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Clinical data and reporting quality in NMDAR-antibody encephalitis and pregnancy: a systematic review

Scarlett L Harris [1,2] Sophie N M Binks [3,4] Donal Skelly,[4,5] Hanine Fourie,[6] Phoebe Cherrington-Walker,[1] Tomasz Bajorek,[3] Sarosh R Irani [3,7] M Isabel Leite,[3] Adam E Handel [3] Adam Al-Diwani [8]

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SNMB and DS contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Scarlett L Harris;
scarlett.harris@imperial.ac.uk

Dr Adam Al-Diwani;
adam.al-diwani@psych.ox.ac.uk

ABSTRACT

Background N-methyl-D-aspartate receptor antibody encephalitis (NMDAR-Ab-E) can have an onset during, after or prior to a pregnancy. In animal models, transplacental NMDAR immunoglobulin G transfer can affect neurodevelopment. In contrast, clinical reports of mothers affected by NMDAR-Ab-E typically are reassuring. We systematically reviewed maternal, infant and childhood clinical data pertaining to NMDAR-Ab-E with an onset before, during or after pregnancy and compared this to our single autoimmune neurology centre experience.

Methods After pre-registration on PROSPERO (CRD42023408447), we searched PubMed and Scopus for NMDAR-Ab-E case reports/series with an onset before, during or after pregnancy (last search 19/10/2023). We extracted maternal, neonatal and childhood outcomes using an idealised checklist to derive summary statistics.

Results After quality control, we identified 66 pregnancies in 61 women from 48 reports or series. 72% of women recovered with minimal or no neurological deficits, comparable to non-pregnancy-associated NMDAR-Ab-E. Likewise, 80% of pregnancies resulted in live births with a single neonatal death reported. Data on neonatal outcome measures were frequently unreported, and childhood follow-up was provided in only 60%. Our centre's experience is consistent: 3/4 mothers recovered with no functional deficits and 7/8 children without evidence of compromise at a median follow-up of 2 years.

Conclusions Current evidence does not overall suggest unfavourable maternal, fetal or childhood outcomes after NMDAR-Ab-E. However, the available sample is small, predominantly single case reports with modest follow-up, lacks standardisation, and data are often incomplete. Future approaches should address these caveats: developing multi-centre collaboration towards an international registry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some animal models of N-methyl-D-aspartate receptor (NMDAR) immunoglobulin G transplacental transfer show adverse effects on brain development. However, caveats include species differences and potentially non-physiological exposures. Moreover, although some case reports identify adverse maternal and fetal outcomes, previous systematic reviews and single-centre summaries of clinical data have been more reassuring.

WHAT THIS STUDY ADDS

⇒ We update and expand on previous systematic reviews by including cases of NMDAR-antibody encephalitis in the postpartum period and cases of pregnancy after recovery, as well as reporting the experiences of our autoimmune neurology centre. Additionally, we also focus on childhood outcomes and have contacted authors of published case reports for further follow-up. These data show generally good outcomes for mothers and children, but reporting is patchy and not standardised.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To overcome these shortcomings in reporting, we recommend collaboration among the autoimmune neurology clinical-research community to consolidate experience. This could include establishing an international registry to foster reporting standardisation and improve understanding of interactions between the illness, pregnancy and potential effects on neonatal and childhood outcomes.

INTRODUCTION

N-methyl-D-aspartate receptor antibody encephalitis (NMDAR-Ab-E) is an autoimmune neurological disorder predominantly affecting women of reproductive age.[1 2] Mediated by IgG autoantibodies against the NR1 (GluN1) subunit of the NMDA receptor (NMDAR-IgG), NMDAR-Ab-E presents with combinations of acute psychiatric disturbance, movement disorders, seizures, dysautonomia, hypoventilation and altered level of consciousness. Increasingly, this condition has been identified during pregnancy or in the postpartum period.[3] Additionally, many who recover from the illness have yet to start or complete their family. They and their clinicians require clarity on potential risks for both mother and baby.

NMDAR-IgGs are typically of the IgG1 subclass. IgG1 autoantibodies can cross the

placenta and induce congenital disease including in the nervous system. For example, in myasthenia gravis, autoantibodies against fetal acetylcholine receptor isoforms can cause fetal acetylcholine receptor antibody-related disorders, a spectrum of disorders ranging from milder myopathic presentations to arthrogryposis multiplex congenita.[4] In these cases, immunomodulation, particularly early in pregnancy, has been shown to improve survival and reduce complications for the developing fetus. Such precedents have raised the question of whether autoantibodies against central nervous system targets could affect fetal brain development. In animal models, CASPR2 and NMDAR-autoantibodies have been shown potentially to affect neurodevelopment.[5 6] Furthermore, NMDAR-IgG seropositivity often persists despite clinical remission,[7 8] and so syncytiotrophoblastic neonatal FcRn receptors could mediate transfer of the dominant IgG1 sub-class autoantibodies.[9 10] Therefore, it is important to consider both illness onset during pregnancy but also cases in which illness onset and recovery have occurred before pregnancy. Nonetheless, real-world clinical outcomes have been more reassuring. For example, a previous systematic review found 10/13 live births with 8/10 healthy neonates,[3] and an experienced autoimmune neurology centre reported 10/11 neonates healthy at birth.[11] Moreover, in cases where there has been proven NMDAR-IgG transfer with sub-optimal neonatal outcomes, potential confounders have included maternal condition, medication and placental factors.[12 13]

Here, we aimed to assess maternal, fetal/neonatal and childhood outcomes with a focus on reporting quality to inform recommendations on future standards. We deployed an idealised checklist of features in pregnancy and developmental features to systematically review literature-reported cases and compare with experience from our own autoimmune neurology centre.

METHODS

We pre-registered the study protocol with NIHR PROSPERO on 17/3/2023 (CRD42023408447) and followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines.

Search strategy

We searched two databases (PubMed and Scopus) without language or date restriction using the search terms (‘*anti-NMDA receptor*’ *OR* ‘*anti-NMDAR*’ *OR* ‘*anti-N-methyl-D-aspartate receptor encephalitis*’ *OR* ‘*NMDAR-antibody encephalitis*’ *OR* ‘*NMDAR-Ab-E*’ *OR* ‘*NMDAR encephalitis*’ *OR NMDARe) AND (pregnancy OR postpartum OR post-partum OR puerperal OR puerperium OR foetus OR fetus OR gestation OR birth OR neonate OR infant OR child OR perinatal*). We screened the reference lists of included papers for additional publications. The search was repeated twice to identify any papers published prior to the final analysis.

Eligibility criteria

We included case reports and series that reported on patients with an onset of NMDAR-Ab-E *before* (‘non-pregnancy-associated’), *during* or *after* pregnancy (‘pregnancy-associated’), as well as reports of children born to these patients. We planned to restrict to cases that strictly met the 2016 consensus criteria for definite anti-NMDAR encephalitis.[14] However, our initial search yielded seven cases, including four published prior to these criteria, which did not fully meet a definite classification due to not measuring cerebrospinal fluid (CSF) NMDAR-IgG. Yet being highly typical for the illness, they met probable criteria, and given the modest sample size and valuable clinical information therein, we chose to include these cases. For the non-pregnancy-associated *before* cases, since NMDAR-IgG testing both outside of acute illness and in neonates is variable, to obtain as full a picture as possible, we did not restrict inclusion of these cases by persisting seropositivity. Rather, a prior episode satisfying our overall criteria was sufficient.

We initially defined postpartum onset as within 42 days as per the World Health Organisation (WHO).[15] However, only two of eight postpartum cases occurred within this period. Further aiming to maximise the inclusion of clinically relevant information, we extended the postpartum definition to include cases where the presenting disorder was classified as postpartum in onset, which here was a maximum of 11 months postpartum.

Outcome measures

The full template for data collection including all extracted outcomes is provided in online supplemental table 1. As primary outcomes, we aimed to ascertain maternal morbidity, mortality and functional status; pregnancy complications; and morbidity, mortality and functional status in neonates (baby<28 days old), and where available, later childhood developmental progress. We defined preterm birth as before 37 weeks and low birth weight at term as <2.5 kg as per the WHO.[16] We defined postpartum haemorrhage as blood loss of >500 mL as per the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines.[17] We defined normal CSF parameters as protein concentration of 15–40 mg/dL and white cell count of 0–5/mm^3.[3 18] As secondary outcomes, we noted whether NMDAR-IgG autoantibodies were reported in cord or neonatal blood samples alongside maternal serology.

Data extraction

We removed duplicate papers to produce a final list of abstracts for screening. Two authors (SH and AAD) independently compared a representative sample (n=21) of the abstracts and reached consensus on inclusion with full agreement. The remaining abstracts were screened, yielding 48 papers eligible for inclusion. SH performed the extraction, which was then independently cross-checked (AAD, DS and HF). Any differences were resolved by discussion. Where data were insufficient, we contacted the report authors to supplement the available published data.

Quality assessment

Studies were assessed for quality using the tool for evaluating the methodological quality of case reports and case series.[19] We made project-specific modifications to prioritise whether there was sufficient information to (1) confirm the diagnosis of NMDAR-Ab-E and (2) allow basic evaluation of neonatal outcomes (online supplemental table 1). Maternal outcome data were not used to determine inclusion as we did not wish to exclude records of children born secondary to pregnancies complicated by NMDAR-Ab-E, which may not report maternal outcome. Those providing information on childhood outcomes and with follow-up of at least 1 year were considered good quality.

Local case series: research ethics and consent

To contextualise the global experience from the systematic review, we reported cases from our autoimmune neurology service who satisfied the same eligibility criteria. All are participants in the Immune Factors in Neurological Disease research study (REC 16/YH/0013) and gave informed consent in accordance with the Declaration of Helsinki. If an assenting participant lacked capacity to consent for themselves, then there was a next of kin declaration. Additional publication-specific consent was obtained for de-identified detailed individual participant data including offspring.

Patient and public involvement

The study was discussed with patients who gave consent to participate in the reporting of our local case series. They read and commented on the proposed manuscript, helping to both guide our presentation and affirm the relevance of the study to patients and the public.

Data analysis

Data were tabulated with Excel version 16.83 (Microsoft). Statistical analyses and visualisation were conducted with Prism version 10.2.1 (GraphPad). Fisher's exact test was used to compare between pregnancy groups, and the binomial or X^2 tests to compare observed to expected results. Statistical significance was inferred where $p<0.05$.

RESULTS

Identification of records

Our initial search identified 1587 records (733 PubMed; 854 Scopus, figure 1). Later repeated searches identified an additional 107 records (49 PubMed, 58 Scopus). 638 duplicate records were removed, leaving 1056 for abstract screening. This was then refined to 60 eligible records, including two identified through abstract screening (online supplemental table 2). Two systematic reviews and two papers with insufficient data were removed.

We then quality-assessed the remaining 56 records, finding 48 of sufficient quality for inclusion (n=8 inadequate, n=33 adequate, n=15 good; figure 1). There were 53 NMDAR-Ab-E illness episodes directly associated with pregnancy, including 45 with an illness onset *during* pregnancy and eight with an illness onset *after* pregnancy. There were 13 instances in which the illness had occurred *before* a pregnancy, which we grouped, in contrast, as 'non-pregnancy-associated'. This group included two women who had NMDAR-Ab-E during a previous pregnancy, and one who had two pregnancies after recovery.

NMDAR-Ab-E description and treatment

The average age of illness onset was consistent across the groups (figure 2). The overall ovarian teratoma rate in the pregnancy-associated cases was 43% (23/53) comparable to the literature-reported rate.[20] This comprised 17/45 (38%) *during* and 6/8 (75%) *after* (non-significant; p=0.065, Fisher's exact test).

The majority of cases that occurred *during* pregnancy were early, with only four in the third trimester (9% (4/45), p=0.001, X^2 test). The overall clinical profile of the cases associated with pregnancy vs non-pregnancy associated cases differed in reduced consciousness (70% vs 10%, p=0.0006, Fisher's exact test) and hypoventilation (49% vs 10%, p=0.034, Fisher's exact test) (online supplemental figure 1A). The rates of these features in the pregnancy-associated group are broadly in keeping with a recent large meta-analysis of 1550 predominantly female patients, where reduced level of consciousness was reported in 55% and central hypoventilation in 43%.[21] Investigation and treatment profiles were also broadly similar across case types (online supplemental figure 1B-D).

Pregnancy outcomes

For cases with an illness onset *during* pregnancy, most resulted in live births (33/45, 73%) (figure 3A). However, 18/33 (55%) were preterm (median gestational age 33 weeks, range 27–36), of which most were iatrogenic, ie, either induced or involved a caesarean section (14/18, 78%; figure 3A–B). 14 women had a live birth at term (14/33, 42%), and 29% (4/14) of these babies were born by caesarean section. We plotted available birth weights against week of delivery, and these clustered at or below the normative median with 1/12 >97th centile and 2/12 <3rd centile (figure 3C). One paper reported a birth weight of 408 g at 33 weeks, which is close to the limit of viability and appeared implausibly low.[22 23] Attempts to contact the authors to clarify were unsuccessful; therefore, we elected to exclude this data point from this analysis (retained and compared for reference in online supplemental figure 2).

Six pregnancies ended spontaneously (four miscarriages and two stillbirths), and another six were terminated (online supplemental table 3). For both stillbirths, sepsis complicated immunotherapy treatment. In the non-pregnancy-associated *before* group, there was one termination, and the rest were live births (12/13, 92%) with two (17%) caesarean sections. All the cases with illness onset *after* pregnancy were live births with no caesarean sections

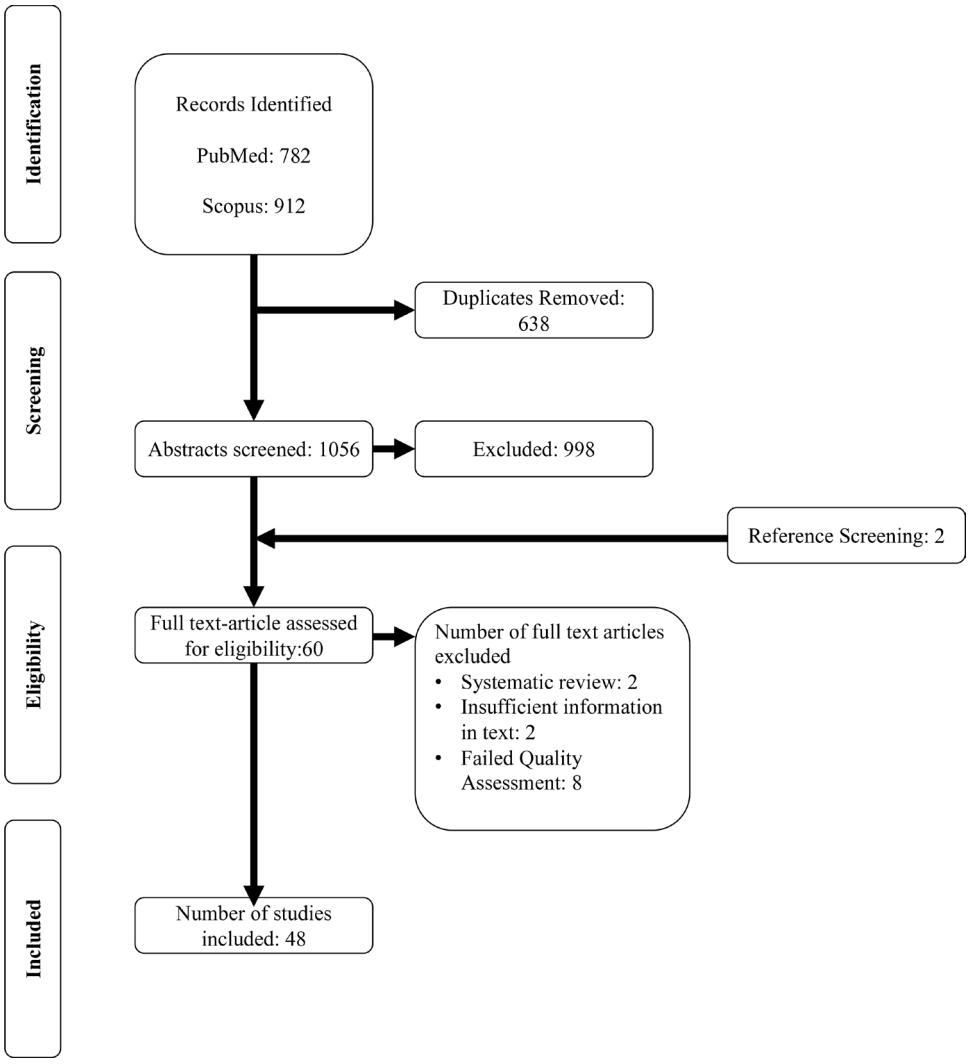

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram. The combined findings of the initial search conducted on 21 March 2023 and subsequent searches on 17 July and 19 October 2023 are shown. After screening, removal of duplicates and quality control, 48 studies were identified as eligible for inclusion.

reported. Generally, antenatal and delivery outcomes were rarely reported (online supplemental figure 3).

Maternal outcomes

Most women recovered fully or with minimal neurological deficit (*before* 8/10, 80%; *during* 31/43, 72%; *after* 5/8, 63%). However, the follow-up duration was modest, with only 12/40 (30%) of the *during* cases reporting maternal follow-up for more than a year. Across all the cases, there were four maternal deaths (4/61, 6.6%; figure 4A – top and online supplemental figure 4). These were predominantly secondary to sepsis, a relatively common cause of maternal death that accounted for 10% of maternal deaths in the UK between 2019 and 2021.[24]

Neonatal outcomes

Overall, while there was little evidence for poor neonatal outcomes (figure 4A—middle), reporting of specific neonatal outcomes was generally sparse (figure 4B). This was especially true for *after* cases where there was only one case of preterm birth reported, secondary to placental abruption (figure 4A—middle). In three of these cases, no specific statement on neonatal health was given, but we could infer the neonate was alive because the mother was breastfeeding, or the delivery was described as normal.

Overall, 7/53 neonates were identified as compromised (five *during* cases and two *before* cases; 13%). This neonatal compromise included low Apgar scores, respiratory insufficiency, neurological abnormality or a combination (online supplemental table 5). Of these seven, five were tested for NMDAR-IgG, of which four (80%) were positive. Five healthy neonates were tested, with only one positive result. In these instances of neonatal compromise with detectable neonatal seropositivity, there were additional maternal factors including medication and sepsis that confounded the role of the autoantibody. For example, we identified a single death reported of an already compromised neonate in which both mother and neonate were seropositive, and the neonate was also treated with intravenous immunoglobulin for possible NMDAR-Ab-E. The mother had previously recovered from

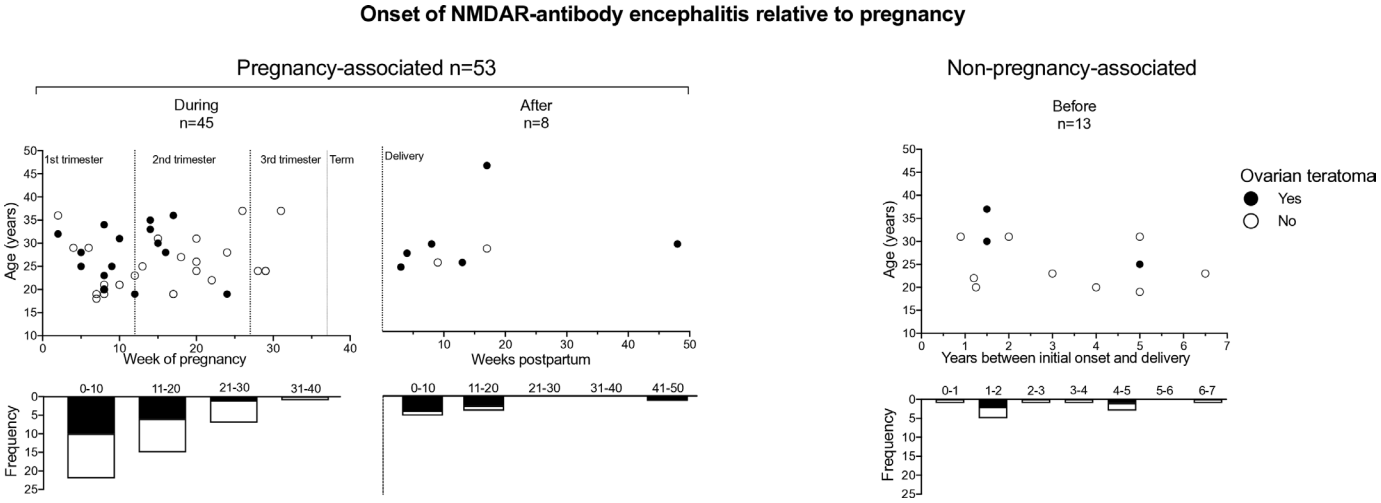

Figure 2 Onset of NMDAR-antibody encephalitis relative to maternal age and pregnancy. Cases of NMDAR-antibody encephalitis are plotted according to the stage of pregnancy and maternal age. They are split into pregnancy-associated (illness onset *during* or *after* pregnancy; left) and non-pregnancy associated (illness onset *before* pregnancy; right). For *during* cases, 41 of the 45 cases are represented since four cases did not give a specific onset time in gestational weeks but were all within the first trimester, and two were associated with a teratoma. One teratoma-associated *before* case is not shown since the time interval was not clearly stated. NMDAR, N-methyl-D-aspartate receptor.

NMDAR-Ab-E, although the interval to the pregnancy was relatively short, with the illness onset preceding delivery by 18 months.[13] While there were concerns regarding an encephalitis relapse, the patient was unaware of her pregnancy and presented with unmodified hypertension and deranged liver function consistent with pre-eclampsia, which could itself explain these clinical features and outcome.

Childhood outcomes

Of the 33 cases in which illness began during pregnancy ending with a live birth, childhood outcomes were provided in 22 (figure 4A—bottom). The level of detail was largely restricted to a general statement in most cases that the children were healthy and/or meeting developmental milestones (figure 4C). However, the duration of follow-up and therefore opportunity to identify more complex neuro-developmental outcomes was limited. For cases with an illness onset during pregnancy, 8/22 (36%) were followed up longer than a year, while this figure was 44% for those born to mothers who had recovered from NMDAR-Ab-E *before* pregnancy (four of nine cases providing childhood follow-up, figure 4D). There was no childhood data provided for cases with an illness onset after pregnancy.

Among the *during* cases, one child had global developmental delay, and in this case, the mother's illness was severe, and she died secondary to infection.[12] The baby's serum was positive for NMDAR-IgG at birth but negative by 1 year. This child was identified as compromised in the neonatal period, but the other three compromised neonates for whom data was available went on to develop normally. For the *before* cases, only one child had reported medical diagnoses, which were torticollis and strabismus.[25] This child was not identified as compromised at birth, and the one surviving compromised child was described as developmentally normal. Maternal, neonatal and child outcomes are summarised in online supplemental figure 4.

Given the number of potential childhood outcomes left unreported and the limited length of reported follow-up, we contacted authors to ascertain if further follow-up was available. Seven of 27 authors contacted responded, of which three were able to provide further follow-up. No new diagnoses were made to alter the existing reported literature.

Oxford autoimmune neurology experience

In addition to a group summary (table 1), where possible we obtained specific consent to report de-identified individual participant data according to our checklist (online supplemental table 6). We have not encountered any patients with a postpartum onset of the illness, but two cases with an onset *during* pregnancy: a relapse and first illness. Both neonates were born premature but live (one spontaneous delivery and one emergency caesarean section secondary to non-reassuring fetal heartbeat). Both were admitted to the special care baby unit and have developed along normal trajectories with a median follow-up of 1.5 years.

Beyond this, most of our experience is non-pregnancy-associated NMDAR-Ab-E, occurring and resolving *before* pregnancy (seven pregnancies from three mothers). All mothers had recovered without residual deficit, with six pregnancies resulting in live births and one in miscarriage. Four of the six neonates were born in good condition. For the other two, one had raised respiratory rate at birth and was treated for possible sepsis. Heel prick blood from this neonate was positive for NMDAR-IgG, but there were no features of NMDAR-Ab-E, and over 5 years of

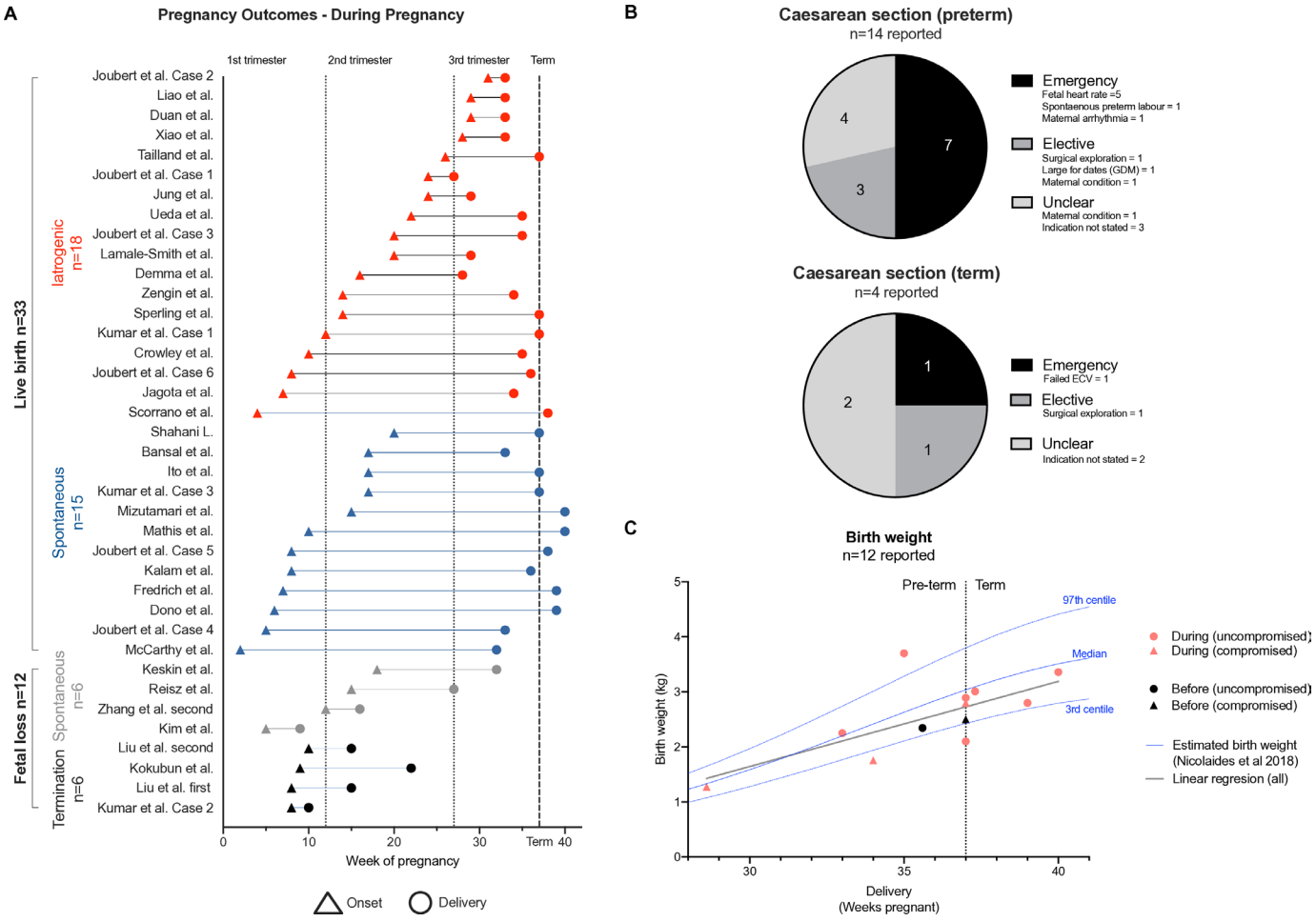

Figure 3 Pregnancy outcomes. (A) Cases of N-methyl-D-aspartate receptor-antibody encephalitis during pregnancy are shown according to illness onset in relation to gestational time and pregnancy outcome (gestational week at presentation, triangles; end of pregnancy, circle; termination, black; spontaneous fetal loss, grey; spontaneous live birth, blue; iatrogenic live birth, red). Vertical dotted lines represent the end of the first and second trimesters, and the dashed line at week 37 demarcates term. Four first trimester cases of fetal loss (two terminations and two miscarriages) are not shown as specific timings were unavailable. Three spontaneous live births are not shown since specific delivery time was not described. (B) In cases with an illness onset during pregnancy, pie charts summarise the proportion and absolute number of indications for caesarean section (preterm deliveries, top; term deliveries, bottom). (C)12 available birthweights are plotted by gestational week (onset *during* pregnancy pink, onset *before* pregnancy black; uncompromised, circle; compromised, triangle) with a line of best fit (grey) in the context of normative birth weight ranges (blue lines; as per Nicolaides et al Ultrasound Obstet Gynecol 2018; 52: 44–51).

follow-up, there have been no developmental concerns. The other was treated for sepsis and jaundice in the context of preterm premature rupture of membranes. Here, the development has been largely as expected, but an assessment for potential neurodiverse needs is awaited. All other children were achieving normal milestones at the most recent follow-up (median 3 years old, range 0.5–5).

DISCUSSION

Overall, we have found a relatively small and still developing literature. The evidence was of sufficient quality to synthesise, but compared with our idealised checklist, there was considerable missing data. While our conclusions are largely reassuring, the strength of the evidence is low and should be considered provisional. However, given the prevalence of case reports (45/48, 94%), a format that is intrinsically potentially biased towards atypicality and concern, their low frequency offers a degree of reassurance.

Maternal outcomes did not differ significantly from a systematic review of the disease overall, with 36/51 (71%) of pregnancy-associated cases either fully recovering or with minimal deficit vs 918/1284 (72%) with mRS 0–2. The rate of maternal deaths was also similar (4/51, 8%, vs 81/1284, 6%).[21] Episodes of NMDAR-Ab-E resolving *before* later pregnancies were generally less severe, plausibly reflecting an inherent selection bias.

With regard to miscarriage, three occurred during the first trimester and one in the second trimester, broadly in keeping with spontaneous fetal loss (15% in the first trimester and 1–2% in the second).[26 27] For pregnancies

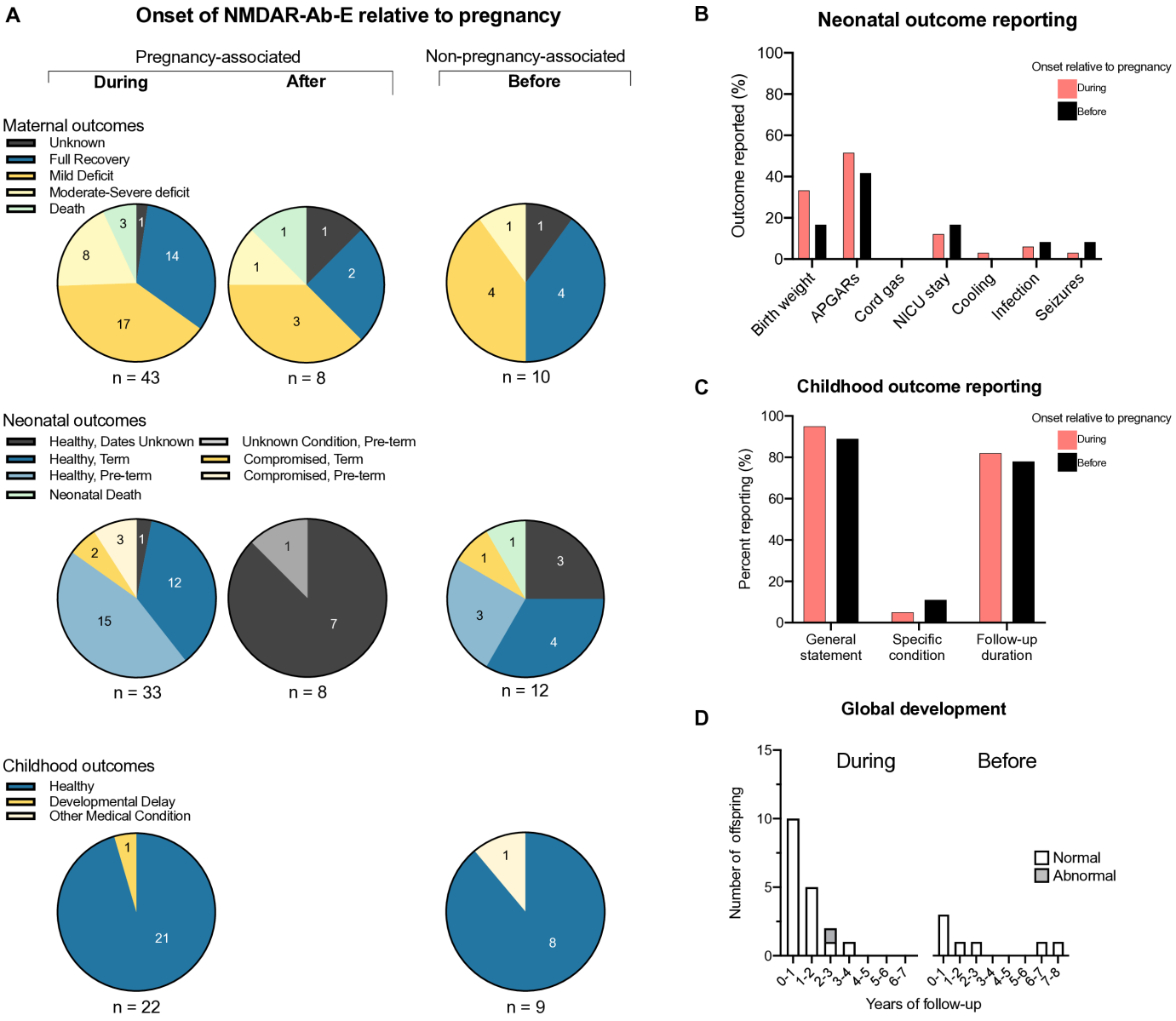

Figure 4 Maternal, neonatal and childhood outcomes. (A) Maternal, neonatal and childhood outcomes are shown divided by the onset of NMDAR-antibody encephalitis in relation to pregnancy. For maternal outcomes, cases where deficit was reported as 'minimal' or mRS of 1–2 are shown as mild deficit. Cases are defined as moderate to severe deficit for mRS 3–5 or clear functional disability described. For neonatal outcomes, infants are specified as compromised if this was specifically stated or as indicated by Apgar scores. (B) Positively reported neonatal outcomes are plotted as percentages for pregnancies with an onset of NMDAR-Ab-E occurring *during* (pink) or *before* (black). (C) Reported childhood outcomes are plotted as percentages for pregnancies with an onset of NMDAR-Ab-E occurring *during* (pink) or *before* (black). A general statement refers to a descriptor of adequate progress such as 'healthy', 'met all developmental milestones', 'developing normally'. Also plotted are statements of a specific condition and whether the duration of follow-up was stated. (D) Where available, specific duration of childhood follow-up of global development is plotted as a bar chart for pregnancies with an onset of NMDAR-Ab-E occurring *during* (left) or *before* (right). Offspring in whom an abnormality was reported are shaded grey. APGAR, Appearance, Pulse, Grimace, Activity and Respiration; mRS, modified Rankin score; NMDAR-Ab-E, N-methyl-D-aspartate receptor-antibody encephalitis; NICU, neonatal intensive care unit.

proceeding past 24 weeks, extended perinatal mortality (stillbirth and neonatal death) was higher than a recent UK rate (3/55, 5.45% vs 5.04/1000, 0.5%).[28] However, to help contextualise for the morbidity associated with NMDAR-Ab-E, extended perinatal mortality reported for pregnant women admitted to intensive care has been estimated to be up to 14%.[29] Importantly, the small sample size of this sub-group of a rare disease derived from a variety of global ante- and peri-natal healthcare settings, further influenced by reporting bias, considerably caveats these comparisons, making future robust epidemiological studies needed before firm conclusions can be drawn.

It is encouraging that the literature and our own experience find cases of pregnancy following resection of

Table 1 Group summary of single-centre experience of N-methyl-D-aspartate receptor-antibody encephalitis and pregnancy with maternal, neonatal and childhood outcomes

NMDAR-Ab-E onset relative to pregnancy	Number of patients (pregnancies), n* (trimester at NMDAR-Ab-E onset)	Miscarriage, n	Live births, N (preterm, term)	Birth timing years post illness onset, median (range)	SCBU admission, n	Years maternal and child follow-up since episode, median (range)	Child outcome within normal limits, n
Before	3 (7) (N/A)	1	6 (1,5)	3.5 (1.5–6)	1†	7 (2-12) 1.75 (0.5–5)	5
During	2 (2) (first and second)	0	2 (2,0)	N/A	2	1.5 (1-2) 1.5 (1-2)	2
After	0 (N/A)	N/A	N/A	N/A	N/A	N/A	N/A

*Number of patients is presented by the onset category such that one mother is reported in both before and during onsets relative to pregnancy (total series n=4).
†Phototherapy for neonatal jaundice in context of preterm premature rupture of membranes.
mRS, modified Rankin score; n, number; N/A, not applicable; NMDAR-Ab-E, N-methyl-D-aspartate receptor-antibody encephalitis; SCBU, special care baby unit.

ovarian teratoma to treat acute NMDAR-Ab-E. Despite published reports of ovary-preserving surgery,[30] given the risk of residual teratoma tissue driving ongoing disease or relapse, oophorectomy remains common. Therefore, consideration of preserving oocytes in young women who have yet to start a family is important. Our multidisciplinary approach includes a specialist gynaecologist with expertise in both teratoma resection and ovarian cryo-preservation to discuss options with patients and their next of kin.[31]

Despite the evidence from animal models, in the available published data we found little positive evidence of developmental disorders in children born to mothers in any of the three sub-groups. We found one reported case of developmental delay reported in 53 (2%) live births, broadly in keeping with the frequency among children under five in the general population (1–3%).[32] Moreover, while this infant's serum was positive for NMDAR-IgG, the infant was also born prematurely secondary to uteroplacental insufficiency, and the mother had severe illness and died of secondary infection.[12] Thus, the potential specific effects of transplacental transfer of NMDAR-IgG in this case are challenging to disentangle from other relevant factors. Similarly, in our case series of children born to mothers with either active or previous NMDAR-Ab-E, only one is being evaluated for neurodiverse needs, and there was no detectable maternal seropositivity during the pregnancy.

Conversely, the quality of the data we have identified makes it impossible to fully exclude an increased risk of neurodevelopmental conditions. First, specific neonatal health outcomes are often missing from reports (figure 4C). Second, the data on long-term outcomes are very limited, and human neurodevelopment manifests over decades. Moreover, outside of our re-contact data, the duration of follow-up has not been updated in the literature. Additionally, the type of cohort study design needed to truly determine the effects of autoantibody transfer to be adequately powered and control sufficiently for confounding variables would require multi-centre co-ordination. Pregnancies occurring after full disease remission may be amenable to this, but those complicated by NMDAR-Ab-E during or after are by definition heavily confounded by the effects of the disease on maternal and placental condition as well as by the multiple supportive medical, interventional and immunotherapeutic interventions needed to survive and recover from the illness.

Finally, testing of trans-placental autoantibody transfer remains rare (figure 5A,B). Compromised neonates were disproportionately likely to be tested, making up five of ten (50%) cases tested despite only seven of the 53 (13%) cases reporting a compromised infant. Four of the five comprised infants tested were positive for NMDAR-IgG, but two went on to meet their developmental milestones at 1 year of age, while one had global developmental delay, and the other died during the neonatal period (online supplemental table 5). Both the latter had relatively high titres at 1:320 and 1:450, respectively, substantially higher than the 1:20 titre of one of the infants who developed normally but comparable to the other where the titre was 1:400. Furthermore, one healthy infant tested positive for serum NMDAR-IgG.[33] Autoantibody testing was available for one neonate in our cohort, and while compromised at birth, they too have subsequently developed normally. Thus, the clinicopathologic sequelae of transplacental NMDAR-IgG in humans remain to be fully elucidated. Certainly, NMDARs are important in the developing fetal brain.[34] Evidence from mouse models indicates that transplacental transfer of patient-derived NMDAR-IgG can result in reduced survival rates in the postnatal period, with reduced brain volume and neurodevelopmental abnormalities in adulthood.[5] However, human and murine neurodevelopment differ with an established blood–brain barrier forming postnatally in mice and between 22 and 32 weeks of gestation in humans.[35]

Overall, the reliance on reports introduces a reporting bias and unsystematic reporting. The development of a global, confidential registry to systematically record disease presentation, treatments and disease course, in addition to obstetric, maternal, neonatal and childhood outcomes could improve evidence quality. This has precedent in obstetric practice with caesarean scar pregnancies and within neurology for multiple sclerosis.[36 37] Our idealised checklist could serve as a starting point,

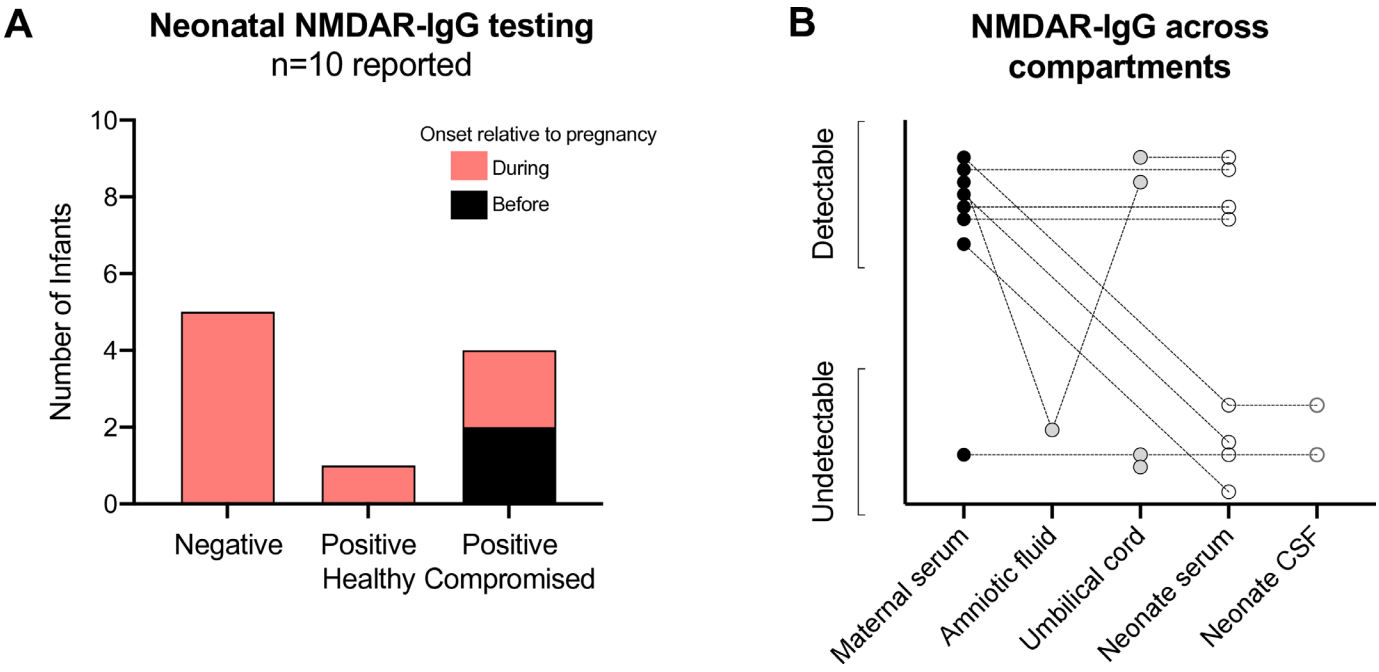

Figure 5 Neonatal NMDAR-autoantibody testing. (A) The absolute number of infants tested for NMDAR IgG autoantibodies is plotted according to the test result. Positive results are divided according to whether the infant was clinically healthy or compromised at the time of testing. The bars are sub-divided according to whether NMDAR-Ab-E occurred *during* (pink) or *before* (black) the associated pregnancy. (B) Results of NMDAR-IgG assays are plotted according to corresponding bio-fluid tested. Dotted lines note samples connected within a maternal–neonatal pair. CSF, cerebrospinal fluid; NMDAR-IgG, immunoglobulin G autoantibody against N-Methyl D-Aspartate receptor.

with further input from existing international clinical-research networks including multi-disciplinary expertise supported by patient advocacy organisations.

Author affiliations
[1]Medical Sciences Division, University of Oxford, Oxford, UK
[2]Faculty of Medicine, Imperial College London, London, UK
[3]Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[4]Department of Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[5]Oxford Centre of Neuroinflammation, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[6]Department of Obstetrics and Gynaecology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[7]Departments of Neurology and Neuroscience, Mayo Clinic, Jacksonville, Florida, USA
[8]Department of Psychiatry, University of Oxford, Oxford, UK

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Contributors Conceptualisation: SLH, DS, HF and AAD. Data collection and curation: SLH, SNMB, PC-W and AAD. Formal analysis: SLH, AH and AAD. Writing—original draft: SLH and AAD. Writing—review and editing: All. AAD is responsible for the overall content as the senior author and guarantor.

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Competing interests SRI is a co-applicant and received royalties on patent application WO/2010/046716 (Neurological Autoimmune Disorders) and has filed two other patents regarding autoantibody diagnostic algorithms. MIL serves on scientific or educational advisory boards for UCB Pharma, argenx and Viela/Horizon. She has received speaker honoraria or travel grants from Biogen Idec, Novartis, argenx, UCB and the Guthy-Jackson Charitable Foundation. None of these are felt to be of direct relevance to the current manuscript. The remaining authors declare no commercial conflicts of interest.

Patient and public involvement statement The study was discussed with patients who gave consent to participate in the reporting of our local case series. They read and commented on the proposed manuscript, helping to both guide our presentation and affirm the relevance of the study to patients and the public.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Immune Factors in Neurological Disease research study (NHS REC 16/YH/0013). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Scarlett L Harris http://orcid.org/0000-0001-5717-4093
Sophie N M Binks http://orcid.org/0000-0003-0991-5998
Sarosh R Irani http://orcid.org/0000-0002-7667-9748
Adam E Handel http://orcid.org/0000-0001-8385-6346
Adam Al-Diwani http://orcid.org/0000-0001-6596-7579

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