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In vivo demonstration of immunologic cross-reactivity to octylisothiazolinone in patients primarily and strongly sensitized to methylisothiazolinone

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Abstract

Background: Notwithstanding that concomitant exposure to different isothiazolinone derivatives may result in concomitant sensitization, clinical and animal studies have suggested cross-reactivity between these derivatives, notably between methylisothiazolinone (MI) and octylisothiazolinone (OIT).

Objective: To investigate if patients sensitized to MI show cross-reactions to OIT and/or to benzoisothiazolinone (BIT) by applying the concept of the re-test method.

Patients And Methods: From March to October 2019 consecutive patients were patch tested with MI 0.2% aqueous in duplicate at the two lower corners of both shoulder blades. Patients sensitized to MI, but not to OIT 0.1% petrolatum (pet.) nor to BIT 0.1% pet., were re-tested, 2 months later, with the latter two derivatives at the skin sites where the MI reactions had fully disappeared.

Results: Of 116 patients, 15 (13%) were sensitized to MI, eight of these not sensitized to BIT nor to OIT. Of these, seven patients, all (very) strongly sensitized to MI, were re-tested: five patients showed positive patch test reactions to OIT 0.1% pet.; one patient to OIT 0.1% pet. and BIT 0.1% pet.; and one other patient showed no reactions.

Conclusion: This study suggests that patients primarily and strongly sensitized to MI may show immunologic cross-reactions to OIT, and to a far lesser extent to BIT.

KEYWORDS

allergic contact dermatitis, benzoisothiazolinone, concomitant sensitization, cross-reaction, methylisothiazolinone, octylisothiazolinone, patch test, re-test method

1 | INTRODUCTION

Until recently methylisothiazolinone (MI) caused an unprecedented outbreak of allergic contact dermatitis in Europe and beyond. No longer allowing this preservative in leave-on cosmetics, and restricting its use concentrations to a maximum of 15 ppm in rinse-off cosmetics, has clearly led to a decreased sensitization rate to MI in Europe.¹ However, in Latin America, and in Argentina in particular, MI is still allowed in concentrations up to 100 ppm in cosmetics. This still

translates in dramatic sensitization prevalences, reaching up to 15.5% in patch tested individuals.² Data from clinical and animal studies have previously suggested that subjects sensitized to MI might show cross-reactions to other isothiazolinone derivatives, octylisothiazolinone (OIT) in particular.³⁻⁷ However, concomitant exposure to isothiazolinone derivatives in daily life makes it very difficult to confirm the existence of such cross-reactivity. In 2002, Rustemeyer et al⁸ described the so-called re-test method to evaluate potential cross-reactions between different haptens in laboratory animals and

humans. It relies on the fact that, upon cutaneous sensitization to a hapten, persisting allergen-specific effector/memory T cells reside in that particular part of the skin, which, upon re-exposure to this chemical, or to a cross-reactive substance, will lead to a faster and/or stronger contact-allergic skin reaction. We here apply the concept of this method (local skin memory) to verify whether immunologic cross-reactions occur to OIT and/or to benzisothiazolinone (BIT) in patients primarily sensitized to MI.

2 | METHODS

From March to October 2019, patients presenting for patch tests at the Dermatology Department of the San Martín Hospital of La Plata, Buenos Aires, Argentina, were consecutively patch tested with the Latin American standard series (Chemotechnique Diagnostics, Vellinge, Sweden) using IQ Ultra patch test chambers (Chemotechnique Diagnostics). MI 0.2% aq., which is a part of this series, was always patch tested in duplicate, using a Finn chamber (12 mm; SmartPractice, Calgary, Alberta, Canada), at the lower corner of both shoulder blades. The derivatives OIT 0.1% pet. (Chemotechnique Diagnostics) and BIT 0.1% pet. (allergEAZE, SmartPractice) were always patch tested on the back as a supplement in each patient using IQ Ultra patch test chambers. Patients who were shown to be sensitized to MI, but not to OIT nor to BIT, were invited to participate in a follow-up patch test session; concomitant sensitization to methylchloroisothiazolinone (MCI)/MI was not an exclusion criterion. Two months later, when all patch test reactions had disappeared, these patients thus underwent re-testing with BIT 0.1% pet. on the left, and OIT 0.1% pet. on the right lower corner of both scapulae (using Finn chambers, 12 mm), respectively, that is, at the skin contact sites where previously the positive patch test reaction to MI had been present.

All patch tests were occluded for 2 days, using 3 M Micropore Surgical Tape (St. Paul, Minnesota), and read on day (D) 2 and D4 according to the ESCD guidelines.⁹ For each patient we evaluated variables such as age, gender, atopy status, occupation, body localizations affected, the degree of MI sensitization and its relevance, concomitant positive patch test reactions, and, in the second patch test session, the degree of sensitization to BIT and/or OIT and their potential relevance.

3 | RESULTS

All results are outlined in Table 1. Out of 116 patients, 72 women and 44 men, 15 patients (13%) were shown to be sensitized to MI 0.2 aq. (Figure 1). Of these, seven were also sensitized to BIT and/or to OIT, among whom three with a cosensitization to MCI/MI 0.01% aq., and were excluded from the second (re-test) patch test session. Of the eight remaining patients, sensitized to MI but not to OIT and/or BIT, seven patients, among them two with a positive reaction to MCI/MI (both +), agreed to be re-tested with OIT and BIT. These included

six females and one male, of whom four had an atopic background, with an age range of 31 to 67 years (median and mean age of 47 and 49 years, respectively). Most patients were very strongly sensitized to MI (extreme positive, +++, three cases), or strongly sensitized (strong positive, ++, three cases), with only one case showing a weak (+) positive reaction. The most commonly affected body localizations were the face (four cases) and the hands (four cases), whereas other localizations included the neck (three cases) and the arms (two cases). The legs and trunk were involved in one case each, and also generalized dermatitis occurred in one patient. MI-containing leave-on products (four cases, among whom one also had used wet wipes) and rinse-off products (four cases) were the culprit allergen sources in the majority of cases; in one case each an MI-containing occupational product was involved, that is, a massage cream, a floor cleaner, and a glue. Interestingly, following the re-testing, five patients now showed positive patch test reactions to OIT 0.1% pet. (all ++), one patient to both OIT 0.1% pet. and BIT 0.1% pet. (++ and +, respectively), and only one patient (with a weak MI sensitization, +) showed no reactions to OIT and/or BIT (Figure 2). The reactions to OIT and BIT were felt to be consistent with immunologic cross-reactions to MI, revealed by exploiting the local skin memory (ie, the specific T-cell clone present at the previously positive patch test sites of MI),⁸ rather than irritant reactions, newly developed sensitizations, or boosting of previously concomitant but false-negative reactions to these derivatives. Of the six patients now showing a positive patch test to OIT and/or BIT at re-testing, 3 (Cases 1, 2, and 4) were considered to have a potentially relevant patch test reaction to these derivatives, due to their potential presence in paint (OIT), a liquid dishwashing agent (BIT), and a leather bag (OIT), respectively. The paint (Case 1) was, however, not labelled and the leather bag (Case 4) could not be chemically analyzed. In the three remaining patients no (current) potential relevance was found for OIT.

4 | DISCUSSION

As indicated by a previous study,² the sensitization rate to MI in Argentinian patients referred for patch tests is still very high (13%, 15/116 patients). Mainly middle-aged women are affected with facial and/or hand dermatitis, mostly attributed to MI-containing cosmetics, which is in good accordance with previous reports from Europe (see, eg,⁴). Besides MI and MCI/MI, OIT and BIT are widely used preservatives, the latter two forbidden in cosmetics, but, similar to the former two, potentially present in household detergents, chemical products such as paints, and numerous industrial applications (eg, in the treatment of leather goods).¹⁰⁻¹⁶

Contact allergens may show cross-reactivity (ie, interact with the same T-cell receptor) if both substances are chemically and structurally (three dimensionally) related.¹⁷ Immunologic cross-reactivity between different isothiazolinone derivatives has often been suggested to occur, although its existence in vivo (ie, in humans) is still controversial, as concomitant exposure to these chemicals readily occurs in daily life, and various studies have yielded conflicting results.

TABLE 1 Patient characteristics and results of initial patch tests and re-tests (all on day 4)

Patient characteristics					First session (initial patch test)					Second session (re-test)		
Case	Age/ sex	Atopy status	Localization	Occupation	MI	Relevance to MI	BIT	OIT	Other positive patch tests	BIT	OIT	Possible relevance
1	67/F	Yes	Generalized	Masseur	+++	Massage cream, body oil	–	–	Ni++, colophonium +, lanolin alcohols ++, MCI/MI+	–	++	Paint
2	43/F	No	Hands	Teacher	+++	Liquid soap	–	–	Formaldehyde+++, caine mix III++	+	++	Liquid dishwashing agent (BIT)
3	31/F	No	Face, hands	Kinesiologist	++	Shampoo, conditioner, bath oil	–	–	Ni++, cobalt++', thiomersal++	–	++	Not found
4	48/F	Yes	Face, hands, neck, trunk, arms	Cleaning lady	++	Body lotion, floor cleaner	–	–	Ni++, formaldehyde ++, FM-I++, FM-II +, Qt15++	–	++	Leather bag
5	64/F	No	Hands, legs	Nurse	+++	Emollient cream	–	–	Formaldehyde+++, lanoline++, MCI/ MI+	–	++	Not found
6	42/M	Yes	Face, neck	Carpenter	+	Glue, shampoo	–	–	–	–	–	N/A
7	47/F	Yes	Face, neck, arms	Nurse	++	Face cleanser, liquid soap, wet wipes	–	–	Thiuram mix++	–	++	Not found

Abbreviations: aq., aqueous; BIT, benzoisothiazolinone 0.1% pet.; F, female; FM, fragrance mix; M, male; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone 0.01% aq.; MI, methylisothiazolinone 0.2% aq.; N/A, not applicable; Ni, nickel; OIT, octylisothiazolinone 0.1% pet.; pet., petrolatum; Qt15, quaternium-15.

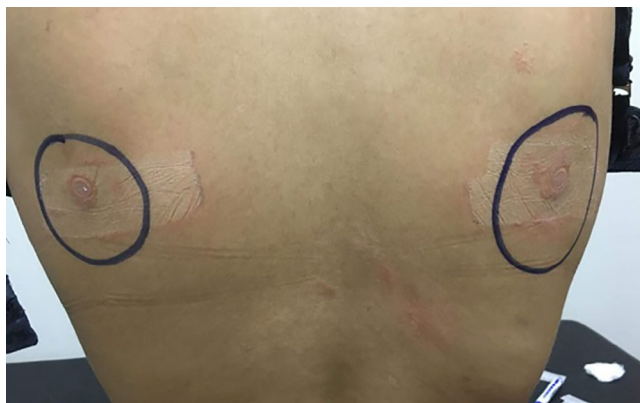


FIGURE 1 Case 3: Strong (++) positive patch test reactions to methylisothiazolinone (MI) 0.2% aqueous (aq.), on day 4, at the lower end of both scapulae. No reactions occurred to benzoisothiazolinone (BIT) 0.1% petrolatum (pet.) nor to octylisothiazolinone (OIT) 0.1% pet. Two months later, once the patch test reactions to MI had fully disappeared, the patient was re-tested with both OIT and BIT at these particular skin sites

Cross-reactivity can be investigated in many ways: (i) by clinical (epidemiological, retrospective) studies, which often only provide indirect evidence and may not exclude concomitant sensitization; (ii) by animal studies, which cannot always be extrapolated to humans; (iii) by statistical analyses, although frequent concomitant positivity to two or more given contact allergens is not necessarily a proof of cross-reactivity (ie, concomitant sensitization being equally likely); (iv) by



FIGURE 2 Case 4: Strong (++) positive patch test reaction to octylisothiazolinone (OIT) 0.1% petrolatum (pet.) on day 4 at the lower end of the right scapula, where previously a strong positive patch test (++) occurred to methylisothiazolinone 0.2% aqueous (aq.) No reaction to benzoisothiazolinone (BIT) 0.1% pet. at the contralateral scapula. Previous patch tests on the upper back, 2 months earlier, were negative to both OIT and BIT

in vitro T-cell studies, which are not always readily available or feasible; and, more recently, (v) by in vitro studies using reconstructed human epidermis.¹⁸ The authors of the latter approach acknowledged that, albeit time consuming, the concept of the re-test method is another interesting way to verify the existence of potential cross-reactivity.

4.1 | Literature data on potential cross-reactivity between MI and MCI/MI

When patients are sensitized to MI, immunologic cross-reactivity to MCI/MI has been considered very likely,^{3,19,20} and also the other way around, that is, when MCI/MI (and thus MCI) is the primary sensitizer, cross-reactivity to MI (especially when it concerns high concentrations) might also occur.^{3,21} However, a recent in vitro study, using reconstituted human epidermis, argued rather against MCI and MI cross-reactivity.¹⁸

4.2 | Literature data on potential cross-reactivity between MI, OIT, and BIT

MI, OIT, and BIT are chemically similar, all of them containing the same isothiazolinone ring; however, structurally, BIT is clearly different, due to its additional benzene ring. In line with results from clinical retrospective studies, this suggests that OIT (the chemical homologue of MI), rather than BIT, might cross-react with MI. With regard to potential cross-reactions between the nonchlorinated derivatives, especially MI and OIT, diverging results have been published. Geier and Schnuch²² initially reported that cross-reactivity between MCI/MI, OIT, and BIT is unlikely to occur (MI not yet being patch-tested at that time), and later on, when MI became available as a separate patch test agent (albeit at the lower test concentration of 0.05% aq.), it was argued that concomitant exposure to MI, OIT, and BIT is still the most reasonable explanation for the observation of concomitant positive patch test reactions to these derivatives.¹⁹ However, the authors added that OIT-sensitized patients, and to a lesser extent BIT-positive patients, were very often co-reacting to MI, potentially indicating cross-reactivity to MI in patients primarily sensitized to OIT.¹⁹ Craig et al confirmed these findings stating that only few patients sensitized to MI reacted to OIT or BIT, but that also a majority of their OIT-sensitized patients co-reacted to MI and/or MCI/MI, again suggesting potential cross-reactivity in this direction.²³ In support of this particular pattern of cross-reactivity, patients sensitized to OIT from its presence in leather items also have been shown to have (non)relevant cross-reactions to MI.¹² However, the opposite (ie, MI-sensitized patients showing cross-reactions to OIT) has been more difficult to establish. Following initial case series (eg, reference 3), a Belgian multicentre study reported the peculiar finding that many MI-sensitized patients showed nonrelevant positive patch test reactions to OIT, and to a much lesser extent to BIT, thereby remarking that only the sole avoidance of MI usually led to resolution of the skin symptoms, indicating that potentially nonrelevant cross-reactivity to

OIT had occurred.⁴ This hypothesis was further supported by Belgian case reports published afterwards.⁵ Eventually, also a retrospective Finnish study came to the same conclusions, stipulating that mainly patients strongly sensitized to MI showed remarkable concomitant positive patch test reactions to OIT, the latter not always explained by concomitant exposure, hence arguing for cross-reactivity.⁶ Meanwhile, market surveys and chemical analytical data on the content of widely used household detergents and water-based paints also showed that such products mainly contain MI and BIT, and only to a lesser extent OIT and MCI/MI, adding to the confusion of some clinicians as to why many of their patients, sensitized to MI, were then cosensitized to OIT, and not to BIT.^{14–16} Ultimately, an animal study also, using a modified local lymph node assay (LLNA), argued in favour of cross-reactivity between MI and OIT, and even BIT, thereby highlighting that this depends on the concentrations used.⁷ The latter correlates with the inherent sensitization potential (EC3 value) of the derivative in question, that is, the chemical with the lowest sensitization potential (that is, BIT) requires the highest concentrations to show cross-reactivity. Somewhat contrary to this animal study, all aforementioned (retrospective) clinical studies highlighted that BIT, which chemically differs from the other isothiazoline derivatives, behaves as an independent sensitizer in humans.^{4,6,19,23,24} Altogether, all the aforementioned clinical and animal studies still only offer indirect evidence for the potential existence of immunologic cross-reactions between the nonchlorinated isothiazolinone derivatives in humans, and between MI and OIT in particular.

4.3 | Results from the current study: Cross-reactivity to OIT in patients primarily and strongly sensitized to MI

Our approach, based on the re-test method,⁸ suggests that individuals, primarily and strongly sensitized to MI, may indeed develop cross-reactions to OIT, and, to a much lesser extent, to BIT. Indeed, six of the seven MI-sensitized patients who were re-tested to OIT and BIT developed positive patch test reactions, almost exclusively and strongly (++) to OIT. All these MI-sensitized patients were very strongly (+++) or strongly (++) sensitized to MI, in line with the Finnish study.⁶ Moreover, the only patient who had reacted to BIT (albeit weakly, +) in the re-testing had also shown an extreme positive patch test reaction to MI (+++). This particular patient (Table 1, Case 2), who had suffered from hand eczema due to the use of an MI-containing liquid soap, had a weak positive patch test reaction (+) to BIT during the first patch test session, on D2, becoming, however, negative by D4. For this reason, she had been included in the re-test to BIT, which, on that occasion, again showed a weak (+), but now lasting positive patch test reaction to this derivative on D4. In retrospect, it cannot be excluded that, besides an immunologic cross-reaction to MI, this particular patient had a weak, independent, concomitant sensitization to BIT, only revealed by re-testing (boostering) with this derivative. The only patient not reacting to OIT, nor to BIT in the re-testing had shown only a weak (+) reaction to MI during the first patch test session. Altogether, these results thus suggest that patients who are (very) strongly sensitized to MI may show immunologic cross-

reactions to OIT, and, debatably and to a far lesser extent, potentially even to BIT. Cross-reactivity to MI in patients primarily sensitized to OIT or BIT, although suggested to occur, was not formally addressed in this study. Moreover, it might be hypothesized that also individuals weakly sensitized to MI might show cross-reactions to OIT, and perhaps even to BIT, depending on the patch test concentrations used, although again this was not evaluated in this study. Nevertheless, it is worth mentioning that, in order to demonstrate potential cross-reactivity between isothiazolinone derivatives, it has been shown that it is important to use sufficiently high patch test concentrations, and with regard to the non-chlorinated isothiazolinone derivatives, this refers to MI at 0.2% aq., instead of the lower concentrations of 0.05% and 0.02% aq., and to OIT at 0.1% pet.^{12,24,25} instead of 0.025% pet.^{19,22} For BIT this might indicate that the 0.1% pet. concentration should perhaps be preferred over the 0.05% pet.²⁴ The former, together with OIT 0.1% pet., recently being added as recommended additions to the new European baseline series.²⁶ Given that BIT has the weakest sensitization potential, even higher test concentrations may be required to show any cross-reactivity to MI in humans, similar to what has been done in the animal LLNA study,⁷ although such concentrations are probably of limited use considering this derivative's irritant potential.^{6,24} It might equally be suggested that besides a sufficient test concentration, later patch test readings, beyond D4, might be helpful to reveal potential cross-reactions.

Whenever a positive patch test reaction occurs, and is interpreted as a cross-reaction, the latter can be nonrelevant, but also relevant,¹² as occurred in three cases (Cases 1, 2, and 4) of the present study. Whether a positive patch test reaction to OIT (contact allergy) also translates into clinical symptoms (allergic contact dermatitis) depends on several factors, such as exposure time and dose/concentration of the allergen. For example, Case 4, a polysensitized patient contact allergic to MI, greatly improved by avoiding MI-containing products, but, later on, developed flare-ups of dermatitis in her neck and right armpit when she came in contact with a leather bag, known to potentially contain OIT.¹² Upon avoidance of the bag, her dermatitis settled. Unfortunately, no chemical analysis of the bag could be performed, but the literature suggests that leather goods may be an overlooked cause of allergic contact dermatitis to OIT.^{12,27} Positive patch test reactions, considered to be cross-reactions, may also remain unexplained and be currently nonrelevant (eg, Cases 3, 5, and 7¹²).

4.4 | Limitations of this study

First, it should be mentioned that OIT and BIT were patch tested and re-tested (i) at different parts of the back, (ii) using different patch test systems (IQ Ultra for the first patch test session, and Finn Chambers for the re-test session), and (iii) the doses of the allergens applied may have slightly differed.²⁸ With regard to the latter variable, the patch test preparations had always been applied by the same nurse, thereby minimizing interindividual variation and making comparison between the two patch test sessions still feasible; the readings were also always performed by the same dermatologist (J.P.R.). Nevertheless, the localizations on the back and the patch test systems used still differed between both patch

test sessions. However, it would appear very coincidental that nearly all patients evolved from negative to strong reactions (++) to OIT, the derivative most suspected of showing cross-reactivity to MI, whereas—under the same conditions—only one patient started to react to BIT, the derivative less suspected of showing a cross-reaction. Moreover, with regard to reproducibility of patch tests, it is usually the weak (+) reactions that may be difficult to reproduce, whereas in the present series the reverse occurred, that is, patients with no reactions at all suddenly started to show strong reactions. The concept of the re-test method is also that a particular skin site, where “local T-cell memory” is present (ie, the lower corner of both scapulae), will most effectively reveal potential immunologic cross-reactivity.⁸

Second, the original “re-test” method is an experimental, animal-based method. Although we applied its concept of local skin memory in this study, we did not perform a full repetition of this method in humans. The results must be cautiously interpreted, specifically with regard to the observation that the majority of patients that were initially (during the first patch test session) MI-positive and OIT-negative all of a sudden became OIT-positive (during the second patch test session) when re-tested with OIT on previously MI-positive skin sites. Unlike animals, under well-controlled conditions, this study is about humans, and we cannot fully exclude that besides false-positive (irritant) reactions to OIT during the second patch test session (albeit unlikely, based on the contact allergic morphology of the patch test results), and apart from the here-proclaimed cross-reactivity (ie, an MI T-cell clone reacting to OIT), concomitant sensitizations to OIT may still have occurred. The latter could then be due to (i) active (silent) sensitization to OIT that might have occurred during the first patch test session, or (ii) that in between the two patch test sessions independent (co)sensitization to OIT still occurred (as these patients might have been in contact with OIT-containing sources), or (iii) that the initial, negative OIT reaction (during the first patch test session) was false negative at the reading on D4, and, eventually, did become positive, at the second patch-test session on D4; a control patch test with OIT, at a previously uninvolved skin site during the second patch test session was, however, not included. An initial, false-negative patch test reaction to OIT can indeed be considered, as during the first patch test session late readings (D7 or later) had not been performed, although late positive reactions to OIT have been occasionally documented in the literature. Nevertheless, reports on the latter are scarce, and, additionally, non-occupational sensitization and active sensitization to OIT only infrequently occur.^{10,29,30} Additionally, it remains striking that the majority of MI-sensitized patients started reacting to OIT, whereas in daily life exposure occurs more readily to (albeit weaker sensitizer) BIT, which—as expected from previous human retrospective clinical studies—hardly resulted in positive patch test reactions during the second patch test session.

4.5 | What practical advice to give to patients?

The main conclusion of this study is that it confirms previous data, from clinical retrospective and animal LLNA studies, that patients

primarily and strongly sensitized to MI may be at risk of developing allergic skin reactions, consistent with cross-reactivity, to OIT, although the latter may only become apparent when re-testing OIT on previously MI-positive patch test sites. Therefore, it seems justified, out of precaution, to at least counsel MI-sensitized patients—especially those strongly sensitized—on the possibility that OIT-containing allergen sources, for instance, leather goods, paints, and detergents, especially when containing high concentrations of this derivative, may lead to allergic skin reactions, even if a patch test to OIT turns out negative. Although debated, and not evident from this study, a similar reasoning can be applied to BIT. Similar advices, to avoid nonchlorinated isothiazolinone derivatives altogether in MI-sensitized individuals, were previously already issued by others.^{7,25}

5 | CONCLUSIONS

In conclusion, notwithstanding that concomitant exposure may lead to concomitant sensitization to different isothiazolinone derivatives, and in spite of a relatively small patient sample, we here showed that patients primarily and strongly sensitized to MI may exhibit (non)relevant, immunologic cross-reactions to OIT, and, albeit debatably and in any case to a far lesser extent, possibly also to BIT. Whether such cross-reactions may also occur in individuals weakly sensitized to MI remains to be demonstrated.

CONFLICT OF INTEREST

None to declare with regard to this study.

AUTHOR CONTRIBUTIONS

Juan Russo: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Olivier Aerts:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing.

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