

research



Low risk of autism with antidepressants p 143



Diet and exercise in pregnancy linked with fewer caesareans p 144



Better reporting of interventions can cut research waste p 146

Prenatal antidepressant use and risk of autism

ORIGINAL RESEARCH Population based cohort study

Antidepressants during pregnancy and autism in offspring

Rai D, Lee BK, Dalman C, et al

Cite this as: *BMJ* 2017;358:j2811

Find this at: <http://dx.doi.org/10.1136/bmj.j2811>

Study question Is there an association between maternal use of antidepressants during pregnancy and autism spectrum disorder (ASD) in the offspring?

Methods Observational prospective cohort study with regression methods, propensity score matching, sibling controls, and a negative control comparison. Participants were 254 610 individuals aged 4-17, including 5378 with autism, living in Stockholm County in 2001-11 who were born to mothers who took antidepressants during pregnancy, mothers with psychiatric disorders who did not take antidepressants during pregnancy, or mothers who did not take antidepressants and did not have any psychiatric disorder. The exposure was maternal antidepressant use recorded during the first antenatal interview or prescription records. The main outcome measure was a diagnosis of autism in the offspring with or without a recorded intellectual disability.

Study answer and limitations Children exposed to antidepressants during pregnancy seemed to have a higher risk of autism compared with those whose mothers had a history of a psychiatric disorder but who did not report antidepressant use during pregnancy (adjusted odds ratio 1.45, 95% confidence interval 1.13 to 1.85). Propensity score analysis led to similar results. The results of the sibling control analysis were also in the same direction but with wider confidence intervals. There was no evidence of any increased risk of autism in children whose fathers were prescribed antidepressants during the mothers' pregnancy (1.13, 0.68 to 1.88). If this is a causal, unconfounded association, an estimated



BBOISSONNET/ALAMY

2% of cases of autism could be prevented if no pregnant woman took antidepressants. In all analyses, the risk increase concerned only autism without intellectual disability.

What this study adds The consistent results across methods with different assumptions suggest that the association between antidepressant use during pregnancy and autism might not be fully explained by confounding. The absolute risks were small so these results should not be considered alarming, but the findings could be useful in a further understanding of the aetiology of autism.

Funding, competing interests, data sharing Swedish Research Council, NIHR Biomedical Research Centre Bristol. There are no competing interests and no data to share.

● See COMMENTARY, p 144

COMMENTARY Risk should be viewed through a kaleidoscope of possible causes

Although the causes of autism spectrum disorder are largely unknown, among the first clues were observations of greater than expected aggregation of psychiatric disorders in families of children with autism.¹⁻³ Molecular genetic studies are beginning to show a complex genetic architecture underlying autism^{4,5} and compelling evidence also points to the importance of non-heritable factors, especially arising in utero.³⁻⁷ Finally, autism is phenotypically heterogeneous with regard to behavioural, cognitive, developmental, and medical characteristics, which could reflect diverse causes.⁸ The findings of the linked paper by Rai and colleagues⁹ should be viewed through these complex features.

The authors observed about a 50% increased risk of autism associated with antidepressant use in pregnancy across the main regression analysis and the three refined analyses, although as sample sizes declined in some of the more refined analyses, so did precision and significance of the corresponding risk estimates. Intriguingly, increased risk associated with antidepressant use seemed confined to the subgroup without concurrent intellectual disability, a phenotype that might be more heritable.

Counterintuitive

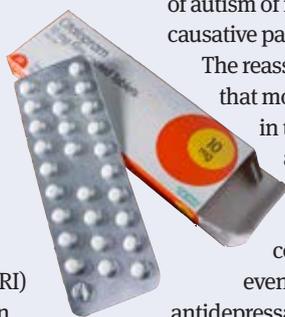
Risk for autism spectrum disorder without intellectual disability was higher in offspring of mothers who had taken non-selective serotonin reuptake inhibitor (non-SSRI) antidepressants rather than SSRI antidepressants, and also with antidepressants with low or moderate affinity for the serotonin transporter receptor compared with antidepressants with high affinity. These results run counter to expectation based on the hypothesised mechanism of risk arising from fetal exposure to serotonergic agents. Overall, the authors could not firmly conclude that

antidepressant use poses a risk for autism spectrum disorder independent of underlying maternal psychiatric illness. The most recent systematic review and meta-analysis reached a similar conclusion.¹⁰

Despite the analytical rigor of the current study, the balance between heritable and non-heritable factors contributing to the association between antidepressant use and autism remains unresolved. Nevertheless, the view of this association through the complex array of factors contributing to autism spectrum disorder is clearer.

The apparent difference in risk associated with antidepressant use and autism with or without concurrent intellectual disability is especially informative because it highlights at least one phenotypic subgroup that could be most relevant. Clarification of the phenotypic subgroup to target could lend analytical efficiency to future studies of autism associated with maternal use of antidepressants—studies that must be better powered than previous ones and include measures of severity of maternal disease, perhaps more reliable measures of antidepressant use, and, ideally, genetic markers contributing to the risk of autism of relevance to the potential causative pathways involved.

The reassuring message was that more than 95% of women in the study who took antidepressants did not have a child with autism spectrum disorder. Rai and colleagues estimated that even if the association between antidepressant use and autism is causal, and with all other factors equal, then only 2% of cases would be prevented if no women with psychiatric disorders used antidepressants during pregnancy.⁹ Although such a small risk within a population might seem too high from an individual's perspective, it must be carefully weighed against the substantial health consequences associated with untreated depression.



Cite this as: *BMJ* 2017;358:j3388

Find the full version with references at <http://dx.doi.org/10.1136/bmj.j3388>

Diana E Schendel diana.schendel@ph.au.dk
See bmj.com for author details

Diet and exercise in pregnancy

ORIGINAL RESEARCH Meta-analysis of individual participant data from randomised trials

Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes

The International Weight Management in Pregnancy (i-WIP) Collaborative Group

Cite this as: *BMJ* 2017;358:j3119

Find this at: <http://dx.doi.org/10.1136/bmj.j3119>

Study question What are the effects of diet and physical activity based interventions on gestational weight gain and pregnancy outcomes, and do they

COMMENTARY Lifestyle interventions are safe in pregnancy, and help control weight gain

Both maternal obesity and excessive weight gain in pregnancy are known to be associated with pregnancy complications for mother and infant.¹⁻³ Maternal obesity is also associated with longer term effects on childhood obesity² and hence potential increases in non-communicable diseases. The prevalence of overweight and obesity is increasing in the maternity population in high resource countries.¹ With the global nutrition transition,⁴ its impact will be more often observed in low and middle income settings.⁵

Information on trends in physical activity in pregnancy is less clear, although the data in the general population are well established—on a worldwide basis physical activity is not increasing.⁶ It is likely this stasis is also occurring in the maternity population; indeed it may be exacerbated by women's, families', and health professionals' concerns over the safety of physical activity during pregnancy.⁷

Summary evidence

Several randomised controlled trials of diet and physical activity based interventions in pregnancy have therefore been conducted over recent years. Rogozinska and colleagues from the i-WIP group conducted an individual

Marian Knight marian.knight@npeu.ox.ac.uk

Charlie Foster

See bmj.com for author details

differ according to women's body mass index, age, parity, ethnicity, or pre-existing medical condition?

Methods The authors undertook an individual participant data (IPD) meta-analysis of randomised trials on diet and physical activity based interventions in pregnancy on gestational weight gain, and maternal and offspring composite outcomes. Statistical models accounted for clustering of participants within trials and heterogeneity across trials, leading to summary mean difference or odds ratios with 95% confidence intervals for the effects overall, and in subgroups (interactions).

Study answer and limitations Women gained less weight in the intervention group than control (mean difference -0.70 kg, 95% confidence interval -0.92 to -0.48 kg; 33 studies, 9320 women); and the reductions in maternal (odds ratio 0.90, 95% confidence



interval 0.79 to 1.03; 24 studies, 8852 women) and offspring (0.94, 0.83 to 1.08; 18 studies, 7981 women) composite outcomes were not significant. No differential intervention effect was found across subgroups, for gestational weight gain or composite outcomes. Interventions reduced the odds of caesarean section (0.91, 0.83 to 0.99; 32 studies, 11 410 women), but not other individual complications. When the authors supplemented IPD with study level data from studies that did not provide IPD, the effect was

similar, with stronger evidence of benefit for gestational diabetes (0.76, 0.65 to 0.89; 59 studies, 16 885 women).

Studies varied in the components of interventions evaluated, such as intensity, setting, and frequency; and in the type and measurements of outcomes. The considerable time needed to obtain and standardise IPD meant that recently published data could not be incorporated in the IPD meta-analysis.

What this study adds Diet and physical activity interventions minimise weight gain and reduce the odds of caesarean section but not other complications, with no difference in effects across subgroups of women.

Funding, competing interests, data sharing The National Institute for Health Research (NIHR) Health Technology Assessment programme provided funding. See bmj.com for competing interests and data sharing. Study registration CRD42013003804.

participant data meta-analysis of these randomised trials, including data on more than 12 000 women, and found a statistically significant mean decrease of 0.7 kg in gestational weight gain among the group of women who had received any diet or physical activity intervention, or both, during pregnancy.⁸ The authors found no differences in maternal or infant composite outcomes between the groups.

Many pregnancy complications are individually rare, or the effects of interventions on individuals are small. The challenge of interpreting research therefore is how to assess apparently positive effects of intervention when those effects are not statistically significant potentially as a result of inadequate sample size. Healthcare practitioners' scepticism about the value of interventions in pregnancy have been shown to be a barrier to implementation of weight management guidelines,⁹ and difficulties interpreting the evidence may play a part in this.

In the context of a recommended weight gain of 11.5-16 kg among women of normal weight,¹⁰ the importance to an individual of a 0.7 kg reduction may be unclear. However, guidelines have been developed for optimal pregnancy weight gain among different body mass index groups to improve maternal and child outcomes,¹⁰ and gestational weight gain above these recommended levels has been shown to be associated with an increased odds of macrosomia and caesarean delivery.¹¹ Therefore across whole populations even a

We can be confident in our advice that physical activity in pregnancy can be maintained

small reduction in gestational weight gain may have an important impact on rates of these outcomes.

Rogozinska and colleagues identified a statistically significant decrease in the caesarean section rate among women who had received any diet or physical activity intervention during pregnancy, with an estimated 9% decrease in odds. Notable, however, was the high caesarean birth rate—34.8% in the intervention group and 37.7% in the control group. This highlights the importance of ongoing research into the underlying causes of increasing medical intervention in pregnancy¹² but also raises our awareness of the possible effect of diet and physical activity on reducing rates.

The work of Rogozinska and colleagues provides little evidence of benefit of physical activity and diet interventions on pregnancy outcomes for either mother or infant.⁸ However, concerns are often expressed about the harms of diet, and particularly physical activity, interventions in pregnancy. This study provides reassuring information for women and healthcare practitioners about safety. The authors found no evidence of an increase in adverse pregnancy outcomes among women participating in dietary, physical activity, or mixed approach interventions (both diet and physical activity).

The direction of the estimates of effect of both composite outcomes and the majority of the individual components of the composite outcomes favoured the intervention groups. We can therefore be confident in our advice to women that physical activity in pregnancy can be maintained.

Sedentary lifestyles

The researchers note that at trial entry, 46% of women took no exercise or were sedentary, and perhaps this is where public health initiatives need to focus in the future. The physical activity interventions included in this meta-analysis were heterogeneous, with differing frequency, intensity, duration, and type of physical activity. The challenge remains for researchers to evaluate specific patterns of physical activity in pregnancy in both low and higher risk populations, and how these change with gestation.

For example, future studies could explore a possible role for strength and balance training in improving pregnancy outcomes, and consider whether pregnancy could be a window of opportunity to change physical activity patterns among women and their families in the longer term. In the context of evidence suggesting that lack of physical activity contributes almost 4% to the population risk of dementia,⁶ this is an opportunity we cannot afford to ignore.

Cite this as: *BMJ* 2017;358:j3283

Find the full version with references at <http://dx.doi.org/10.1136/bmj.j3283>

Enhancing usability of systematic reviews by improving the consideration and description of interventions

Hoffmann TC, Oxman AD, Ioannidis JPA, et al

Cite this as: *BMJ* 2017;358:j2998

Find this at: <http://dx.doi.org/10.1136/bmj.j2998>

The importance of adequate intervention descriptions in minimising research waste has gained attention in the past few years. But the focus has been on randomised trials, whereas clinicians are encouraged to use systematic reviews to inform their practice. The extent to which clinicians can do this is hampered by a lack of full consideration and complete description of interventions in systematic reviews. Historically, the development of systematic review techniques, methods, and technologies has focused on aspects such as searching, assessing and reporting risk of bias, and statistical methods. The clinical usability of the results of systematic reviews has had less attention, and intervention use and reporting in reviews has had almost none.

To identify a common approach for improving the consideration and reporting of intervention details in systematic reviews, a group of experts—including systematic review authors, trial authors, journal editors, methodologists, and statisticians with expertise in intervention descriptions, reporting guidelines, trials, and systematic reviews—held a meeting, along with other stakeholders. Hoffmann and colleagues summarise the discussion and recommendations that arose from this meeting. They describe the stages of the systematic review process at which intervention details should be sufficiently considered and described—from question formulation to decisions about eligibility and analyses, results interpretation, and use of the review findings.

The article contains a list of recommendations that systematic review authors should undertake to improve the consideration of interventions when planning, conducting, and reporting their reviews (box). Improving the completeness of intervention descriptions in systematic reviews is likely to be a cost effective contribution towards facilitating evidence implementation from reviews and reducing the research waste that is caused by reviews failing to consider and provide sufficient details about the interventions. With implications for being able to reproduce and implement systematic reviews, all of those with a role in producing, reviewing, and publishing systematic reviews should commit to helping to solve this remediable barrier.

Recommendations for authors to improve the consideration of interventions when planning, conducting, and reporting systematic reviews

Planning the review

Consider intervention details during question formulation

Use the Template of Intervention Description and Replication (TIDieR) guide to identify any important details of the intervention that will determine the questions that the review will ask, including how broad or narrow the review should be and what the main comparison will be.

Describe intervention considerations in the review protocol

Describe the intervention and its relevant components and characteristics in the protocol. Relevant protocol sections might include: the review question, background, search terms, eligibility criteria, data items, and quantitative synthesis plans.

Conducting the review

Extract intervention details as part of data extraction

Use TIDieR as a guide to the essential intervention characteristics to include in the data extraction form and extract accordingly.

Request missing intervention details

When feasible, request missing details from the authors, using TIDieR as a guide to which details to request, and note when details are not available.

Consider intervention characteristics during statistical analyses and exploration of heterogeneity when appropriate

Where appropriate and feasible, consider intervention characteristics as specified in the protocol when grouping studies, conducting analyses, and exploring heterogeneity.

Reporting the review

Report intervention details in a summary table

Provide a table that summarises the intervention details for each study (see article online).

Share intervention materials where possible

Where intervention materials are available, share or provide their location details in the review's intervention summary table.

Describe implications for future research

If the summary of intervention details reveals important gaps in existing research or if the analyses identify a significant association between effect and the presence or absence of intervention components or characteristics, then describe the future research implications of this in the review.

The *BMJ* is an Open Access journal. We set no word limits on *BMJ* research articles but they are abridged for print.

The full text of each *BMJ* research article is freely available on bmj.com.

The online version is published along with peer and patient reviews for the paper, and a statement about how the authors will share data from their study. It also includes a description of whether and how patients were included in the design or reporting of the research.

The linked commentaries in this section appear on bmj.com as editorials. Use the citation given at the end of commentaries to cite an article or find it online.