In vitro gastrointestinal digestion and bioavailability of lithium from processed lithiated and nonlithiated white *Agaricus bisporus* mushrooms

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Abstract

Aim: In order to avoid side effects of lithium doses in some patients, some commonly cultivated mushroom species including A. bisporus have been successfully lithiated, with the potential to provide more acceptable sources of Li. This study assessed the in vitro release (potential bioaccessibility) and possible intake of Li using the action of artificial gastrointestinal juices on lithiated and nonlithiated (control) button mushrooms (Agaricus bisporus) that were subjected to certain modes of culinary processing. Methods: In the in vitro release study, mushrooms were processed using a number of routinely used domestic treatments including rehydrating dried mushrooms, blanching and blanching followed by pickling of fresh or frozen mushrooms. The in vitro digestion procedure used artificial gastrointestinal juices in a two- stage methodology that was adapted from 'The Bioaccessibility Research Group of Europe' method. The Li concentrations were determined using an inductively coupled argon plasma– dynamic reactive cell– mass spectrometer.

1 Results: Lithium was found to be more bioaccessible from caps of lithiated mushrooms compared with nonlithiated. Releases from the caps and stipes of blanched or blanched and then pickled mushrooms through gastric digestion ranged from 32 ± 2 to 50 ± 1% relative to the dried product and was lower for gastrointestinal digestion, which ranged from 16 ± 1 to 20 ± 1%.

2 Conclusion: Losses of Li sustained through blanching or blanching followed by pickling of fresh mushrooms (41–87% wet weight) combined with limited accessibility during gastrointestinal release (16– 55%) result in much lower bioavailability of the dose from lithiated products. A 300- g meal would provide <5% of the Li (6 mg) required for potential preventative treatments, such as reducing suicide rates and lowering dementia risk.

3 K E Y W O R D S

bioavailability, biofortification, food toxicology, lithium treatment, mental health

4 INTRODUCTION

Lithium (Li), mainly in the form of Li_2CO_3, is used in psychiatric medicine to treat bipolar disorder.[1] There is also a wider debate on other potential health benefits from medicinal or dietary Li, possible side effects, as well as on the essentiality and role of Li in human health and nutrition.[1– 5] A more practical aspect of harnessing the promedicinal potential of intentionally lithiated foods is the effective Li dosage that can be realised from these products. This involves the extent to which they can be enriched, the effects of culinary treatment and intestinal digestion and absorption of Li from such foods.[6–9] The ability of macromycetes to efficiently bioconcentrate some metallic and metalloid elements in their fruiting bodies (mushrooms) is widely known.[10] Some of these elements such as selenium (Se) and lithium (Li) are reported to have a protective or therapeutic effect on neurological function in humans, but their occurrence (particularly of Li) in many foods including edible mushrooms (wild or cultivated varieties) could be considered irrelevant for therapeutic purposes. This has prompted attempts by a number of research groups to enrich the fruiting bodies or mycelia of known fungal species with these elements by fortifying the substrates in which they are cultivated.[11–1 3] Li is a very minor constituent of foodstuffs including edible wild and cultivated mushrooms or potable water.[12,14]

Unlike some vegetables, a number of mushroom species (including most common edible varieties) have to be cooked, because when raw, they are rather hard to digest, cause gastric disorders and in some cases can also be toxic. Early studies on digestion and absorption of minerals from mushrooms used the volunteer or animal (mouse) models. For example, a study reported the use of five volunteers who were provided meals composed of several species of wild *Agaricus* containing Cd and Cu at varying concentrations.[15] The amount of faecal cadmium and copper increased after the meals, suggesting that the elements contained in the mushrooms passed through the intestinal tract without much absorption. In another investigation using volunteers (a group of young female Finns), intestinal digestion, absorption and turnover of Se from a diet composed of freeze- dried and pulverised *Boletus edulis* (King Bolete) mushrooms were studied.[16] The dosage of Se was 150 μg per day over a period of 4 weeks. Plasma and erythrocyte Se levels in the volunteers were then followed for 8 weeks (the mushrooms were also found to have 'elevated' Cd and Hg (resulting in a Cd and Hg dose of 40 μg and 20 μg per day, respectively)). The erythrocyte Se levels increased significantly by 26%, but plasma Se and plasma or platelet GSH- Px activity were only slightly elevated, leading the study to suggest that the

bioavailability of mushroom- Se was reasonably low.[15] In more recent times, experiments with mushrooms and human volunteers and laboratory animals have been largely followed by the use of in vitro release (accessibility, digestion and pseudo bioavailability) models.[17,18]

This study aimed to assess the in vitro release and possible bioavailability of Li from both lithiated and nonlithiated (control) button mushrooms (*Agaricus bisporus*) that were subjected to certain modes of culinary processing.[9,19] The BARGE (the Bioaccessibility Research Group of Europe) method— used for the analysis of the bioavailability of metallic elements of processed mushroom samples— consists of two consecutive processes, gastric and intestinal digestion.[20,21] This in vitro physiologically based ingestion bioaccessibility method gives comparable results to the in vivo relative bioavailability studies in animal models.[22]

5 | MATERIALS AND METHODS

5.1 | Mushrooms

The lithiated and nonlithiated *A. bisporus* mushrooms used in this study were obtained from a cultivation experiment.[19] Lithiation was achieved by raising mushrooms in Li_2CO_3 fortified (at two different compost fortification levels of 50 and 100 mg kg^{-1} compost dw) substrate. The concentration of Li in the caps and stipes of nonlithiated mushrooms was 0.48 and 0.49 mg kg^{-1} dw (means), respectively. Mushrooms were processed using a number of routinely used domestic treatments including rehydrating dried mushrooms, blanching, and blanching and pickling of fresh or frozen mushrooms.[9] In short, nonlithiated mushrooms (separately caps and stipes) were divided accordingly into six equal parts while lithiated mushrooms (separate caps and stipes from 50 and 100 mg kg^{-1} dw growing compost) were divided into two equal by weight parts and then subsequently processed (Table 1). The processed products were lyophilised, then ground into a powder and used in the in vitro digestion study with artificial gastric and gastrointestinal juices. All culinary processing methods substantially decreased the quantity of Li that could potentially be available in a final product such as a mushroom meal. After culinary processing, these concentrations reduced to a range from 0.10 ± 0.09 to 0.18 ± 0.02 mg kg^{-1} dw (caps) and 0.22 ± 0.11 to 0.45 ± 0.02 mg kg^{-1} dw (stipes). The corresponding Li concentration in raw lithiated mushrooms ranged from 11 ± 1 to 11 ± 7 mg kg^{-1} dw (caps) and 12 ± 2 to 15 ± 10 mg kg^{-1} dw (stipes). Culinary processing losses of Li lowered these ranges from 2.6 ± 0.5 to 5.9 ± 0.9 mg kg^{-1} dw (caps) and 5.1 ± 0.8 to 9.1 ± 0.9 mg kg^{-1} dw (stipes).[9] The recorded decreases, integrated for whole fruiting bodies of both lithiated and nonlithiated mushrooms, were as follows:

- after macerating and blanching of rehydrated mushrooms, 83% wet weight (ww) and 80% dry weight (dw),
- after blanching of fresh mushrooms, by 41– 50% ww (33– 41% dw),
- after blanching of deep- frozen mushrooms, by 63% ww (55% dw),
- after blanching and pickling of fresh mushrooms, by 47– 87% ww (72– 77%) dw,
- after blanching and pickling of deep- frozen mushrooms, by 51% (ww) and 57% (dw).[9]

5.2 | Digestion in vitro

The in vitro digestion method used to study the release of Li from mushroom meals used artificial gastrointestinal juices

TABLE 1 Estimated effect of processing (%) and release (%) of Li from nonlithiated and lithiated* *A. bisporus*

Material	Kind of processing	Original concentration (mg kg^{-1} dw)	Gastric release—equivalent concentration (mg kg^{-1} dw)	Gastric release (%)	Gastrointestinal release—equivalent concentration (mg kg^{-1} dw)	Gastrointestinal release (%)
Caps	Fresh → dried (raw)	0.48 ± 0.28	0.021 ± 0.005	4.4 ± 1.0	0.029 ± 0.000	6.1 ± 0.3
Nonlithiated champignons	Fresh → dried → macerated → blanched	0.10 ± 0.09	0.016 ± 0.002	16 ± 2	0.033 ± 0.002	33 ± 2
	Fresh → blanched	0.14 ± 0.10	<MQL	WD	<MQL	WD
	Fresh → blanched → pickled	0.18 ± 0.02	<MQL	WD	<MQL	WD
	Fresh → deep frozen → blanched	0.11 ± 0.01	0.033 ± 0.008	30 ± 7	0.029 ± 0.002	26 ± 2
	Fresh → deep frozen → blanched → pickled	0.16 ± 0.01	0.035 ± 0.001	22 ± 0	0.007 ± 0.003	4.4 ± 1.7
Lithiated champignons	Fresh → dried (raw)[a]	11 ± 1	4.6 ± 0.1	42 ± 1	1.8 ± 0.1	16 ± 1
	Fresh → blanched[a]	5.9 ± 0.9	1.9 ± 0.1	32 ± 2	0.94 ± 0.08	16 ± 1
	Fresh → dried (raw)[b]	11 ± 7	4.8 ± 0.4	44 ± 4	2.2 ± 0.2	20 ± 2
	Fresh → blanched → pickled[b]	2.6 ± 0.5	1.3 ± 0.0	50 ± 1	0.53 ± 0.03	20 ± 1
Stipes	Fresh → dried (raw)	0.49 ± 0.17	0.15 ± 0.02	31 ± 4	0.080 ± 0.002	16 ± 0
Nonlithiated champignons	Fresh → dried → macerated → blanched	0.22 ± 0.11	<MQL	WD	0.050 ± 0.004	23 ± 2
	Fresh → blanched	0.45 ± 0.02	<MQL	WD	<MQL	WD
	Fresh → blanched → pickled	0.34 ± 0.02	<MQL	WD	<MQL	WD
	Fresh → deep frozen → blanched	0.35 ± 0.02	0.041 ± 0.004	12 ± 1	0.081 ± 0.030	23 ± 9
	Fresh → deep frozen → blanched → pickled	0.23 ± 0.02	0.011 ± 0.001	4.8 ± 0.6	0.013 ± 0.002	5.6 ± 0.8
Lithiated champignons	Fresh → dried (raw)[a]	12 ± 2	5.9 ± 1.4	49 ± 12	2.3 ± 0.1	19 ± 1
	Fresh → blanched[a]	9.1 ± 0.9	3.6 ± 0.1	40 ± 1	1.5 ± 0.1	17 ± 1
	Fresh → dried (raw)[b]	15 ± 10	8.2 ± 0.2	55 ± 2	3.2 ± 0.3	21 ± 2
	Fresh → blanched → pickled[b]	5.1 ± 0.8	1.8 ± 0.2	35 ± 3	0.94 ± 0.05	18 ± 1

WD, without data.

*Grown in compost with added Li at the concentrations of 50 mg kg^{-1} dw[a] or 100 mg kg^{-1} dw[b], and in reference (commercial) compost, respectively (n = 5; five replicates of gastric and gastrointestinal digestion for each fungal material were made and examined); method limit of quantification (MQL) = 0.021 mg kg^{-1} dw.

in a two- stage methodology that was adapted from 'The Bioaccessibility Research Group of Europe' method.[20–22] A more elaborated description is provided in Supporting Information, but in short, the method simulates digestive process taking place in the human alimentary tract through the use of four digestive juices: artificial saliva (S), gastric juice (G1), gastrointestinal juice (G2) and bile (B). A mixture of S and G1 yields an artificial digestive fluid for gastric digestion (phase I), and a mix of G2 and B comprises the fluid for gastrointestinal digestion (phase II). The formulas used in the digestive fluids for phases I and II were prepared in 500 ml polypropylene bottles 1 day before the study, using the components, quantities and conditions listed in Table S1. The percentage release of Li in gastric and gastrointestinal digestion of the fungal materials (five replicate analyses per each material) was calculated as the ratio of the leached fraction to the value of the absolute concentration.

5.3 | ICP- DRC- MS analysis

The gastric and gastrointestinal digests obtained were diluted with nitric acid, and the Li concentrations were determined using an inductively coupled argon plasma– dynamic reactive cell– mass spectrometer (ICP- DRC- MS; Perkin- Elmer ELAN DRC II SCIEX, Canada) with a Meinhard concentric nebuliser, cyclonic spray chamber, Pt cones and a quadruple mass analyser. The analytical method was fully validated through the use of standard procedures (standard solutions, quality assurance and quality control (QA/QC), procedural blank samples, duplicates and replicates. Additionally, the instrument was calibrated for each analytical cycle. The quality control parameters obtained from these measurements were found to be suitable for the reliable measurement of Li, as reported earlier[8,19] The limit of detection (LOD) achieved for Li in the gastric and gastrointestinal digests was 0.02 μg L^{-1}.

6 | RESULTS

Data from the in vitro experiments on the digestive release of Li from raw (dried and pulverised) lithiated and nonlithiated button mushrooms that had been culinarily processed were assessed in relation to the original Li concentration prior to processing. An overview of the levels of Li released during the digestion experiments can be visualised for both lithiated and nonlithiated caps and stipes in Figure 1.

The percentage releases of Li from unprocessed raw (dried and powdered) nonlithiated caps in the gastric digestion (with saliva) and the gastrointestinal digestion experiments were 4.4 ± 1.0 and 6.1 ± 0.3%, respectively. The corresponding releases for lithiated mushrooms (both fortification levels) in these digestion experiments were in the ranges from 42 ± 1 to 44 ± 4 and 16 ± 1 to 20 ± 2%, respectively. In the case of the raw (dried and powdered) nonlithiated stipes, the release of Li from the gastric digestion was 31 ± 4% and 16 ± 0% from the gastrointestinal digestion. Corresponding figures for the lithiated stipes ranged from 49 ± 12 to 55 ± 2% and from 19 ± 1 to 21 ± 2%, respectively (Table 1). This suggests that the release of Li was greater from lithiated caps but in the case of stipes, the results were not so clear- cut.

7 | DISCUSSION

Foods are chemically complex mixtures of nutrients such as carbohydrates, lipids, proteins, vitamins and minerals. The extent to which these components are released from ingested food into the human gastrointestinal tract is an important factor when assessing the benefits or toxicological risks associated with dietary intake, for example, of elements contained in edible mushrooms. The available scientific literature does not provide information on the degree of Li release from button mushrooms and its preserves under the influence of digestive juices or the absorption of the element from the intestinal lumen into the blood.

Data on the release of Li during in vitro gastrointestinal digestion of raw (dried and ground) mushrooms have very recently been reported for lithiated fruiting bodies of *Pleurotus* spp.[7] The *Pleurotus* spp. specified were *P. djamor* and *P. ostreatus* (no information was provided on repetitions for in vitro digestion, nor on the reference/ baseline sample concentrations). The reported release of Li through gastrointestinal digestion in vitro of mushrooms was in the range from 67 to 92%, and using the same procedure for a Li drug (Li_2CO_3 in tablets), the release was in the range from 63 to 78%.[7] Curiously, an earlier study reported the release of Li from Li_2CO_3 tablets subjected to in vitro gastrointestinal digestion at 0.00 ± 0.00% (presumably, no evidence of release), while under the same digestion conditions, the reported release (rounded data) of Li from raw (dried and ground) nonlithiated and lithiated *P. ostreatus* was 27 ± 13% and 70 ± 7%, respectively (although the background concentration of Li in the coffee husk substrate appeared elevated at a reported level of 94 mg kg^{-1} dw).[6]

There is no information in the scientific literature on the degree of Li release from culinarily processed mushrooms under the influence of a digestive juice. In this study, the concentration of Li in the gastric and gastrointestinal digests of fresh nonlithiated caps and stipes subjected to blanching alone or those blanched and then pickled was below the limit of detection, which suggests only a minimal release, if at all (Table 1). The rehydrated caps of nonlithiated mushrooms, which were further macerated and blanched and then subjected to gastric and gastrointestinal digestion, released 16 ± 2% and 33 ± 2% Li, respectively. In the case of similarly treated stipes, no release from the gastric digestion was observed but the gastrointestinal digestion release was 23 ± 2%.

The rate of Li release through gastric digestion of initially deep- frozen nonlithiated caps that were then blanched was 30 ± 7%, with 12 ± 1% release for the stipes; for gastrointestinal digestion, the corresponding releases were 26 ± 2% and 23 ± 9%, respectively. In comparison, the release of Li through the gastric and gastrointestinal digestion of the pickled caps and stipes of nonlithiated mushrooms, which were initially deep- frozen and then blanched, was roughly lower, that is 22 ± 1% and 4.8 ± 0.6%, respectively, for the gastric digestion and 4.4 ± 1.7% and 5.6 ± 0.8%, respectively, for the gastrointestinal digestion. In the case of lithiated mushrooms, the rates of Li release were clearly lower in the gastrointestinal digestion for both caps and stipes of the blanched or blanched and then pickled mushrooms (releases ranged from 16 ± 1 to 20 ± 1%) than through gastric digestion alone (releases ranged from 32

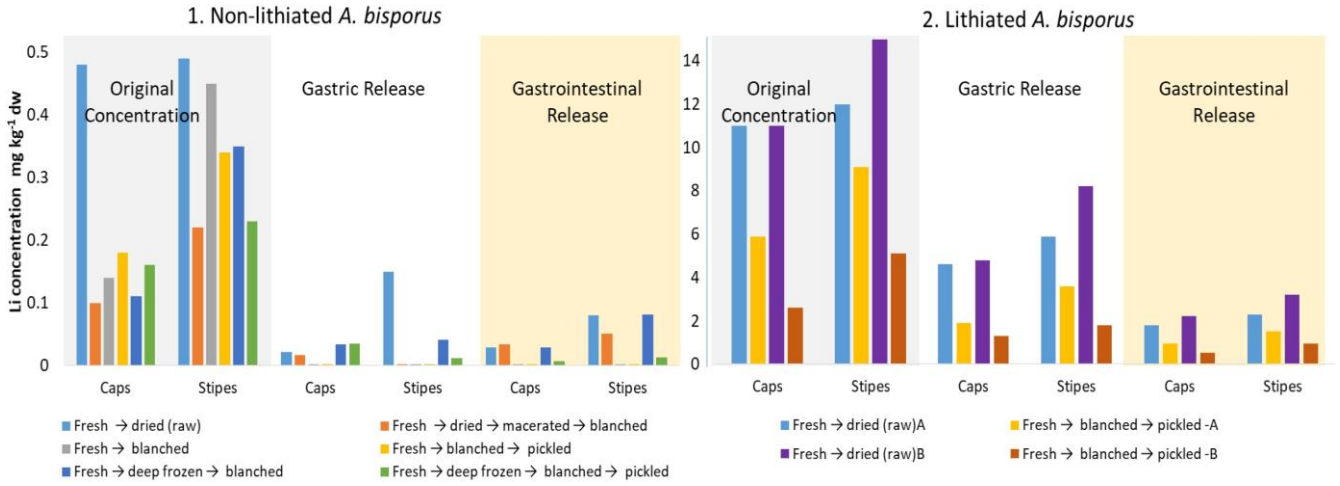

FIGURE 1 Lithiated *A. bisporus* are comprised of separate caps and stipes from specimens grown on Li_2CO_3 fortified compost at 50 mg kg^{-1} dw (samples labelled A) and 100 mg kg^{-1} dw (samples labelled B)

± 2 to 50 ± 1%). Lithiated mushrooms, which were just dried and ground, nominally contained more 'original' Li than the lithiated specimens which were culinarily treated and lost a portion of the element because of processing but this did not seem to affect the release of Li during the gastric and gastrointestinal digestion experiments.

The obtained results suggest that Li is released roughly to the same extent from both raw (dried and ground) mushrooms and those subjected to the culinary processing procedures used in this study, although the volume of materials that were tested (a number of batches for nonlithiated and lithiated mushrooms and levels of lithiation for each process) was too limited to be confirmed through statistical analysis. Simulated modelling of the gastrointestinal release of a compound in the lumen of the digestive tract can provide a quantitative estimate of the accessibility of an element while taking into account the basic factors that influence this process. In the current study, it provides a key indication of the bioavailability of Li, as elements and minerals that are highly bioaccessible are also considered to be more bioavailable (additionally, the Li is incorporated into a mushroom matrix where it is likely to occur as a peptide

complex, a form that is seen to be more bioaccessible). More specific factors relating to individuals (age, sex, physical condition, microbiome, etc.) would also influence the release of Li from a foodstuff but would require additional investigation, which is beyond the scope of the present work. Thus, taking into account the potential losses, data from gastrointestinal release using foods that are culinarily processed can be seen to provide an indication of a worst- case scenario in terms of the bioavailability of targeted constituents such as Li, in the present case.

The button mushrooms in the current study are seen as a common and popular food, and although they were processed in a number of ways, other popular cooking methods, for example frying in a wok, flat pan frying, grilling or braising, were not investigated. Frying of mushrooms in a pan or wok reduces the extent to which metallic elements (e.g. monovalent potassium or radiocaesium) leach from the flesh in a prepared mushroom meal (on a wet weight basis).[23,24] Also, braising largely prevents the leaching of potassium but also radiocaesium, mercury and methylmercury from a mushroom (*B. edulis*) meal (on a wet weight basis).[25,26] Thus, frying or braising of fresh (or deep- frozen) fruiting bodies of some species of mushrooms could provide a better alternative to retain lithium in the flesh of the mushroom rather than macerating, blanching or blanching and pickling of the fresh or deep- frozen mushrooms.

The manner in which mushrooms are processed and the species- specific texture of a fruiting body can have different impacts on the behaviour of the fungal matrix. Processes such as rehydration, thawing of deep- frozen product, boiling water and/or vinegar can result in the loss/retention of intracellular fluid including dissolved or the colloidal fraction of organic matter and the metallic elements therein, disruption of the bonds between metallic elements and the organic matrix, etc. Vinegar absorbed by pickled mushrooms could prompt the release of Li into the digestive tract due to suspected acidifying and chelating impact within the meal, but as observed in this study it can be rather small or negligible (Table 1).

One of the objectives of the study was to assess the potential of lithiated mushrooms to provide a recommended Li dose to patients who have been prescribed Li treatment, that is the bioaccessibility of lithium through consumption of this common food. Due to the substantial loss of Li from lithiated button mushrooms during their blanching, blanching and pickling processes and the demonstrated degree of Li release from such products in simulated in vitro gastrointestinal digestion, only a small amount of the Li originally accumulated in lithiated fruiting bodies would be bioaccessible in a typical portion size of 100– 300 g ww. The degree to which the recommended therapeutic dose (e.g. 600– 1200 mg of Li_2CO_3 is equivalent to 113– 226 mg of elemental Li) was reached was below 0.02% for blanched caps and up to 0.04% for the blanched stipes, while for blanched and pickled caps, it was even lower, that is up to 0.014% and up to 0.025% for the stipes. In the simulated in vitro gastrointestinal digestion experiments, 10– 30- g portions of the dried and powdered lithiated product provided only 0.02– 0.11% of the recommended therapeutic dose.

This is a negligible amount relative to bipolar treatment doses but may be a little more relevant for other therapies which require lower doses, for example 6 mg of Li. Lithiated mushrooms subjected to these culinary treatments could provide from 0.22 to 0.6% of the dose from a 100 g meal or from 0.65 to 1.8% if the intake was increased to 300 g ww. Here, the maximal degree of dose coverage from 10- to 30- g portions of dried and powdered lithiated button mushrooms in simulated in vitro digestion was 1.4% and 4.1%, respectively.

Preventive therapies, for example reducing suicide rates, lowering dementia risk and stabilising mild Alzheimer's dementia, would require daily intake of lower concentration doses— 1- 2 mg/d (reduction of suicide risk) or lower— of the order of micrograms per day.[27]

In considering the possible therapeutic potential of lithiated *A. bisporus*, it is important to bear in mind that these mushrooms could be supplied and retailed as fresh produce, in much the same way that button mushrooms are commonly available throughout the year in green grocery stores and other similar outlets. This easy availability in the last few decades has led to this popular mushroom being consumed as a fresh product rather than as a dried or preserved product. Thus, the availability estimated through the experiments in this study could be realistically viewed as a worst- case scenario, as the consumption of fresh lithiated mushrooms (e.g. pan or stir- fried, or added sliced or whole to a stew) would avoid many of the losses seen for the dried (maceration fluids) and pickled (preservation fluid (vinegar or brine)). Equally, dried and powdered lithiated mushrooms added as a soup or stew ingredient represent the potential of the entire incorporated Li content for release.

AUTHOR CONTRIBUTIONS

SP performed the experiments, contributed to reagents, methodology, formal analysis, investigation and data curation and helped with quaerenda. JF contributed to conceptualisation, formal analysis, investigation, resources, data curation, writing— original draft preparation, review and editing and supervision. HE contributed to formal analysis and draft preparation and helped with quaerenda. DB contributed to analytical methodology, validation, formal analysis, investigation, resources and data curation. ARF contributed to data curation and manuscript writing and editing and helped with quaerenda.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

All authors have given approval to this version of the manuscript.

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