research

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ORIGINAL RESEARCH Prospective register based study

Role of maternal age and pregnancy history in risk of miscarriage

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Study question What is the burden of miscarriage in the Norwegian population and is it associated with maternal age and pregnancy history?

Methods This study used Norwegian health registers (medical birth register, patient register, and the induced abortion register) to identify all pregnancies in Norway between 2009 and 2013 (n=421 201). The risk of miscarriage was estimated according to the woman's age and pregnancy history by using logistic regression, taking into account the competing risk as a result of induced abortions.

Study answer and limitations The risk of miscarriage was lowest among women aged 25-29 (10%), and increased rapidly after age 30, reaching 53% among women aged 45 years and older. There was a strong recurrence risk of miscarriage, with age adjusted odds ratios of 1.54 (95% confidence interval 1.48 to 1.60) after one miscarriage, 2.21 (2.03 to 2.41) after two, and 3.97 (3.29 to 4.78) after three consecutive miscarriages. Risk was modestly increased if the previous birth ended in a preterm delivery (adjusted odds ratio 1.22, 95% confidence interval 1.12 to 1.29), stillbirth (1.30, 1.11 to 1.53), caesarean section (1.16, 1.12 to 1.21), or if the woman had gestational diabetes in the previous pregnancy (1.19, 1.05 to 1.36). Future studies with more comprehensive information on potential common risk factors (eg, ethnicity and body mass index) should examine possible explanations for the association between previous pregnancy complications and the risk of miscarriage.

What this study adds The risk of miscarriage varies greatly with maternal age, shows a strong pattern of recurrence, and is increased after some adverse pregnancy outcomes.

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Risk of miscarriage in Norway between 2009 and 2013 according to the outcome of the previous pregnancy (n=315 963*)

Previous pregnancy	Total No of pregnancies excluding induced abortions	No of miscarriages (%)	Age adjusted odds ratio (95% CI)
None	127 150	14 791 (11.6)	Ref
Live birth	157 763	19 170 (12.2)	0.91 (0.89 to 0.94)
Stillbirth	1175	205 (17.5)	1.30 (1.11 to 1.53)
Miscarriage	29 434	6214 (21.1)	1.65 (1.59 to 1.71)
Neonatal death	441	75 (17.0)	1.28 (0.97 to 1.64)

*105 238 pregnancies excluded from analysis because of unknown pregnancy history or because previous or current pregnancy was an induced abortion.

Pesticides and autism

ORIGINAL RESEARCH Population based case-control study

Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children

von Ehrenstein OS, Ling C, Cui X, et al

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Study question What is the association between risk of autism spectrum disorder and exposure to ambient pesticide during early development up to the first year of life?

Methods This registry linkage study used California birth records from 1998-2010. 2961 patients with a diagnosis of autism spectrum disorder (based on the DSM IV-R (up to 31 December 2013)), including 445 with intellectual disability comorbidity, were identified through records at the California Department of Developmental Services and linked to their birth records. Controls derived from birth records were matched to cases 10:1 by sex and birth year. Data from the California state mandated Pesticide Use Reporting were integrated into a geographic information system tool to estimate prenatal and infant exposure to pesticides (calculated as pounds applied per acre each month within 2000 m distance from the maternal residence), in California's main agricultural region (Central Valley). High use pesticides were a priori selected according to previous evidence of experimental neurodevelopmental toxicity, including chlorpyrifos, permethrin, methylbromide, and glyphosate. Multivariable logistic regression assessed associations between pesticide exposure (ever versus never for each pesticide during specific developmental periods) and autism spectrum disorder (with or without intellectual disabilities) in offspring, adjusting for confounders.

Study answer and limitations Risk of autism spectrum disorder was associated with prenatal exposure to glyphosate (odds ratio 1.16, 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13, 1.05 to 1.23), diazinon (1.11, 1.01 to 1.21), malathion (1.11, 1.01 to 1.22), and permethrin (1.10, 1.01 to 1.20). For the disorder with intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure to glyphosate, chlorpyrifos, diazinon, permethrin, methylbromide, and myclobutanil; exposure in the first year of life increased the odds for the disorder with comorbid intellectual disability by up to 50% for some pesticide substances. Exposure assessment was based on maternal residence at birth; however, misclassification of exposure would be

COMMENTARY Prenatal and early life pesticide exposure linked to modest increases in risk of autism

Autism spectrum disorder is a complex and heterogeneous condition and much uncertainty surrounds the cause. Twin[3] and family based[4] studies have shown that it is a highly heritable condition, with inherited[5] and de novo[6] genetic sources contributing considerably to risk. Genetic risk, however, does not entirely explain autism's aetiology, indicating that autism also has environmental origins. A growing body of scientific literature implicates exposure to ambient pesticides during pregnancy and early childhood as an environmental risk factor for autism spectrum disorder.[7-10]

The linked study by von Ehrenstein and colleagues using population based data from California represents the largest epidemiological effort to date investigating the relations among exposures to ambient pesticides during pregnancy and early childhood and risk of autism spectrum disorder. The study focused on 11 common pesticides, and exposure was assessed within 2000 m of the maternal birth addresses of women residing in California's San Joaquin Valley, a heavily agricultural region.

The study identified modest increases in risk of autism spectrum disorder (adjusted odds ratios ranged from 1.10 to 1.60) associated with exposure to certain pesticides in the prenatal period and first year of life, including the organophosphates chlorpyrifos, diazinon, and malathion; the pyrethroids permethrin and bifenthrin; and glyphosate, avermectin, and methylbromide. Associations were strongest in offspring with autism spectrum disorder and co-occurring intellectual disability, which represent the more severe end of the autism spectrum.

The findings by von Ehrenstein and colleagues corroborate some earlier work,[7-9] much of which has been done in California using similar data resources.[7 9] But the new study moves our understanding of the science linking pesticides with autism spectrum disorder forward in several ways.

What's new?

First, children with autism spectrum disorder and co-occurring intellectual disability were examined as a separate

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expected to be non-differential because moving residence would happen before diagnosis of autism spectrum disorder; thus any related bias would likely be towards the null. Uncontrolled residual confounding always remains a concern.

What this study adds Findings suggest that prenatal or infant ambient exposure to a priori selected pesticides (including glyphosate, chlorpyrifos, diazinon, and permethrin) within 2000 m of the maternal residence is associated with increased odds of developing autism spectrum disorder, compared with offspring of women from the same region without such exposure.

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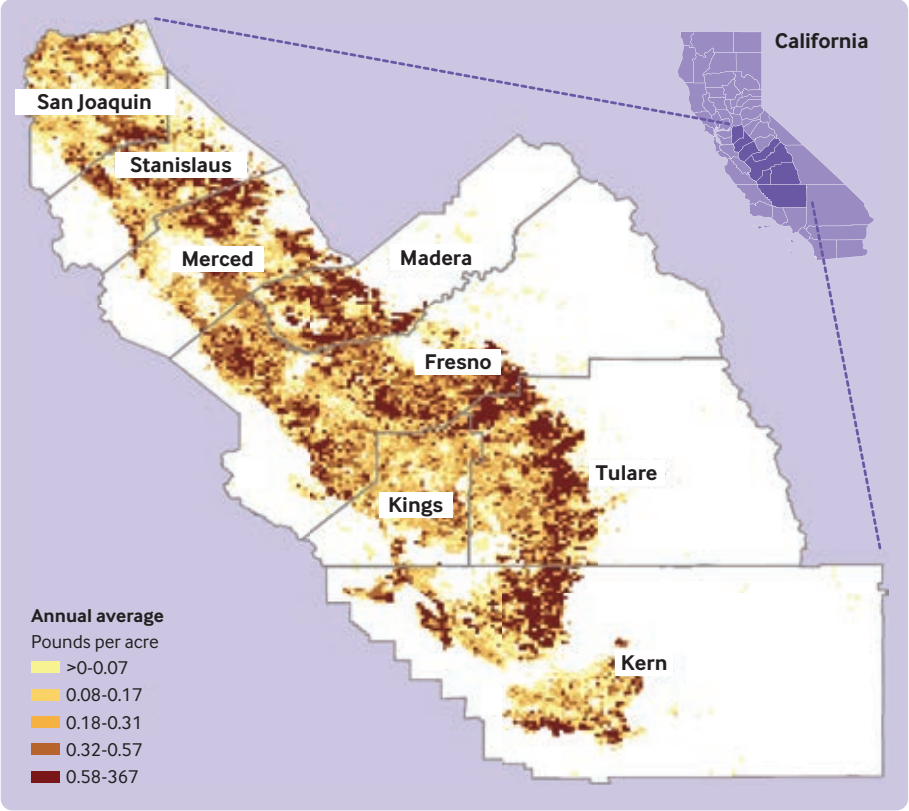

Pesticide application of glyphosate in Central Valley, California, 1998-2010

outcome. Higher odds ratios linked to pesticide exposure in offspring with autism spectrum disorder and comorbid intellectual disability might provide insight into how pesticide exposure relates to autism severity.

Second, the authors formulated multi-pesticide models, including two or three pesticides from different chemical classes. This is important, as residents of California's San Joaquin Valley are likely to be exposed daily to a complex mixture of ambient pesticides.

One limitation, however, is that the study included only children with a diagnosis of "autistic disorder" by the California Department of Developmental Services, based on criteria described in the *Diagnostic and Statistical Manual of Mental Disorders* version IV-R.[13] Children with milder forms of autism spectrum disorder, including those with Asperger's syndrome or pervasive developmental disorders, were excluded, so we cannot know how the findings generalise to the entire autism spectrum.

What's next?

Findings from observational epidemiological studies, such as this, are important for motivating follow-up work intended to elucidate underlying biological mechanisms and inform public policy. As most research on this topic has been conducted in California, future work should aim to replicate this study's findings in diverse regions of the world to determine generalisability.

Associations were strongest in offspring with autism spectrum disorder and co-occurring intellectual disability

Although exposure to ambient pesticide is likely to follow a continuous distribution, von Ehrenstein and colleagues treated such exposure as a dichotomous "ever versus never" measure resulting in a loss of information and risk of misclassification.[14] Future research should examine biologically plausible dose-response and non-linear relations between exposure to ambient pesticide and autism spectrum disorder.

Finally, little is known about the individual level maternal and child characteristics that underlie an offspring's vulnerability to autism spectrum disorder after exposure to ambient pesticides in the prenatal period and early childhood. Next steps in this line of inquiry should include identifying genetic and individual level characteristics that moderate and mediate the relation between exposure to ambient pesticide and risk of autism spectrum disorder.

The "ever versus never" dichotomisation of pesticide exposure also has implications for the public health interventions that could follow. The risk of autism spectrum disorder was increased among offspring exposed to certain pesticides during pregnancy and early life, including glyphosate, the most commonly used herbicide worldwide.[15] Yet, reducing maternal exposure to zero for a pesticide such as glyphosate might be close to impossible in some populations.

Although reducing maternal exposure to pesticides during pregnancy is sensible public health policy based on this study, future research exploring dose-response and non-linear relations and individual susceptibilities could help to translate these study findings into more refined public health actions for pregnant women residing in areas of high pesticide use.

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Data sharing practices of medicines related apps and the mobile ecosystem

Grundy Q, Chiu K, Held F, Continella A, Bero L, Holz R

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Study question Do developers of medicines related applications (apps) share user data, and, if so, with whom?

Methods Using an app store crawling program and purposive sampling strategies, the authors sampled top rated medicines related apps for the Android mobile platform available in the Medical store category of Google Play in the UK, US, Canada, and Australia. 821 apps were screened and 24 included that pertained to medicines information, dispensing, administration, prescribing, or use, and were interactive. In a laboratory setting, a traffic analysis was carried out of each app downloaded onto a smartphone, simulating real world use with four dummy scripts. The authors observed the app's baseline traffic related to 28 different types of user data and then, to identify privacy leaks, modified one source of user data and observed deviations in the resulting traffic and identified the recipient. Using content analysis of companies' websites and policies, they characterised the recipients of user data and performed network analysis to understand their data sharing relations.

Study answer and limitations 19 out of 24 apps transmitted user data to the network. 55 unique entities, owned by 46 parent companies, received or processed app user data; 18/55 (33%) provided infrastructure related services such as cloud services and 37/55 (67%) provided services related to the collection and analysis of user data. This analysis is cross sectional and limited to apps for the Android platform.

What this study adds Medicines related apps, which collect sensitive and personal health data, share user data within the mobile ecosystem in much the same way as other types of apps. A small number of commercial entities have the potential to aggregate and perhaps re-identify user data as result of their network position.

Types and frequency of user data shared with third parties in traffic analysis

User data type	Explanation	No (%) of apps sharing*
Device name	Name of device (eg, Google Pixel)	15 (63)
OS version	Version of device's Android operating system	10 (42)
Browsing	App related activity performed by user (eg, view pharmacies, search for medicines)	9 (38)
Email†‡	User's email address	9 (38)
Android ID†‡	Unique ID to each Android device (ie, used to identify devices for market downloads)	8 (33)
Drugs list‡	List of drugs taken by user	6 (25)
Name/Last name†‡	User's name and/or last name	5 (21)
Time zone	Time zone in which device is located (eg, GMT+11)	5 (21)
Connection type	Cellular data or wi-fi	4 (17)
Medical conditions‡	Users' medical conditions (eg, diabetes, depression)	4 (17)
Birthday‡	User's date of birth	3 (13)
Device ID†‡	Unique 15 digit International Mobile Equipment Identity code of device	3 (13)
Sex	User's sex	3 (13)
Carrier	Mobile network operator, provider of network communications services (eg, AT&T)	2 (8)
Country	Country in which device is located (eg, Australia)	2 (8)
Coarse grain location‡	Non-precise location. Usually city in which device is located (eg, Sydney)	2 (8)
Drug instructions	Instructions related to user's drugs (eg, orally, with food)	2 (8)
Drug schedule	Times for drug administration (eg, 8 pm, in the morning)	2 (8)
Personal conditions‡	Users' personal conditions (eg, smoker, pregnant)	2 (8)
Personal factors‡	Includes user's anthropometric measurements or vital signs (eg, height, weight, blood pressure)	2 (8)
Symptoms‡	User's symptoms (eg, headache, nausea)	2 (8)
Doctor's name‡	Name of the user's doctor	1 (4)
Doses‡	Dose of user's drug (eg, 100 mg aspirin per day).	1 (4)
Feelings	User's current feelings (eg, happy, sad, anxious)	1 (4)
Pharmacy name‡	Information about user's favourite pharmacies (eg, name, location)	1 (4)

*Total number is 24; percentages do not add up to 100% as apps could share multiple types of user data.
†Unique identifier.
‡May be considered personal data under the General Data Protection Rules—that is, "any information relating to an identified or identifiable natural person."

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