



Geriatrics, Gerontology and Aging

ISSN: 2447-2115

ISSN: 2447-2123

Sociedade Brasileira de Geriatria e Gerontologia, SBGG

Pinto, Eliz Cassieli Pereira; Silva, Ana Maria Rigo; Cabrera, Marcos Aparecido Sarria;
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Geriatrics, Gerontology and Aging, vol. 17, e230029, 2023
Sociedade Brasileira de Geriatria e Gerontologia, SBGG

DOI: <https://doi.org/10.53886/gga.e0230029>

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Relationship between anticholinergic load and self-perceived health in a population aged 44 years or older

Relação entre carga anticolinérgica e autopercepção de saúde em população com mais de 44 anos

Eliz Cassieli Pereira Pinto^a , Ana Maria Rigo Silva^a , Marcos Aparecido Sarria Cabrera^a ,
André de Oliveira Baldoni^b , Daniela Frizon Alfieri^a , Renne Rodrigues^a , Edmarlon Giroto^a  

^aUniversidade Estadual de Londrina – Londrina (PR), Brazil.

^bUniversidade Federal de São João del-Rei – Divinópolis (MG), Brazil.

Correspondence data

Edmarlon Giroto – Avenida Robert Koch, 60 – CEP: 86039-440 – Londrina (PR), Brazil.
E-mail: edmarlon78@gmail.com

Received on: 04/24/2023.

Accepted on: 06/19/2023.

Associate Editor in Charge: Patrick Alexander Wachholz

How to cite this article: Pinto ECP, Silva AMR, Cabrera MAS, Baldoni AO, Alfieri DF, Rodrigues R, et al. Relationship between anticholinergic load and self-perceived health in a population aged 44 years or older. *Geriatr Gerontol Aging*. 2023;17:e230029. <https://doi.org/10.53886/gga.e0230029>

Abstract

Objective: To investigate the relationship between anticholinergic load (ACL) and self-perceived general health in adults in a medium-sized municipality in southern Brazil. **Methods:** This cross-sectional study was based on 2015 data from a medium-sized municipality in southern Brazil. All respondents aged 44 years or older who reported using drugs in the 2 weeks before the interview were included (n = 662). The Anticholinergic Drug Scale was used to measure the ACL. Self-perceived health was categorized as positive self-perception (PSP) or negative self-perception (NSP). Crude and adjusted Poisson regression analyses were conducted to investigate the association between ACL and self-perceived health. **Results:** NSP was found in 50.91% of 662 respondents. Significant ACL, older age, lower economic status, lower education, polypharmacy, and depression correlated with a higher frequency of NSP. Individuals with significant ACL had a prevalence of NSP of 1.27 (95% confidence interval: 1.02 – 1.58), and each additional ACL level represented a 6.10% higher chance of worse self-perceived health, regardless of confounding factors. **Conclusions:** An association was found between significant ACL and NSP, with an effect dependent on ACL level.

Keywords: adverse drug reactions; cholinergic antagonists; pharmacoepidemiology; healthy aging.

Resumo

Objetivo: Investigar a relação entre carga anticolinérgica (CAC) e autopercepção de saúde em adultos de um município de médio porte do sul do Brasil. **Metodologia:** Trata-se de um estudo transversal com dados de 2015, realizado em um município de médio porte do sul do Brasil. Todos os entrevistados com 44 anos ou mais que relataram uso de drogas nas duas semanas anteriores à entrevista foram incluídos (n = 662). A *Anticholinergic Drug Scale* (ADS) foi utilizada para medir a CAC. A autopercepção da saúde foi categorizada em autopercepção positiva (APP) ou autopercepção negativa (APN). Análises de regressão de Poisson bruta e ajustada foram realizadas para investigar a associação entre CAC e autopercepção de saúde. **Resultados:** Entre os 662 participantes, a CAC foi encontrada em 50,91% dos respondentes. CAC significativa, idade avançada, situação econômica mais baixa, menor escolaridade, polifarmácia e depressão foram correlacionados com maior frequência de APN. Indivíduos com CAC significativo apresentaram prevalência de APN de 1,27 (intervalo de confiança de 95%: 1,02 – 1,58), e cada nível adicional de CAC representou uma chance 6,10% maior de pior autopercepção de saúde, independentemente de fatores de confusão. **Conclusões:** Encontrou-se associação entre ACL significativo e APN, com efeito dependente do valor do CAC.

Palavras-chave: reações adversas e efeitos colaterais relacionados a medicamentos, anticolinérgicos, pharmacoepidemiologia, envelhecimento saudável.



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INTRODUCTION

The increase in life expectancy in the last century is due to several sociodemographic and health factors, including access to health services and the development of modern therapies.¹ Parallel to the aging of the population, care for chronic health conditions has increased, together with the use of drugs.²

If, on the one hand, drugs are essential in the recovery and maintenance of health, on the other hand, they pose a risk of adverse drug reactions (ADRs), facilitated by the physiological changes inherent to aging. Examples of such effects are decreased muscle mass, body water, and liver and kidney metabolism, which may favor the accumulation of toxic substances and thus the onset of ADRs.³ Despite the effects that organic changes resulting from aging cause in the response to drugs, pharmacological intervention is still the most common therapy in older people care.⁴

Inappropriate prescribing is a public health problem given its association with morbidity and mortality, with additional costs to health services resulting from ADRs.⁵ In many cases, the treatment of an ADR leads to the addition of new drugs to the pharmacotherapy, thus increasing the risk of polypharmacy and iatrogenic cascade.⁶ In the geriatric field in particular, a comprehensive evaluation of pharmacotherapy is essential.⁷ In this scenario, especially in recent decades, criteria and recommendations aiming for more judicious use of drugs have been developed.^{5,8} Recently, drugs that exert anticholinergic action have received special attention from researchers.^{9,10} Criteria and lists have been published in an attempt to estimate a patient's anticholinergic load (ACL) and provide support for a more cautious use of these agents,¹⁰ since they have been associated with several clinical outcomes.⁹

Self-perceived health has been used as a valid marker of morbidity and mortality and of general health status.¹¹ Self-assessment is one of the main factors that lead people to seek medical care,¹² and this can increase their use of health services¹³ and even influence the assessment performed by professionals.¹² Thus, the objective of the present study was to investigate the association between ACL and self-perceived general health in middle-aged and older adults in a medium-sized municipality in southern Brazil.

METHODS

This cross-sectional and analytical study was based on data from the *VigiCardio* project (2015), a broader survey that examined cardiovascular diseases in the state of Paraná, including mortality, risk profile, drug therapy, and complications.¹⁴ The baseline data of the *VigiCardio* project were collected in 2011 using a population-based design in adults aged 40

years or older in the municipality of Cambé, northern Paraná state. Then, they were followed up in 2015.

The sample size was calculated using data from the 2007 population count performed by the Brazilian Institute of Geography and Statistics, when 92,888 people lived in the municipality — 33.10% were 40 years or older. The StatCalc[®] tool of the Epi Info[®] 3.5.3 software was used, with a margin of error of 3,00%, outcome prevalence of 50,00%, and confidence level of 95,00%, resulting in a sample size of 1066 participants. Assuming eventual losses and refusals, the sample size was increased by 25,00%, totaling 1332 people to be interviewed. Baseline data were collected between February and June 2011. To ensure greater representativeness, the spatial distribution of participants to be interviewed was arranged based on the 86 census tracts of the urban region of the municipality. After the total number of participants to be interviewed was calculated, the number of individuals to be interviewed in each census tract was determined, considering the number of residents in each tract, according to sex and age group. Based on the maps of the census divisions, the sampling route was systematically defined to ensure full coverage of the tract and random selection of households. The routes traveled by the researchers, the households visited (1 of every 2), and 1 individual per household were randomly selected to be included in the study.¹⁴

A loss was deemed to have happened when the individual selected in the household was not found after at least 3 visits on alternate days and/or times or the person refused to be interviewed. There were 159 losses, 93 due to refusals and 66 due to not finding the individual after 3 attempts. Thus, the sample in 2011 was composed of 1180 individuals (88.10%). For the 2015 follow-up of the *VigiCardio* study (age ≥ 44 years), the same individuals were invited to participate, by telephone or home visit. The same criteria used in 2011 were adopted to account for losses. After the losses were added to deaths, a total of 885 individuals were interviewed in the follow-up.¹⁴

The final sample of the present study was composed of the individuals in the 2015 database and excluded individuals who had not taken medications in the last 15 days. For this purpose, the response to the following question was evaluated: "In the last 15 days, did you take any medications?" Those who answered "Yes" and presented the medical prescription, primary and/or secondary packaging, and/or drug package insert were included. The final definition of the sample is shown in detail in Figure 1.

Interviewers were trained before baseline data collection, and a pilot study was conducted to investigate possible weaknesses in the data collection instrument, selection strategy,

and approach. In both years, the data were collected during a home interview using a semistructured questionnaire, and the number of questions was increased in the follow-up.

The independent variable (ACL) was measured by the Anticholinergic Drug Scale (ADS).¹⁵ The ADS has a list of 117 drugs with estimated ACLs ranging from 1 to 3. The total ACL score is the number of drugs used by the individual, assuming that a load of different drugs respects a linear additive model.¹⁵ The ADS scale was used in the present study because there are similarities between the drugs used in Brazil and the United States;¹⁶ the ADS scale is more suitable for American pharmacotherapy¹⁰ and its validation was done according to the Anticholinergic Activity Scale (AAS).

The ADS scale was applied to the drug therapy reported by the patient in the last 15 days, and the total load was obtained by summing the values of all drugs used in this period. Therapies with scores of 3 or higher were considered significant,¹⁵ while those with scores lower than 3 were considered non-significant.

The dependent variable was self-perceived health, determined with the following question: “How do you rate your health status?” The results were grouped into positive self-perception (PSP) (responses: very good and good) and negative self-perception (NSP) (responses: fair, poor, and very poor).^{17,18} Self-perception of health is an important indicator of morbidity and mortality¹² and a relevant factor for the use of health services,¹² and this simple question has been one of the most frequently employed health indicators in health research.¹⁹ Sociodemographic and health characteristics were included as control variables. The sociodemographic variables were sex (female; male), age (continuous), marital status (with a partner; without a partner), educational level (0 – 4; 5 – 8; > 8 years of study), and economic status (based on the classification of the Brazilian Association of Research Companies,²⁰ which considers the purchasing power and educational level of the head of the family, categorized as A/B and C/D/E). The health variables were polypharmacy (categorized as yes or no), defined as the use of five or more active ingredients, according to the vast majority of studies on the subject,²¹ depression, hypertension, and diabetes mellitus (self-report of medical diagnosis).

The data collected with paper forms were entered twice in Microsoft Office Excel® spreadsheets and then compared using the Microsoft Office Spreadsheet Compare®. In 2015, approximately one-third of the data were collected with electronic forms, which were first stored on the server and then exported to Microsoft Office Excel® spreadsheets, thus eliminating data transcription.

The associations between the variables were analyzed by Poisson logistic regression with robust variance to obtain prevalence ratios (PRs). First, univariate (crude) analyses were performed between each control variable and ACL with the outcome of self-perceived health. Next, models were constructed progressively and cumulatively including the control variables. The models consisted of the following:

- Model 1 - sex and age (continuous);
- Model 2 - model 1 plus marital status, education, and economic status;
- Model 3 - model 2 plus polypharmacy; and
- Model 4 - model 3 plus depression, hypertension, and diabetes mellitus.

Significant associations were those with $p < 0.05$, considering the 95% confidence interval (95%CI). To analyze the effect of each ACL level (continuous) on self-perceived health, a regression model with generalized estimating equations was adopted, with the following parameters: normal

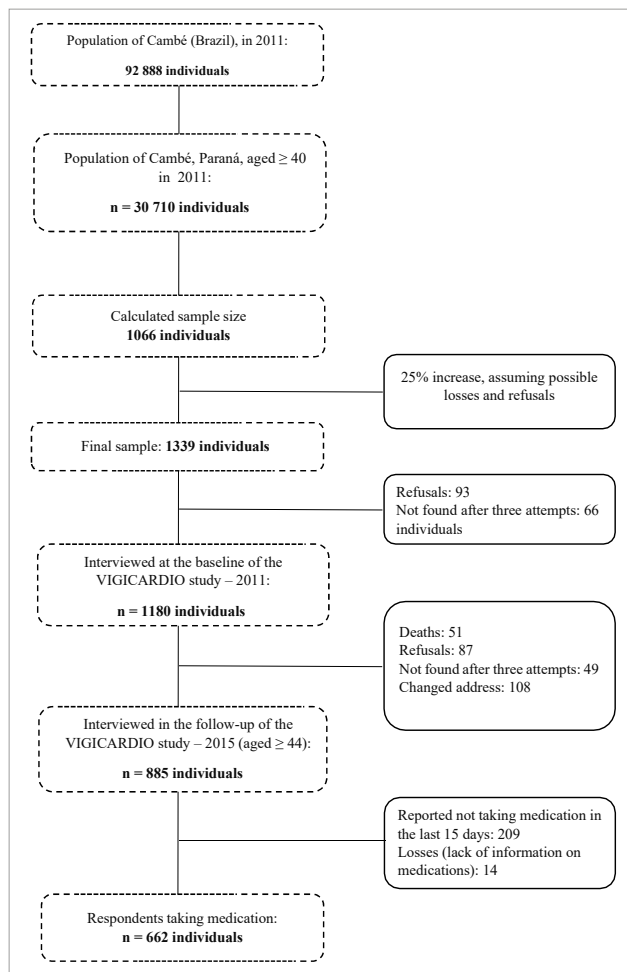


FIGURE 1. Flowchart for determining inclusion in the study sample. Cambé (Brazil), 2015.

distribution of the outcome, log link, permutation matrix, and robust variance. The analyses were performed within the Statistical Package for the Social Sciences (SPSS), version 20.0.

The participants were informed about the content of the study and signed an informed consent form. In addition, all research procedures were approved by the Human Research Ethics Committee of State University of Londrina (Universidade Estadual de Londrina) with certificate no. 0192.0.268.000-10 (2011) and certificate no. 39595614.4.0000.5231 (2015).

RESULTS

The prevalence of NSP among the 662 individuals evaluated in the present study was 50.91%. The population was predominantly female (61.78%), aged between 50 and 59 years (35.20%), of economic status C/D/E (66.16%), had a low educational level (53.32%), and lived with a partner (68.08%). Also, about one-quarter of the participants underwent polypharmacy treatment and reported having a diagnosis of depression. Approximately 60,00% and 20,00% of the participants reported a medical diagnosis of hypertension and diabetes mellitus, respectively (Table 1).

TABLE 1. Frequency of sociodemographic, economic, and health variables, according to self-perceived health, in individuals aged 44 years or older.

Variable	Self-perceived health					
	Positive		Negative		Total	
	n	%	n	%	n	%
Anticholinergic load						
0 to 2	272	51.81	253	48.19	525	79.31
≥ 3	53	38.69	84	61.31	137	20.69
Sex						
Female	192	46.94	217	53.06	409	61.78
Male	133	52.56	120	47.44	253	38.22
Age group (years)						
44 – 59	74	62.71	44	37.29	118	17.82
50 – 59	108	46.35	125	53.65	233	35.20
60 – 69	96	48.48	102	51.52	198	29.91
≥ 70	47	41.59	66	58.41	113	17.07
Economic status*						
A/B	130	58.04	94	41.96	224	33.84
C/D/E	195	44.52	243	55.48	438	66.16
Education level (years of study)						
0 – 4	141	39.94	212	60.06	353	53.32
5 – 8	73	51.05	70	48.95	143	21.60
≥ 9	111	66.87	55	33.13	166	25.08
Marital status						
With a partner	232	51.56	218	48.44	450	68.08
Without a partner	93	44.08	118	55.92	211	31.92
Polypharmacy†						
Yes	59	34.30	113	65.70	172	25.98
No	266	54.29	224	45.71	490	74.02
Depression						
Yes	69	39.43	106	60.57	175	26.44
No	256	52.57	231	47.43	487	73.56
Hypertension						
Yes	183	44.96	224	55.04	407	61.48
No	142	55.69	113	44.31	255	38.52
Diabetes mellitus						
Yes	60	41.67	84	58.33	144	21.75
No	265	51.16	253	48.84	518	78.25

*Economic status: considers the purchasing power and educational level of the head of the family;²⁰ categorized as A/B/C and D/E; †Use of five or more active ingredients.²¹

Of the 662 respondents who used some type of medication, 137 had significant ACL (20.69%). In those individuals, NSP was more prevalent (61.31%) than in those whose ACL was not significant (48.19%). Participants of female sex, older age, lower economic status, lower education, or no partner had a higher frequency of NSP. Those who underwent polypharmacy treatment and reported a diagnosis of depression, hypertension, and diabetes mellitus also had a higher prevalence of NSP (Table 1).

Fluoxetine, orphenadrine, and amitriptyline were the most common medications with an ACL among middle-aged adults (44 to 59 years). The top three medications for older adults (60 years or older) were furosemide, clonazepam, and amitriptyline.

As shown in Table 2, when the crude analysis was performed, significant ACL, age (in years), lower economic status, lower education, polypharmacy, and reported diagnosis of depression and hypertension were significantly associated with a higher prevalence of NSP.

In the adjusted analysis, a significant association between ACL and NSP was found in all models (Table 3). Linear regression adjusted for sex, age (continuous), economic status, educational level, marital status, polypharmacy, and reported diagnosis of depression, hypertension, and diabetes mellitus showed that, with each additional ACL level, the chance of worse self-perceived health was 6.10% higher (95%CI 2.70 – 9.50; $p < 0.001$).

DISCUSSION

The main objective of this study was to investigate the association between ACL and self-perceived health. A significant association was found between these variables, regardless of confounding factors. Considering the multidimensionality of self-perceived health, in addition to the conditions investigated in this analysis, it is plausible to assume that many factors influence self-perceived health status. For this reason,

TABLE 2. Prevalence ratio (PR) of socioeconomic and health variables according to self-perceived health in adults aged 44 years or older ($n = 662$).

Variable	Negative self-perception of health (NSP)		p-value*
	PR	95%CI	
Anticholinergic load			
< 3	1.00		
≥ 3	1.34	1.07 – 1.68	0.011
Sex			
Female	1.12	0.96 – 1.31	0.155
Male	1.00		
Age			
In years (continuous)	1.01	1.00 – 1.02	0.003
Marital status			
With a partner	1.00		
Without a partner	1.18	0.99 – 1.40	0.073
Economic status [†]			
A/B	1.00		
C/D/E	1.30	1.12 – 1.52	0.001
Education level (years of study)			
0 – 4	1.67	1.42 – 1.98	< 0.001
5 – 8	1.28	1.04 – 1.57	0.019
≥ 9	1.00		
Polypharmacy [‡]			
Yes	1.58	1.27 – 1.98	< 0.001
No	1.00		
Depression			
Yes	1.33	1.09 – 1.63	0.005
No	1.00		
Hypertension			
Yes	1.24	1.06 – 1.44	0.006
No	1.00		
Diabetes mellitus			
Yes	1.23	0.99 – 1.52	0.056
No	1.00		

*Poisson logistic regression with robust variance; [†]Economic status: considers the purchasing power and educational level of the head of the family;²⁰ categorized as A/B and C/D/E; [‡]Use of five or more active ingredients.²¹

TABLE 3. Prevalence ratio for the association between anticholinergic load and negative self-perceived health, according to different statistical models, in adults aged 44 years or older ($n = 662$).

	Model 1*	Model 2*	Model 3*	Model 4*
Prevalence ratio				
ACL < 3	1.00	1.00	1.00	1.00
ACL ≥ 3	1.36	1.33	1.26	1.27
95% confidence interval	1.09 – 1.71	1.06 – 1.66	1.01 – 1.58	1.02 – 1.58
p-value	0.007	0.013	0.037	0.037

*Prevalence ratio obtained by Poisson regression with robust variance. ACL: anticholinergic load. Model 1: adjusted for the variables sex and age (continuous); Model 2: adjusted for model 1 plus economic status, marital status, and education; Model 3: adjusted for model 2 plus polypharmacy; Model 4: adjusted for model 3 plus reported diagnosis of depression, hypertension and diabetes mellitus.

an analytic model for confounding factors including polypharmacy and depression was adopted, as these variables are associated with NSP.²²

In the present study, the prevalence of NSP was 50.90%. This finding is similar to those of other Brazilian studies in the older population.^{19,23} A similar prevalence was also found in Serbia,²⁴ but a significantly lower rate was reported in Canada (NSP < 20,00%) in a study with a similar age range and design.²⁵ Because self-perceived health is a subjective, multifactorial concept that includes individual, collective, and socioenvironmental aspects,²⁶ the discrepancies may be due to socioeconomic and cultural differences between countries. Therefore, comparisons of this dimension between populations with such divergent characteristics should be made with caution.

Regarding the use of drugs, those exposed to significant ACL had a higher prevalence of NSP. Self-perceived health is a widely used dimension and is described as an indicator of morbidity and mortality. Thus, variables that are associated with self-perceived health may also be indirectly associated with increased morbidity and mortality.¹¹ In fact, a meta-analysis showed that a higher ACL is associated with an increased risk of mortality.²⁷

Self-perceived health is recognized as an indicator of both the use of health services and the medical assessment of health conditions.^{12,13} Although our hypothesis assumes that NSP is a consequence of high ACL, the bidirectionality of these factors cannot be ignored. Thus, indirectly, the presence of significant ACL might lead to a worse self-perception of health, and this perception, in turn, might lead the patients to demand more health services and even influence their assessment of their medical condition.¹⁴ Moreover, a cyclical phenomenon may be observed, as the demand for health services has been a risk factor for the use of anticholinergic drugs.²⁸

According to López-Alvarez et al.,⁹ some recommendations are essential to guide health professionals in safer prescription of anticholinergic drugs. Those authors say that if prescribing an anticholinergic medication is necessary, the drug with lower anticholinergic potential and greater affinity for its site of action should be prioritized.⁹ Whenever a drug is added and, in some way, affects functions sensitive to anticholinergic actions, a global assessment of the pharmacotherapy should be performed, along with the avoidable or unavoidable ACL, and nonpharmacological approaches should be considered.⁹ Finally, given the potential risk of irreversible cognitive decline from the prolonged use of high-anticholinergic-potential drugs, treatment should not exceed 3 months without a reassessment.⁹

Among other aspects to be considered, the perception that patients have about their care should be a point of attention during clinical evaluation.²⁹ Shared care and person-centered therapy are some of the topics that encompass the perceptions and expectations of patients and professionals. Therefore, such topics should be a common subject in the training of health professionals to ensure that, once provided with information, they can use the available tools and resources, including medications, in a rational manner.

Our findings are another indicator of morbidity and mortality related to the use of anticholinergic drugs. In addition to the results found in this population, we sought to reflect on the complexity of drug use and its impact on self-perceived health.

The limitations of this study are those inherent to a cross-sectional design — although associations between the variables can be observed, no temporal relationship can be defined. In this sense, although the hypothesis that the side effects caused by anticholinergics lead to a negative self-perception of health, which in turn leads to the use of other drugs, is supported, this relationship may be bidirectional, and the opposite directionality cannot be excluded. Additionally, the study was conducted in only 1 city in southern Brazil, which limits the extrapolation of the results to the entire country.

Conversely, the systematic process adopted from sampling to data analysis contributes to the quality of the information presented. The study of adults enabled us to investigate the action of anticholinergic drugs beyond the older population, a demographic known to be polymedicated and more susceptible to side effects, and may have provided evidence of anticholinergic action before older age. In addition, the results were controlled for possible confounding factors, including age, which gives us greater confidence in the associations found. Additionally, it should be highlighted that the literature supports the use of polypharmacy with a multimorbidity proxy because there is a systematic correlation with the existence of chronic conditions (pattern of multimorbidity and polypharmacy).

CONCLUSION

Individuals taking drugs with anticholinergic activity have a higher prevalence of negative self-perceived health, with a load-dependent effect. That is, the higher the ACL, the greater the chances of worse self-perceived health. Longitudinal studies are suggested to investigate the causality of the links between the associated variables in order to elucidate the possible bidirectionality of this relationship.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

ECPP: conceptualization, formal analysis, methodology, validation, writing – original draft, visualization. AMRS:

conceptualization, funding acquisition, investigation, methodology, project administration, validation, resources, writing – original draft. MASC: funding acquisition, investigation, methodology, project administration, resources, validation, writing – review & editing. AOB: validation, visualization, writing – review & editing. DFA: validation, visualization, writing – review & editing. RR: validation, visualization, writing – review & editing. EG: conceptualization, formal analysis, methodology, supervision, validation, visualization, writing – original draft.

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