair Stands Test than participants with no exposure. Moreover, those with high exposure had poorer performance on the Cardigan Test and had lower Functional Independence than participants with no exposure (Table 3). The strengths of these associations (βs = 0.02, 0.54, and −1.17) were, respectively, comparable with the associations between sex and the Cardigan Test (β = −0.09), Chair Stands Test, (β = 0.41), and Functional Independence (β = −0.95). No associations were observed for the Walking Test and the Balance Test. See Supplementary Appendix 3 for unadjusted results and results from the sensitivity analysis with a DBI calculated for anticholinergic and sedative medications that had been prescribed for at least ≥1 year(s).

## Discussion

This longitudinal analysis of data collected over 20 years showed that higher long-term cumulative exposure to anticholinergic and sedative medications was found to be associated with poorer cognitive and physical functioning. Given the follow-up period of the LASA study spanning two decades of late adulthood, the present findings are an important complement to previous findings from cross-sectional studies as well as longitudinal studies with shorter follow-ups. Extrapolations of short to medium term findings to the long term may not be necessarily valid. Our findings seem to be consistent with the previously observed association between anticholinergic exposure and potentially irreversible brain atrophy (23) while they do not seem to confirm tolerance to these medications and likewise a reduction of adverse effects over time (13).

The associations between higher cumulative exposure to anticholinergic and sedative medications and poorer cognitive functioning are in line with several previous findings (20,24,34) but inconsistent with others (6,19,22). This variability between studies can be attributed to differences between studies regarding use of different measures of cumulative drug exposure, different measures of physical and cognitive outcomes and the study of different populations (35). The associations with poorer physical functioning are in line with previous cross-sectional studies and studies with shorter follow-ups (5,10,24). Of note, the associations found in the present study between the DBI and physical functioning were not only found on performance tests (the Walking and the Cardigan Test), which reflect what people can actually do, but were also found for

**Table 3.** Twenty-Year Associations Between Cognitive and Physical Functioning and Cumulative Anticholinergic and Sedative Exposure (DBI) Adjusted for Covariates

| | | | Measurement Occasions (y) (*M*, *SD*) | | | Adjusted Parameter | | |
|---|---|---|---|---|---|---|---|---|
| Outcome × DBI | 92/93 | 95/96 | 98/99 | 01/02 | 05/06 | 08/09 | 11/12 | (95% CI)[a] |
| *N* | 2,627 | 2,252 | 1,891 | 1,566 | 1,182 | 925 | 726 | |
| Cognitive functioning | | | | | | | | |
| MMSE score[b] | | | | | | | | |
| None (DBI = 0) | 27.3 ± 2.6 | 27.1 ± 2.9 | 27.1 ± 3.2 | 26.9 ± 3.4 | 26.9 ± 3.2 | 26.8 ± 3.3 | 27.0 ± 3.1 | Reference |
| Medium (0 < DBI < 1) | 26.5 ± 3.5 | 26.0 ± 3.9 | 26.4 ± 3.5 | 27.1 ± 2.9 | 26.9 ± 2.8 | 26.8 ± 3.0 | 27.1 ± 2.5 | β 0.01 (–0.02; 0.04)[a,†] |
| High (DBI ≥ 1) | 25.8 ± 3.6 | 26.2 ± 3.3 | 26.3 ± 3.5 | 26.4 ± 3.3 | 26.2 ± 3.4 | 26.8 ± 2.6 | 26.0 ± 3.7 | β 0.03 (–0.01; 0.08)[a,†] |
| Alphabet Coding Task[d] | | | | | | | | |
| Trial 1 | | | | | | | | |
| None (DBI = 0) | 23.1 ± 7.7 | 21.9 ± 7.3 | 22.4 ± 7.2 | 23.6 ± 7.2 | 23.8 ± 6.8 | 22.8 ± 7.4 | 21.9 ± 7.2 | Reference |
| Medium (0 < DBI < 1) | 20.6 ± 7.2 | 19.9 ± 7.3 | 20.7 ± 7.2 | 22.1 ± 7.2 | 21.9 ± 6.6 | 21.5 ± 7.4 | 21.2 ± 7.1 | **β –0.31 (–0.58; –0.05)**[e,§] |
| High (DBI ≥ 1) | 18.1 ± 6.7 | 18.7 ± 6.7 | 19.2 ± 7.3 | 20.2 ± 6.9 | 19.6 ± 7.2 | 20.2 ± 6.2 | 18.9 ± 7.1 | **β –0.84 (–1.25; –0.42)**[e,§] |
| Trial 2 | | | | | | | | |
| None (DBI = 0) | 25.2 ± 7.9 | 24.0 ± 7.6 | 24.3 ± 7.4 | 25.4 ± 7.6 | 25.6 ± 7.2 | 24.7 ± 7.5 | 24.2 ± 7.2 | Reference |
| Medium (0 < DBI < 1) | 22.6 ± 7.3 | 21.9 ± 7.8 | 22.6 ± 7.4 | 23.8 ± 7.3 | 24.1 ± 7.2 | 23.2 ± 7.2 | 22.8 ± 7.9 | **β –0.28 (–0.55; –0.01)**[e,§] |
| High (DBI ≥ 1) | 20.0 ± 7.1 | 20.5 ± 7.5 | 20.9 ± 7.1 | 21.6 ± 7.0 | 22.2 ± 7.3 | 22.0 ± 6.8 | 21.1 ± 7.6 | **β –0.94 (–1.34; –0.55)**[e,§] |
| Trial 3 | | | | | | | | |
| None (DBI = 0) | 26.2 ± 7.8 | 25.1 ± 7.7 | 25.4 ± 7.4 | 26.3 ± 7.5 | 26.5 ± 7.3 | 25.7 ± 7.3 | 24.9 ± 7.1 | Reference |
| Medium (0 < DBI < 1) | 23.9 ± 7.5 | 22.8 ± 7.8 | 23.3 ± 7.7 | 24.7 ± 7.2 | 25.1 ± 7.2 | 24.2 ± 7.4 | 23.4 ± 8.1 | **β –0.36 (–0.63; –0.09)**[e,§] |
| High (DBI ≥ 1) | 20.9 ± 7.0 | 21.5 ± 7.5 | 22.0 ± 7.2 | 22.6 ± 6.9 | 22.8 ± 7.7 | 23.1 ± 6.6 | 21.9 ± 7.7 | **β –0.92 (–1.31; –0.54)**[e,§] |
| 15 AVLT Learning[f] | | | | | | | | |
| None (DBI = 0) | 8.0 ± 2.5 | 8.2 ± 2.6 | 8.1 ± 2.7 | 8.8 ± 2.7 | 7.6 ± 2.7 | 7.4 ± 2.5 | 8.3 ± 2.8 | Reference |
| Medium (0 < DBI < 1) | 7.6 ± 2.4 | 7.5 ± 2.7 | 7.5 ± 2.9 | 8.3 ± 2.7 | 8.1 ± 2.6 | 6.7 ± 2.4 | 8.3 ± 2.5 | **β –0.14 (–0.26; –0.02)**[§] |
| High (DBI ≥ 1) | 6.6 ± 2.4 | 7.4 ± 2.7 | 7.5 ± 2.7 | 8.0 ± 2.9 | 6.8 ± 2.5 | 7.0 ± 2.3 | 7.7 ± 2.6 | **β –0.24 (–0.42; –0.07)**[§] |
| 15 AVLT Retention[g] | | | | | | | | |
| None (DBI = 0) | 62.4 ± 25.3 | 68.2 ± 25.9 | 65.0 ± 26.7 | 69.6 ± 24.8 | 65.3 ± 26.0 | 62.8 ± 27.0 | 67.6 ± 27.1 | Reference |
| Medium (0 < DBI < 1) | 57.9 ± 27.5 | 62.7 ± 28.6 | 62.4 ± 27.4 | 65.5 ± 26.7 | 67.2 ± 29.2 | 60.2 ± 20.9 | 66.1 ± 29.0 | β –1.50 (–2.94; –0.06)[§] |
| High (DBI ≥ 1) | 55.4 ± 28.5 | 64.5 ± 27.6 | 59.0 ± 26.9 | 69.6 ± 26.9 | 66.1 ± 29.0 | 61.6 ± 27.0 | 67.9 ± 28.9 | β –0.70 (–2.77; 1.36)[§] |
| Raven Colored Progressive Matrices[e] | | | | | | | | |
| Set A | | | | | | | | |
| None (DBI = 0) | 10.2 ± 1.7 | 10.3 ± 1.7 | 10.2 ± 1.8 | 10.3 ± 1.6 | 10.4 ± 1.6 | 10.1 ± 1.6 | —[h] | Reference |
| Medium (0 < DBI < 1) | 9.8 ± 1.8 | 9.6 ± 2.0 | 9.7 ± 1.9 | 9.9 ± 1.6 | 10.2 ± 1.6 | 10.0 ± 1.9 | —[h] | β 0.03 (–0.003; 0.06)[i,†] |
| High (DBI ≥ 1) | 9.4 ± 2.1 | 9.4 ± 1.9 | 9.5 ± 1.9 | 9.7 ± 1.8 | 9.8 ± 1.7 | 9.7 ± 1.8 | —[h] | **β 0.08 (0.03; 0.12)**[i,†] |
| Set B | | | | | | | | |
| None (DBI = 0) | 8.0 ± 2.8 | 8.1 ± 2.8 | 8.0 ± 2.8 | 8.1 ± 2.7 | 8.1 ± 2.6 | 8.1 ± 2.5 | —[h] | Reference |
| Medium (0 < DBI < 1) | 7.3 ± 2.8 | 6.8 ± 2.7 | 6.9 ± 2.7 | 7.4 ± 2.7 | 7.7 ± 2.7 | 7.6 ± 2.5 | —[h] | β 0.03 (–0.002; 0.06)[i,†] |
| High (DBI ≥ 1) | 6.8 ± 2.8 | 6.4 ± 2.7 | 6.9 ± 2.5 | 6.6 ± 2.9 | 7.1 ± 2.6 | 7.0 ± 2.4 | —[h] | **β 0.07 (0.02; 0.11)**[i,†] |
| Physical functioning | | | | | | | | |
| Walking Test | | | | | | | | |
| None (DBI = 0) | 7.9 ± 3.3 | 7.9 ± 3.6 | 8.9 ± 4.7 | 9.0 ± 4.4 | 8.8 ± 4.2 | 9.3 ± 4.2 | 9.6 ± 4.3 | Reference |
| Medium (0 < DBI < 1) | 9.4 ± 4.5 | 9.4 ± 4.5 | 10.3 ± 5.1 | 9.7 ± 4.5 | 9.6 ± 4.5 | 10.7 ± 5.8 | 10.3 ± 5.0 | β 0.01 (0.00; 0.02)[j,†] |
| High (DBI ≥ 1) | 9.9 ± 4.7 | 10.1 ± 4.9 | 11.6 ± 6.1 | 11.0 ± 5.2 | 11.6 ± 5.5 | 12.2 ± 5.5 | 12.6 ± 5.9 | β 0.01 (0.00; 0.02)[j,†] |
| Cardigan Test | | | | | | | | |
| None (DBI = 0) | 12.9 ± 6.4 | 12.6 ± 6.4 | 13.0 ± 6.5 | 13.7 ± 8.0 | 13.7 ± 6.8 | 15.0 ± 7.8 | 15.9 ± 8.7 | Reference |
| Medium (0 < DBI < 1) | 14.7 ± 7.6 | 14.4 ± 8.1 | 14.5 ± 7.8 | 14.3 ± 8.8 | 14.9 ± 7.8 | 15.6 ± 8.7 | 15.7 ± 7.4 | β 0.00 (–0.01; 0.01)[j,†] |
| High (DBI ≥ 1) | 15.9 ± 8.9 | 15.7 ± 8.5 | 18.1 ± 11.2 | 15.8 ± 10.4 | 17.1 ± 8.9 | 16.7 ± 8.8 | 18.7 ± 10.1 | **β 0.02 (0.01; 0.04)**[j,†] |
| Chair Stands Test | | | | | | | | |
| None (DBI = 0) | 12.4 ± 3.8 | 12.8 ± 3.7 | 13.2 ± 4.2 | 13.0 ± 3.8 | 13.3 ± 3.5 | 13.6 ± 3.8 | 14.1 ± 4.2 | Reference |
| Medium (0 < DBI < 1) | 13.6 ± 4.0 | 14.3 ± 4.1 | 14.3 ± 4.2 | 14.3 ± 4.7 | 14.1 ± 3.3 | 14.4 ± 4.3 | 14.9 ± 4.0 | **β 0.27 (0.09; 0.46)**[k,†] |
| High (DBI ≥ 1) | 15.1 ± 4.4 | 14.7 ± 4.7 | 15.4 ± 5.8 | 15.4 ± 5.1 | 15.5 ± 3.9 | 15.6 ± 3.9 | 16.2 ± 5.2 | **β 0.54 (0.22; 0.86)**[k,†] |
| Balance Test | | | | | | | | |
| None (DBI = 0) | —[h] | 9.7 ± 1.1 | 9.9 ± 0.7 | 9.8 ± 1.0 | 9.8 ± 0.7 | 9.8 ± 0.9 | 9.6 ± 1.2 | Reference |
| Medium (0 < DBI < 1) | —[h] | 9.6 ± 1.1 | 9.8 ± 0.9 | 9.8 ± 0.9 | 9.8 ± 0.8 | 9.8 ± 0.8 | 9.9 ± 0.6 | OR 1.09 (0.86; 1.38)[l,§] |
| High (DBI ≥ 1) | —[h] | 9.6 ± 1.3 | 9.8 ± 0.9 | 9.9 ± 0.6 | 9.8 ± 0.8 | 9.7 ± 1.2 | 9.8 ± 0.9 | OR 1.27 (0.90; 1.77)[l,§] |

**Table 3.** Continued

| Outcome × DBI | 92/93 | 95/96 | Measurement Occasions (y) (*M*, *SD*) 98/99 | 01/02 | 05/06 | 08/09 | 11/12 | Adjusted Parameter (95% CI)[a] |
|---|---|---|---|---|---|---|---|---|
| Functional independence | | | | | | | | |
| None (DBI = 0) | —[h] | 21.6 ± 4.2 | 21.2 ± 4.6 | 20.7 ± 4.9 | 20.4 ± 5.1 | 20.1 ± 5.0 | 19.4 ± 5.3 | Reference |
| Medium (0 < DBI < 1) | —[h] | 19.2 ± 5.6 | 19.2 ± 5.4 | 19.3 ± 5.5 | 19.0 ± 5.2 | 18.5 ± 5.6 | 18.1 ± 5.6 | β −0.23 (−0.50; 0.03)[m,§] |
| High (DBI ≥ 1) | —[h] | 17.4 ± 5.9 | 16.7 ± 6.6 | 17.8 ± 5.6 | 15.9 ± 5.8 | 15.6 ± 6.2 | 14.7 ± 6.4 | **β −1.17 (−1.57; −0.76)**[m,§] |

*Note:* Higher parameter value indicates †: poorer functioning §: better functioning. DBI = drug burden index; CI = confidence interval; MMSE = Mini-Mental State Examination; AVLT = Auditory Verbal Learning Test; β = unstandardized regression coefficient; OR = odds ratio.

[a]Adjusted for participants' sex, age, years of education, marital status, BMI, depressive symptoms as measured with the Center for Epidemiologic Studies Depression (CES-D) scale, number of comorbidities, and number of non-DBI medications.

[b]Max. 30 points.

[c]ln(31-MMSE score).

[d]Each trial lasting 1 min.

[e]Number correct.

[f]Maximum score achieved on three trials.

[g]Number of recalled words/maximum score from learning trials and expressed as a percentage.

[h]Not measured on measurement occasion.

[i]ln(13-Raven score).

[j]log10(number of seconds on test).

[k]Seconds needed to complete test.

[l]Seconds dichotomized: 4–9 = 0 vs 10 = 1.

[m]Self-reported functional independence.

a self-reported measure of functional independence which reflects what people think they are able to do.

The present findings have two implications. First, in research, the DBI could serve as an important covariate that may be controlled for particularly when studying cognitive and physical aging in community-dwelling older people (36). Second, in clinical practice, the DBI may be useful to identify individuals with polypharmacy who are at risk of cognitive and physical decline which may be medication-induced. Given that the DBI is based on patients' medication prescriptions and does not require blood withdrawal, it is noninvasive and feasible for large-scale routine use (37). Associations between the DBI and cognitive and physical impairments remained significant even after controlling for other causes such as comorbidities that were likely to increase over time. Therefore, even for patients with prolonged use of these medications, it may still be worthwhile to "deprescribe" inappropriate anticholinergic and sedative medications and to minimize doses if these medications are appropriate (38,39). Follow-up investigations of the DBI with regard to these issues are warranted.

A number of methodological issues need to be considered. Although strength of the LASA study is its long-term follow-up of 20 years, a longer follow-up also increases the risk of differential attrition. To anticipate on this, older people and men were oversampled to reduce potential differential loss-to-follow-up with regard to sex and age. Nevertheless, selection still occurred. However, it should also be noted that selective loss-to-follow-up of participants with these characteristics is inherent to studying an aging population. Thus, while the largest source of attrition in the sample, that is, mortality, leads to an increasingly selective sample over time, it does not necessarily follow from this that the sample becomes less representative. Mortality occurs in the overall population as well and minor differences were previously shown between estimated mortality rates among participants of the LASA study and the total Dutch age-related population (40). As in all observational studies, we cannot rule out residual confounding. However, we attempted to minimize this by excluding participants who were potential problem drinkers or who had sensory deficits, conditions which are likely to compromise test performance. Furthermore, we adjusted for the number of comorbidities and the number of prescribed medications other than those included in the DBI. Although the LASA study is representative for the indigenous older Dutch population, replications in, for example, migrants would be worthwhile to pursue. Strength of the data from the LASA study was the measurement of physical functioning using both objective and subjective tests, and the measurement of cognitive functioning in specific areas (executive functioning, memory, and fluid intelligence) with tests sensitive to more subtle decline in addition to the MMSE as a measure of global cognitive functioning.

Currently, there is neither international consensus on the list of anticholinergic or sedative medications nor the minimal dose to use. There are a number of scales other than the DBI available to estimate cumulative exposure to anticholinergic medications, which may yield different results (41). Strength of the DBI compared with these other scales is that the DBI includes sedative medications in addition to anticholinergic medications and that it takes the dosages of medications into account. We did not have information about anticholinergic and sedative exposure in-between measurement occasions. However, the sensitivity analysis in which we calculated a DBI for anticholinergic and sedative medications that had been prescribed ≥1 year(s) before the measurement occasion, gave similar results as the primary analysis.

In conclusion, this longitudinal analysis of data collected over 20 years showed that prolonged cumulative exposure to anticholinergic and sedative medications was associated with poorer cognitive and physical functioning.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Author Contributions

H.W., S.N.H., J.P.V.C., P.D., and K.T. were involved in conception of research question/study design. H.W., D.G., M.T., H.G.V.D.M., L.A.S., M.H., and H.C.C. were involved in data analysis. H.W., S.N.H., J.P.V.C., M.T., L.A.S., M.H., H.C.C., and K.T. were involved in drafting the article. S.N.H., D.G., J.P.V.C., M.T., H.G.V.D.M., L.A.S., M.H., H.C.C., P.D., C.J.L., and K.T. were involved in critical appraisal of manuscript for intellectual content.

## Conflict of interest statement

None declared.

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