

# A Drug Burden Index to Define the Functional Burden of Medications in Older People

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**Background:** Older people carry a high burden of illness for which medications are indicated, along with increased risk of adverse drug reactions. We developed an index to determine drug burden based on pharmacologic principles. We evaluated the relationship of this index to physical and cognitive performance apart from disease indication.

**Methods:** Data from the Health, Aging, and Body Composition Study on 3075 well-functioning community-dwelling persons aged 70 to 79 years were analyzed by multiple linear regression to assess the cross-sectional association of drug burden index with a validated composite continuous measure for physical function, and with the Digit Symbol Substitution Test for cognitive performance.

**Results:** Use of anticholinergic and sedative medications was associated with poorer physical performance score (anticholinergic exposure, 2.08 vs 2.21,  $P < .001$ ; sedative exposure, 2.09 vs 2.19,  $P < .001$ ) and cognitive per-

formance on the Digit Symbol Substitution Test (anticholinergic exposure, 34.5 vs 35.5,  $P = .045$ ; sedative exposure, 34.0 vs 35.5,  $P = .01$ ). Associations were strengthened when exposure was calculated by principles of dose response. An increase of 1 U in drug burden index was associated with a deficit of 0.15 point ( $P < .001$ ) on the physical function scale and 1.5 points ( $P = .01$ ) on the Digit Symbol Substitution Test. These values were more than 3 times those associated with a single comorbid illness.

**Conclusions:** The drug burden index demonstrates that anticholinergic and sedative drug exposure is associated with poorer function in community-dwelling older people. This pharmacologic approach provides a useful evidence-based tool for assessing the functional effect of exposure to medications in this population.

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OLDER PEOPLE CARRY BOTH a high burden of illness for which medications are indicated and an incompletely understood increased risk of adverse drug reactions.<sup>1-3</sup> Evidence to guide prescribing is limited by the exclusion of older adults with multiple medical conditions from participation in

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controlled clinical trials. Determination of potentially inappropriate medication use in older people is guided predominantly by expert consensus statements such as the updated Beers criteria.<sup>4</sup> Use of medications described as inappropriate by the Beers criteria has been associated with adverse health outcomes in nursing home residents<sup>5</sup> and with poorer self-perceived health<sup>6</sup> but not with decline in self-reported function.<sup>7</sup> Development of an evidence-based approach to guide appropriate medication use, linking clinically relevant data such as functional measures to medication exposure, would

be consistent with current practices in clinical decision making.<sup>8</sup>

The use of drugs with central nervous system depressant effects is associated with an estimated 50% increased risk of falling in older people.<sup>9,10</sup> Hip fracture has been associated with the use of barbiturates,<sup>11</sup> benzodiazepines,<sup>12</sup> tricyclic antidepressants,<sup>13</sup> antipsychotics,<sup>13</sup> and selective serotonin reuptake inhibitors.<sup>14</sup> Memory test scores are lower in people taking benzodiazepines.<sup>15</sup> Benzodiazepine use has been associated with lower functional status in cross-sectional studies<sup>16</sup> and with decline in physical performance after 4 years.<sup>17</sup> High serum anticholinergic activity, a measure of peripheral blood anticholinergic burden, has been associated with decreased Mini-Mental State Examination scores<sup>18</sup> in community-dwelling older people.

Balancing the risks of polypharmacy with underuse of potentially beneficial drugs in older people presents a major challenge. The association between polypharmacy and increased risk of inappropriate prescribing<sup>19</sup> and adverse drug events<sup>20,21</sup> has been well described. Number of medications has also

been correlated with markers of frailty, such as involuntary weight loss and impaired balance.<sup>22</sup> However, awareness that polypharmacy carries risk is insufficient because it provides no guidance for identifying the drugs that should be reduced or eliminated to minimize drug-related risk. A more sophisticated model than simply counting the number of concurrent medications may assist physicians in the risk-benefit assessment when prescribing for older people.<sup>23,24</sup>

One potential methodologic improvement would involve testing associations of potentially harmful drugs with physical or cognitive function in healthier older adults. Physical and cognitive function represent important dimensions of life quality for older adults that are necessary for independent living.<sup>25,26</sup> Performance measures of lower-extremity function predict disability and mortality.<sup>27,28</sup> Examination of associations in a higher-functioning population minimizes the potential for the diseases for which the drugs are prescribed, rather than the drugs themselves, to influence outcomes.

In this study we describe and report an index for “drug burden” developed according to pharmacologic principles that has been applied to a community-dwelling population of persons aged 70 to 79 years (the Health, Aging, and Body Composition [Health ABC] Study cohort) to examine the association between medication use and physical and cognitive performance. This drug burden index provides insight into potential drug-related sources of impaired function in older adults. This index is proposed as a tool that, if validated in other populations, will provide an evidence-based guide for prescribing in older people.

## METHODS

### STUDY POPULATION

The Health ABC study population consists of 3075 community-resident Medicare recipients aged 70 to 79 years, recruited from April 1997 to June 1998 from the areas around Pittsburgh, Pa, and Memphis, Tenn. To participate, subjects were required to report no difficulty in walking one-quarter mile, climbing 10 steps, or performing activities of daily living. Baseline assessments consisted of a questionnaire administered during a home visit followed by further questioning and objective assessments during a clinic visit.<sup>29</sup>

### MEDICATION INVENTORY

A medication inventory was conducted by research personnel during the baseline clinic visit. Participants were instructed to bring all prescription and over-the-counter medications used in the past 2 weeks with them to the clinic visit. The researchers took a structured medication history to confirm the medications actually taken by the participants in the previous 2 weeks. For each medication, the name, Iowa Drug Information System ingredient code, route of administration, and dose and frequency in which the medication was taken were recorded. Of the 3075 subjects, 338 had a medication inventory that reported no medications. Ten did not have a medication inventory recorded and were assumed to be taking no medications. Of the 775 individuals who reported taking an anticholinergic drug, 29 did not have dose or frequency recorded. When numbers of anticholinergic drugs were counted, these 29 individuals were included; however, for calculation of drug burden, they were considered to have zero drug burden. Of the 433

individuals taking a sedative drug, 12 did not have dose or frequency recorded and were treated in the same way.

## MEDICATION BURDEN

With the use of data from existing studies on the effects of medications on physical and mental function in older people, a formula for drug burden was derived. Medications were characterized with respect to risk into 3 groups: (1) drugs with anticholinergic effects, (2) drugs with sedative effects, and (3) total number of medications. Each of these has been associated with increased risk of adverse drug events, falls, and confusion in older people, and these factors were used in our equation for total drug burden (TDB):

$$(1) \quad TDB = B_{AC} + B_S + B_{NW},$$

where AC indicates anticholinergic; B, burden; NW, total number of drugs with no anticholinergic or sedative effects; and S, sedative. Medications with clinically significant anticholinergic or sedative effects were identified by means of *Mosby's Drug Consult*<sup>30</sup> and the *Physicians' Desk Reference*.<sup>31</sup> Medications with both anticholinergic and sedative effects were classified as anticholinergic.

We hypothesized that  $B_{AC}$  and  $B_S$  may be proportional to a linear additive model of pharmacological effect ( $E$ ):

$$(2) \quad \frac{E}{\alpha} = \sum \frac{D}{DR_{50} + D},$$

where  $\alpha$  is a proportionality constant,  $D$  is the daily dose, and  $DR_{50}$  is the daily dose to achieve 50% of maximal contributory effect at steady state.

Because a general  $DR_{50}$  of anticholinergic or sedative effect is not identifiable and the need for normalizing doses remains, we redefined  $DR_{50}$  to represent a recommended minimum daily dose ( $\delta$ ) as approved by the US Food and Drug Administration:

$$(3) \quad \frac{E}{\alpha} = \sum \frac{D}{\delta + D}.$$

This expression represents a hyperbolic function ranging in value from 0 to 1 for each drug that will shift depending on the choice of  $\delta$ . This expression has a pharmacologic basis, whereby effect intensities ranging from 20% to 80% of maximal will be directly proportional to the logarithm of dose.<sup>32</sup>

Although anticholinergic and sedative drugs act on multiple receptor types and subtypes, we hypothesized that their cumulative effect would be linear, rather than one of drug synergism.<sup>33</sup> Thus, a simple linear additive model was used to estimate the total  $B_{AC}$  and  $B_S$ . We hypothesized that both the presence of a medication from these groups and the degree of exposure to drugs in these groups would be negatively associated with objective measures of function.

Both prescription and over-the-counter drugs were included in the analysis. Topical preparations without significant systemic effects were excluded. Analyses were performed with and without “as-needed” medications. Where a dose was missing for an anticholinergic or sedative medication ( $n = 18$  medications), the median dose for the population was used in the calculations.

Finally, a composite “drug burden” equation was developed. The weight assigned to each of the 3 components was based on the strength of association of each individual component with Health ABC score and Digit Symbol Substitution Test (DSST).

## COVARIATES

Prevalent medical conditions were determined from self-report of physician diagnoses, assessments, and medication use.<sup>29,34</sup> A

comorbidity score was calculated as the sum of the number of each of the following conditions: cancer, osteoporosis, osteoarthritis, cerebrovascular disease, cardiac disease, peripheral vascular disease, hypertension, diabetes mellitus, pulmonary disease, and visual impairment. Hospitalization in the previous 12 months was also included. The presence or absence of cognitive impairment (Teng and Chui's modified Mini-Mental Status Examination<sup>35</sup> score <80), depression (Center for Epidemiological Studies–Depression Scale<sup>36</sup> score >15), and anxiety (Hopkins Symptom Checklist<sup>37</sup> response for fear, tense, or nervous included at least 1 moderate or at least 2 mild) were separate covariates.

Sociodemographic characteristics (age, race, sex, study site, and high school completion) were also included as covariates because these factors have been associated with health, medication use, and physical and cognitive performance.<sup>29,34</sup>

## OUTCOME MEASURES

### Physical Function

Physical function was determined with the Health ABC performance score, a modification of the Established Populations for Epidemiologic Studies of the Elderly summary performance score, developed for use with higher-functioning older adults.<sup>29</sup> The performance battery comprises 4 timed tests: time to complete 5 chair stands; time held for 3 progressively more difficult stands: semi-tandem, full tandem, and single-leg up; and gait speed over 6 m on a normal and a narrow (20-cm wide) course. Ratio scores from 0 to 1 were calculated for each test, where 1 represents the maximal performance of a healthy older adult. Participants unable to perform a test were assigned a score of 0. Ratio scores for each test were summed to create a continuous scale from 0 to 4, with higher scores representing better function.

### Attention and Concentration

Attention and concentration were assessed by means of the DSST as adapted from the Wechsler Adult Intelligence Scale.<sup>38</sup> The DSST measures psychomotor performance, concentration, and short-term memory, reflected in speed of motor response, recognition of sensory information, and visuomotor coordination. The score represents the number of correct symbols written within 90 seconds.

## STATISTICAL ANALYSES

The relationships between each factor in our hypothesized drug burden index and Health ABC physical function score and DSST score, controlling for comorbidities and sociodemographic characteristics, were assessed by means of analysis of covariance and multiple linear regression analysis. The individual contribution of each hypothesized factor in the drug burden index to the functional outcomes was used to make a weighted equation for total drug burden. The association of this calculated total drug burden with function was assessed by multiple linear regression.

Statistical analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC). All tests were 2-tailed, and  $P < .05$  was considered statistically significant.

## RESULTS

At baseline, Health ABC Study participants were aged  $73.6 \pm 2.9$  years, 48% were men, 42% were black, 50% were from each site, and 75% had completed high school. With respect to drug exposure, 25% had been exposed to anticholinergic drugs (including those with sedative ef-

**Table 1. Baseline Characteristics of Health ABC Study Population**

Characteristic	Value*
Age, y	73.6 ± 2.9
Sex, % male	48
Ethnicity, % black	42
Secondary education, % completed	75
Site, % Memphis, Tenn	50
Comorbidity score	2.0 ± 1.3
Depression, anxiety, or cognitive impairment, %	23.8
Health ABC score	2.2 ± 0.6
DSST score	35.2 ± 14.8
No. of medications excluding those with anticholinergic and sedative effects	3.1 ± 3.3
Exposed to anticholinergic medications, %	25
Exposed to sedative medications, %	14
Drug burden index	0.18 ± 0.35

Abbreviations: DSST, Digit Symbol Substitution Test; Health ABC, Health, Aging, and Body Composition.

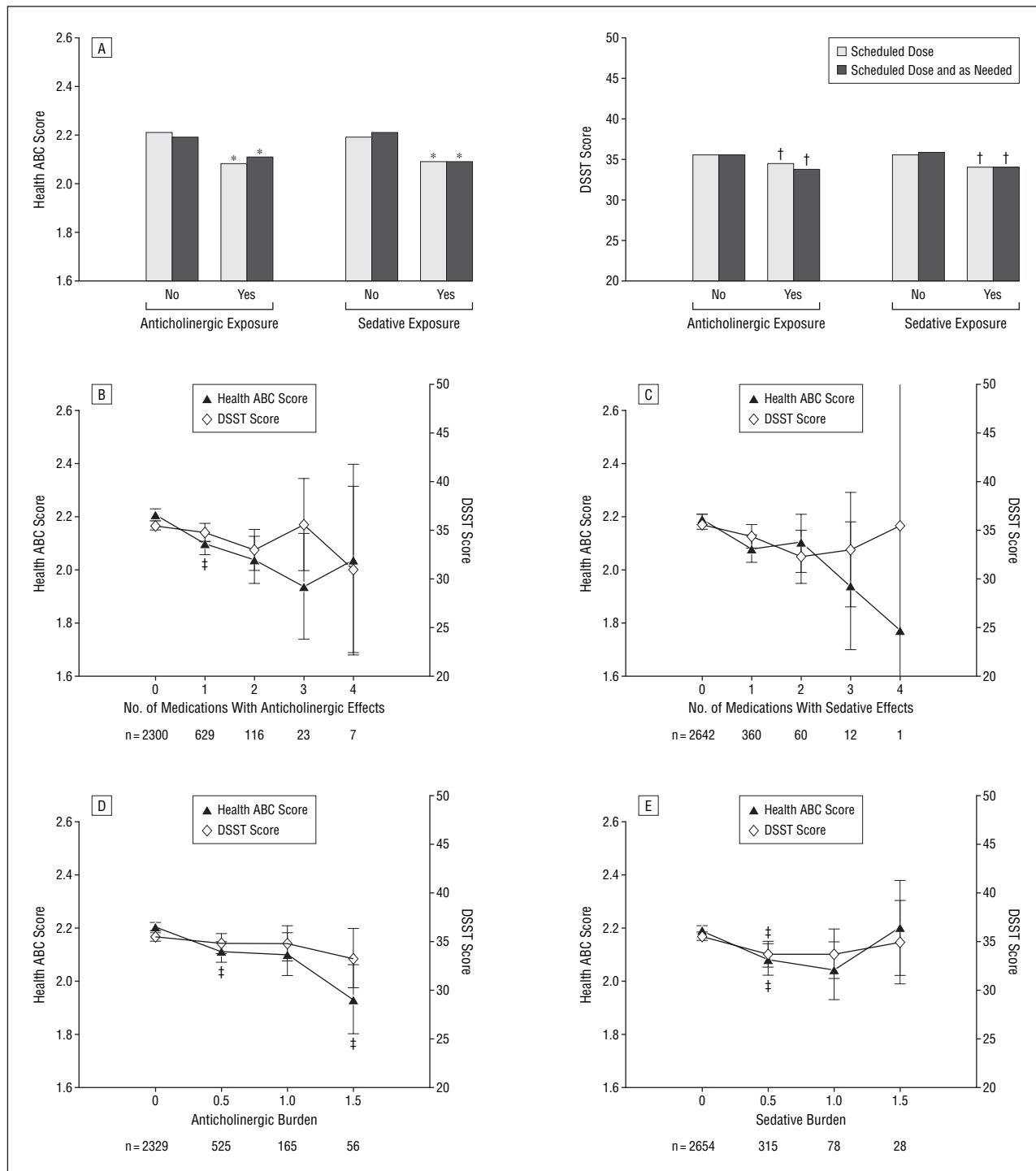
\*Data are mean ± SD unless otherwise stated.

fects as well) and 14% had been exposed to sedative drugs (**Table 1**). Drug assignment to anticholinergic or sedative groups, the Iowa Drug Information System code, the recommended minimum daily dose ( $\delta$ ), and number of individuals exposed to each drug are available on request from the authors.

Findings from the analyses of covariance between exposure to medications with anticholinergic and sedative properties and Health ABC and DSST scores, adjusting for age, sex, race, education, study site, and comorbidity, are presented in **Figure 1**. In contrast to no exposure, any exposure to medications with anticholinergic and sedative effects was associated with poorer physical performance score (anticholinergic exposure, 2.08 vs 2.21,  $P < .001$ ; sedative exposure, 2.09 vs 2.19,  $P < .001$ ) and cognitive performance on DSST score (anticholinergic exposure, 34.5 vs 35.5,  $P = .045$ ; sedative exposure, 34.0 vs 35.5,  $P = .01$ ) (**Figure 1A**). The inclusion of “as-needed” medications had minimal effect on the associations. Associations persisted when the number of drugs with anticholinergic or sedative effects was considered (**Figure 1B and C**) and were stronger when exposure was calculated with the principles of dose-response and maximal effect (**Figure 1D and E**).

**Figure 2** presents the relationships between total number of drugs, with and without drugs with anticholinergic and sedative effects, and physical and cognitive performance scores. The trend toward poorer physical function with increasing number of medications was no longer observed when drugs with sedative and anticholinergic actions were excluded. There was no association between number of drugs and DSST, with a trend toward higher cognitive performance with exposure to increasing numbers of drugs.

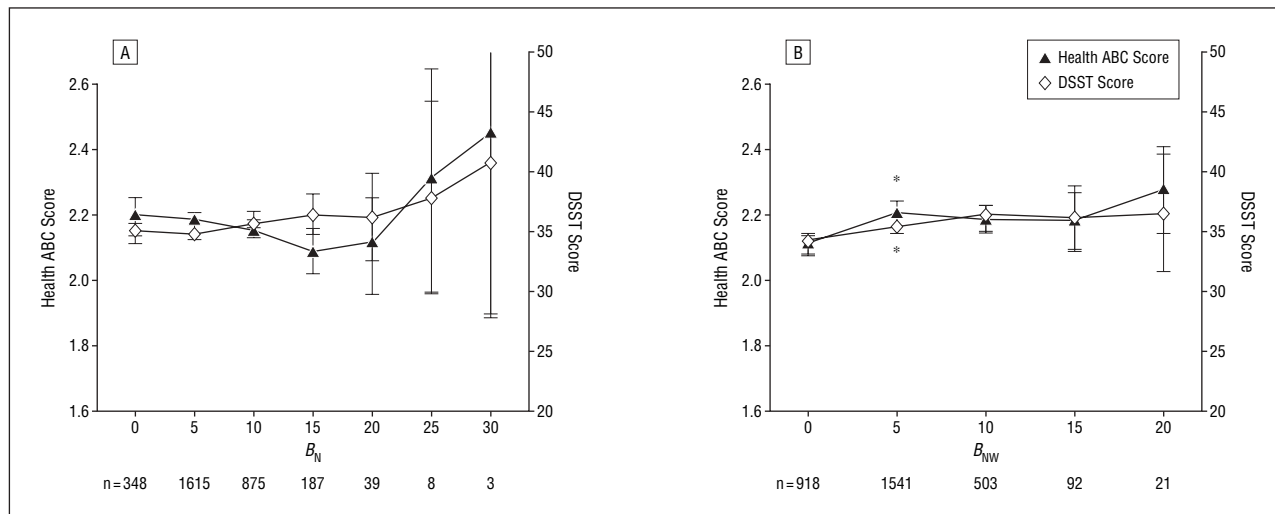
As described in the “Methods” section, the total drug burden equation was derived from the associations found between its components and functional performance. The sedative burden and the anticholinergic burden were equally weighted because they had similar associations



**Figure 1.** Association between exposure to drugs with anticholinergic or sedative effects and physical function or cognition, controlling for comorbidities and sociodemographic factors by means of analysis of covariance. A, Subjects who were exposed to drugs with anticholinergic or sedative effects had significantly lower Health, Aging, and Body Composition (Health ABC) scores and Digit Symbol Substitution Test (DSST) scores than those who were not exposed. Similar results were seen when as-needed medications were included. \* $P < .001$  and † $P < .05$  for differences in Health ABC and DSST scores with exposure to medications. B and C, Anticholinergic and sedative burden, respectively, calculated as the number of drugs in each class. Weak associations with physical function and cognition are shown. D and E, Anticholinergic and sedative burdens, respectively, calculated by means of standardized doses of the drugs and the principles of maximal effect. The associations with physical function and cognition are stronger. The anticholinergic and sedative burdens are rounded in intervals of 0.5 and capped at 1.5. In B through E, error bars show 95% confidence intervals. ‡ $P < .05$  for the difference between the marked point and the previous point on the graph.

with physical and cognitive outcomes. Total number of drugs, when sedatives and anticholinergics were excluded, did not correlate with physical performance or cognition. Consequently, total number of drugs was considered an interactive variable with anticholinergic and

sedative load. Thus, the equation for total drug burden, TDB (equation 1), was reduced to  $TDB = B_{AC} + B_S$ , where  $B_{AC}$  and  $B_S$  are each the linear additive sum of  $D/(\delta + D)$  for every anticholinergic or sedative drug to which the subject is exposed (equation 3).



**Figure 2.** Association of Health, Aging, and Body Composition (Health ABC) physical function score and Digit Symbol Substitution Test (DSST) score with the total number of drugs ( $B_N$ ) (A) or the total number of drugs excluding those with anticholinergic or sedative effects ( $B_{NW}$ ) (B), rounded to the nearest 5. Error bars show 95% confidence intervals. \* $P < .05$  for the difference between the marked point and the previous point on the graph.

On testing the association between drug burden and function, increasing anticholinergic and sedative drug burden was associated with poorer physical function, as shown in the regression table (**Table 2**) (**Figure 3**). Each additional unit of drug burden had a negative effect on physical function (measured by Health ABC score) similar to that of 3 additional physical comorbidities, and a greater effect than anxiety, depression, or cognitive impairment. Each additional unit of drug burden had a negative effect on DSST similar to that of 4 additional physical comorbidities, and half the effect of anxiety, depression, or cognitive impairment.

### COMMENT

In this study of well-functioning community-dwelling older people, the degree of exposure to medications with anticholinergic or sedating effects was associated with poorer performance on physical mobility and cognitive tasks. Using the definition of drug burden developed herein that accounts for dose and frequency of use to determine exposure strengthens the association. This association was not attributable to sociodemographic factors or comorbidity. The total number of drugs taken was not associated with poorer objective functioning when drugs with anticholinergic and sedative effects were excluded.

The lack of association between total medications and function is of particular interest because previous studies<sup>39</sup> have shown an association between number of medications and falls, and an intervention that reduced the number of medications decreased the likelihood of falling in community-dwelling older persons.<sup>39</sup> Our data indicate that when drugs that impair function are excluded, the association of number of drugs taken with poorer function is lost. This may be influenced by the association with better function of some drugs, such as angiotensin-converting enzyme inhibitors, hydroxymethylglutaryl coenzyme A reductase inhibitors, and testosterone, in older people.

The model of drug burden described herein incorporates dose-response relationships and empirical data. The

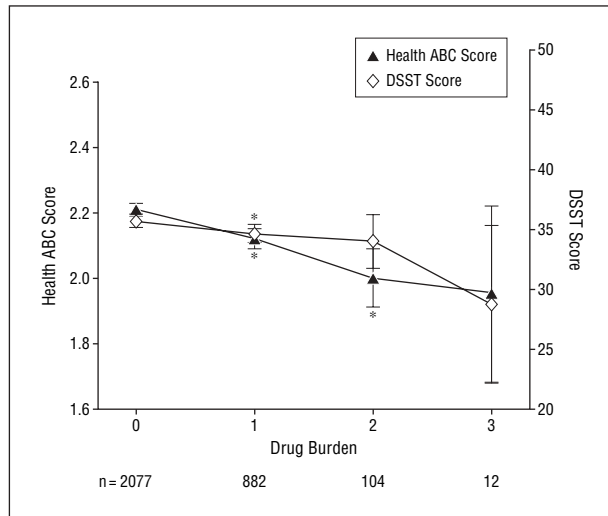
**Table 2. Multiple Regression Analyses for Association of Drug Burden With Physical Function (Health ABC Score) and DSST Score\***

Factor	Parameter Estimate	t	Pr> t	R <sup>2</sup>	
<b>Model for Health ABC Score</b>					
Age	-0.04	-12.18	<.001	0.23	
Sex, F	-0.27	-15.34	<.001		
Race, black	-0.24	-12.20	<.001		
Study site, Memphis, Tenn	-0.04	-2.34	<.05		
Secondary education, absent	-0.16	-6.91	<.001		
Comorbidity	-0.05	-7.30	<.001		
Anxiety, depression, or cognitive impairment	-0.09	-5.67	<.001		
Drug burden	-0.15	-5.73	<.001		
<b>Model for DSST Score</b>					
Age	-0.78	-10.60	<.001		0.40
Sex, F	3.84	9.07	<.001		
Race, black	-10.77	-23.25	<.001		
Study site, Memphis	-3.92	-9.16	<.001		
Secondary education, absent	-10.62	-19.83	<.001		
Comorbidity	-0.36	-2.24	<.05		
Anxiety, depression, or cognitive impairment	-3.07	-8.08	<.001		
Drug burden	-1.51	-2.50	.01		

Abbreviations: DSST, Digit Symbol Substitution Test; Health ABC, Health, Aging, and Body Composition.

\*The parameter estimates tell the amount of change in functional score that would be predicted by a 1-U change in the predictor. The *t* and *Pr>|t|* columns provide the *t* value and 2-tailed *P* value used in testing the null hypothesis that the parameter estimate is 0. The *R*<sup>2</sup> is the proportion of variance in the functional score that can be predicted from the independent variables.

role of dose in adverse outcomes associated with benzodiazepines has been demonstrated empirically for sedation,<sup>2</sup> falls,<sup>15,17</sup> and injuries.<sup>39</sup> These studies either looked



**Figure 3.** Association of increasing drug burden with decreasing scores for physical function and cognition. Drug burden was rounded to integers and capped at 3 (1 subject had a drug burden >3). Error bars show 95% confidence intervals. \* $P < .05$  for the difference between the marked point and the previous point on the graph. Health ABC indicates Health, Aging, and Body Composition; DSST, Digit Symbol Substitution Test.

for a linear dose-response effect or used number of drugs prescribed as a surrogate for dose. Our calculation of drug burden incorporated a classic dose-response relationship assuming linear additive effects.<sup>32</sup>

There are limitations to this pharmacologic model as an index of drug burden. The substitution of the minimum efficacious dose for the dose that gives 50% of the effect is an estimate. The degree of error in this estimate probably varies among drugs and among subjects with different pharmacokinetic and pharmacodynamic profiles. It is possible that the accuracy of our model could be further improved by including drug-drug interactions, considering the relative affinity of different drugs for cholinergic receptors, and including the complexities of drug synergism.<sup>33</sup> However, the drug burden index calculated by this relatively straightforward model has an effect on physical function and cognition as measured by the DSST that is comparable to and independent of that of physical or mental comorbidity.

This study's focus on high-functioning, community-resident older adults provides a unique perspective from which drug burden is examined. The recording of actual medication use was based on inspection of all medications brought by the subject during a clinic visit. This gives more accurate information on exposure than does information obtained from databases, medical records, pharmacy records, or subject questionnaires or interviews.<sup>40,41</sup> The outcomes used in this study were both objective and clinically relevant. Objective measures of physical function are superior to self-reported function, particularly to differentiate among well-functioning subjects who are independent in activities of daily living. The Health ABC Study performance scale distinguishes the physical functional capacity of older people at the higher end of the functional spectrum<sup>29</sup> and is based on the Established Populations for Epidemiologic Studies of the Elderly scale, which has been shown to predict nursing home admission, mortality, and disability in older people

over time.<sup>27</sup> The significant association of drug burden with poorer physical function (Figure 3) is similar in magnitude (0.2 SD, statistically small) to the difference in physical function scores in individuals with and without diabetes mellitus from the Health ABC Study population,<sup>42</sup> suggesting a clinically relevant degree of change. The DSST is a well-established measure of cognition influenced by drug use.<sup>43</sup> Health ABC and DSST scores, the 2 outcomes used in this study, were independent of each other, with only 10% covariance on linear regression analysis. Despite incorporating most factors known to influence function, this model captures only 23% of the variability in Health ABC functional score and 40% in the DSST, which may reflect the well-recognized, poorly understood significant interindividual variability in older people.<sup>44</sup>

We have established an association between increasing drug burden index and function in a cross-sectional data set from which the index was derived. The strength of the association with these outcomes could be further tested in the Health ABC Study cohort and other populations of older people by means of cross-sectional and longitudinal data analysis. Analysis of associations between drug burden index at baseline and future function, and change in drug burden index and change in function over time, may clarify this relationship.

Finally, the study's careful adjustment for comorbid illnesses is required on the basis of the established relationship between comorbidity and functional limitations.<sup>42,45,46</sup> This study's rigorous assessment of medical conditions as potential confounders increases our confidence with which the relationship between drug burden and functional limitations can be reported. Future studies will be required to determine the association between drug burden and function in frail older people.

## CONCLUSIONS

This study demonstrates that objective mobility and cognitive performance in well-functioning older people is associated with a drug burden index that accounts for the degree of exposure to drugs with anticholinergic and sedative effects. These findings provide a basis for evaluating drug burden when prescribing for even high-functioning older people in the community. The drug burden index could be easily calculated by means of prescribing software to inform prescribers of the likely functional implications of an older person's medications.

The drug burden calculated in this study correlates well with objective functional measures, providing an evidence base for the association between medication use and functional impairment in high-functioning older people. Provided that this correlation is also found in other populations, the calculation of drug burden may be useful in predicting the effects of medication on function and therefore guide prescribing for older people.

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