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Effects on hearing after long-term use of iron chelators in beta-thalassemia: Over twenty years of longitudinal follow-up

Mirko Aldè [a, b, *], Umberto Ambrosetti [a], Marianna Giuditta [a, c], Elena Cassinerio [a, c], Gioia Piatti [d]

[a] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[b] Audiology Unit, Department of Specialist Surgical Sciences, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[c] Unit of Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[d] Department of Pathophysiology and Transplantation, University of Milan and Unit of Bronchopneumology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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ABSTRACT

Objective: The role of iron chelation in causing hearing loss (HL) is still unclear. The present study assessed the prevalence of HL among transfusion-dependent thalassemia (TDT) patients who underwent audiological follow-up over a 20-year period.
Methods: We retrospectively analyzed clinical records and audiological tests from January 1990 (T0) to December 2022 (T22) of a group of TDT patients who received iron chelation therapy with deferoxamine (DFO), deferiprone (DFP) or deferasirox (DFX), in monotherapy or as part of combination therapy.
Results: A total of 42 adult TDT patients (18 male, 24 female; age range: 41–55 years; mean age: 49.2 ± 3.7 years) were included in the study. At the T22 assessment, the overall prevalence of sensorineural HL was 23.8 % (10/42). When patients were stratified into two groups, with and without ototoxicity, no differences were observed for sex, age, BMI, creatinine level, pre-transfusional hemoglobin, start of transfusions, cardiac or hepatic T2 MRI; only ferritin serum values and duration of chelation were significantly higher ($p = 0.02$ and $p = 0.01$, respectively) in patients with hearing impairment in comparison to those with normal hearing.
Conclusion: This study with long-term follow-up suggests that iron chelation therapy might induce ototoxicity; therefore, a long and accurate audiological follow-up should be performed in TDT patients.

1. Introduction

In beta-thalassemia, regular blood transfusions to correct anemia, and iron chelation therapy to reduce secondary hemosiderosis, are the treatment choices to improve patients' quality of life [1]. It is generally recommended to start iron chelation treatment after completion of 10–20 transfusions or when the serum ferritin levels reach 1000 ng/ml [2].

The first iron chelating agent, deferoxamine (DFO) (Desferal®, Novartis Pharma Stein AG, Switzerland) was introduced in 1962; it has been a revolution in the field of thalassemia and nowadays is the most common chelating agent in use, even if it can only be administered parentally. Subsequently, many new oral chelating agents have been introduced in the market, such as deferiprone (DFP) (Ferriprox®, ApoPharma USA, Inc. Rockville, MD) and deferasirox (DFX) (Exjade®, Novartis Pharma Stein AG, Switzerland) which have better compliance and fewer side effects than DFO [3].

Some studies have highlighted the occurrence of hearing disorders associated with the use of DFO [4–10]; however, ototoxicity with this agent has been shown to be dose-dependent, and currently the recommended therapeutic dosage is 20 to 40 mg/kg/day, which usually felt to be low risk for ototoxicity [10]. The negative effects on hearing seem occur more frequently in patients treated for a long duration of time at high doses and in patients with lower ferritin levels (< 2000 ng/ml) [7], although most of these observations are from the 1980s and 1990s, when higher DFO dosages were used; today there is more attention to treatment monitoring, and toxic chelation levels are rarely achieved [11].

Hearing loss (HL) has also been reported in patients undergoing iron chelation with DFP and DFX, but to date there is limited data concerning the otologic side effects profile for these new generation iron chelators [12–14]. Typically, pharmacological ototoxicity follows a cochlear base-to-apex gradient: the high frequency range is affected first, and HL may progress to lower frequencies with an increase in dosage and/or

* Corresponding author: Via Pace 9 - 20122 Milano (ITALY).
E-mail address: mirko.alde@unimi.it (M. Aldè).

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treatment duration [11]. Hearing impairment in beta-thalassemia is expected to have progressive course over time, due to the presumed cumulative toxic effect of chelation therapy. However, very few longitudinal studies are available so far.

To elucidate the adverse impact on the auditory function by the iron chelation therapy, we re-assessed a group of transfusion-dependent thalassemia (TDT) patients, object of a previous publication over twenty years ago [15].

2. Materials and methods

We retrospectively analyzed our clinical records and audiological tests from January 1990 (T0) to December 2022 (T22) of a group of TDT patients who received iron chelation therapy with DFO, DFP (in monotherapy or as part of combination therapy), or DFX.

All adult TDT patients, regularly followed-up at the Center for Hemoglobinopathies of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (Milan, Italy), were included in the present study.

They were periodically transfused, every 21–25 days, since the first years of life, in order to maintain a pre-transfusional hemoglobin concentration within 9–10 g/dl range.

Patients were receiving chelation therapy with DFX (5–28 mg/Kg/day, oral tablets) or either DFO (25–50 mg/Kg/day) or DFP (25–100 mg/kg/day, oral tablets) or both. Mean daily dosage (mg/Kg/day) was calculated as the total 12 months dose divided by 365 divided by weight.

Duration of treatment was calculated as the time from the beginning of the therapy to the time of follow-up study. Mean serum ferritin and pre-iron chelation hemoglobin levels over the last year were recorded.

Whereas renal impairment constitutes one of the most common conditions that could be associated with audio-vestibular disorders because the larger part of ototoxic drugs is eliminated at the kidney level, such as DFO and DFP, at T22 we examined creatinine values of TDT patients.

At T22 we also included the magnetic resonance data (MRI T2*) for iron evaluation in the heart and in the liver, annually performed only in recent years as routine control for iron status.

None of patients had active or recent ear diseases, underwent to ear surgery, referred exposition to acoustic trauma, or had a family history for genetic deafness; no treatment with known ototoxic drugs were taken.

All subjects underwent routine otolaryngologic examination by otomicroscopy, pure-tone audiometry and tympanometry to verify the normal condition of the middle ear, as part of an annual follow-up. Conventional audiometric evaluations were performed with an Amplaid 309 audiometry device (Amplifon, Italy) in a standard sound-treated room with noise levels within permissible limits according to the International Standards Organization. The methodology described in the "Guidelines for manual pure-tone threshold audiometry" of the American Speech-Language Hearing Association was followed: pure-tone audiometric threshold were determined between 0.25 and 8 kHz (0.25, 0.5, 1, 2, 4, 6 and 8 kHz) and measured in both ears separately. Tympanometry and stapedial reflex tests were performed with the Interacoustic AZ26 tympanometer (Assens, Denmark).

Normal hearing refers to a pure tone average (PTA) equal to or lower than 25 dB (hearing level) and HL to a PTA above 25 dB (hearing level). PTA is the average of hearing sensitivity at 0.5, 1, and 2 kHz. The degree of HL was classified as "*slight*" when the PTA was between 26 and 40 dB, "*moderate*" between 41 and 60 dB, "*severe*" between 61 and 80 dB and "*profound*" more than 81 dB, according to World Health Organization – Grades of Hearing Impairment in different levels of severity [16].

The type of HL was classified according to the audiometric results by comparing air and bone conduction threshold: *conductive hearing loss* (CHL) was defined by normal bone conduction threshold (< 15 dB) with air-bone gap > 15 dB, averaged over 0.5, 1 and 2 kHz; *sensorineural hearing loss* (SNHL) was defined by an equal amount of loss for air and bone conduction thresholds with air-bone gap < 15 dB, averaged over 0.5, 1 and 2 kHz; *mixed hearing loss* (MHL) was defined as bone conduction threshold and air-bone gap > 15 dB, averaged over 0.5, 1 and 2 kHz.

HL was considered *progressive* if the PTA deteriorated more than 15 dB within a 10 years period [17].

The hearing thresholds recorded during 2022 (T22) were compared to those obtained over twenty years ago at the first visit (T0). Furthermore, by comparing the pure tone thresholds with the 95th percentile value for sex and age-related hearing thresholds (International Organization for Standardization - "ISO-7029 standard") [18], thalassemia-related HL could be distinguished from presbycusis. The degree of HL related to thalassemia and its therapies was calculated as the difference between the measured loss for a specific frequency and the expected value at 95th percentile.

Ototoxicity severity was graded according to the NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for Adverse Events) ototoxicity grades for adults [19]:

Grade 1: Threshold shift or loss of 15–25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear;

Grade 2: Threshold shift or loss of 26–90 dB, averaged at two contiguous test frequencies in at least one ear;

Grade 3: HL sufficient to indicate therapeutic intervention, including hearing aids; threshold shift or loss >25–90 dB, averaged at three contiguous test frequencies in at least one ear;

Grade 4: Profound bilateral HL >90 dB; indication for cochlear implant.

This retrospective study was conducted according to the World Medical Association's Declaration of Helsinki and approved by the local ethics committee.

2.1. Statistical analysis

The demographic and clinical characteristics were described by means with SDs for normally distributed continuous data or as absolute frequency and percentages for categorical data. Differences between the percentages were tested by Fisher test while those from means by ANOVA analysis; correlation analyses were performed with the Pearson's test; statistical significance was estimated for $p < 0.05$. Statistical analysis was performed using R software.

3. Results

A total of 42 adult TDT patients (18 males, 24 females; age range: 41–55 years; mean age: 49.2 ± 3.7 years) regularly transfused with packed red cells, were included in the present study: their clinical data and audiometric tests were compared with those obtained over twenty years ago. Although 57 patients were examined at T0, only 42 patients were included at T22, as 15 subjects (5 of them with slight SNHL at T0) moved to other centers or died.

Table 1 shows the mean demographic and clinical features of TDT patients at T0 and T22; out of 42, 31 (73.8 %) patients had previously undergone to splenectomy; one subject experienced cardiac overload, while 5 patients experienced hepatic overload. Regarding iron chelating therapy, at T0 all subjects received DFO, while since 2010 most of them were treated with DFX (oral tablets have been available since about 2018); the average ongoing dosages of iron chelator employed were 46.7 ± 9.3 (mg/kg/die) for DFO, 17.9 ± 6 (mg/kg/die) for DFX and 63.2 ± 10.6 (mg/kg/die) for DFP.

At the T22 assessment, all subjects had intact tympanic membranes. The hearing threshold was normal in 29 patients, while pure tone audiometry revealed hearing impairment in 13 patients (31.0 %). In particular, SNHL was identified in 10 patients (76.9 %), while 3 patients (23.1 %) were found to have a CHL. The 3 patients with CHL did not

Table 1
Demographic and clinical features of transfusion-dependent thalassemia patients.

	T0	T22
Age (years)	23.8 ± 3.5	49.2 ± 3.7
BMI	22.5 ± 2.8	23.1 ± 3.2
Mean pre-transfusional hemoglobin (g/L)	9.3 ± 0.5	9.7 ± 0.5
Ferritin (ng/mL)	1380.6 ± 715.7	706.5 ± 605.6
Years of transfusion	24 ± 4	52 ± 4.2
Years of chelation	22.3 ± 3.8	50.5 ± 3.5
Iron chelator type		
DFO (Number of patients,%)	57 (100.0)	6 (14.3)
DFX (Number of patients,%)	0 (0.0)	33 (78.6)
DFP + DFO (Number of patients,%)	0 (0.0)	3 (7.1)
Splenectomy (Number of patients,%)	38 (66.7)	31 (73.8)
Cardiac T2* (> 20 ms)	–	35.7 ± 8.4
Hepatic T2* (> 6.3 ms)	-	14.7 ± 8

have otitis media with effusion, but showed tympanosclerosis resulting from inflammatory conditions that occurred during childhood. Both acoustic immittance (type A tympanogram) tests and acoustic-reflex thresholds for ipsilateral and contralateral ears were normal in all patients except in the 3 subjects with CHL, having a type B tympanogram and absent acoustic-reflex thresholds.

Table 2 reports PTA results in TDT patients at T0 and T22. In all 10 patients with SNHL at T22, HL was slight.

At T0, 15 patients had SNHL (13 of slight and 2 of moderate severity): of the 13 patients with slight SNHL, 5 were lost to follow-up because they moved to other centers or died, while 8 showed a slight SNHL at T22. The PTA of the 2 patients with moderate SNHL at T0 improved to slight SNHL at T22. Moreover, 2 patients with no hearing impairment at T0 showed high-frequency SNHL at T22, although they still had a PTA corresponding to normal hearing.

The frequency analysis comparing the threshold values at T0 and T22 revealed a statistically significant difference at 1.0 kHz ($p = 0.02$), while above 2.0 kHz all differences were highly statistically significant ($p < 0.001$) (Table 3).

According to NCI CTCAE criteria ototoxicity we detected ototoxicity grade 2 in all 10 patients, particularly evident above 3 kHz. Fig. 1 shows the area of hearing impairment due to ototoxicity which is more evident in the field of high frequencies. No patients had HL combined with vertigo complaints or tinnitus. When patients were stratified into two groups, with and without ototoxicity, no differences were observed for sex, age, BMI, creatinine level, pre-transfusional hemoglobin, start of transfusions, cardiac or hepatic T2*; only ferritin and duration of chelation were significantly higher ($p = 0.02$ and $p = 0.01$, respectively) in patients with SNHL in comparison to those with normal hearing (Table 4).

A negative correlation was found between ferritin level and cardiac T2* ($p = 0.02$, $r = -0.37$) and between ferritin level and hepatic T2* ($p = 0.002$, $r = -0.47$).

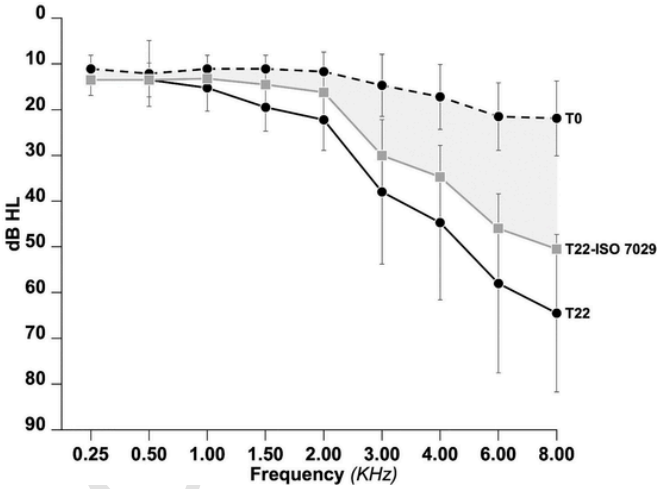

Fig. 1. Auditory frequencies distribution in both ears in thalassemia patients with sensorineural hearing loss. The dotted black line shows the hearing thresholds at T0; the continuous black line shows the hearing thresholds at T22; the gray line shows the difference between the measured threshold for the specific frequency and the expected values due to presbycusis at 95th percentile, according to ISO 7029 (T22-ISO7029). The gray band indicates the hearing impairment due to ototoxicity. The differences between T0 and T22 were significant ($p = 0.01$) at 1.0 kHz; above 1.5 kHz they were highly significant ($p < 0.001$).

Table 2
Hearing threshold in transfusion-dependent thalassemia patients.

	T0 (N,%)	T22 (N,%)
Normal hearing (≤ 25 dB)	38 (66.7)	29 (69.0)
Slight SNHL (26–40 dB)	13 (22.8)	10 (23.8)
Moderate SNHL (41–60 dB)	2 (3.5)	0
Severe SNHL (61–80 dB)	0	0
Profound (≥ 81 dB)	0	0
Conductive HL	4 (7.0)	3 (7.1)
Total	57 (100.0)	42 (100.0)

HL = Hearing loss; SNHL = Sensorineural hearing loss.

Table 3
Comparison between T0 and T22 of threshold values (mean of both ears ± SD) at the different frequencies.

KHz	T0	T22	*P-Value*
0.25	11.1 ± 3	13.5 ± 3.4	0.09
0.50	13.1 ± 7.2	13.5 ± 3.7	0.87
1	11.1 ± 3	15.2 ± 5.1	0.02*
2	11.7 ± 4.3	22.2 ± 6.7	< 0.001**
3	14.8 ± 6.8	38 ± 15.8	< 0.001**
4	17.1 ± 7.1	44.7 ± 16.9	< 0.001**
6	21.5 ± 7.4	58 ± 19.6	< 0.001**
8	21.9 ± 8.3	64.5 ± 17.2	< 0.001**

Table 4
Features of transfusion-dependent thalassemia patients with normal hearing and with sensorineural hearing loss at T22.

	Normal hearing ($N = 29$)	Sensorineural hearing loss ($N = 10$)	*p*-value
Sex (males)	11 (37.9%)	6 (60%)	0.3
Age (years)	49.31 ± 3.7	48.6 ± 2.8	0.58
BMI (Kg/m^2)	23.1 ± 3.3	23.4 ± 2.9	0.8
Pre-transfusional hemoglobin (g/L)	9.7 ± 0.4	9.7 ± 0.8	1.0
Ferritin (ng/mL)	576.7 ± 260.5	1082.6 ± 1061.1	0.02*
Splenectomy	23 (79.3%)	5 (50%)	0.1
Creatinine (mg/dL)	0.81 ± 0.2	0.93 ± 0.2	0.11
Start of transfusions (months)	15.4 ± 17.6	15 ± 14.7	0.94
Years of chelation	46.1 ± 3.7	50 ± 4.2	0.01*
Iron chelator type			
DFX (Number of patients,%)	23 (79.3)	9 (90.0)	0.65
DFO (Number of patients,%)	4 (13.8)	0 (0.0)	0.55
DFO + DFP (Number of patients,%)	2 (6.9)	1 (10.0)	1.0
Cardiac T2*(> 20 ms)	36.1 ± 8.2	38.4 ± 5.3	0.41
Hepatic T2*(> 6.3 ms)	16.2 ± 7.6	12.9 ± 8.9	0.26

*Statistically significant result.

4. Discussion

Regular blood transfusions and iron chelation treatments have ameliorated the quality of life and improved survival of TDT patients, however allowing the emergence of treatment-related comorbidities, such as SHL.

The first evidences of ototoxicity were described for DFO, demonstrating to cause a dose-related SNHL [4,5,11]; this has led to routine auditory assessment for early detection of hearing impairment and to a careful dosage adjustment and/or a reasoned pharmacological shift. DFO may have toxic effects directly on the cochlea: sections of the inner ear showed cytoplasmic protrusions of the hair cells at the base of the cochlea, which is consistent with hypoxic injury [20]; furthermore, it is believed that DFO could chelate and remove other trace elements (e.g. Zn, Cu and Mn) useful to hearing function [8,21]. However, ototoxicity was also reported for other iron chelators such as DFP and DFX [12–14]. Hearing disorders have been shown to occur mainly in patients treated for a long period with high doses and in those with increased ferritin levels; in most cases, the damage appears to be reversible with discontinuation of treatment [14]. However, ototoxicity may be influenced by high interindividual variability due to genetic factors, age, gender, pharmacokinetic and pharmacodynamic characteristics, comorbidities and polytherapy [22].

Particularly, pediatric patients seem to have a greater SNHL, probably due to increased cochlear sensitivity in younger subjects [23]; in the pediatric population a transient CHL is also common [11].

In our study, the prevalence of SNHL detected by pure tone audiometry in TDT patients taking iron chelating therapies for many years was 23.8 %, in line with the literature data [11]. All patients with HL showed a grade 2 of ototoxicity; among them, 9 patients had been taken DFX for more than 10 years (previously DFO) and 1 DFO and DFP since 2017.

To date, there are few reports on the course of HL in TDT patients and the maximum length of follow-up is six years [24]; therefore, this is the first study performed with a such long period of follow-up.

SNHL in patients with TDT is supposed to have a progressive course over time due to a cumulative toxic effect of chelation therapy [11]. However, although a slow deterioration of hearing threshold is quite common [24], HL may improve with reduction or discontinuation of chelation therapy [11].

In our sample, 2 patients who had received a diagnosis of moderate SNHL at T0 showed an improvement in their hearing threshold at T22, probably due to an optimization of the chelation treatment over the years.

Interestingly, the hearing impairment did not correlate with age, sex and laboratory findings.

As a matter of fact, the available data show a poor or absent correlation between HL and age, suggesting that within the TDT patients some subjects are more vulnerable to hearing deterioration while others are almost refractory to auditory impairment [11]. In agreement with most studies [4,7,13,15] we failed to find a correlation between HL and age in thalassemic patients, although in these subjects, as in the general population, one might expect a worsening of the hearing threshold with age. It is believed that probably only some individuals are susceptible to auditory impairment, as several factors, including genetic and constitutional features, may be important for manifesting ototoxicity [11,22].

Manara et al., examining brain perfusion MRI in adult thalassemic patients, recently found a bilateral relative hypoperfusion and hypometabolism of the auditory cortex, which seem to represent an early hallmark of this hemoglobinopathy, largely independent of clinical phenotype (TDT vs NTDT) and HL condition [25].

No correlations were detected between HL and sex and neither with mean annual hemoglobin level or age at first transfusion or duration of transfusion treatment.

The relationship between serum ferritin level and HL is still debated: initiation of iron chelation therapy is currently recommended after serum ferritin level is above 1000 ng/mL, and levels lower than 1000 ng/mL are associated to better outcomes such as protection from heart disease and improved survival [26]. Both iron overload and excessive iron chelation should be avoided to prevent HL [26], but it was also observed that even patients naive for iron chelation may present a sensorineural deficit [25]. Our results seem to indicate that high serum ferritin level and longer duration of chelation therapy are significantly related to SNHL. Although the duration of chelating treatment in patients with normal hearing and those who experienced SNHL does not appear so impressive, we observed a statistically significant difference. Other studies have provided similar results after a longer duration of DFX use, but further investigation is needed to clarify this issue [14]. Indeed, the relationship between SNHL and duration of chelation may be another crucial factor in identifying TDT patients at risk for hearing deterioration.

Despite the importance of the major findings, the study has several limitations. First, we did not perform both high-frequency audiometry (HFA), i.e. pure-tone air conduction threshold testing for frequencies above 8 kHz, that is the most sensitive measure to detect most of the early cochleotoxic changes as well as the study of distortion product otoacoustic emissions (DPOAEs), an accurate and sensible method for early assessing the dysfunction of the outer hair cochlear cells. However, unlike the conventional frequency range of 0.25–8 kHz where the normal range of hearing is well-established, no “normal range” for frequencies above 8 kHz in adults is defined and intersubject variability for HFA threshold is high [27]. Therefore, some tests may reveal “preclinical” damage to the ear, prior to the development of HL in the conventional test range: HFA and DPOAEs study would be an area of future research in TDT patients because an early detection of ototoxicity can lead to prompt management and prevention of HL progression.

Secondly, over the course of 20 years, it is possible that some patients might have mild progression of HL based upon other factors as SNHL in adults is typically multifactorial and often influenced by genetic factors and comorbidities. Therefore, it would have been interesting to examine a control group with similar general health status, age, and gender. However, for obvious medical and ethical reasons, it was not possible to study a control group of thalassemic patients who did not receive these treatments.

Finally, the application of the ISO-7029 standard could be subject to some limitations: it is based upon large population estimates; the ototoxicity definitions and grading scales are designed to be used with acute exposure to a medication, and not specifically with long term changes.

5. Conclusions

Our study with over twenty years of follow-up suggests that iron chelation therapy might induce ototoxicity; after long-term treatments with these agents, the severity of ototoxicity was grade 2. Particular attention must be paid to balance between serum ferritin values and an adequate dosage adjustment of iron chelating therapies according to baseline and ongoing iron intake. A periodic monitoring of hearing conditions is mandatory, especially in patients presenting with an initial hearing impairment.

Author declarations

Author agreement

All authors have approved the manuscript and agree with its submission

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Ethics approval

The present retrospective study was conducted according to the World Medical Association's Declaration of Helsinki and was approved by the local ethical committee.

Author contributions

MA: substantial contributions to the conception, interpretation, analysis of data for the work; giving final approval of the version to be published; agreement to be accountable for all aspects of the work.

UA: substantial contributions to the acquisition and interpretation of data; giving final approval of the version to be published; agreement to be accountable for all aspects of the work.

MG: substantial contributions to the conception, design, acquisition of data for the work; giving final approval of the version to be published; agreement to be accountable for all aspects of the work.

EC: revising the work critically for important intellectual content; giving final approval of the version to be published; agreement to be accountable for all aspects of the work.

GP: substantial contributions to the conception, design, and interpretation, analysis of data; drafting the work; giving final approval of the version to be published; agreement to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest/competing interests.

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