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ATTENTION-DEFICIT DISORDER (A ROSTAIN, SECTION EDITOR)

Prenatal Risk Factors and the Etiology of ADHD—Review of Existing Evidence

Emma Sciberras[1,2,3] · **Melissa Mulraney**[2] · **Desiree Silva**[4] · **David Coghill**[2,3,5]

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Abstract While it is well accepted that attention-deficit/hyperactivity disorder (ADHD) is a highly heritable disorder, not all of the risk is genetic. It is estimated that between 10 and 40% of the variance associated with ADHD is likely to be accounted for by environmental factors. There is considerable interest in the role that the prenatal environment might play in the development of ADHD with previous reviews concluding that despite demonstration of associations between prenatal risk factors (e.g. prematurity, maternal smoking during pregnancy) and ADHD, there remains insufficient evidence to support a definite causal relationship. This article provides an update of research investigating the relationship between prenatal risk factors and ADHD published over the past 3 years. Recently, several epidemiological and data linkage studies have made substantial contributions to our understanding of this relationship. In particular, these studies have started to account for some of the genetic and familial confounds that, when taken into account, throw several established findings into doubt. None of the proposed prenatal risk factors can be confirmed as causal for ADHD, and the stronger the study design, the less likely it is to support an association. We need a new benchmark for studies investigating the etiology of ADHD whereby there is an expectation not only that data will be collected prospectively but also that the design allows the broad range of genetic and familial factors to be accounted for.

Keywords ADHD · Etiology · Prenatal · Environmental · Pregnancy

This article is part of the Topical Collection on *Attention-Deficit Disorder*

✉ David Coghill
david.coghill@unimelb.edu.au

[1] Deakin University, Melbourne, VIC, Australia

[2] Murdoch Childrens Research Institute, Parkville, VIC, Australia

[3] The Royal Children's Hospital, Level 2 East, 50 Flemington Road, Parkville 3052, Victoria, Australia

[4] School of Paediatrics and Child Health, University of Western, Perth, Australia

[5] Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia

Introduction

Although attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent and widely researched developmental conditions affecting young children and adolescents, we still have much to learn about the underlying etiology of the disorder. While it is well accepted that the disorder is highly heritable (>70%) [1], the search for the genes underlying the phenotypic expression of ADHD has been slow. Early research in this area focused on candidate gene approaches which have yielded evidence of a small number of potential genes each having a small effect in predicting ADHD [2, 3] (e.g. DRD4, DRD5, DAT1, HTR1B, SLC6A4, SNAP25). Genome-wide association studies have started to appear, and while to date, no significant genome-wide hits have been published; this is probably due to limitations of sample size, and it is anticipated that these will soon be announced. Clearly, not all of the risk for ADHD is genetic, and it should be noted that in addition to the pure environmental risk, estimates of heritability also include an element of gene environment interaction. It is estimated that between 10 to 40% of the variance associated with ADHD is accounted for environmental factors [4].

ADHD appears early in life, and there is significant interest in the potential role that the prenatal environment might play in the development of the disorder. Studies have identified

numerous prenatal risk factors, which appear to be associated with ADHD including maternal substance use and stress during pregnancy, prematurity, low birth weight and a number of other pregnancy, labour, delivery or infancy complications. Previous reviews have concluded that, despite the demonstration of association, there is as yet insufficient evidence to support the notion of a truly causal relationship between those prenatal risk factors identified to date and the later outcome of ADHD [3, 5].

It is particularly difficult to disentangle prenatal risk from postnatal risk factors such as social adversity, as well as parental mental health and maternally transmitted inherited factors. A recent study of children born through in vitro fertilization, contrasted the prenatal environment provided by a related versus unrelated mother enabling comparisons of between those who did and those who did not smoke during pregnancy on birth weight and antisocial behaviour outcomes, while controlling for genetic risk [6]. Antisocial behaviour was higher in related but not unrelated offspring of prenatal smokers and non-smokers. Similarly, Obel and colleagues [7] used a sibling-matched design to control for genetic confounding when comparing the frequency of ADHD between children of smoking and non-smoking mothers. In the genetically sensitive analysis, the relationship between prenatal smoking and ADHD was attenuated. These studies highlight that genetic risk may be the more likely explanatory factor underpinning the relationship between some prenatal risk factors and later ADHD.

Several recent large-scale population-based studies have advanced our understanding of the prenatal risk factors of ADHD [e.g. 8•, 9•, 10, 11]. These population-based study designs have the advantage of having sufficient statistical power to allow adjustment of and for multiple potentially confounding variables and the detection of small effects. A widespread limitation in the literature is the reliance on retrospective recall of events during pregnancy. Population data linkage studies can access prospectively collected patient medical records thus minimising recall bias and reducing socially desirable responding.

This article aims to provide a recent update of the research examining the relationship between ADHD and prenatal factors from 2013 to 2015. We start each section with a summary of what was known about the relationship between prenatal risk factors and ADHD (where applicable) using updated findings from a systematic review, which was originally submitted to the England and Wales Department of Health in 2011 [5]. This review was updated but not published in 2013.

Prematurity

Summary from Previous Review Sufficient evidence of a temporally ordered association, with a risk ratio (RR) of 2.64 (range 1.7 to 3.3) [5].

Recent Findings Three population-based data linkage studies have examined the risk of ADHD related to a range of pregnancy/labour factors. Halmøy et al. [10] conducted one such study using data from Norwegian national registries. The sample comprised all adults born between 1967 and 1987 who survived until 18 years of age (n = ~1.17 million) including 2323 cases of adult ADHD who were approved for stimulant treatment between 1997 and 2005. Similarly, Silva et al. [9•] conducted a population-based record linkage case–control study of children prescribed stimulant medication for ADHD in Western Australia (N = 12,991) compared to 30,071 children not taking stimulant medication. Lastly, Henriksen et al. [8•] conducted a nationwide cohort study of all live singleton births in Denmark between 2000 and 2008 after spontaneous onset of labour (N = 546,146), of which 4617 had a diagnosis of ADHD. All three of these studies found an association between prematurity and risk of ADHD whereby the risk increases as gestational age decreases. For example, in children born late pre-term (33- to <37-week gestation), risk estimates range from hazard ratio (HR) = 0.96 to RR = 1.3, while in children born extremely pre-term (<29 weeks), risk estimates range from odds ratio (OR) = 1.2 to RR = 5.0 [8•, 9•, 10]. These relationships held in adjusted models (controlling for maternal age, maternal education, and marital status, year of child birth, gender, and all pregnancy/labour/newborn factors of interest), indicating that prematurity may independently increase risk.

A study in the USA failed to replicate this association between gestational age and risk of ADHD [12]. This study only compared children born late pre-term (34- to <37-week gestation) with those born at term, providing further support for a possible inverse linear association between gestational age and risk of ADHD. Similarly, a case–control study from the USA reported that children with ADHD (N = 2243) were no more likely than controls (N = 5631) to have been born prematurely [13]. It seems biologically plausible that prematurity would be associated with ADHD, as there is less time for neural development, but it is likely that the association operates through a number of mechanisms such as increased incidence of obstetric complications that may lead to neural insult [14] or to genetic factors which may confer risk for both ADHD and premature birth. There is little evidence to suggest that post-term birth is associated with ADHD.

Low Birth Weight

Summary from Previous Review Some suggestive evidence of an association with adjusted OR/RR 1.5 to 9.6 across 19 studies (n = 129,858) but inconsistency across studies [5]. Many studies did not report the proportion of low birth weight children that were also premature.

Recent Findings Consistent with the findings regarding prematurity, Clements et al. [13] found no association between low birth weight and ADHD. In contrast, the large population-based studies by Halmøy et al. [10], Henriksen et al. [8•] and Silva et al. [9•] all reported that low birth weight conferred risk for ADHD in unadjusted analyses. Two of these studies [9•, 10] reported that children who are born small for gestational age (SGA) were at increased risk for ADHD (OR males = 1.13, OR females = 1.16 [9•]; RR = 1.3 [10]). However Silva et al. [9•] found the relationships between ADHD and both low birth weight and SGA attenuated in their fully adjusted model (accounting for maternal smoking, preterm labour, oxytocin use). Neither Halmøy et al. [10] nor Henriksen et al. [8•] were able to adjust for maternal smoking. The inconsistencies in the literature may therefore relate to methodological issues with the observed association between low birth weight and ADHD being driven by other, unmeasured, factors such as maternal smoking during pregnancy.

Other Pregnancy, Labour/Delivery and Neonatal/Infancy Complications

Summary from Previous Review Insufficient evidence of a relationship. No overall estimate available as the 24 studies (n = 179,017) had examined different factors [5].

Recent Findings Halmøy et al. [10] reported that birth by caesarean section (RR = 1.3), pre-eclampsia (RR = 1.2), induced labour (RR = 1.2) and low Apgar score at 5 min (RR = 2.8) all increased risk for ADHD in fully adjusted models that did not include smoking during pregnancy. There was also an increased risk of ADHD in children born with an oral cleft (RR = 2.8), an association which has not previously been reported. Similarly, Silva et al. [9•] found a number of pregnancy/labour factors to be associated with ADHD in their adjusted model including maternal urinary tract infection (OR males and females = 1.3), pre-eclampsia (OR males = 1.2, OR females = 1.3), induced labour (OR females = 1.2), cord prolapse (OR females = 2.8) and threatened pre-term labour (<37 weeks—OR males = 1.8). Information on smoking during pregnancy was available for approximately 10% of the total sample. When analyses were restricted to this subgroup and maternal smoking was entered into the model, almost all other relationships attenuated. Clements et al. [13] found no relationship between mode of delivery and ADHD in their case–control study. In a Danish nationwide cohort study [8•] and an Australian study [9•], both indicated that oxytocin for labour augmentation does not increase risk for ADHD. There is evidence that exposure to ischemic-hypoxic conditions in pregnancy (e.g. placental abruption, pre-eclampsia) increases risk for ADHD [14]. This association was strongly related to gestational age indicating that some of the risk attributable to gestational age may be due to increased incidence of ischemic-hypoxic events in utero in those born prematurely.

Maternal Substance Use in Pregnancy

Alcohol

Summary from Previous Review Inconclusive evidence with prior 16 studies (n = 94,921) generally of low quality [5]. Adjusted ORs of 2.8 to 11.7 in studies showing significant association.

Recent Findings Langley et al. [15] recently found that maternal alcohol use during pregnancy was associated with elevated ADHD symptoms but did not elaborate on this as it was not a key focus of their investigation. Sundquist et al. [16] found that ADHD was elevated in those with a biological parental with a history of alcohol use disorders (standardized incidence ratio of 2.19; 95% CI 2.15, 2.23), compared to that in individuals without an affected parent. The risk was even higher where the parents were diagnosed with an alcohol use disorder prior to the child's birth (standardized incidence ratio of 2.70; 95% CI 2.59–2.81) which may suggest that germ cell mutation may increase the risks of developing ADHD. The study was unfortunately unable to separate the risk from alcohol use disorders from genetic and familial level confounding.

Tobacco

Summary from Previous Review Some suggestive evidence of a relationship with an OR of 2.4 from a meta-analysis of 33 studies (n = 1,059,416) [5]. Adjusted OR/HRs from other studies not included in the meta-analysis ranged from 1.5 to 4.0.

Recent Findings The recent population-based linkage study by Silva and colleagues [9•] reported an association between smoking during pregnancy and ADHD for both males (OR = 1.9) and females (OR = 1.7); however, maternal psychiatric history was not taken into account. There are plausible biological mechanisms that may account for this relationship. Nicotine impacts on serotonin and dopaminergic systems, brain cell growth, as well as DNA and RNA synthesis of the foetal brain; thus, it is possible that exposure could disrupt normal brain development, which could lead to the phenotypic expression of ADHD [17, 18].

However, a number of recent studies with more sophisticated study designs continue to suggest that the relationship between ADHD and maternal smoking during pregnancy is driven by genetic risk factors. Langley et al. [15] demonstrated that both maternal ($\beta = 0.25$) and paternal ($\beta = 0.21$) smoking

during pregnancy was associated with increased parent-reported ADHD symptoms at age 7.6 years, using data from a large prospective cohort study ($N = 8234$). Their findings were also replicated using teacher-reported ADHD symptoms. These findings are partially consistent with those by Zhu et al. [11] ($N = 84,803$; 2009 with ADHD). Although Zhu et al. [11] found a relationship between both maternal and paternal smoking during pregnancy and ADHD, risk was greater for maternal smoking. Furthermore, there was higher ADHD risk for mothers who used nicotine replacement during pregnancy suggesting a possible prenatal programming effect associated with nicotine exposure.

Skoglund et al. [19••] demonstrated the role of unmeasured familial confounding in explaining the relationship between maternal smoking during pregnancy and ADHD status using a Swedish population-based cohort study ($N = 813,030$; 19,891 ADHD cases). Although maternal smoking during pregnancy predicted ADHD status initially (HR ranged from 1.89 to 2.50 for moderate to high smoking, respectively), results weakened when accounting for covariates and in a cousin-comparison model (i.e. adjusting for unmeasured confounding shared within the extended family). The relationship was no longer significant when accounting for unmeasured confounders within the nuclear family using the sibling-comparison design.

Children with ADHD who were exposed to prenatal smoking may represent a more severe phenotype of the disorder. Thakur et al. [20] reported that the children with ADHD exposed ($n = 165$) versus not exposed ($n = 271$) to maternal smoking during pregnancy had a more severe presentation including greater externalizing symptoms, lower verbal IQ and elevated neurocognitive deficits. Furthermore, there was a dose–response relationship between the average number of cigarettes smoked per day during pregnancy and verbal IQ and other aspects of neurocognitive functioning. The authors later extended these findings to show that mothers and fathers of children with ADHD who were exposed to smoking during pregnancy ($n = 168$) compared to those who were not ($n = 346$) presented with a much higher burden of mental health difficulties including increased frequency of antisocial personality disorder, substance use disorders and major depressive disorder [21]. In contrast, Biederman and colleagues [17] did not uncover any differences in the clinical characteristics of children with ADHD who were and were not exposed to prenatal smoking but this finding is also at odds with earlier studies in the area [22–24].

Illicit Drug Use

Summary from Prior Review Four case–control studies comprising of ~1500 participants failed to find an association between drug use in pregnancy and ADHD [5], with few mothers in these studies reporting using drugs during pregnancy.

Recent Findings Although it is biologically plausible that a relationship between drug use and ADHD would exist, recent studies in this area were not identified, and it appears that previous studies are limited in their ability to identify relationships given the small sample sizes of women reporting drug use in pregnancy. This is clearly an area in need of further investigation.

Maternal Anti-depressant Use

Summary from Prior Review No studies met criteria for inclusion in the previous review [5].

Recent Findings Clements et al. [13] used a case–control design to examine the impact of maternal anti-depressant use (measured by prescriptions recorded in the patient's electronic health record) in children with ADHD ($n = 2243$) and non-ADHD controls ($n = 5631$). Maternal anti-depressant use at any stage during pregnancy increased risk of ADHD (adjusted OR = 1.8), with risk highest for anti-depressant use preconception i.e. 3 months preceding last menstrual period (OR = 2.15) and during the first trimester (OR = 2.03). Analyses controlled for a broad range of socio-demographic characteristics and the presence or absence of maternal major depressive disorder. However, the study design did not allow for measurement of genetic of familial factors which may contribute to both ADHD and the use of anti-depressants in pregnancy and also used a proxy for anti-depressant use (prescription).

An earlier study by Laugesen et al. [25•] used a nationwide cohort study ($N = 877,778$) in Denmark in order to examine the association between anti-depressant exposure (redemption of a prescription) and ADHD status. Children exposed to anti-depressants in utero were compared with children of former users, and children of never users. A sibling-comparison design was also used whereby siblings discordant for exposure were compared for risk of ADHD. Anti-depressant use increased risk for ADHD (adjusted HR 1.2) when accounting for a number of risk factors including maternal age, smoking during pregnancy, gestational age and birth weight. However, in the sibling-comparison analysis, the association attenuated (adjusted OR 0.7).

Paracetamol (Acetaminophen) Use

Summary from Prior Review No studies met criteria for inclusion in the previous review [5].

Recent Findings Data from a Danish Birth Cohort Study ($N = 64,322$) found that paracetamol use during pregnancy was associated with elevated risk for hyperkinetic disorder diagnosis (adjusted HR = 1.34), ADHD medication use (adjusted HR = 1.29), and total behaviour problems measured using the strengths and difficulties questionnaire (adjusted

RR = 1.13); ADHD risk increased with higher frequency of paracetamol use [26]. The findings did not appear to be confounded by maternal inflammation or infection during pregnancy, maternal mental health, or other prenatal exposures such as smoking and alcohol use during pregnancy. The authors put forth that acetaminophen may impact the brain development of the foetus via its endocrine-disrupted properties.

These findings were replicated using data from the Auckland birthweight collaborative study (n = 871) [27]. In multivariable models, acetaminophen use during pregnancy was associated with increased hyperactivity/impulsivity symptoms at age 7; however, this finding attenuated at age 11 years. A broad range of confounding variables were accounted for including socio-demographic characteristics, maternal smoking during pregnancy and maternal health including mental health. This study also demonstrated that risk was specifically associated with acetaminophen use and not other commonly used medications including aspirin, antacids and antibiotics. Although both studies were rigorous in considering a range of confounding variables, the design did not take into account genetic factors pertaining to ADHD. Further research is needed to clarify these findings.

Maternal Age at Child Birth

Summary from Prior Review No studies met criteria for inclusion in the previous review [5].

Recent Findings In the large population-based study by Halmøy and colleagues [10], adults with ADHD were more likely to be firstborns and to have a younger maternal age at delivery. Similarly, Clements et al. [13] found that younger maternal age was associated with ADHD (OR = 0.97). However, it is possible that this association may be driven by other unmeasured factors. For example, young people with ADHD are more likely to engage in risky sexual behaviours [28] which may put them at risk of teenage pregnancy [29]. Chang et al. [30] used a nationwide cohort study from Sweden (N = 1,495,543; 30,674 with ADHD) to clarify the relationship between maternal age and offspring ADHD using sibling- and cousin-comparison analyses. At a population level, teenage childbirth increased risk for ADHD (HR = 1.78), and although the risk remained significant in the cousin-comparison model (HR = 1.33), the relationship was no longer significant in the sibling model.

In contrast, Park at al. [31], using a case–control cross-sectional design, reported that advanced rather than younger maternal age at pregnancy was independently associated with both ADHD-inattentive (OR = 1.6) and ADHD-combined types (OR = 1.4) in their multivariable logistic regression analyses. Interestingly, they found that younger paternal age at pregnancy was associated with increased risk for both ADHD subtypes (inattentive, OR = 0.7; combined, OR = 0.8). It is important to note the sample size of this study was comparatively small compared to that other studies (inattentive, n = 82; combined, n = 65), that it was limited by retrospective recall and that maternal smoking during pregnancy was not included in their adjusted models.

Maternal Physical and Mental Health

Summary from Previous Review Twelve studies assessed a broad range of exposures (e.g. stress, depression, marital problems, life events) (n = 86,137), which meant that an overall estimate was not available [5]. ORs for different factors ranged from 1.04 to 6.8, with the largest study having OR 2.37 for maternal stress in pregnancy. There was limited prior research examining other maternal physical health risk factors.

Recent Findings Clements et al. [13] reported that maternal history of major depressive disorder (OR = 2.3) increased risk of ADHD; however, genetic confounding was unaccounted for. Park et al. [31] reported a relationship between maternal stress during pregnancy and ADHD-inattentive (OR = 2.2) and ADHD-combined (OR = 1.9) type; however, this study was relatively small and again used retrospective reports of stress during pregnancy. Stress in pregnancy is likely an indicator of other maternal health or family psychosocial factors which may confer risk for ADHD but these were not taken into account in this study.

Although Chen and colleagues [32] initially identified a relationship between maternal BMI and ADHD risk in their Swedish cohort study (N = 673,632; 17,380 ADHD) (overweight HR = 1.23, obese HR = 1.64), this attenuated in their sibling-matched design (HR = 0.99), again strongly suggesting that the initial finding was driven by familial confounding. Andersen and colleagues [33] found an association between maternal hyperthyroidism and increased risk of ADHD (adjusted HR = 1.14) in a Danish nationwide cohort study (N = 857,014; ADHD 11,351). Stratified analyses suggested that only maternal diagnosis of hyperthyroidism after birth (mean of 6.5 years later) was associated with ADHD even when taking into account a broad range of potentially confounding variables including maternal smoking during pregnancy. The highest risk for ADHD was in those diagnosed with hyperthyroidism within 2 years of the birth of the child, suggesting untreated, subclinical or developing maternal hyperthyroidism during pregnancy may be the reason for increased risk of ADHD in the child. Halmøy et al. [10] found a relationship between maternal epilepsy and ADHD status (adjusted RR = 1.7) but the mechanism for this relationship is unclear, and findings may be due to unmeasured factors such as use of antiepileptic medications during pregnancy.

Exposure to Environmental Toxins

Summary from Previous Review No studies met criteria for inclusion in the previous review [5].

Recent Findings Data from the Danish birth cohort study did not find a relationship between perfluoroalkyl substances (persistent pollutants) measured in maternal plasma and ADHD status [34], despite some prior evidence from cross-sectional studies [35, 36]. Similar findings were detected by Ode et al. [37] using measurements from umbilical cord serum. Although Ode et al. [38] found no relationship between continuous levels of manganese and selenium in umbilical cord serum and ADHD, they did find that children with high selenium concentrations (>90th percentile) had a 2.5 increased odds of ADHD compared to children with lower readings between the 10th and 90th percentiles. The latter finding was unexpected as selenium has strong antioxidant properties and was expected to be protective against ADHD. The meta-analysis by Yoshimasu et al. [39] found limited evidence between prenatal/early infancy mercury exposure and later ADHD. Although they initially found a relationship between environmental mercury exposure and ADHD (OR 1.60; 95% CI 1.10, 2.33), the relationship attenuated when excluding studies that did not adjust for confounding variables.

A recent study by Malin et al. [40] reported a relationship between state prevalence of artificial water fluoridation and state prevalence of ADHD. However, this study merely correlated group-level data from two large data sets and did not have individual-level data available. The study was also limited by weak case ascertainment of ADHD (parent report of previous diagnosis), which could be subject to both under- or over-reporting. Nonetheless, the study proposes a plausible biological mechanism through which fluoride increases lead levels in the blood or contributes to suppression of the thyroid gland, both of which could leads to expressed ADHD symptoms. This finding is very far from suggesting a causal relationship and requires replication.

Conclusions

The findings from several epidemiological and data linkage studies over the past 3 years have made a substantial contribution to our understanding of the relationships between prenatal risk factors and the development of ADHD in offspring. However, they have also emphasised the complexity of moving from associations to causal relationships and the shortcomings of many of the existing studies. These complexities are further highlighted by a series of methodologically superior studies that have started to account for some of the genetic and familial confounds that when taken into account throw several "established" findings into doubt.

Prematurity, especially extreme prematurity, has the strongest relationship with ADHD, considering all of the other prenatal risk factors that have been implicated. While the evidence for an effect of low birth weight is less clear, there is some evidence that supports an increased risk of ADHD, independent of prematurity, in those that are small for gestational age. For prematurity, low birth weight and the many other pregnancy, labour/delivery and neonatal/infancy complications that have been reported to increase the risk for ADHD, it is unfortunate that the vast majority of studies have failed to account for other risks like smoking or alcohol use during pregnancy. Studies that were able to control for these factors have tended to report either lower risk ratios or non-significant findings. Even the strong associations between ADHD and smoking during pregnancy seem to be better accounted for by genetic and familial level factors than the actual exposure. Similar criticisms can be made about the studies highlighting associations between maternal age and ADHD and for various maternal physical and mental health problems both during and shortly after delivery. The limited evidence linking ADHD with prenatal exposure to a variety of environmental toxins is difficult to interpret, and further well-designed studies are clearly required.

In general, it is still the case that none of these proposed prenatal risk factors can be confirmed as causal for ADHD. And indeed based on current evidence, it would appear that the stronger the study design, the less likely it is to support a causal association. The overall message is that we need a new benchmark for this type of study whereby there is an expectation not only that data will be collected prospectively but also that the design will allow the broad range of genetic and familial factors to be accounted for. This will be of particular importance to new birth cohort studies and places an emphasis on collecting high quality data from parents at baseline and to follow them up alongside their offspring. Studies also need to focus on postnatal risk factors, which may have an epigenetic effect during vulnerable developmental periods via an inflammatory pathway.

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Compliance with Ethical Standards

Conflict of Interest Emma Sciberras, Melissa Mulraney and Desiree Silva declare that they have no conflict of interest.

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- •• Of major importance

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