RESEARCH ARTICLE

Polypharmacy in Alzheimer's disease patients in Brazil: Guidance for pharmaceutical assistance [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Elderly patients frequently have concomitant diseases, triggering the necessity of utilizing several different medications, which can cause adverse events associated with therapy, called polypharmacy. This study aimed to evaluate the main concomitant diseases with Alzheimer's disease (AD) and discuss possible interactions between drugs utilized to treat dementia and its comorbidities, and indicate safe medicines for patients with AD.
Methods: 41 individuals with AD who withdraw medicines for dementia from the Brazilian public health system (SUS) participated in this study. Data collection was performed using three questionnaires: 1) Clinical Dementia Rating, to verify disease stage; 2) Mini–mental state examination, to measure cognitive impairment; and 3) Sociodemographic analysis, to evaluate concomitant diseases, utilized drugs, drug-drug interactions, among other demographic variables. Statistical analyses were performed using SPSS and data was presented as relative frequency.
Results: The results of this study showed that the most frequent concomitant diseases with AD are: systemic arterial hypertension, depression, diabetes mellitus, and hypercholesterolemia. Polypharmacy was observed in 95.12% of patients. The pharmacologic classes that presented interactions with AD medications were anxiolytics, antidepressants, antipsychotics, antihypertensives, and antidiabetics.
Conclusion: In the present study, polypharmacy in patients with AD and other concomitant diseases has been characterized. The average number of drugs that these patients ingested was seven per day, and this leads to drug interactions, which are potentially damaging to the

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body. Consequently, we have tried to reduce these interactions, by suggesting drugs that are safer, for example furosemide instead of amlodipine to treat hypertension.

Keywords
Medicine usage, Elderly, Pharmacoepidemiology, Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is characterized by beta-amyloid (βA) peptide production and aggregation in specific regions of the brain, such as the hippocampus, and ventral and entorhinal cortex[1]. AD is the most common dementia, marked by progressive cognitive and motor impairments. This disease compromises patients' daily life activities[2], affecting attention, language, visual-spatial ability, locomotion and primarily, memory[3].

Elderly patients are at considerably higher risk of developing conditions such as cancer, diabetes, inflammations, and cardiovascular and neurodegenerative diseases, e.g., AD and Parkinson's disease[4]. Therefore, elderly patients frequently have concomitant diseases, triggering the necessity of utilizing several different medications.

Pharmacology is distinct in elderly patients because, during the process of aging, some alterations are observed in body composition and renal and hepatic functions, interfering in the pharmacokinetics and pharmacodynamics of several drugs; for these reasons, elderly patients are more vulnerable to iatrogenesis[4].

Adverse events caused by the concomitant use of several drugs may be prevented by making an adequate prescription. Potential inappropriate medications (PIMs) are drugs with a high-risk of provoking more side effects than benefits, even though there are available alternatives that can be substituted[5]. In Brazil, PIMs are still being prescribed and used as top-notch treatments for the majority of elderly patients, although there is evidence of negative results[6,7]. This occurs because these medications are in the Brazilian National Essential Medicines List (RENAME) and are distributed free of charge by the Brazilian public health system (SUS)[5].

Among elderly patients, adverse events associated with medications are caused by polypharmacy, which facilitates adverse drug reaction (ADR) and drug interactions[8]. According to Ribeiro and colleagues (2013)[9], polypharmacy may be classified as mild, moderate and grave, depending on if the patients utilize 2-3, 4-5, or 5+ medications, respectively[10,11].

Individualized healthcare is essential for elderly patients with polypharmacy. Therefore, protocols have been developed that aim to establish appropriate drug prescription for elderly patients. The most employed protocols are the PRISCUS list[12] and Beers-Fick criteria[13]. PRISCUS list is more updated and inclusive; however, both protocols are not complete or adapted to Brazilian ambulatory reality. For that reason, the present study aimed to verify the most frequent diseases concomitant with AD and analyze the interactions between medications and these diseases, to indicate a safer alternative treatment for AD patients.

Methods

This research was approved by the Ethics Committee of Research of Midwest State University (COMEP/ UNICENTRO; Guarapuava, Brazil), approval no. 968931.

Participants

This study was conducted between March 2015 and July 2016. Elderly patients invited to participate in this study had a confirmed AD diagnosis (inclusion criteria), issued by a geriatric or neurologist, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS- ADRDA) criteria[14]. All participants received free medicines from SUS for disease treatment. Those without confirmed diagnosis, that were absent after three consecutive home visits, that changed residence or died before blood collection were excluded from the study.

57 elderly patients with AD were randomly invited to participate in this study, but only 41 reached the end of the study. Initially, phone calls were made by the researchers to explain the objective and purpose of the research, who were recruited at Basic Health Unit (UBS) of Vila Carli, Industrial, Santana, Santa Cruz e Paz e Bem. All are characterized as low level health facilities in Guarapuava/PR city. If the participant accepted the invitation, a meeting was scheduled (home visit) with the caregivers to present and sign the informed consent form (if patients were lucid, they signed a consent form, but, if not, the caregivers provided the written consent). Subsequently, by an interviewer, three questionnaires were applied to the AD patients: Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE) and a sociodemographic questionnaire.

Data collection

Clinical Dementia Rating (CDR)[14] aims to classify the disease's stage in CDR-1, 2 or 3, which indicates mild, moderate and severe dementia, respectively. In contrast, Mini-Mental State Examination (MMSE)[15] evaluates global cognitive functions and was applied as a psychometric analysis of orientation, attention, calculation, and language. The maximum score for MMSE is 30, and this indicates cognitive impairment. The sociodemographic questionnaire (Supplementary File 1) analyzed the patient's profile, knowledge about their diseases and identifying drugs and dosages utilized daily.

After discussing patients' characteristics, a drug-interaction analysis was performed by Scientific studies, Beers-Fick and PRISCUS protocols, and medical studies were analyzed to verify drug-drug interactions, in addition to using the drugs.com database, in which, for each patient, a folder was created and inserted all medicines. At the end of the process the drugs.com base returned a report with the interactions. Each medication received a code: 0 to the absence of interaction and 1 to the presence of any interaction with an AD medication (Supplementary File 2).

Data analysis

Statistical analyses were performed using SPSS® software version 20.0, utilizing operational system Windows 10 Pro® and Office 2016® package. The results were presented in relative and absolute frequency.

Results

From the initial sample of 57 individuals, eight (14.04%) died before data collection, and eight (14.04%) were absent after three consecutive home visits. The final sample total 41 patients.

Results of CDR test showed most of the patients were in CDR 3, AD severe stage (Table 1). Because of that, patients presented with higher cognitive impairment, and consequently, the proposed questionnaires could not be responded to properly. Therefore, the mean number of correct answers in MMSE was 10.80. Regarding concomitant diseases, systemic arterial hypertension was the most frequent (58.54%), followed by depression (46.34%), diabetes mellitus (27.28%), and hypercholesterolemia (26.80%).

63.42% (n=26) of the patients took AD medications that interacted with drugs taken to treat other diseases (Table 2). Drug-interactions occurred more frequently in patients with the moderate stage of AD (CDR-2, 68.76%), followed by the mild stage (CDR-1, 66.67%) and lastly, patients with severe stage AD (CDR-3, 57.89%).

According to the results shown in Table 3, 34 of 41 elderly patients, took AD medications. Of these, half (50%; n=17) utilized Donepezil hydrochloride and 38.24% (n=13) utilized rivastigmine, both acetylcholinesterase inhibitors (AChEI). Only four patients (11.76%) utilized memantine, an adjuvant drug to AD treatment, which blocks N-Methyl-D-aspartate receptor (NMDAR), decreasing mitochondrial oxidative stress. Memantine must only be used during mild and moderate stages of AD (CDR-1 and 2). Thus, two patients diagnosed with severe AD (CDR-3), were ineffectively treated with memantine.

From 19 patients with CDR 3, 36.84% (n=7) did not use any AD-specific drug, due to Brazilian legislation (Ordinance SAS/MS No. 1.298 of November 21, 2013). This legislation does not allow patients in AD severe stage (CDR 3) to withdraw medications from SUS, claiming a low efficiency of AChEI treatment. Medications utilized to treat concomitant diseases are fully described in Table 4.

AD treatment consists of AChEI (rivastigmine and donepezil) and NMDAR antagonists (memantine). Therefore, knowing which medications interact with these drugs is fundamental to indicate the correct treatment for secondary diseases and, even, predict drug-interactions. The main drug interactions found in the drug-interaction analysis are shown in Table 5.

Table 1. Characteristics of elderly Alzheimer's disease patients in Brazil.

		Frequency, % (n=41)
Sex	*Male*	34.14 (n=14)
	Female	65.86 (n=27)
Age (years)	*Men*	79.27 ± 8.20
	Women	77.70 ± 14.12
CDR	*1*	14.64 (n=6)
	2	39.02 (n=16)
	3	46.34 (n=19)
Cancer		19.51 (n=8)
Parkinson's disease		17.70 (n=7)
Stroke		17.70 (n=7)
Smoking		7.30 (n=3)
Systemic arterial hypertension		58.54 (n=24)
Hypercholesterolemia		26.80 (n=11)
Depression		46.34 (n=19)
Psychosis		12.19 (n=5)
Diabetes mellitus		28.27 (n=12)
Polypharmacy[9]	*No* *Mild* *Moderate* *Severe*	4.88 (n=2) 14.64 (n=6) 29.26 (n=12) 51.22 (n=21)
MMSE score		10.80 ± 6.60

Data are presented as mean ± standard deviation; relative frequency.
CDR: Clinical Dementia Rating[14]; MMSE: Mini-Mental State Examination[15].

Table 2. Presence of drug-interactions in Alzheimer's patients in Brazil.

Drug-interaction	General, % (n=41)	CDR 1 (n=6)	CDR 2 (n=16)	CDR 3 (n=19)
		Mild, %	Moderate, %	Severe, %
No	36.58 (n=15)	33.33 (n=2)	31.24 (n=5)	42.11 (n=8)
Yes	63.42 (n=26)	66.67 (n=4)	68.76 (n=11)	57.89 (n=11)
Total	*100.00 (n=41)*	*100.00 (n=6)*	*100.00 (n=16)*	*100.00 (n=19)*

Data were presented in relative frequency.

Table 3. Drugs taken by elderly Alzheimer's disease patients in Brazil.

Drug	% (n=41)
AChEI and/or NMDAR antagonists	82.93 (n=34)
- *Rivastigmine hemitartrate*	38.24 (n=13)
- *Donepezil hydrochloride*	50.00 (n=17)
- *Memantine hydrochloride*	11.76 (n=04)

Data presented as relative frequency.

Table 4. Drugs and/or therapeutic classes utilized to treat concomitant diseases in elderly Alzheimer's disease patients in Brazil.

DISEASE	PHARMACOLOGICAL TREATMENT
Depression	Serotonin reuptake inhibitor (SRI); Serotonin-norepinephrine reuptake inhibitors (SNRIs); Tricyclic antidepressants; Tetracyclic antidepressants.
Psychosis	Atypical and typical antipsychotic;
Parkinson's disease	Dopamine Analogues, Catechol-O-methyltransferase (COMT) inhibitors; Monoamine oxidase inhibitors (MAOIs); DOPA decarboxylase inhibitor; Levodopa.
Systemic arterial hypertension	Angiotensin II inhibitors; Angiotensin-converting-enzyme inhibitor (ACE inhibitor); Calcium channel blockers (CCBs); aliskiren; diuretics.
Hypercholesterolemia	Statins; fibrates; ezetimibe, niacin; resins; Omega-3 fatty acids.
Diabetes mellitus	Insulins; metformin; sulfonylureas; thiazolidinedione; DPP-4 inhibitors; analogues of the incretins

Source: GOODMAN & GILMAN[16], 2012; Sociodemographic questionnaire.

Discussion

In the present study, AD prevalence was higher in women [65.86% (n=27)]. This data corroborates Silva and collaborators (2012)[17] results and may be justified by female longevity. Women tend to live longer than men, therefore, they spend more time of their lives with chronic diseases[18].

Approximately 80% of patients presented moderate and severe polypharmacy (Table 1). From 251 analyzed medications (corresponding 41 patients diagnosed with AD), the mean number of drugs taken was 7. Passareli and Filho (2007)[19] showed a mean number of 6 drugs taken by AD patients, while other authors, such as Barbosa *et al.* (2008)[20], demonstrated patients took approximately 8.6 medicaments concomitantly, indicating grave polypharmacy in this part of the population.

Drug-interactions may occur for several reasons, such as pharmacokinetics, physiological antagonisms, additive effects, etc. The utilization of three drugs (donepezil, rivastigmine and memantine) to treat AD creates the false impression that controlling drug-interactions is simple. AD patients and caregivers are not aware of the interaction between drugs and enzymes. These enzymes may trigger inductive or inhibitory responses or serve as a substrate to other reactions.

Table 5. Main drug-interactions with AChEI and NMDAR antagonists for AD treatment.

AD TREATMENTS	DRUG-INTERACTIONS	EXPECTED EFFECTS
Rivastigmine	Amlodipine (anti-hypertensive)	The association may decrease blood pressure and cause bradycardia.
	Nifedipine (anti-hypertensive)	
	Beta-blockers	
	Amitriptyline (Antidepressant)	Drug opposite effect may worsen cognitive impairment, decreasing AChEI activity.
	Perphenazine (Antipsychotic)	
	Imipramine (Antidepressant)	
	Risperidone (Antipsychotic)	
	Olanzapine (Antipsychotic)	
	Biperiden (Anticholinergic)	Biperiden must be avoided by patients with AD or other cognitive impairments. Biperiden decreases rivastigmine effects and vice versa.
Donepezil	Imipramine (Antidepressant)	Drug opposite effect may worsen cognitive impairment, decreasing AChEI activity.
	Ranitidine (Antiulcer)	
	Perphenazine (Antidepressant)	
	Olanzapine (Antipsychotic)	
	Quetiapine (Antipsychotic)	
	Risperidone (Antipsychotic)	
	Amiodarone (Anti-arrhythmia)	The association may decrease blood pressure and cause bradycardia.
	Metoprolol (anti-hypertensive)	
	Atenolol (anti-hypertensive)	
	Digoxin (Anti-arrhythmia)	
	Paroxetine (Antidepressant)	The inhibition of enzymes that degrade Donepezil (cytochrome P450, 2D6 or 3A4), increase plasmatic concentrations of AChEI.
	Sertraline (Antidepressant)	
	Phenobarbital (Barbituric)	
	Ciprofloxacin (Antibiotic)	
	Acetylsalicylic acid (Non-steroidal anti-inflammatory)	Donepezil indirectly increases cholinergic activity in stomach, releasing more gastric acid.
	Risperidone (Antipsychotic)	The association decreases AChEI effects and cause drowsiness, confusion and mental deficiency.
	Bupropion (Antidepressant)	Seizures may occur, depending on drug dosage.
Memantine	Metformin (Antidiabetic)	Bioavailability of both drugs decrease.
	Hydrochlorothiazide (diuretic)	

Source: GOODMAN & GILMAN[16], 2012; www.drugs.com[21]. AD, Alzheimer's disease.

Only pharmacokinetic interactions originated from AD drugs metabolism were utilized in the present study. A total of 30 possible drug-interactions between AChEI and other medications were identified. These interactions may be associated with increased risk and severity of ADRs, cumulative toxicity, medication errors, treatment adherence reduction, increase morbimortality and may also worsen patients' cognitive functions[22].

Rivastigmine is primarily metabolized through hydrolysis by esterase, but this drug does not appear to be a substrate for cytochrome P450 isozymes[23,24,25]. Therefore, drugs that modify the activities of isoenzymes do not alter kinetics characteristics of rivastigmine. When analyzing calcium channel antagonists, antidiabetics, non-steroidal anti-inflammatory drugs, antihistamines and anti-acids, no pharmacokinetic interaction with rivastigmine was found.

However, the association of antihypertensive and beta-blockers with rivastigmine may contribute to additive effects that trigger bradycardia. Bradycardia might happen due to the block of beta-1-adrenergic receptors in the heart that, associated with

acetylcholinesterase inhibition, cause an increase in acetylcholine levels, triggering a greater parasympathetic activity[23,26,27].

Association of antipsychotics and antidepressants with AChEI may inhibit the effects of AChEI, by the inhibition of cytochrome P450 2D6, which metabolizes AD medicaments. Due to this fact, the patient presents greater cognitive impairment[23,28].

Donepezil is also metabolized in the liver by cytochrome P450 isoenzymes 2D6 and 3A4. According to Pasquelati *et al*. (2015)[28], an additive effect or a drug metabolism inhibition may occur when the cytochromes find specific substrates. These substrates may be, for example, antiarrhythmic (e.g., amiodarone) and antidepressant (e.g., Paroxetine, Perphenazine) drugs. In cases of such drug interactions, donepezil metabolism inhibition may potentiate the drug's effects because donepezil's active principles are, for a longer time, available in blood circulation.

The metabolism intensification and the decreased effects of donepezil may be observed with concomitant use of some antipsychotics (e.g., Quetiapine, Risperidone) or antidepressants (e.g. Sertraline), drugs that may be substrates to cytochrome P450[29,30]. Amiodarone, for example, may induce or retard AD drug metabolism, by being an antagonist and also a substrate of enzymes[31].

A common association of high-risk is the use of donepezil with no-steroidal anti-inflammatory agents, such as acetylsalicylic acid. The results of this interaction may be increased gastric acid secretion, and subsequently increased cholinergic activity, causing gastrointestinal hemorrhage[32].

Memantine is a weak base, excreted unchanged in urine; therefore, when analyzing its interaction with other drugs, urinary pH may be measured. Diuretics (e.g., Hydrochlorothiazide) increase body liquid elimination, which may cause a faster active principle clearance. When memantine and diuretics are taken together, blood concentrations of the diuretic may be reduced[33].

The interaction of memantine with biguanide results in an activation of renal tubular excretion caused by metformin, increasing memantine clearance, which is similar to a diuretic effect[34]. However, no clinical study has been performed about this interaction.

Prescriptions must be personalized according to the patients. In Brazil, if an AD patient uses SUS, they are influenced by the free of charge medications available in this system. Therefore, the list of medications dispensed by SUS should also be reevaluated and made adequate to elderly patients.

An ongoing evaluation of patients' prescriptions is important since the majority of comorbidities begin between the 4th and 5th decade of life. At this age, comorbidities are treated with drugs appropriated to adults, but these medicaments are not changed when the individual reaches 60 years old[9].

In summary, the present study verified drug-interactions that need particular attention, in order to improve the quality of life for the elderly population and decrease possible adverse effects. Some drug-interactions may begin after some years and are erroneously interpreted as a new disease, which complicates treatment and causes greater cognitive impairment in patients[35].

AChEI and NMDAR antagonist drugs interact with several drug classes (e.g., anxiolytics, antidepressants, antipsychotics, antihypertensive and antidiabetics), triggering polypharmacy. According to Hammes *et al*. (2008)[36,37] polypharmacy is one of the leading causes of drug-interactions. Additionally, the authors reported that the risk of drug-interactions in patients who take eight or more medications increases by 100%.

Several possible drug-interactions during AD treatment have been discussed by the present study. Consequently, a list of safe medications is indicated in Table 6 to treat AD patients with depression, anxiety, psychosis, hypertension, diabetes mellitus, cardiovascular diseases, inflammatory and fluid retention conditions, without interaction with AChEI and NMDAR antagonist drugs.

Table 6. Examples of safe medications to treat AD without interaction with AChEI and NMDAR antagonist drugs.

DISEASE/SYNDROMES	DRUG
Hypertension	Furosemide; Doxazosin; Captopril; Losartan; Aliskiren.
Depression	Mirtazapine; Venlafaxine; Cisapride.
Inflammatory conditions	Betamethasone; Prednisone; Prednisolone.
Gastric ulcers	Pantoprazole; Lansoprazole.
Psychosis	Paliperidone; Droperidol.
Seizures	Lamotrigine; Sodium valproate; Zonisamide; Gabapentin.
Anxiety	Diazepam; Clonazepam.
Diabetes mellitus	Glibenclamide; Glimepiride; Rosiglitazone.

Source: GOODMAN & GILMAN, 2012; www.drugs.com. AD, Alzheimer's disease.

Conclusion

The present study showed the most frequent concomitant disease with AD were systemic arterial hypertension, depression, diabetes mellitus and hypercholesterolemia. To treat these concomitant diseases, patients took a mean of 7 medications daily, characterizing polypharmacy, which often triggers drug-interactions. The main pharmacological classes that result in drug-interaction were anxiolytics, antidepressants, antipsychotics, antihypertensives, and antidiabetics. Alternative treatments were proposed by the present study to replace PIM for elderly patients with AD.

To improve clinical safety, professionals must know the consequences of certain medications used in elderly patients, to identify these drugs and mainly, not to prescribe them. In Brazil, the implementation of a specific list in RENAME, including adequate drugs to elderly patients is necessary, as well as expanding the availability of these medications to elderly patients through the SUS.

In this study, polypharmacy was characterized in our patients. The mean number of drugs that they took was seven daily, used to treat concomitant diseases, which often trigger drug-interactions. We aimed to decrease these interactions and suggest drugs that no have interactions with concomitant disease.

Data availability

Raw data for this article are available on OSF: http://doi.org/10.17605/OSF.IO/8UVR2[38].

Competing interests

No competing interests were disclosed.

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Supplementary material

Supplementary File 1: Sociodemographic questionnaire.

Click here to access the data.

Supplementary File 2: Drug interactions. In this file are completely arranged, all interactions found of drugs ingested by patients. The analyzes were carried out through the literature GOODMAN AND GILMAN[16] and also through the search in the database "drugs.com", in which the drugs ingested were inserted individually and a report of the interactions was reported.

Click here to access the data.

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The authors presented a study aiming to evaluate the most frequent diseases concomitant with AD, analyze the interactions between medications and these diseases, and suggest a potentially safer alternative treatment for concomitant diseases. The topic is indeed very interesting, and of a crucial importance for the geriatric population. The work presented is potentially interesting, but unfortunately there are several major points to take into consideration.

- In the definition of AD, I would include the tau deposition and the cortical atrophy as hallmark of the disease, together with the deposition of Amyloid β (Aβ). Moreover, I would mention about the amyloid deposition distribution pattern, which is more represented into the neocortex.

- The use of the CDR scale should be better specified; if the score utilized to stratify the impairment is the “global” CDR or the sum of boxes and, should be referenced accordingly. (I assume it has been used the global, therefore I would suggest to reference Hughes et al. (1982)[1].

- In the session “data collection” the MMSE is explained as follows “The maximum score for MMSE is 30, and this indicates cognitive impairment”; considering that 30 in the MMSE is indicative of better performance, I would suggest to rephrase the sentence correctly.

- “Memantine must only be used during mild and moderate stages of AD” is not in agreement with the guidelines of using Memantine, which should be rather used in “moderate to severe dementia in Alzheimer’s Disease”

- “Therefore, knowing which medications interact with these drugs is fundamental to indicate the correct treatment for secondary diseases and, even, predict drug-interactions” I wouldn’t use the word “secondary” since the disease the authors are evaluating are

concomitant and not “secondary” to AD.

- In the discussion, when the authors write “AD patients and caregivers are not aware of the interaction between drugs and enzymes. These enzymes may trigger inductive or inhibitory responses or serve as a substrate to other reactions” it would be advisable to mention which enzymes/isoenzyme are they talking about (i.e Cytochrome P450)

- In Table 5, I think it would be clearer if what the authors mean for “Drug opposite effect may worsen cognitive impairment, decreasing AChEI activity” will be more clearly specified.

- In Table 6, some medications are suggested as “not interacting with Ache-I or NMDAR antagonists”. Considering that we are talking about a geriatric population, I don’t particularly agree with the definition of “safe”. For example, BDZ are considered safe for treating anxiety, according to the table. However, it is known that the CNS sensitivity to BDZs in increased, determining sedation at lower concentration. I would strongly recommend to carefully review this information, in light of the population taken into consideration in this paper, constituted not only by elderly, but demented.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.