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Neurodevelopmental outcomes in individuals with fetal alcohol spectrum disorder (FASD) with and without exposure to neglect: Clinical cohort data from a national FASD diagnostic clinic

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ABSTRACT

Disentangling the relative developmental impact of prenatal alcohol exposure from postnatal neglect is clinically valuable for informing future service provision. In this study, developmental outcomes across groups are compared in a 'natural experiment'.

Methods: Clinical data from 99 persons with fetal alcohol spectrum disorder (FASD) diagnoses were audited. Developmental outcomes (diagnosis of attention deficit hyperactivity disorder, ADHD; social and communication disorder, SCD; or Autistic Spectrum Disorder, ASD; Short Sensory Profile, SSP; Vineland II Adaptive Behaviour Scales) were compared across two exposure groups: prenatal alcohol only; and mixed prenatal alcohol and neglect.

Results: ADHD (74%) and ASD/SCD (68%) were common, with no significant difference between groups (ADHD, $p = 0.924$; ASD, $p = 0.742$). Vineland age equivalence scores were lower than chronological age (11.1 years − prenatal alcohol only, and 12.7 years − neglect) across all domains, especially receptive language (3.7 years for both groups). Age equivalence did not differ between groups, with the exception of domestic daily living (neglect: 7.7 years vs. prenatal alcohol only: 5.8 years, $p = 0.027$). A probable/definite difference on SSP was more common in the prenatal alcohol only (96% vs. 67%, $p = 0.006$). For the individual subscales of SSP, there were no significant differences by neglect category.

Discussion: Postnatal neglect in this group did not make the developmental outcome any worse, suggesting that prenatal alcohol influences these outcomes independently. Professionals who support families looking after a child with both FASD and a history of neglect should be aware that the behavioral difficulties are likely to be related to prenatal alcohol exposure and not necessarily reflective of parenting quality.

Introduction

Making a diagnosis of fetal alcohol spectrum disorder (FASD), which incorporates the range of diagnostic profiles from full Fetal Alcohol Syndrome (FAS) to Alcohol Related Neurodevelopmental Disorder (ARND), remains a challenge for many (Mukherjee, Wray, Curfs, & Hollins, 2015). It is often a complex diagnosis that requires not only the features of the disorder to be established but also overlapping factors to be ruled out (British Medical Association, 2016; Douzgou et al., 2012). This diagnosis by exclusion was made explicit in proposed new DSM-V guidance. Neurodevelopmental disorder associated with prenatal alcohol exposure (NDPAE; American Psychiatric Association, 2013) is a profile encompassing much, but not all, of the wider FASD presentation (Johnson, Moyer, Klug, & Burd, 2017; Kable & Mukherjee, 2016). A subpart of the cohort studied here has previously been mapped against the different diagnostic methods used internationally, including NDPAE (British Medical Association, 2016; Kable & Mukherjee, 2016). In order for a diagnosis of NDPAE to be made, other factors that better explain the presentation need to be ruled out. One such potential other cause is neglect (American Psychiatric Association, 2013). Yet, to date, there has been inconsistent recognition for the role of neglect. For instance, a report of the effects of drugs and alcohol use in pregnancy produced by the American

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Academy of Pediatrics (2013) underscored that, of all the illicit, non-illicit, and non-prescribed compounds, alcohol had the most significant impact on the development of the fetus (Behnke & Smith, 2013). However, this report did not address neglect and its effects. In contrast, neglect was specifically mentioned in DSM-V as a contributing factor to consider for the proposed criteria of NDPAE. Therefore, it is important to understand the impact of neglect on the clinical presentation, especially since neglect commonly occurs alongside prenatal alcohol exposure.

The effects of neglect on neurodevelopment have been demonstrated in various settings. For example, early animal studies in rhesus monkeys demonstrated that increasing exposure to neglect led to differing behaviors, including autistic-like patterns (Harlow, Harlow, & Suomi, 1971). Studies of institutionalized children have also shown neurodevelopmental effects (Sonuga-Barke et al., 2017; Tizard & Hodges, 1977). As was the case in the animal studies, these studies on children demonstrate that increased length and severity of neglect have greater impacts on outcome. For example, where the staff to child ratio was very low (i.e., the more severe neglect as seen in the Romanian adoptees' study), those children adopted after 6 months had poorer neurodevelopmental outcomes than those adopted earlier (Sonuga-Barke et al., 2017). This is in contrast to research in situations with more favorable staff to child ratios: such negative outcomes were not seen and there were no significant deficits in cognitive function identified (Tizard & Hodges, 1977).

A review by De Bellis (2005) highlighted that abuse and neglect were the most common reasons for children to be taken into care in the United States in 2002. The authors report that some 60% of these children had experienced neglect. Yet many of the research papers published regarding neglect had failed to consider the impact of prenatal alcohol and drugs as a confounding factor (De Bellis, 2005).

To date, research into substance use in pregnancy, when combined with studies also looking at neglect, has focused more on illicit drugs and nicotine rather than alcohol exposure. One such study of children born to opiate-using mothers showed that children had worse developmental outcomes when left with biological parents with limited stimuli, compared to being adopted (Onroy, Segal, Bar-Hamburger, & Greenbaum, 2001). This study, however, failed to take account of any prenatal alcohol exposure and only accounted for prematurity and gestational diabetes. Later research has gone on to show that exposure to opiates alone has no clear impact on the child's cognition, while alcohol can have a strong effect (Behnke & Smith, 2013). Similar issues have been shown for nicotine, where initial research suggested links to attention deficit hyperactivity disorder (ADHD) and cognitive difficulties (Gillies & Wakefield, 1993; Jauniaux & Greenough, 2007), yet later research has demonstrated that many of these effects can be accounted for by inherited factors (Thapar et al., 2009). These studies of other substances demonstrate that alcohol is frequently overlooked as a cause for developmental and behavioral issues.

A recent systematic review (Price, Cook, Norgate, & Mukherjee, 2017) found that only five studies have currently been published on the dual impact of prenatal alcohol exposure and childhood maltreatment (abuse and/or neglect). Three of these compared dual exposure with PAE only, and two compared dual exposure with maltreatment only. Children with both PAE and maltreatment were more likely to have deficits in speech and language, memory, attention, intelligence, and behavioral difficulties, or were more likely to have more severe deficits in these areas. The conclusion of the review was that a dual exposure of PAE and maltreatment appears to carry a higher risk of neurodevelopmental deficits than either exposure alone, but more high quality research is required.

Despite the complexity of the ethics of studying this subject in humans, it remains necessary to demonstrate biological plausibility for the reported harmful effects of alcohol and neglect. Prenatal alcohol has been studied with multiple mechanisms identified through animal models (Hannigan, 1996) and also human studies (Kodituwakku, 2009; Riley et al., 2003), correlating with damage to neurological functioning. This increases the plausibility of alcohol consumption in pregnancy having direct long-term effects on the developmental outcomes for the child. However, research determining the relationship between prenatal alcohol exposure and neglect in a research sample remains challenging.

Methods to elucidate biological plausibility have been suggested. One such approach is the use of natural experiments where samples occur by chance (Gray, Mukherjee, & Rutter, 2009). While such studies have inherent biases, they pose fewer ethical challenges for the study of FASD and its risk factors. This paper presents the findings of one such cohort from a national clinic-based sample that was carried out as part of a wider service evaluation project. All patients diagnosed with FASD in the clinic were included in an analysis that compared those who had experienced significant neglect to those who had experienced only very minimal to no neglect.

Methods

The clinic

The National FASD clinic was established in 2007, and was expanded in 2009. Taking referrals from all four nations of the UK, the clinic has seen over 150 of the most complex cases since 2007. The types of patient presenting often have more comorbid difficulties than in the general population of persons with FASD, but in every case, the same approach to diagnosis and wider evaluation is taken. This ensures that there is comparability across cases. Service users or their parental guardians provided informed consent to use anonymized data for the purpose of annual audits of the service. These annual service audits have been registered under the clinical governance procedures. We evaluated data from 106 patients who had been assessed in the first seven years as part of the 2014 audit. Since these data were collected as part as of a clinical process, over the years the information collected has been refined. Through the process of annual service reviews, different measures have been added to offer wider clinical information in later years. For this reason, not all patients have the same amount of information compiled, and sample sizes varied depending on which measure was being evaluated.

Process and source of referrals

Referrals to the FASD clinic were received via a healthcare professional. The diagnostic process has been described in detail elsewhere (Gray & Mukherjee, 2007; Mukherjee, Carlisle, & Livesey, 2017). In summary, however, each case had over 12 h of direct testing (over two days) and a similar amount of time for report analysis and compilation. The process assessed physical, cognitive, communicatory, sensory, behavioral, educational, functional, and neurodevelopmental domains. All cases had a microarray analysis (a genetic test to assess the genetic profile of the individual and detect common abnormalities) prior to acceptance in order to rule out other known common genetic causes of developmental delay (Douzgou et al., 2012). The first day focused on direct observation and assessment of the individual. The second involved the collating of informant-based information using a standardized developmental interview, originally designed to assesses autism (DISCO; Wing & Gould, 2003), but used primarily in this context as a developmental history. The two days were separated by a short period of between 4 and 6 weeks to allow the

collating of other informant-based information using structured standardized questionnaires. Overall, this allowed basic cognition, executive function, communication, sensory processing (using the Short Sensory Profile; Dunn, 1999), function, behavior including psychiatric presentations, and comorbid outcomes such as ADHD and Autistic Spectrum Disorder (ASD) to be assessed. When taken alongside other collated reports from education, prior testing, and wider assessments, a comprehensive understanding was achieved for each individual. The 2005 Canadian guidance was applied to the profile of each individual to achieve FASD diagnostic criteria (Chudley et al., 2005). Initial findings from a smaller case series highlight the ASD and ADHD diagnostic process in more detail, and initial findings are described elsewhere (Mukherjee, 2016; Mukherjee, Layton, Yacoub, & Turk, 2011).

Most referrals were from those who had been adopted or fostered; however, a proportion of guardians were birth parents who were not aware of the risks of alcohol exposure in pregnancy. The neglect history was obtained from a mixture of self-report, adoption paperwork, and wider medical and social work records provided as part of the assessment. Due to this being a clinical sample, it was not always possible to obtain wider information. Consequently, it was not possible to construct a refined and detailed categorization of neglect. However, using more than one source of information made allocation of the neglect classification more reliable than using one source of information alone. In these cases, neglect or the potential for neglect, i.e., where the birth family had prior children removed for neglect, was the primary reason for the child to be taken into care. The point at which individuals were taken into care varied within those attending the clinic.

From these referrals, three groups of patients were identified. First, those taken into care immediately from birth or not neglected by the birth parents (FASD-B) who experienced limited duration of exposure to neglect (Neg); second, those who remained in neglectful environments (FASD-Neg) taken into care within the first 6 months of life (FASD-Neg < 6); finally, those who continued to remain in a neglectful situation for a longer period (FASD-Neg > 6). Of the 106 individuals seen by the service, seven did not have a confirmed FASD diagnosis, and a further two had uncertain history in terms of neglect, leaving 97 cases with an FASD diagnosis and a neglect classification. The FASD-B group was compared with the two FASD-Neg groups in terms of the proportion of those with ASD and ADHD (a single category of ASD included three individuals with Social Communication Disorder [SCD]). Data were 100% complete for the ADHD diagnosis (all 97 cases), but diagnoses were not always available for ASD, so fewer cases were available for analysis (n = 91).

There were substantial missing data on performance on psychometrics of the Short Sensory Profile (SSP) (n = 48) and the Vineland II Adaptive Behaviour Scales (n = 82). This was partly due to changing in clinical practice over the period of the audit; for example, SSP was only routinely carried out since November 2010. It was therefore not possible to split the cohort into three categories for analysis. In the light of the Romanian orphanage study (Sonuga-Barke et al., 2017), which concluded that developmental outcomes in children taken into care within 6 months did not differ from controls, our FASD-B and FASD-Neg <6 groups were combined into a 'no significant neglect' group. The SSP is a norm-referenced, standardized questionnaire designed to assess the sensory processing patterns of children. It is a tool frequently used in screening of sensory issues in both clinical and research practice. The outcomes are automatically coded, based on scores received, against the normed population to one of the three outcomes: Typical, Probable Difference, and Definite Difference. SSP subscale scores were coded into one of two nominal outcomes – either 'Typical' or 'Probable/Definite Difference'.

The degree of association between neglect groups and i) ADHD; ii) ASD/SCD, and iii) SSP categories were assessed using chi-square analysis. Age equivalent Vineland II scores were compared with ANOVA. Analysis was carried out using SPSS version 23.

Results

The age of the patients ranged from 6 years to 26 years, with the majority (78%) being aged 14 years or younger. Only eight individuals were aged 20 years or over. The sample was 60% male. FASD diagnoses recorded were FAS (n = 13), partial FAS (n = 17), and ARND (n = 67). Over half (54%) had experienced prolonged neglect (FASD-Neg > 6). A third (32%) had no history of neglect (FASD-B), and a further 13% had experienced neglect in early infancy only (FASD-Neg < 6).

Table 1 highlights that the majority (74%) of those with FASD also had an ADHD diagnosis, and 68% had an ASD or SCD diagnosis. There was no significant association between neglect category and ADHD (chi square = 0.158, p = 0.924) or ASD/SCD (chi square = 0.597, p = 0.742).

Table 2 shows that the adaptive behavior age equivalent scores in the cohort were substantially lower than chronological age (chronological age: 11.1 years for the no significant neglect group and 12.7 years for the FASD-Neg > 6 group). Receptive language scores showed the lowest age equivalence, with an average of 3.7 years (for both neglect groups). Age equivalence was the highest for written language (7.9 years for the no significant neglect group and 8.5 years for the FASD-Neg > 6 group). There was no difference between groups in terms of adaptive behavior, with the exception of domestic daily living skills, where the FASD-Neg >6 group had an

Table 1
Neurodevelopmental outcomes by neglect category.

	No neglect FASD-B[a]	Some neglect FASD-Neg < 6[b]	Prolonged neglect FASD-Neg > 6[c]	Total	Chi	*p*
Neurodevelopmental outcome						
Autistic Spectrum Disorder (ASD) or Social Communication Disorder (SCD)						
No ASD/SCD (n, %)	10 (34.5%)	5 (35.5%)	14 (26.6%)	29 (31.9%)		
ASD/SCD (n, %)	19 (65.5%)	8 (61.5%)	35 (71.4%)	62 (68.1%)	0.597	0.742
Total (n)	29	13	49	91		
Attention Deficit Hyperactivity Disorder (ADHD)						
No ADHD (n, %)	9 (28.1%)	3 (23.1%)	13 (25.0%)	25 (25.8%)		
ADHD (n, %)	23 (71.9%)	10 (76.9%)	39 (75.0%)	72 (74.2%)	0.158	0.924
Total (n)	32	13	52	97		

No significant neglect: individuals with no history of postnatal neglect and those removed from situations of neglect before the age of 6 months.
[a] FASD-B Taken into care straight from hospital or with parents who demonstrated good parenting.
[b] FASD-Neg <6 Some Neglect (up to 6 months).
[c] FASD-Neg >6 Prolonged Neglect individuals neglected for more than 6 months in childhood.

Table 2
Comparison of Vineland mean age equivalence between two neglect groups.

	No significant neglect	Prolonged neglect (FASD-Neg > 6)	F[a]	*p*
Sample size	**N = 38**	**N = 44**		
Chronological age	**11.1 (9.75–12.4)**	**12.7 (11.3–14.2)**	2.271	0.104
Receptive language	3.7 (2.98–4.33)	3.7 (2.86–4.48)	0.001	0.973
Expressive language	5.5 (4.87–6.23)	6.2 (5.21–7.17)	1.105	0.296
Written language	7.9 (7.10–8.76)	8.5 (7.78–9.29)	1.197	0.277
Personal daily living skills	5.8 (4.90–6.60)	7.0 (5.65–8.29)	2.294	0.134
Domestic daily living skills	5.8 (4.88–6.77)	7.7 (6.38–9.06)	5.109	0.027
Community daily living skills	7.1 (6.16–8.00)	8.2 (7.10–9.33)	2.412	0.124
Interpersonal relationship socialisation	4.5 (3.57–5.44)	4.8 (3.87–5.70)	0.179	0.673
Play and leisure time socialisation	5.0 (4.05–5.97)	4.9 (4.06–5.75)	0.028	0.867
Coping skills socialisation	4.8 (3.84–5.80)	4.9 (4.25–5.63)	0.046	0.830

No significant neglect: individuals with no history of postnatal neglect and those removed from situations of neglect before the age of 6 months.
Prolonged neglect (FASD-Neg > 6): individuals neglected for more than 6 months in childhood.
[a] Analysis of Variance.

age equivalence of 7.7 years compared to the no significant neglect group, where the age equivalence was 5.8 years (see Table 1).

Fig. 1 shows that overall, 83% of the cohort showed probable/definite difference on the total SSP profile. This was significantly higher in the no significant neglect group, with 96% having a probable/definite difference, compared with 67% of the FASD-Neg >6 group (chi-square = 7.47, $p = 0.006$). For the individual subscales of SSP, there were no significant differences by neglect category, although the no significant neglect group tended to be more likely to have a probable/definite difference in all subscales.

Analyses were repeated excluding those aged over 15 years (no significant neglect mean age = 9.8 years; FASD-Neg >6 = 10.7 years). Patterns remained the same across analyses, although both previously significant comparisons became non-significant due to small sample size.

Discussion

Our findings would suggest, when taken on their own, that prenatal exposure to alcohol has an impact on these specific neurodevelopmental presentations, independent of neglect. In addition, the neglect does not appear, in our sample, to have any further impact on the neurodevelopmental outcomes. On their own, these data do not tell the whole story, as we did not study a group with neglect but without any prenatal alcohol exposure. However, we can infer that prenatal alcohol exposure likely has an independent effect on neurological outcomes, and therefore subsequent neurodevelopmental outcomes, regardless of whether the individual is subsequently exposed to neglect.

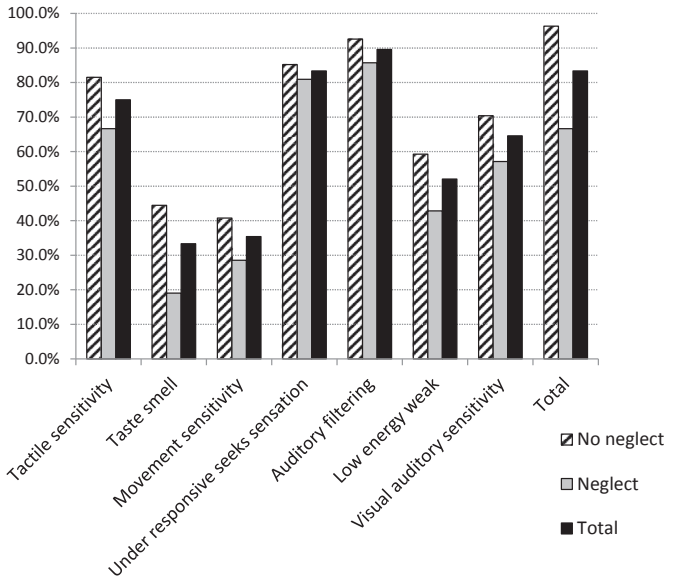

Fig. 1. Percent with probable/definite difference on Short Sensory Profiles, stratified by neglect (FASD-Neg > 6, n = 27) and no significant neglect (n = 21). No significant neglect: individuals with FASD but no history of postnatal neglect and those removed from situations of neglect before the age of 6 months. FASD-Neg >6: individuals neglected for more than 6 months in childhood.

No study has looked at neurodevelopmental conditions using the same methods that we report here. However, the systematic review of PAE and maltreatment (Price et al., 2017) did identify five studies that assessed the impact of dual exposure on a range of cognitive and behavioral outcomes. The review concluded that dual exposure appeared to carry a higher risk of neurodevelopmental deficit, but further studies were needed in order to develop this conclusion. In light of the findings of the present study, a pattern may now be emerging. Two of the studies in the review compared children with both exposures to children with maltreatment alone. These studies found that children with dual exposure had lower scores on intelligence, attention, memory, and language, and were rated as more problematic in terms of hyperactivity, impulsivity, restlessness, oppositional behavior, and social problems compared to children with maltreatment only. The same two studies found no differences in visual processing, motor control, or social communication. The other three studies in the review found that attachment and behavioral problems were more likely in children with dual exposure compared to those with PAE alone. The same studies found no differences in language, social communication, or developmental level. The present study found that children with both neglect and PAE were no worse off in terms of language, socialization, or daily living skills, and were no more likely to meet diagnostic criteria for ASD or ADHD, compared to children with PAE alone. With the addition of these results to those of the systematic review, it appears that prenatal alcohol exposure may be responsible for more harm than postnatal maltreatment or neglect in samples where both exposures are present.

The finding that prenatal alcohol exposure alone can account for the neurodevelopmental outcomes in children with FASD has wider potential implications, for example, on attachment behaviors and parenting. Our own previous studies involving caregivers have identified that parental stress is high in adoptive parents of children with FASD (Mukherjee, Wray, Commers, Hollins, & Curfs, 2013). Using the parental stress index, it was highlighted that childhood factors were a significant component in the dynamic of stress. It was also found that parents are often blamed for the difficulties faced by their children. Health care professionals should be aware that children may be developmentally challenged due to a prenatal

insult, and that the neurological deficits caused by alcohol exposure may be the single biggest impact on the presentation.

It has also been shown that attachment behaviors may be influenced by the underlying neurological deficit caused by alcohol exposure. Children with FASD may be more likely to have a disorganized attachment pattern compared to those without FASD (O'Connor, Sigman, & Brill, 1987). The clinical assessment process used in this study was not specifically designed to assess attachment behaviors in a quantified manner, highlighting the need for further work in this area.

Taken together, this work has implications for clinical practice in terms of recognition, prevention, and long-term management of behavioral difficulties in people with FASD. The findings will aid understanding of why these difficulties occur and therefore how to support those individuals affected. In particular, when investigating NDPAE as a possible diagnosis, we urge caution in using the presence of neglect as an explanation for developmental difficulties, since it seems likely that the coexistence of the two exposures (prenatal alcohol exposure and neglect) has meant that damage due to alcohol may be being wrongly attributed to neglect.

This study had several limitations. Firstly, as a specialist clinic-based sample it is not necessarily representative of the wider population with FASD, as it tends to be a group of individuals who have a larger number of comorbid conditions and therefore present with a greater range of complexities compared to more 'straightforward' presentations of FASD. For example, compared with other studies of FASD and ASD, we find a far higher prevalence of ASD and ADHD in our sample (Mukherjee, 2016; Mukherjee et al., 2011). Comorbid diagnoses may add to the complexity of the presentation of FASD, and may lead these individuals to be over-represented in our cohort. Generalizing the results thus requires some caution. The results do highlight a trend that warrants further exploration to identify whether the important findings seen here are seen in a wider, non-clinical population.

Further, the measures that were collected were chosen primarily for clinical reasons; therefore, it is entirely possible that some information bias may be present. While there was no clear evidence of differences in these areas between neglect groups, it cannot be excluded completely. The sample size was relatively small, especially for the SSP analysis. The statistically significant findings were in fact counter-intuitive, with the FASD-Neg >six group having fewer deficits as measured by the SSP and a higher age equivalence on one subscale of the Vineland scale. Findings were no longer significant when older individuals (>15 years) were excluded from the analysis. This may suggest that the sample size was too small to form robust conclusions. Alternatively, phenotypic expression could change with age, thus confounding our results, or factors related to the measure may have influenced the findings, as the SSP was designed primarily for children (even though the measure is often used in adults). The impact of these potential explanations is unclear from these data alone.

The study does identify the prenatal effects of alcohol on the development of the child, and adds to the understanding that the neurodevelopmental presentation is vital for appropriate understanding and management of affected children and adults. When considering that some of the highest rates of FASD are found in children in care (Lange et al., 2017), and these children are likely to have been exposed to neglect, these findings have particular significance. Further studies are required to understand how a parent influences the behavior of these children. Future research into areas of neglect should take prenatal alcohol exposure into account as a potential confounding covariate in order to exclude its effect. In clinical practice, understanding that neurological damage caused may be prenatal, and therefore not necessarily related to parenting quality, is important if families are to be supported appropriately by multi-professional groups.

Ethical approval

This is registered as a service evaluation with RM NHS Trust. It is an evaluation of clinical cases with patient/parental consent, and therefore research ethics approval was not sought.

Funding

There was no funding for this study.

Contributions

RM runs the clinic where data were collected. PC supported data analysis with RM. SN and AP contributed to article development and corrections alongside RM and PC.

Conflicts of interest

RM has received honoraria for talks related to FASD and is an unpaid medical advisor to various UK FASD charities. PC, AP, and SN: no declaration of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.alcohol.2018.06.002.

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