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Parental perspectives about information and deferred versus two-stage consent in studies of neonatal asphyxia

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ABSTRACT

Objective The ALBINO Trial (NCT03162653) investigates effects of very early postnatal allopurinol on neurocognitive outcome following perinatal asphyxia where prenatal informed consent (IC) is impossible. Ethically and legally, waiver of consent and/or deferred consent (DC) is acceptable in such an emergency. Short oral/two-step consent (SOC, brief information and oral consent followed by IC) has recently been investigated.

Methods Mixed-methods analysis of parental opinions on DC versus SOC in the context of neonatal asphyxia in a survey at two German centres. Prospective parents (ProP), parents of healthy newborns (PNeo) and parents of asphyxiated infants (PAx) born between 2006 and 2016 were invited.

Results 108 of 422 parents participated (ProP:43; PNeo:35; PAx:30). Most parents trusted physicians, wanted preinterventional information and agreed that in emergencies interventions should begin immediately. Intergroup and intragroup variability existed for questions about DC and SOC. In the ALBINO Trial situation, 55% preferred SOC, and 26% reported DC without information might adversely affect their trust. Only 3% reported to potentially take legal action after DC. PAx were significantly more likely to support DC. PAx more frequently expressed positive emotions and appreciation for neonatal research. In open-ended questions, parents gave many constructive recommendations.

Conclusion In this survey, parents expressed diverse opinions on consent, but the majority preferred SOC over DC. Parents who had experienced emergency admission of their asphyxiated neonates were more trusting. Obtaining parental perspectives is essential when designing studies, while being cognisant that these groups of parents may not represent the opinion of all parents.

WHAT'S IS ALREADY KNOWN ON THIS SUBJECT

⇒ Obtaining parental consent for investigations in emergencies (eg, perinatal asphyxia) is ethically complex and sometimes impossible.

⇒ Deferred/waiver of consent is a controversial topic where parental/stakeholders' perspectives are scarce.

WHAT THIS STUDY ADDS

⇒ Stakeholders can have diverse opinions. In the context of asphyxia, the majority of parents preferred short oral consent followed by informed consent over deferred consent.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Considering parental perspectives when designing studies including waiver/deferred consent is essential.

⇒ Two-(or multi-)stage consent with the opportunity to opt-out may be a good approach and following participants in those studies for their perspectives is recommended.

OBJECTIVE

According to current legislation, guidelines on Good Clinical Practice and the Declaration of Helsinki[1] ethically justified research in humans requires informed consent (IC).[2 3] In paediatrics, parents/guardians provide consent for their children.[4]

In emergencies, 'deferred consent (DC)' can be used[1] and interventions started with later IC for continuing participation and data analysis.[2]

In neonatal research, this may be considered in trials on delivery room management,[5] where DC has been used before,[6] but is deemed ethically and legally complex.[7] The alternative, prenatal consent, was reported to negatively impact on validity and representativeness.[8 9] Recently, short oral/two-step consent (SOC) has been described, where researchers seek oral opt-out assent for participation during time-critical periods, followed by later IC.[10]

The ALBINO Trial (NCT03162653) investigates the effects of early allopurinol versus placebo, administered ≤45 min after birth, on neurocognitive outcome following perinatal asphyxia,[11 12] where prenatal and detailed IC before enrolment is not feasible because birth asphyxia is unpredictable and parents are burdened in such situations.[13] Nevertheless, research in these situations is essential to improve outcomes.[14]

Designing the ALBINO Trial, investigators, ethicists and parent advocates discussed the consent methodology and sought guidance by surveying parental perspectives about DC and SOC in perinatal emergencies.

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METHODS

Questionnaire

The anonymous semistandardised questionnaire was co-developed by clinicians and experts in parental perspectives and qualitative healthcare research. The original questionnaire was in German (online supplemental appendix 1, online). Data were collected from October 2016 to October 2017.

In the standardised section, parents were asked about their general trust in physicians/paediatricians, decisions about medical interventions for their child, decision-making during emergencies, and consent in the context of ALBINO and other pharmaceutical trials. Answers were given on a 4-point Likert-Scale ('I fully agree' to 'I fully disagree') or, alternatively, 'I don't know/cannot judge this'.

Additionally, open-ended questions inquired parental perspectives on their child's participation in trials (eg, ALBINO), their reaction after DC and recommendations for the ALBINO team.

Subjects and recruitment

Three parent groups were invited:

1. Prospective parents (ProP) recruited during routine prenatal outpatient appointments.
2. Parents of healthy newborns (PNeo) recruited during inpatient maternity care.
3. Parents of neonates treated for perinatal asphyxia (PAx) in 2006–2016 (meeting ALBINO Trial inclusion criteria), invited by letter and reminded once.

ProP and PNeo received a brief verbal explanation before receiving the study documents.

Formal sample size calculation was not performed due to the exploratory and qualitative character of the study. The initial sample size was determined based on the prevalence of perinatal asphyxia in the preceding 10 years at Dresden and Tübingen, and an expected response rate of 30% in PAx.

Data analysis

Analyses of the standardised questions were descriptive using percentages, means and SDs. Couples were treated as independent observations. Likert-Scale results were dichotomised (positive vs negative). The neutral answer ('I don't know/cannot judge this') was set to 'missing'. Associations between answers (positive vs negative) and parent groups, gender, religious affiliation and education were evaluated exploratively by χ^2 test for questions with (predefined) differences of >10%. χ^2 tests were done with SPSS (Statistics V.25; IBM Corp.; Armonk, New York, USA). Significance level for alpha was <0.05 without adjustment for multiple comparisons.

Answers to open-ended questions were analysed using descriptive content analysis.[15 16] Themes were developed simultaneously and independently by three investigators. After reaching consensus on codes/definitions, answers were coded independently by two investigators, resolving discrepancies with a third.

Ethics

Parents signed a consent form before participation. The anonymity of respondents was preserved by having an evaluation-independent person open the return envelopes, file the consent forms and hand the sealed, anonymous questionnaires to the investigators.

RESULTS

Demographics

There were 108 participants (ProP: 43/120; PNeo: 35/114; PAx: 30/188; figure 1); overall return rate was 25.6%; mean age was 34 years (SD 4.9); 63% were mothers; 57% were Christians, 41% non-religious or stated that religion had no influence on their decisions; 58% had a university degree.

Standardised answers

The following section summarises the main results (all answers detailed in online supplemental appendix 1, online).

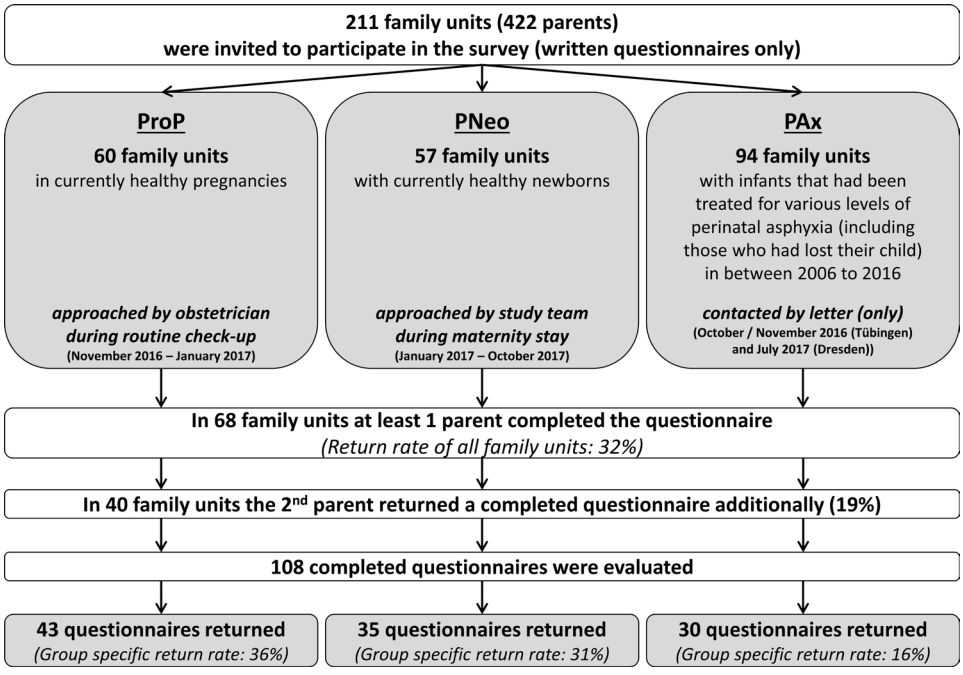

Figure 1 Trial flow chart. PAx, parents of neonates treated for perinatal asphyxia; PNeo, parents of healthy newborns; ProP, prospective parents.

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Table 1 Most relevant questions for the ALBINO scenario

% agreement	Total	ProP	PNeo	PAx
5.8 'I think that I would make the right decision even in this emergency. Therefore, I would prefer to only be informed in a few sentences and to be asked for short (oral) consent before administering the study medication.'	55 %	54 %	60 %	50 %
5.9 'In the emergency described, I would be glad not to have been asked for permission to give the study medication, because I would have felt helpless and unable to make decisions, and I would probably have followed the advice of the physicians anyway.'	43 % (disagree: 47 %)	40 % (disagree: 54 %)	34 % (disagree: 54 %)	57 % (disagree: 30 %)
5.16 'If my child has been given study medication in an emergency without my prior consent, I would decide afterwards as follows (after detailed information):'				
'I would agree to participate afterwards.' (deferred consent)	48 %	40 %	43 %	67 %
'I would refuse to participate afterwards.' (deferred consent)	4 %	7 %	0 %	3 %
'I would have refused to participate before the birth.' (prenatal consent)	2 %	2 %	3 %	0 %
'I do not know/ I am not sure for any scenario.'	46 %	51 %	54 %	30 %
5.17 'I think that giving a study medication in this situation without my knowledge is so inappropriate that I would take legal action against the investigators.'	8 %	14 %	0 %	10 %

PAx, parents of neonates treated for perinatal asphyxia ; PNeo, parents of healthy newborns; ProP, prospective parents.

Trust in physicians

The majority (88%) trusted their own physicians to make the right decisions/recommendations. Only 27% would generally seek a second opinion. Parents with university degree tended to rely less on the opinion of their child's physician than those without (76 vs 92%; p=0.028).

Medical interventions (in general)

The majority (95%) wanted to be informed before agreeing to a medical treatment for their child. Half insisted on information beforehand, even if this delay would reduce the intervention's benefit (50%); Some (44%) favoured starting treatment immediately.

Emergencies

Almost all (97%) agreed that in emergencies treatment must begin immediately and no time should be wasted on information; most (84%) reported that, especially in emergencies, more research should be done in order to better prevent serious harm (3% disagreed).

DC in the context of perinatal asphyxia

The majority thought they would be able to cope better with a situation of perinatal asphyxia and administration of study medication without prior information/consent if they had already heard about this (eg, by community engagement; 78%).

When asked for their preferences in the ALBINO Trial context, 55% preferred SOC, while 43% preferred DC. PAx more frequently favoured DC over SOC (54% vs 30%; p=0.032) (table 1).

In the ALBINO scenario, 91% would wish the medication to be given even without their prior consent, provided its therapeutic effect had been proven in previous studies. Administration of study medication in an emergency was acceptable without consent for 80%, provided it was safe (minor side effects only).

If the study medication had been administered without prior information/consent, 26% responded that it might adversely affect trust in their paediatrician. Men (40% vs 18%; p=0.029) and non-religious parents (36% vs 18%, p=0.040) reported this more frequently. Twenty-three per cent would later suspect that new health problems of their child might have been caused by the study medication. 74% would not consider legal action against the study team, whereas 3% would and 6% would at least consider it (table 1).

Concerning DC, 57% of respondents thought that information about such a study with flyers or posters in the delivery area and/or information in the media would be sufficient. PAx more frequently agreed with this point (70% vs 52%; p=0.149).

An 'emergency card' indicating the intention to participate in a study for perinatal asphyxia (yes/no) was considered helpful by 83%, while only 41% would use such a card.

Contemplating the 'ALBINO situation', 48% would consent to continued participation following detailed information in a DC scenario; 4% would not consent and 2% would have refused participation before birth if they had had the chance, for example, by community engagement; 46% were uncertain (table 1).

Pharmaceutical studies (in general)

Almost all (94%) agreed to participate in pharmaceutical trials, if there was a good chance for benefit and a low risk for harm.

Some (40%) would prefer a safe treatment with a proven small therapeutic effect over an experimental treatment with a potentially greater therapeutic effect.

Open-ended answers

When parents were asked which factors would impact on their decision to give consent in a study, 87 answers in the following main themes emerged: information and transparency of study (24%); side effects of study medication (23%); benefits of study (22%); risk-benefit ratio (16%); condition of the child (15%); relationship with the study team (14%); personal views regarding the necessity for study participation (14%); safety of/experience with the drug (11%); burden of the study intervention (9%); time needed to participate (8%) and reputation/commitment of the study team (7%).

Parents often invoked multiple themes. Examples of parental responses (each from a different participant) included:

- *'If there were the (smallest) possibility of a "cure" or improvement, I would take part. The side effects shouldn't be too bad either.'* (ProP-mother)
- *'[…] Do I have the feeling that I know exactly what is being done, what is being observed, what the goals are?'* (ProP-mother)

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Table 2 Examples of parental quotes and emotions. When asked the following question: 'If a study drug was administered to your baby as part of an emergency trial without informing you; please tell us what would be your reaction when you would be informed later and asked for consent for continued participation in that trial.' (examples associated with only one emotion, for the complete list see online supplemental appendix II)

Parent group	Example of parental quotes and emotions associated with them		
	Positive (total: 19%)	Neutral (total: 55%)	Negative (total 26%)
ProP (n=36)	(17%) 'Positive thoughts: it's good that the doctors thought of the possibility; Hopefully the drug will work for my child; What would it have been like without it?' 'I would be glad that everything possible was done for my child.'	(53%) 'Assuming prior information: I would try to remain calm, thinking that by doing so you have done everything possible to help the child.' 'Possibly confusion; good or bad depends on the situation' 'Uncertainty at first, but if someone would explain to me what it's about, then it would be ok.' 'Concern and the right to be informed in detail afterwards. Side effects. What if the drug had not been administered.' 'I'd probably be fine with that, if it successfully helped. In the event of complications, I cannot judge how I will react. In general, I have to trust the knowledge and actions of the doctors in such a situation.'	(31%) 'Aggravation. After all, it is a drug that has not yet been approved.' 'Doctors ask why there was no brief explanation beforehand! There was enough time!' 'I wouldn't like that, it's still a study drug. A tested drug would be more ok! Especially in the case of study drugs, prior information would be particularly important to me!' 'That would probably depend very much on the success of the treatment. A certain feeling of deceit would probably not be avoidable, even if it is irrational.'
PNeo (n=23)	(13%) 'If the application brings a positive result, this would lead to joy. It's better to try something than to refrain from helping.' 'It's good that my child was given the best possible help. I am grateful because I know the sequalae and damage that can happen after a lack of oxygen' I would think: 'The doctors did everything they could to help my child.'	(67%) 'I would like a full explanation and exact reasons why the doctors chose this drug and why they acted the way they did.'	(21%) 'Disappointment, possibly anger because I wasn't asked in advance!' 'I would lose confidence in the doctors and possibly take legal action against them'
PAx (n=25)	(28%) 'I would hope that this would be as helpful to my child as possible, and even if not, that there would be a sense of progress that would help other children in a similar situation.' 'This triggered so much relief in me. The hope that my child could do well is irreplaceable!' 'I would be grateful if I knew that everything is being tried to save my child. I also expect that from a university hospital, which is why I go there and not to a birth center'	(48%) 'I would first get clarification from the doctor. But basically, I would trust his expertise.'	(24%) 'I would be shocked! Extremely angry. Depending on the side effects my child would have afterwards. If there were no adverse effects, I would probably just be shocked that something was done without permission.' 'Incomprehension, anger, doubts about legality; Would rate the approach as arrogant and high-handed.' 'That would harm my trust and my confidence. I would then question everything and suspect several things about which I was not informed.'

PAx, parents of neonates treated for perinatal asphyxia ; PNeo, parents of healthy newborns; ProP, prospective parents.

- *'Are the doctors concerned with the well-being of my child or just with participating in the study? […]'* (PNeo-mother)
- *'Follow-up examinations: time required, travel routes? […] child-friendly setting? […]'* (PNeo-mother)

Many of the 84 answers to the question on how parents would react after DC in an emergency trial were emotional: 19% reported only positive emotions (gratitude, satisfaction, relief, trust, etc), 26% only negative (anger, irritation, mistrust, frustration, sadness, etc), while about half answered without expressing emotions (table 2). Some parents also answered in a positive and negative manner, for example:

- '*Fear and hope, anger or gratitude depending on success of the drug*' (ProP-father)
- '*Worry about whether it might harm the child. Reassurance because everything has been done that is possible according to current research*' (ProP-father)

PAx more frequently reported positive feelings (28% vs 15%).

Fifty-six parents made recommendations for the ALBINO investigators, generally on 'information' and 'communication'. Many encouraged researchers to continue with the ALBINO Trial:

- *'I think flyers are great! Also, to inform parents in advance about the consequences of a lack of oxygen. […] because the public is not sufficiently informed and educated about rare conditions or disabilities. Always talk plainly, it can be difficult at first, but it is the best solution. […]'* (ProP-mother)
- *'Information brochures with the essential facts for expectant parents, as well as an emergency card on the maternity booklet are definitely helpful to avoid misunderstandings/conflicts […].'* (ProP-father)
- *'Humanity comes first, followed by honesty, openness, respect and professional competence. Don't make us feel like a lab animal! Child-friendliness must be a prerequisite.'* (PAx-mother)

DISCUSSION

To our knowledge, this is the first investigation on parental perspectives on consent for a trial in the context of neonatal asphyxia in a high-income country, and the only one asking a variety of parents with different pregnancy and birth experiences.

Previous poststudy surveys or hypothetical research studies indicated that parents may initially be upset by a study intervention started without their prior consent or short verbal information,[17 18] although this can often be mitigated by further explanations.[17] Parents wanted to be involved and asked for consent (even in an emergency),[19] and they were more willing to accept DC in an emergency.[18] We confirmed these findings

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in our survey. In contrast, after the randomised controlled PREMOD Trial, a low risk comparison between two standard-of-care interventions (cord-milking vs delayed cord-clamping), parents reported to be generally satisfied with the use of DC.[20] However, in this online survey, several parents reported that physicians spoke about the study *before* delivery, and only half the respondents explicitly recalled that they had been informed *after* their baby's inclusion. Another successful DC example might be the 'milking in non-vigorous' trial.[21]

Seeking parental perspectives for an investigation about neonatal asphyxia raises the question which parents should be asked. ProPs (whose unborn child is at risk of asphyxia), parents of newborns (at the time when detailed IC would be obtained in the ALBINO Trial), parents of children who met ALBINO inclusion criteria in the past (both bereaved and non-bereaved parents)? When involving stakeholders, researchers generally seek the information of parents of living children who met inclusion criteria, generally those engaged in support groups. Such stakeholders may be more positive towards research. However, when consent is obtained in a suddenly evolving emergency (like perinatal asphyxia), parents are in a different frame of mind and acutely anxious whether their child will survive. This distinguishes them from parents of premature infants, who frequently have some time to prepare for the upcoming situation. Perhaps the best way to obtain stakeholders' opinions is to ask a variety of stakeholders.

In our case, participants agreed about some issues: almost all parents, when placing themselves in the ALBINO scenario, wished medication of proven efficacy to be given, even without their prior consent, and they were also in favour of research. However, when asked about DC and SOC, parents within and between groups were far from unanimous, for example, a large proportion favoured SOC over DC. However, parents of children having experienced perinatal asphyxia were different: Although their response rate was lower (presumably because of the method of contact), they preferred DC more often, were more often positive about emergency research and expressed more positive feelings and gratitude. Possibly, their experience resulted in a different understanding of the need for such research procedures and the limitations to judicious decision making in acute emergencies, whereas the purely hypothetical idea of a DC situation led to more emotional rejection/distrust.[22]

This survey has several limitations. The generalisability of the findings is limited by the low response rate, even if comparable to other surveys.[20 23] Additionally, predominantly well-educated parents participated with little diversity concerning religious background, which limits our findings to this group of parents. Possibly, German parents may also have a different ethical approach to DC than others. In other contexts, where parental decisions about participation are guided by unreserved trust in physicians, parental perspectives about the most appropriate consent procedure may differ.[24] Additional challenges for SOC have also been identified in low-income settings.[25]

Questionnaire studies have inherent biases, which we tried to reduce by asking different groups of parents. Because of their variety of perspectives and demographic factors, the results may represent the range of perspectives of parents in our centres. We even asked parents of children who had died of neonatal asphyxia, as their opinions were deemed to be particularly valuable, hoping that the chance for benefit from their potential participation, in the memory of their child, would exceed the risk of harm.[26] Another limitation is that we did not ask what information parents needed for their decision to participate in an emergency study, for example, legislation and ethics committees insist on detailed information about data protection, whereas this may not be important to parents.

Supported by these results, the ALBINO investigators asked national ethics committees to choose between DC and SOC.[11] DC was approved in Austria, Belgium, Estonia, Finland and Norway, whereas SOC was approved in Germany, Italy, the Netherlands, Portugal, Spain and Switzerland. In Poland, the leading ethics committee insisted on written IC from both parents before enrolment. Ethics committees considered the validity of parental consent in an emergency situation, burden to parents and legal requirements (eg, the European clinical trial regulation 536/2014 had not yet entered into force[2]). During the ongoing ALBINO Trial, parental satisfaction with the SOC/DC process will be evaluated.

CONCLUSION

The vast majority of parents wanted to be informed about study participation in an emergency such as perinatal asphyxia. SOC may improve parental satisfaction and safeguard their autonomy (parents can opt-out if they have concerns after receiving at least the most relevant information), while enabling emergency studies that are representative and valid. SOC could be complemented by prior study-related information such as provided in the delivery room. Parents' perspectives on these issues are essential for future research and should be sought in trials using DC or SOC. Additionally, future trials may compare these consent approaches by randomly allocating the consent process prior to a randomised-controlled trial.

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Correction notice The licence for this article has been updated to Open Access.

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Contributors CAM conceptualised the study, designed the survey, recruited parents on the maternity ward in Tübingen and drafted the first version of the manuscript (including translation of the survey and the answers). CAM approved the final version of the manuscript and agreed to be accountable for all aspects of the work. CR contributed to the design of the survey, recruited parents on the maternity ward in Tübingen and coordinated the data collection in the obstetric practices and in Dresden. CR revised the manuscript, making important contributions, approved the final version of the manuscript and agreed to be accountable for all aspects of the work. MR coordinated data collection in Dresden. MR and CFP supervised the project as heads of the neonatal departments involved and critically reviewed the manuscript for important intellectual content and translations. Both authors revised the manuscript, making important contributions, approved the final version of the manuscript and agreed to be accountable for all aspects of the work. HS and MM assisted in the design of the survey from a perspective of healthcare research and critically reviewed the manuscript. Both authors made important contributions and approved the final version of the manuscript. AJ encouraged this study by critically commenting on 'deferred consent' for ALBINO as member of the ALBINO Ethics Advisory Board. AJ revised the manuscript critically for important intellectual content and with regard to the English language as a native speaker. AJ agreed to the final version of the article and agreed to be accountable for all aspects of the work. GM made important contributions as member of the ALBINO ethics advisory board. GM revised the manuscript critically for important intellectual content, agreed to the final version of the article and agreed to be accountable for all aspects of the work. H-JE made important contributions as member of the ALBINO ethics advisory board. H-JE revised the manuscript critically for important intellectual content, agreed to the final version of the article and agreed to be accountable for all aspects of the work. ARF conceptualised the study and designed the survey and was coordinator of the project. ARF was responsible for concept and design and supervised assessment of the data. ARF revised the manuscript, making important contributions, approved the final version of the manuscript and the translations and agreed to be accountable for all aspects of the work. ARF and CAM are guarantors.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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