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Investigations of prenatal exposure to low doses of alcohol and psychological outcomes in childhood: *methodological issues*

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A few facts about Denmark…

Who drinks and how much:

- 5.5 million people in Denmark
- Most people drink alcohol on a regular basis
- 7% of women and 3% of men are abstainers
- Average yearly intake: 12 litres of pure alcohol (age 16 and over)
- People with tertiary education drink more than those less educated

- App. 65.000 births per year
- Official guidelines: Are you pregnant – avoid alcohol. Are you trying to become pregnant – avoid alcohol just in case….

What does the literature show?
Prenatal exposure to low doses of alcohol...

Contradictory findings:

Some studies have reported an association between prenatal exposure to low doses of alcohol and *externalising behaviours* (Sood et al 2001), *mental health* (Sayal et al 2007), *IQ* (Streissguth et al 1990), *learning difficulties* (Olson et al 1997), *attention* (Streissguth et al 1994, 1986)

Other studies have reported no such associations with mental health (Niclasen submitted, Kelly et al 2010), hyperactivity/ inattention (Rodriquez et al 2009), IQ (Eriksen et al 2012), attention (Underbjerg et al 2012), executive functions (Skogerbo et al 2012).

Even other studies have reported on a J-alcohol shape including cognitive outcomes (Kelly et al 2009, 2010) and mental health (Robinson et al 2010)

No dose-response associations have been established in human studies……

What does the literature show?
Prenatal exposure to low doses of alcohol...

Contradictory findings:

One thorough review by Henderson, Gray and Brocklehurst (2007) and an extensive report by Gray and Henderson (2007) concluded that there is no convincing evidence that prenatal exposure to low doses of alcohol is negatively associated with neurobehavioural development. Concluded:

- Many studies had methodological weaknesses
- Controlled insufficiently for confounding factors
- "healthy drinker effect"

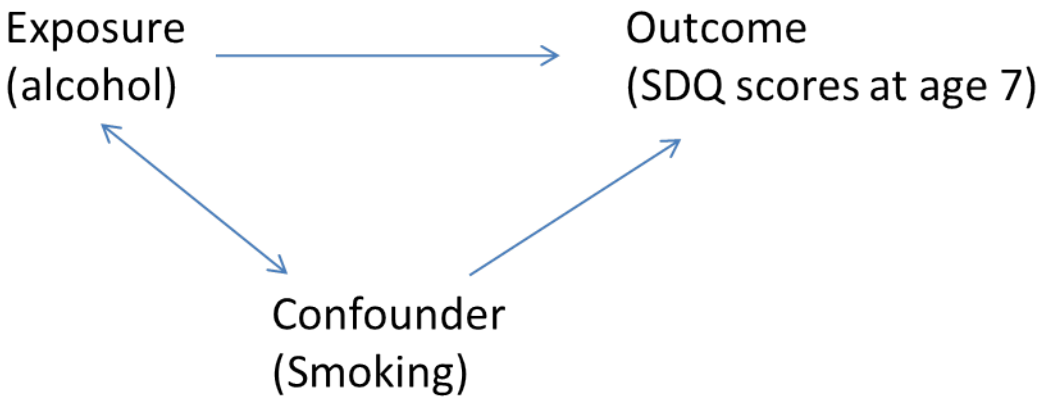
Possible explanations for the lack of consistency in the literature…

Six possible factors that may (in part) explain the lack of consistency in the observational literature:

1. The issue of confounding
2. The issue of mediation
3. The issue of "dose", "pattern" and "timing"
4. The issue of defining the alcohol categories
5. The issue of the applied outcome measures
6. The issue of the age at which the child was assessed

1. The issue of confounding

A confounder is defined as the mixing together of the effect of an exposure with a factor that is statistically associated with the exposure and causally associated with the outcome (Porta 2008)



1. The issue of confounding

- Normal to control for some confounding factors including maternal age, smoking, education, psychiatric diagnoses, illicit drugs, socioeconomic status etc.
- Other factors are rarely controlled for including psychotropic medication, having a partner, parental criminal behaviour, personality, IQ, social support, physical activity, caffeine. Also on the paternal side.

- Accepted for publication in 'Alcohol and Alcoholism' (September 2013)
- Based on data from the Danish National Birth Cohort
- 100.000 pregnancies
- 1996-2002
- Register-based

1. The issue of confounding

		Cumulated alcohol intake (no. drinks/ full pregnancy)				
Alcohol	Full	0	>0-10	>10-30	>30-90	>90
N	63,464	7204	19111	15054	16619	5476
Socio-demographic factors						
Age (M)	30.5	29.5	29.8	30.5	31.1	32.5
Age (P)	32.3	31.5	31.6	32.2	32.9	34.6
Married (no)	2.3%	3.5%	2.5%	2.1%	1.9%	2.4%
Tenant (yes)	26.7%	30.6%	28.0%	26.2%	25.5%	22.8%

1. The issue of confounding

		Cumulated alcohol intake (no. drink/ full pregnancy)				
Alcohol	Full	0	>0-10	>10-30	>30-90	>90
N	63,464	7204	19111	15054	16619	5476
Education						
Mandatory (M)	8.4%	17.8%	9.3%	6.6%	5.4%	6.5%
University (M)	14.6%	5.8%	11.3%	15.4%	19.2%	21.2%
Mandatory (P)	13.3%	22.9%	14.8%	11.5%	9.8%	10.6%
University (P)	15.3%	7.1%	12.4%	15.8%	19.6%	21.7%

1. The issue of confounding

		Cumulated alcohol intake (no. drink/ full pregnancy)				
Alcohol	Full	0	>0-10	>10-30	>30-90	>90
N	63,464	7204	19111	15054	16619	5476
Pre-preg. psychiatric diagnoses (M)	2.9%	4.8%	3.0%	2.4%	2.4%	3.0%
Pre-preg. psychiatric diagnoses (P)	1.9%	2.8%	1.9%	1.7%	1.5%	1.9%
Binge drinking (yes)	30.3%	10.2%	22.4%	31.7%	39.8%	52.7%
Pre-preg. alc. intake	3.0	0	1.4	2.8	4.6	8.3

1. The issue of confounding

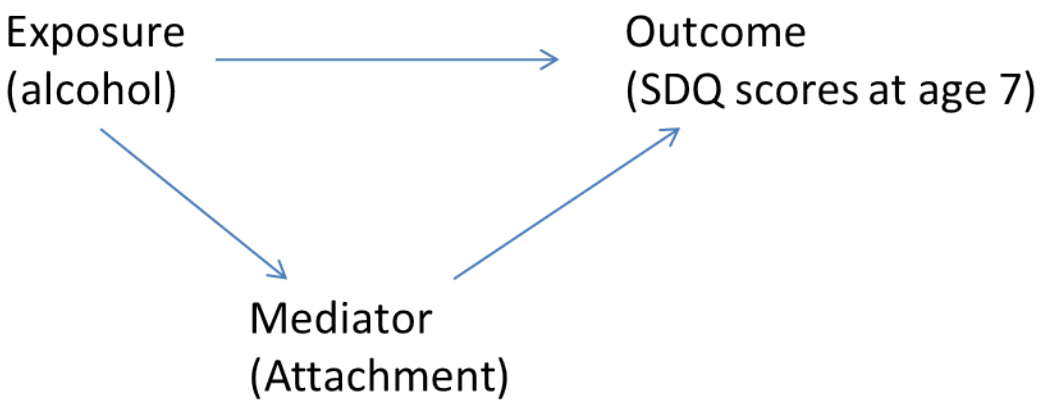
		Cumulated alcohol intake (no. drink/ full pregnancy)				
Alcohol	Full	0	>0-10	>10-30	>30-90	>90
N	63,464	7204	19111	15054	16619	5476
Lifestyle factors						
Cumulated smoking (cig.)	63	100	62	54	50	78
Smoking (yes)	25.2%	31.5%	24.1%	23.3%	23.5%	30.9%
Partner smoking (yes)	29.6%	37.0%	29.6%	27.9%	27.1%	31.2%

1. The issue of confounding

		Cumulated alcohol intake (no. drink/ full pregnancy)				
Alcohol	Full	0	>0-10	>10-30	>30-90	>90
N	63,464	7204	19111	15054	16619	5476
Lifestyle factors						
BMI	67.6%	56.8%	64.0%	68.4%	72.8%	76.0%
Cola	16.5%	24.0%	17.2%	15.0%	14.1%	15.4%
TV	21.1%	29.6%	23.4%	20.1%	17.4%	15.7%

2. The issue of mediation

Mediation can be defined as 'a variable that occurs in a causal pathway from a causal (independent) variable to an outcome (dependent) variable. It causes variation in the outcome variable and itself is caused to vary by the original causal variable. Such a variable will be associated with both the causal and the outcome variable



Relevant mediators that could be controlled for: IQ on part of the child, parental mental health, home environment, violence, social support, attachment, personality

2. The issue of mediation

- Mediating factors are rarely controlled for
- John Bowlby and attachment theory (1950s): was the first to demonstrate the lasting consequences that the quality of the mother-child relationship has for a wide range of developmental cognitive and mental health outcomes.
- He concluded that infants who develop a secure attachment style are those with a history of sensitive and responsive maternal care and this style is later associated with better emotional regulation, higher self-esteem, and more develop coping skills. This in turn makes the child better able to handle stressful or challenging situations and reversely lowers the risk for poorer mental health outcomes later in life. On the other hand, children with an insecure attachment are at greater risk for poor mental health outcomes
- Possibly similar inter-group differences would be observed for the childhood-related mediating variables
- Abel (1998) "*that a child's postnatal environment affects his/ her behaviour is hardly surprising, but it has not received the attention it deserves in the present context*" (p. 127)

3. The issue of “dose”, “pattern” and “timing”

- “Dose”: how much alcohol is consumed – usually “average per week”
- “Pattern”: how much is consumed on a typical occasion? Distinction between average doses and binge drinking…
- “Timing”: at what point in pregnancy did the consumption take place

- These three parameters are most often insufficiently incorporated into the exposure categories
- Studies focus on one, or at best, two of these three parameters
- “Dose”: larger doses, worse that smaller doses
- “Pattern”: binge drinking worse than same amount spread over several days
- “Timing”: maybe worse in third and first trimester

4. The issue of defining the alcohol categories

1. On the basis of what information has the alcohol categories been defined?

Average alc. intake 1st trim. (N= 37,315)	Full sample	0	>0-2	>2-4	>4
Mandatory	6.8 %	8.3 %	4.9 %	6.3 %	8.3 %
University	15.8 %	14.0 %	17.6 %	20.8 %	13.7 %

Full preg. (N= 63,464)	Full sample	0	>0-10	>10-30	>30-90	>90
Mandatory	8.4%	17.8%	9.3%	6.6%	5.4%	6.5%
University	14.6%	5.8%	11.3%	15.4%	19.2%	21.2%

4. The issue of defining the alcohol categories

2. On the basis of what information are the abstainers and the high intakers categorised?

Abstainers (N= 63,464)	Full sample	All-time abstainers	Pregnancy-abstainers
Mandatory	8.4%	17.8%	9.4%
University	14.6%	5.8%	12.6%

High-intakers (N= 63,464)	Full sample	>90-180	>180
Mandatory	8.4%	6.0%	9.1%
University	14.6%	21.7%	18.2%

4. The issue of defining the alcohol categories

3. Is a substantial number of women misclassified into the wrong exposure categories?

There may be an issue of reporting bias:

- Women who drink deny: women with a high intake may be misclassified into the abstaining group
- Women who admit drinking do not remember correctly
- Women purposely under-report their alcohol intake

Underreporting will probably vary between exposure groups → differential misclassification

4. The issue of defining the alcohol categories

4. There is a confusion about what is meant with "low", "moderate" and "high" doses of alcohol

5. The issue of the applied outcome measures

- Generally very little information on psychologically-oriented outcomes in the large scale cohorts
- Many cohorts use brief questionnaires (SDQ) as outcome measures, chosen for practical reasons, not for theoretical reasons
- Children exposure to alcohol exhibit impairments on the performance of relative complex and novel tasks – the outcome measures may not be sensitive enough to grasp potential damage
- The applied measures may not be critically evaluated

6. The issue of the age at which the child was assessed

- In cohort studies the ages for the follow-up is chosen from practical and logistic reasons rather than theoretical reasons.
- When the outcome is neurodevelopment the follow-up time should be theory-driven rather that practicality-driven
- Often the children are assessed at too early ages

- One study with 2600 children with FAS 50 % were found to have normal developmental scores at pre-school whereas all had severe brain dysfunction at age ten. In the same group of children 10 % were found to have attention problems at age five, whereas 60 % had attention problems at age ten (Astley (2010)).

Conclusion

- On the basis of the six issues presented above, no firm conclusion can be drawn as to whether exposure to low doses of alcohol is negatively associated with neurodevelopmental outcomes in childhood
- Currently, it cannot be concluded that exposure to low doses of alcohol is negatively associated with neurodevelopmental outcomes.
- However, it cannot be concluded either that it is *not* negatively associated with neurodevelopmental outcomes in childhood
- Therefore, as long as our research designs are so full of methodological faults and limitations the only reasonable thing to do is to recommend abstinence – for the sake of the unborn children
- Stop spending more money on these very expensive studies – put the money into prevention instead
- Quoting Garcia-Algar and colleagues (2012): *"no evidence of harm does not mean evidence of no harm"*.

THANK YOU FOR YOUR ATTENTION!!!

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