effective for acute mania with a response rate up to 55% (Table 1). Three reviews reported some evidence of long-term maintenance efficacy. Only Pisano et al. included both patients with BD and major depressive disorder (MDD). Authors found that efficacy on depression is not clear (Pisano et al. 2019).

Safety

All the studies specified that lithium was generally well tolerated with common side effects similar to those reported in adults. Two studies (Amerio et al. 2018; Pisano et al. 2019) specified that most common adverse effects were gastrointestinal, polyuria or headache. (Yee et al. 2019) found that mean adverse-effect risks for lithium was 23.9%. Long term studies specifically designed to assess safety issues are lacking.

Peripartum

The ten systematic reviews included in the peripartum section involved a total of 3872 individuals treated with lithium (Table 1). Four of the included reviews specifically focused on lithium (Imaz et al. 2019; Fornaro et al. 2020; Newmark et al. 2019; Poels et al. 2018b), while the others reported results also on other drugs used in mood disorders during the peripartum period. Most reviews included a limited number of studies (< 20); Fornaro et al. (Fornaro et al. 2020) was the larger meta-analysis and systematic review. The design of primary studies varied across reviews, including retrospective and prospective, open label, observational, and interventional studies (Table 1). Some reviews only included case reports and case series (Imaz et al. 2019; Newmark et al. 2019; Uguz and Sharma 2016; Pacchiarotti et al. 2016). Six of the included reviews focused on women with mood disorders exposed to lithium during pregnancy (Fornaro et al. 2020; Poels et al. 2018b; Doucet et al. 2011; Haskey and Galbally 2017; Galbally et al. 2010; Uguz 2020) and four during lactation (Imaz et al. 2019; Newmark et al. 2019; Uguz and Sharma 2016; Pacchiarotti et al. 2016). One study exclusively focused on postpartum psychosis (Doucet et al. 2011). Seven of the included reviews focused only on lithium safety, two focused on lithium efficacy (Table 1) and only one provided data on both efficacy and safety (Fornaro et al. 2020). The same study was also the only one providing meta-analytic findings.

Efficacy

Fornaro et al. (Fornaro et al. 2020) specified that lithium use during pregnancy show superior efficacy compared to non-lithium in BD relapse prevention (OR = 0.16, 95%CI = 0.03 to 0.89). The other two studies providing results on the efficacy of lithium during pregnancy were Uguz et al. (2020) and Doucet et al. (2011). The first specified that recurrence rates in women with BD using lithium during pregnancy and post-partum were 23% and 20%, respectively (Uguz 2020). The second supported the prophylactic effect of lithium in the prevention and treatment of postpartum psychosis (Doucet et al. 2011).

Safety

Fornaro et al. reported that lithium was associated with congenital anomalies (OR = 1.81, 95% CI = 1.35–2.41), cardiac anomalies (OR = 1.86, 95% CI = 1.16–2.96) and spontaneous abortion (OR = 3.37, 95% CI = 1.15–12.39). They specified that risk associated with lithium exposure at any time during pregnancy was low and higher for first-trimester or higher-dosage exposure (Fornaro et al. 2020). The other reviews investigating lithium safety during pregnancy were basically in line with Fornaro et al. (Fornaro et al. 2020), reporting a low absolute risk of congenital abnormalities and no adverse effects on child developmental outcomes (Table 1). Nevertheless, they underlined the dearth of available data.

The reviews focusing on lactation provided only safety results (Imaz et al. 2019; Newmark et al. 2019; Uguz and Sharma 2016; Pacchiarotti et al. 2016). The rates of adverse effects ranged between 0 and 20% (Table 1), but the reviews warned about the dearth and low quality of the primary studies.

Old age

The five systematic reviews included in the elderly section involved a total of 1676 individuals treated with lithium (Table 1). All the included reviews exclusively focused on lithium, except one (Cooper et al. 2011). Specifically, Cooper et al. (2011) systematically reviewed studies on treatments, including lithium, for refractory depression in older people. Most reviews included a limited number of studies (< 20); only Sun et al. (2018) summarised more than 37 studies, but presented only case report data. Across the reviews, the design of primary studies varied, including retrospective and prospective, open label, and observational studies, as well as randomized controlled trials (Table 1). The included reviews presented with a high level of heterogeneity in terms of study population and specific outcomes. Two studies focused on efficacy, two on safety and only one review assessed efficacy and safety of lithium exclusively in the treatment and prevention of mania.

Efficacy

Two studies supported the efficacy of lithium in geriatric patients with resistant MDD (Cooper et al. 2011; Ross 2008). Nevertheless, the two reviews were substantially different with respect to study design (Table 1). Cooper et al. (2011) was the only review providing meta-analytic

data for the evaluation of treatment response in resistant MDD; they specified that the overall response rate for lithium augmentation was 42%. Ross et al. (2008) aimed at quantifying the risk of relapse when lithium augmentation is discontinued in geriatric patients with MDD. Recurrence rates was 50% relapse over approximately 6 month follow-up. Considering lithium efficacy on manic symptoms, De Fazio et al (2017) found that lithium was superior to placebo and to other mood stabilizers in treating mania.

Safety

Three other reviews focused on lithium toxicity in patients > 65 years with mood disorders (Sun et al. 2018; Fazio et al. 2017; Rej et al. 2012).The first one focused on renal adverse events (Rej et al. 2012); the second one reviewed all the effects associated with lithium toxicity (Sun et al. 2018), the third one assessed lithium tolerability in treating mania (Fazio et al. 2017). The studies suggested that lithium may be relatively well-tolerated, but low doses should be used in the elderly. Adverse events were dose-dependent.

Risk of bias

The ROBIS tool was used to assess the risk of bias of the included systematic reviews. According to the results of phase 1, in all the included studies participants, exposures, comparators, and outcomes matched the target question. The results of phase 2 are shown in Fig. 1 and further detailed in Additional file 1 Results.

Analysis of the degree of overlap in studies

Corrected covered areas (CCAs) were calculated for systematic reviews on paediatric age and peripartum. It was not possible to calculate CCAs for the old-age category, as primary studies presented with a high level of heterogeneity in terms of sample population and specific outcomes (Table 1).

Regarding the paediatric age section, the CCA for the four reviews considered was 23%. Considering in the citation matrix only randomised controlled trials, which evaluated more homogenous parameters, results in a CCA increase to 38%.

Based on the results of studies on peripartum, we decided to divide the studies into two groups, i.e., those focusing on the use of lithium during pregnancy and those focusing on lactation (Table 1). For studies on lithium use during pregnancy, the overall CCA was 10%. An additional CCA was also repeated excluding from the citation matrix case reports and case series, not consistently included in the systematic reviews on pregnancy. A CCA of 13% was obtained. All four reviews on lactation focused on safety, specifically on infant adverse events and neurodevelopmental consequences for the child after lithium exposure. The CCA for these reviews was 47%. All citation matrices can be found in the Supplement.

Discussion

To the best of our knowledge, this is the first umbrella review assessing efficacy and safety of lithium across the lifespan by simultaneously targeting three specific life stages: childhood and adolescence, peripartum (pregnancy, postpartum and lactation), and old age.

Children and adolescents

Regarding childhood and adolescence, the findings outline a dearth of systematic reviews on the topic. We found five systematic reviews, most of them including a small number of studies (< 10), with only one review reporting data from 30 primary studies and more than 1000 patients (Amerio et al. 2018). Nevertheless, the risk of bias for this group of studies was relatively low, with the 80% of reviews being at low risk (Fig. 1). This result corroborates the substantial agreement among the conclusions of included systematic reviews. They all supported lithium as a potential reasonably safe and effective treatment in children and adolescents (Table 1); however, they strongly underlined the limited number of available studies.

The only meta-analysis included in our review restricted this observation to prepubertal children protracted manic/mixed episodes and comorbid attention ADHD, specifying that lithium may be superior to placebo, it is comparable to sodium divalproex, and inferior to risperidone (Duffy et al. 2018). Results are not surprising and in line with robust evidences in adults, showing that antipsychotic drugs were more effective than mood stabilizers in treating mania in the short-term (Cipriani et al. 2011). Authors specifically warned about the lack of evidence to inform the question as to the effectiveness of lithium in paediatric BD of the classical type. The other included reviews reported that lithium was effective for acute mania with a response rate up to 55%. Included studies provided some evidence of long-term maintenance efficacy. Pisano et al. (2019) specified that the efficacy of lithium use in MDD is not clear. Further primary studies with larger primary sample size, as existing in the adult populations (Nunes et al. 2020), are necessary to determine lithium response rates in different mood states and in the long-term.

The included systematic reviews agreed that lithium was generally well-tolerated, with common adverse events that were similar to those experienced by adults and that usually showed a dose–response pattern. This is in line with a recent pharmacokinetic study conducted in 61 children with BD, showing that, when adjusting

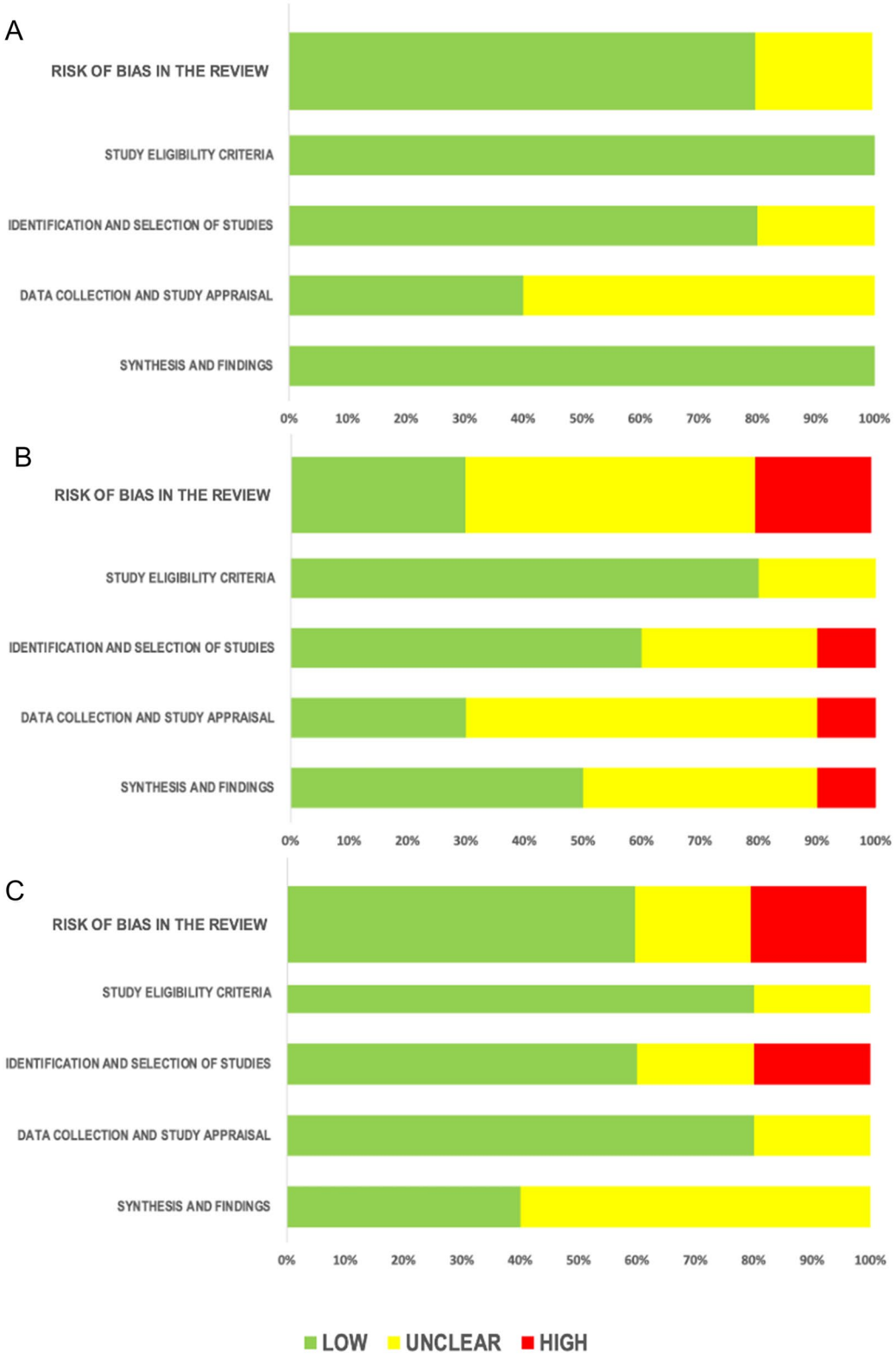

Fig. 1 Results of risk of bias assessment. **A**, Children and adolescents; **B**, Peripartum; **C**, Old age. Phase 2 and 3 of ROBIS are depicted for all the studies included in the umbrella review. Results are presented as percentages of studies at low, unclear or high risk

for body size, the pharmacokinetic parameters in paediatric patients were within the range of estimates from adults (Landersdorfer et al. 2017). Results are also in line with a large scale systematic meta-review on the adverse effects of medications in paediatric psychiatric illnesses highlighting that lithium showed the safer profile among mood stabilizers (Solmi et al. 2020).

With respect to the overlap in primary studies across systematic reviews, the CCA for the five reviews included in the paediatric group, was 23%. The main reason of this relatively small overlap could be identified in the high level of heterogeneity in the primary studies included in the systematic reviews. Heterogeneity may derive from virtual differences in different studies or be caused by various biases. Different inclusion criteria and definition may primarily cause clinical heterogeneity. Sources of heterogeneity may also derive from different study designs, specific outcomes and quality. For example, there were both randomised-control trials (RCTs) and open label studies in different systematic reviews (Table 1). Accordingly, when we considered in the citation matrix only RCTs, the CCA increased to 38%.

It is worth noticing that none of the included reviews focused on the efficacy of lithium in juvenile suicide prevention. This is an important gap to fill, given that recent meta-analytic findings, including over 2000 youths diagnosed with mood disorder, specified that the pooled incidence of suicide attempts in juvenile BD was 31.5% (Crescenzo et al. 2017). Based on the convincingly proved prophylactic activity of lithium in adulthood (Wilkinson et al. 2022), further systematic reviews and meta-analyses are required to find out whether the efficacy of lithium in suicide prevention may extend to the paediatric age as well.

Peripartum

Regarding the peripartum period, we included a relatively large number of studies (N = 10). Based on the results, we decided to divide the systematic reviews in two groups, those focusing on lithium use during pregnancy and postpartum and those focusing on lactation (Table 1). The most comprehensive and recent meta-analysis on pregnancy and the postpartum was conducted by Fornaro and colleagues (Fornaro et al. 2020). Authors reported data on lithium efficacy and safety from over 2,000 pregnancies, comparing women treated with lithium to unexposed control subjects (both women in the general population and patients with affective disorders not exposed to lithium) (Fornaro et al. 2020). Providing meta-analytic findings, Fornaro et al. (Fornaro et al. 2020) concluded that lithium was superior to non-lithium in relapse prevention) and that the risk of any congenital anomaly associated with lithium exposure at any time during pregnancy was low. In line with recent large cohort data (Munk-Olsen et al. 2018), the risk was higher for first-trimester or higher-dosage exposures (Fornaro et al. 2020). Interestingly, the risk significantly decreased if lithium-taking patients were compared only to patients with affective disorders not taking lithium (Fornaro et al. 2020). This result highlights the importance of taking as reference adequate control groups in pregnancy studies, so to balance the benefits and risks of pharmacological intervention (Viswanathan et al. 2021; Scrandis 2017). Recent meta-analytic findings confirmed previous naturalistic observations (Rosso et al. 2016) and showed that postpartum relapse rates in BD were significantly higher among patients who were medication-free during pregnancy (66%; 95% CI = 57–75) than among those using prophylactic medication (23%; 95% CI = 14–37) (Wesseloo et al. 2016). Medication showed the same protective effect on relapse rates during pregnancy (Stevens et al. 2019). The other systematic reviews investigating lithium efficacy and safety during pregnancy were basically in line with Fornaro et al. (Poels et al. 2018a).

Three of the included reviews specifically investigated neurodevelopmental outcomes for those children exposed to lithium during pregnancy (Poels et al. 2018b; Haskey and Galbally 2017; Galbally et al. 2010). Available data were reassuring, although limited, and suggest that lithium use during pregnancy is associated with normal child neurodevelopment. This observation is in line with a very recent study founding no evidence for significantly altered neuropsychological functioning of lithium-exposed children at the age of 6–14 years (Poels et al. 2022). Specifically, authors found no association between prenatal lithium exposure and IQ and no relationship between lithium blood level during pregnancy and neuropsychological functioning (Poels et al. 2022).

Considering the studies on lactation, they were only focused on lithium safety. Authors reported lithium adverse events ranging between 0 and 20% (Table 1) during the lactation period. It should be stressed that results were based on few primary included studies, which were all case reports and case series. Future control group studies with longitudinal designs are needed to find the balance between the risk associated with lithium intake and the benefit of breastfeeding in mood disorders. This might be of particular importance, because recent data showed that there is no differences in oxytocin levels between women with depression and asymptomatic ones during observed infant feeding sessions (Whitley et al. 2020).

The overall risk of bias for the group of systematic reviews on the peripartum period was moderately high (Fig. 1). Only 30% of studies showed low risk, preventing us from being able to generalise the results from this

group of studies. The main reasons are (1) several reviews failed to adopt measures to prevent the biases in the identification and selection of the primary studies; and (2) they also failed in using appropriate criteria for data collection and study appraisal and data synthesis (Additional file 1: Figure S2; Additional file 1 Results). This result may be explained by the fact the articles spanned from 2011 to 2020, a period during which the methodological standards to apply to systematic reviews changed. The same explanation could apply to the low level of overlap in primary studies across systematic reviews (10% and 13%, excluding case reports), indicating a high level of heterogeneity. A higher overlap was found for lactation studies (47%), probably depending on the small number of primary studies available on the topic (only case reports and case series) and consequently on the relatively unrestricted inclusion criteria adopted by these systematic reviews.

Old age

Considering the geriatric population, included reviews were few and remarkably heterogeneous. Available studies supported the efficacy of lithium in geriatric patients with treatment-resistant MDD (Cooper et al. 2011; Ross 2008), or mania (Fazio et al. 2017). Remarkably, no systematic reviews summarised the efficacy of lithium in BD relapse prevention. This is an important gap that needs to be bridged, since first manic episodes rarely occur in this age group, while recurrence of BD episodes is frequent (Dunner 2017). Furthermore, none of the included reviews considered the effect of lithium on cognitive symptoms. A growing body of evidence supports the neuroprotective effects of lithium (Malhi et al. 2013). In elderly patients, in particular, a recent study showed that lithium use may influence the volume of the hippocampus (Zung et al. 2016). Starting from the first evidence obtained by Kessing and colleagues (Kessing 2004), it is also well established that lithium significantly reduces the risk to develop Dementia in elderly patients with BD (Ishii et al. 2021; Nunes et al. 2007; Velosa et al. 2020). Accordingly, a more comprehensive review of lithium efficacy on cognition may help understanding the mechanisms underlying neuroprotection in the elderly with mood disorders (Bersani et al. 2016).

Regarding safety, three of the included reviews focused on lithium toxicity and found that lithium is relatively well-tolerated in the elderly, provided that low doses are used (Sun et al. 2018; Fazio et al. 2017; Rej et al. 2012). Adverse events were dose-dependent, including all renal effects. Data are in line with previous observations in BD (Fotso Soh et al. 2019; Ljubic et al. 2021; Arnold et al. 2021) and with a 6 year follow-up study showing that median lithium serum concentration in elderly patients was 0.55 mmol/l, at the lower end of the therapeutic window of younger adults (Bocchetta et al. 2017). Another large study confirmed that higher serum lithium concentration is a risk factor for renal functioning decline in long-term lithium exposure (Tondo et al. 2017).

The overall risk of bias for systematic reviews included in the geriatric group was moderate, with 60% of studies showing a low risk (Fig. 1). It was not possible to calculate the overlap in primary studies across systematic reviews because, as shown in Table 1, articles had an extremely high level of heterogeneity in terms of efficacy and safety outcomes and patient populations. A critical point emerging from this overview is the need to establish a clear cut-off age for future systematic reviews on lithium use in the elderly. In fact, the included reviews provided different cut-offs to define the geriatric population. The adopted cut-off ranged between > 50 and > 65 years. This heterogeneity reflects the uncertainty expressed by the scientific community on this particular topic. Recently, the International Society for Bipolar Disorders Task Force proposed to consider > 50 years as a demarcation for older-age BD (Sajatovic et al. 2015). Nevertheless, it reported that many studies considered older-age BD as BD in individuals aged ≥ 60 years (Sajatovic et al. 2015).

Limitations

Before presenting our conclusions, we must acknowledge some points that might limit the generalisability of our results. First, only published systematic reviews and meta-analyses on lithium use in paediatric age, peripartum, and old age were included, which may have omitted some important recently published individual studies. Second, the results of bias assessment showed that the included reviews, in particular peripartum and old age, had a moderately high risk of bias. This finding demonstrates that investigators should use more appropriate study eligibility criteria and data synthesis methods in future systematic reviews. Third, the number of included reviews, in particular for paediatric and old ages, was small. Future studies focused on the extremes of the Gaussian age curve are surely needed. Fourth, the relatively low degree of overlap in studies, as assessed by the CCA, requires that further systematic reviews and meta-analyses should standardise inclusion/exclusion criteria and search strategies (including an appropriate number of databases).

Conclusions

In conclusion, this umbrella review supports the use of lithium across the lifespan, with particular reference to paediatric age, peripartum period, and old age. Lithium appears to be effective and relatively safe in these special life stages and emerges as a viable treatment option

to antipsychotic drugs, already widely used (Centorrino et al. 2005). Low doses should be used in the elderly. Further studies are needed, in particular for paediatric and old ages, to confirm these initial observations. Given the high level of heterogeneity among the systematic reviews, studies with increased methodological homogeneity need to be performed from now and onwards, so that meta-analyses could obtain more sound results and inform improved patient outcomes across the lifespan.

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
BD	Bipolar disorders
CCA	Corrected Covered Area
MDD	Major depressive disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria
RCTs	Randomised-control trials
ROBIS	Risk of Bias Assessment Tool for Systematic Reviews

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40345-023-00287-7.

Additional file 1: Figure S1. PRISMA flow diagram of included studies. **Figure S2.** Risk of bias assessment for each systematic review. **Table S1.** CCA of the primary studies included in the systematic reviews on pediatric population. **Table S2.** CCA of all the randomized controlled trials (RCT) included in the systematic reviews on pediatric population. **Table S3.** CCA of the primary studies included in the systematic reviews on pregnancy and peripartum. **Table S4.** CCA of the primary studies included in the systematic reviews on pregnancy and peripartum without case reports

Author contributions

DJ, GSam, UA, FC, GM, GS, AT, AZ, AF, GSan contributed to the conception and design of the work; DJ, GSam, AF, GSan performed the search, established eligibility and performed data extraction; DJ, GSam, UA, FC, GM, GS, AT, AZ, AF, GSan interpreted the data and contributed to the manuscript's drafting. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its Additional file 1].

Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

No competing interests to declare.

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