**Supplemental material contains calculation equations for the drug dose calculations and final total calculations from the TAPH database.**

* 1. Average daily dose measure

Score boundaries range from 0 to an upper boundary that depends on the highest score and number of medications included. No suggested categorization of values is provided. The score is independent of follow-up time. Average daily dose may be calculated by summing the total anticholinergic potency of all anticholinergics prescribed over the period considered by the ACB scales and dividing the resulting value by the number of days in the period:

**∑** (Drug A # days supplied x ACB score)

Mean total ACB score = + (Drug B # days supplied x ACB score ) + (Drug X...)

# days in *the exposure period*

* 1. Cumulative dose measure

To calculate scores based on this measure, medication doses are first standardized and then summed to derive an estimate of cumulative exposure, described as cumulative total standardized daily dose (TSDD).1,2 Steps to calculate TSDD are: 1) calculate total medication dose for each prescription dispensation of a medication considered by ant anticholinergic scale, by multiplying the tablet strength by the number of tablets dispensed; 2) for each prescription dispensation, calculate the standardized daily dose (SDD) by dividing the estimated total medication dose by the minimum-effective dose per day (MED) recommended for use in older adults; and 3) for each participant, sum the SDD for all anticholinergic pharmacy dispensations during the exposure period to generate a TSDD. Our team used Greta Lozano-Orega, 2020 as a guide to categorized the resulting TSDD into “no use” (score of 0); 1–90; 91–365; 366–1095; or greater than 1095, with cut points based on clinical interpretability and the observed exposure distribution.1,3

s

* 1. CAB

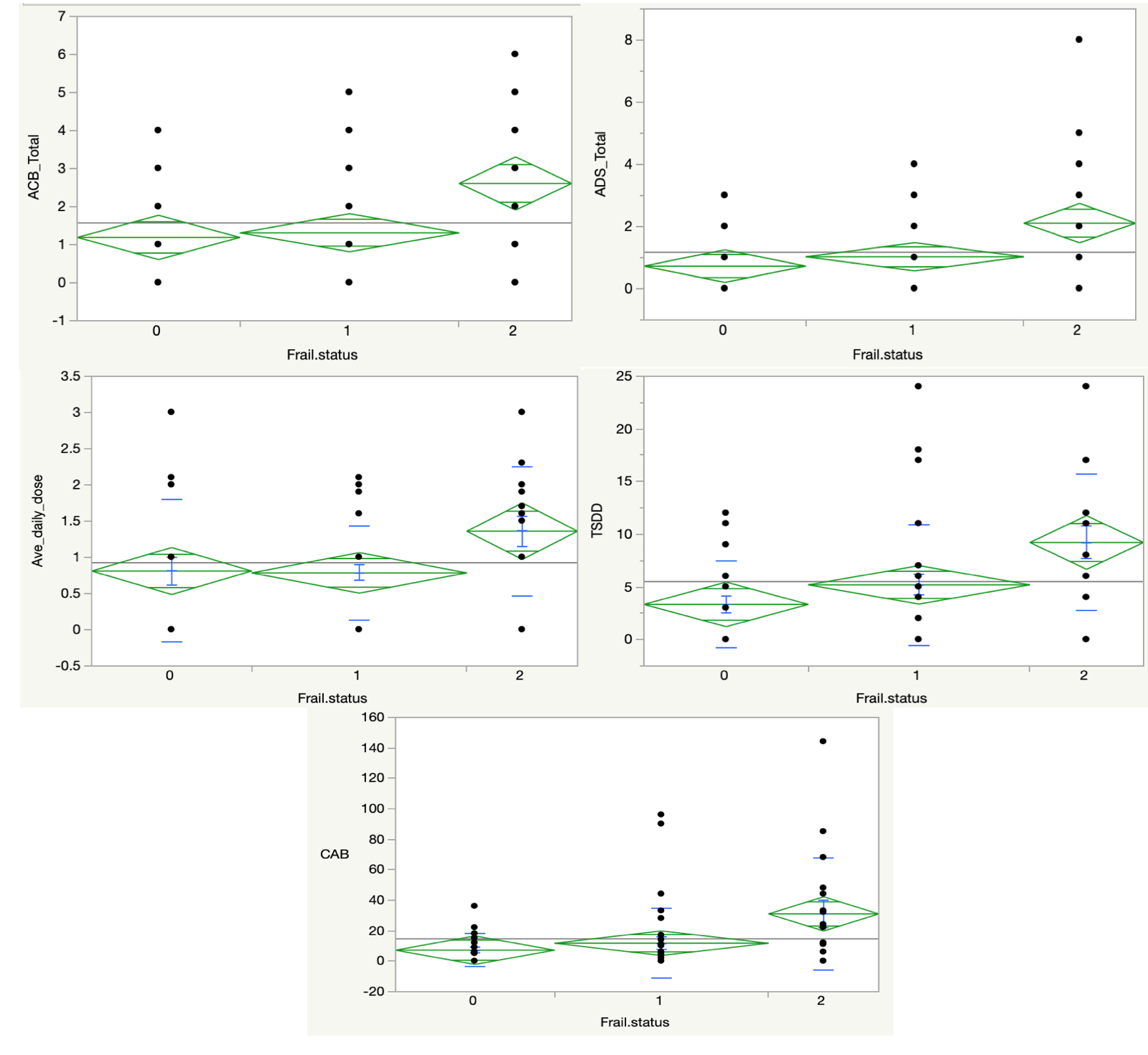
The World Health Organization (WHO) defined daily dose (DDD), the average daily maintenance dose for a medication’s main indication in adults, was used to standardize dosing across different medications, and the drug-specific ACB score provided strength of anticholinergic activity.4 Steps to estimate cumulative exposure were: (1) determine the DDD4,5 of each medication considered by the ACB scale; (2) calculate the standardized daily dose (SDD) for each anticholinergic dispensing according to the following equation:

SDD=Number of Daily Units×Unit DoseDDD.SDD=Number of Daily Units×Unit DoseDDD.

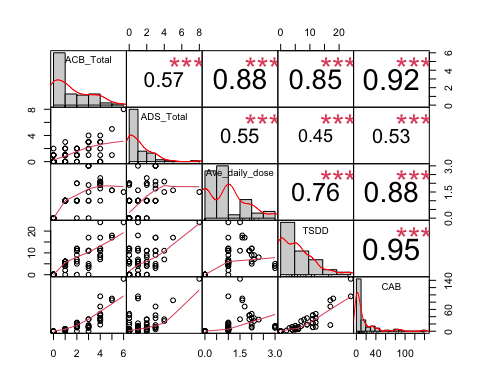
(3) multiply the SDD by the medication’s ACB scale score to yield a drug- and patient-specific measure of standardized daily anticholinergic exposure (SDACE); (4) sum the drug-specific SDACE for all anticholinergic medications for individuals treated with multiple anticholinergic medications on a given day to give a summed standardized daily anticholinergic exposure (SumSDACE); and (5) calculate cumulative exposure by summing SumSDACE for all days during the exposure period. As DDDs are often unavailable in administrative databases, they were extracted from the WHO Collaborating Centre for Drug Statistics Methodology website.6

**S.Table 1. Anticholinergic medications cumulative** **scores across selected scales**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ACB: 1** | **ACB: 2** | **ACB: 3** | **Total ACB Score** | **Level 1** | **Level 2** | **Level 3** | **Total ADS Score** |  | **Average daily dose** | **Cumulative Dose Measure (TSDD)** | **CAB Measure** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 3 | 3 | 0 | 0 | 3 | 3 |  | 3 | 4 | 12 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 2 | 2 |
| 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 2 | 0 | 3 | 2 | 0 | 0 | 2 |  | 0 | 0 | 0 |
| 1 | 0 | 3 | 4 | 0 | 0 | 3 | 3 |  | 2.1 | 9 | 36 |
| 0 | 0 | 3 | 3 | 1 | 0 | 0 | 1 |  | 3 | 5 | 15 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 3 | 3 | 0 | 0 | 3 | 3 |  | 3 | 3 | 9 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 6 | 6 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 5 | 5 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 3 | 4 | 0 | 0 | 0 | 0 |  | 1.9 | 11 | 44 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 |  | 1 | 4 | 4 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 2 | 0 | 0 | 2 | 1 | 0 | 0 | 1 |  | 1 | 11 | 11 |
| 1 | 0 | 0 | 1 | 2 | 0 | 0 | 2 |  | 1 | 4 | 4 |
| 1 | 0 | 0 | 1 | 1 | 2 | 0 | 3 |  | 1 | 5 | 5 |
| 2 | 0 | 0 | 2 | 1 | 0 | 0 | 1 |  | 1 | 12 | 12 |
| 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 |  | 2 | 6 | 12 |
| 3 | 0 | 0 | 3 | 3 | 0 | 0 | 3 |  | 1 | 11 | 11 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 2 | 0 | 3 | 5 | 2 | 0 | 3 | 5 |  | 1.6 | 17 | 85 |
| 3 | 0 | 0 | 3 | 1 | 2 | 0 | 3 |  | 1 | 17 | 17 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 5 | 5 |
| 1 | 0 | 3 | 4 | 0 | 0 | 0 | 0 |  | 2 | 12 | 48 |
| 1 | 0 | 0 | 1 | 2 | 0 | 0 | 2 |  | 1 | 6 | 6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 2 | 0 | 3 | 2 | 2 | 0 | 4 |  | 1.5 | 11 | 33 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 |  | 0 | 0 | 0 |
| 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 |  | 1 | 11 | 22 |
| 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 |  | 2 | 5 | 10 |
| 2 | 0 | 0 | 2 | 1 | 0 | 0 | 1 |  | 1 | 11 | 22 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 1 | 0 | 3 | 4 | 0 | 0 | 0 | 0 |  | 2 | 12 | 36 |
| 0 | 0 | 3 | 3 | 0 | 0 | 3 | 3 |  | 3 | 4 | 12 |
| 1 | 0 | 3 | 4 | 1 | 0 | 3 | 4 |  | 2.1 | 7 | 28 |
| 2 | 0 | 3 | 5 | 1 | 0 | 0 | 1 |  | 1.6 | 18 | 90 |
| 1 | 0 | 3 | 4 | 2 | 0 | 0 | 2 |  | 2.3 | 8 | 32 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 6 | 6 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 5 | 5 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 1 | 0 | 3 | 4 | 0 | 0 | 3 | 3 |  | 1.9 | 11 | 44 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 3 | 0 | 3 | 6 | 3 | 2 | 3 | 8 |  | 1.5 | 24 | 144 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 6 | 6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 6 | 6 |
| 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |  | 1 | 12 | 24 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 6 | 6 |
| 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 |  | 1 | 9 | 18 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 2 | 2 | 0 | 4 | 0 | 0 | 0 | 0 |  | 2 | 9 | 18 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  | 0 | 0 | 0 |
| 1 | 2 | 0 | 3 | 0 | 2 | 0 | 2 |  | 1.9 | 11 | 33 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |  | 1 | 6 | 6 |
| 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |  | 1 | 0 | 0 |
| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |  | 0 | 0 | 0 |
| 2 | 0 | 0 | 2 | 1 | 0 | 0 | 1 |  | 1 | 7 | 14 |
| 4 | 0 | 0 | 4 | 1 | 0 | 0 | 1 |  | 1 | 24 | 96 |
| 1 | 0 | 3 | 4 | 0 | 0 | 0 | 0 |  | 1.9 | 11 | 44 |
| 2 | 2 | 0 | 4 | 1 | 2 | 0 | 3 |  | 1.7 | 17 | 68 |

**S.Figure 1. Anticholinergic scale differences by frailty phenotype**

**S.Figure 2. Correlation matrix by anticholinergic burden scale**



Spearman Correlation matrix: Distribution of each variable is shown on the diagonal, each significance level is associated to p=0.001\*\*\*

References

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