University of BRISTOL

Fetal exposure to alcohol and cognitive development: results from a Mendelian randomization study

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Is moderate drinking during pregnancy really harmful?

Alcohol and pregnancy - conflict and confusion

Shouldn't pregnant women be afforded the right to exercise personal choice when deciding whether to drink alcohol?

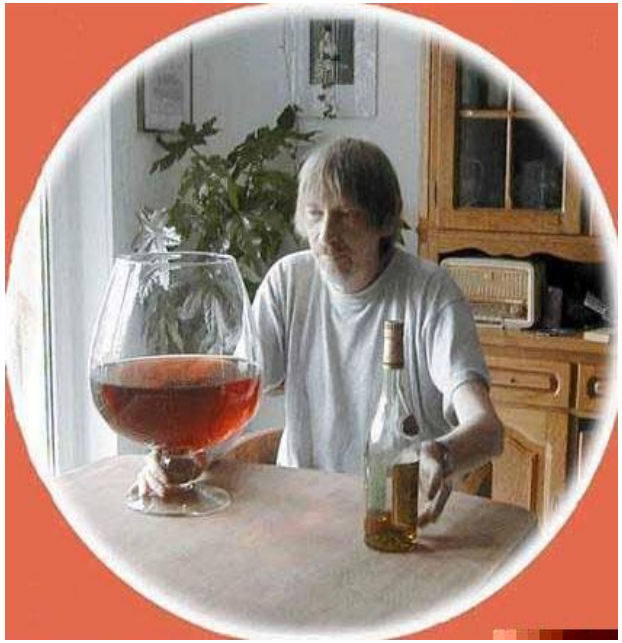
-GUARDIAN NOVEMBER 12,2009

Drinking alcohol occasionally when pregnant 'does no harm

- Times 30 October, 2008

Problems of observational studies of alcohol intake and cancer

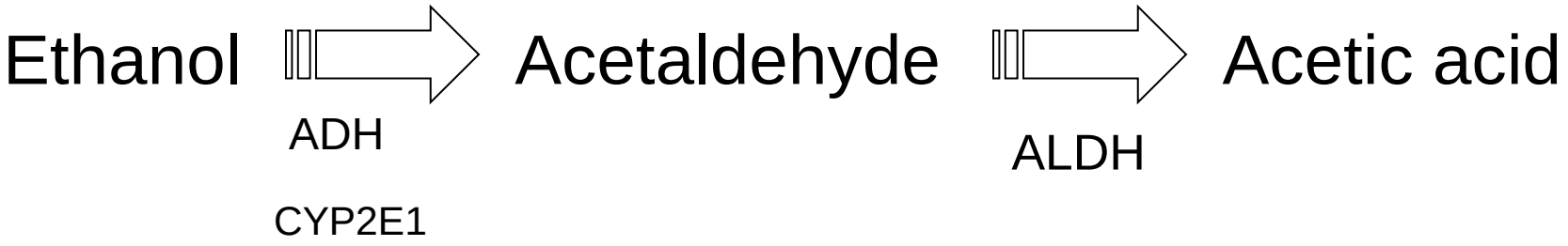
- Measurement error
- Reporting/interviewer bias
- Disease affects drinking habits
- CONFOUNDING



Aim of the project

- To investigate associations between polymorphisms of the main alcohol metabolizing genes in mother and child and growth and neurodevelopmental outcomes in infants and children.

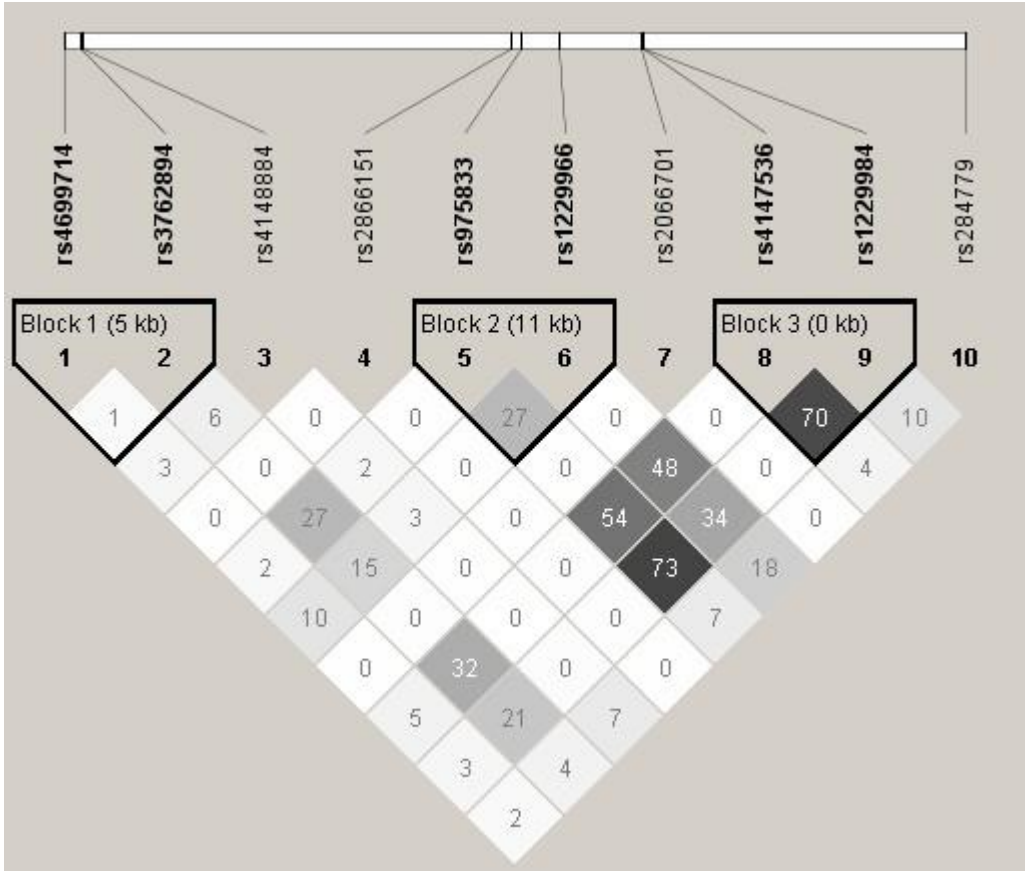
Metabolism of alcohol



* Mainly occurs in the liver, but some activity is also present in the oral cavity and digestive tract

ADH genes and SNPs investigated

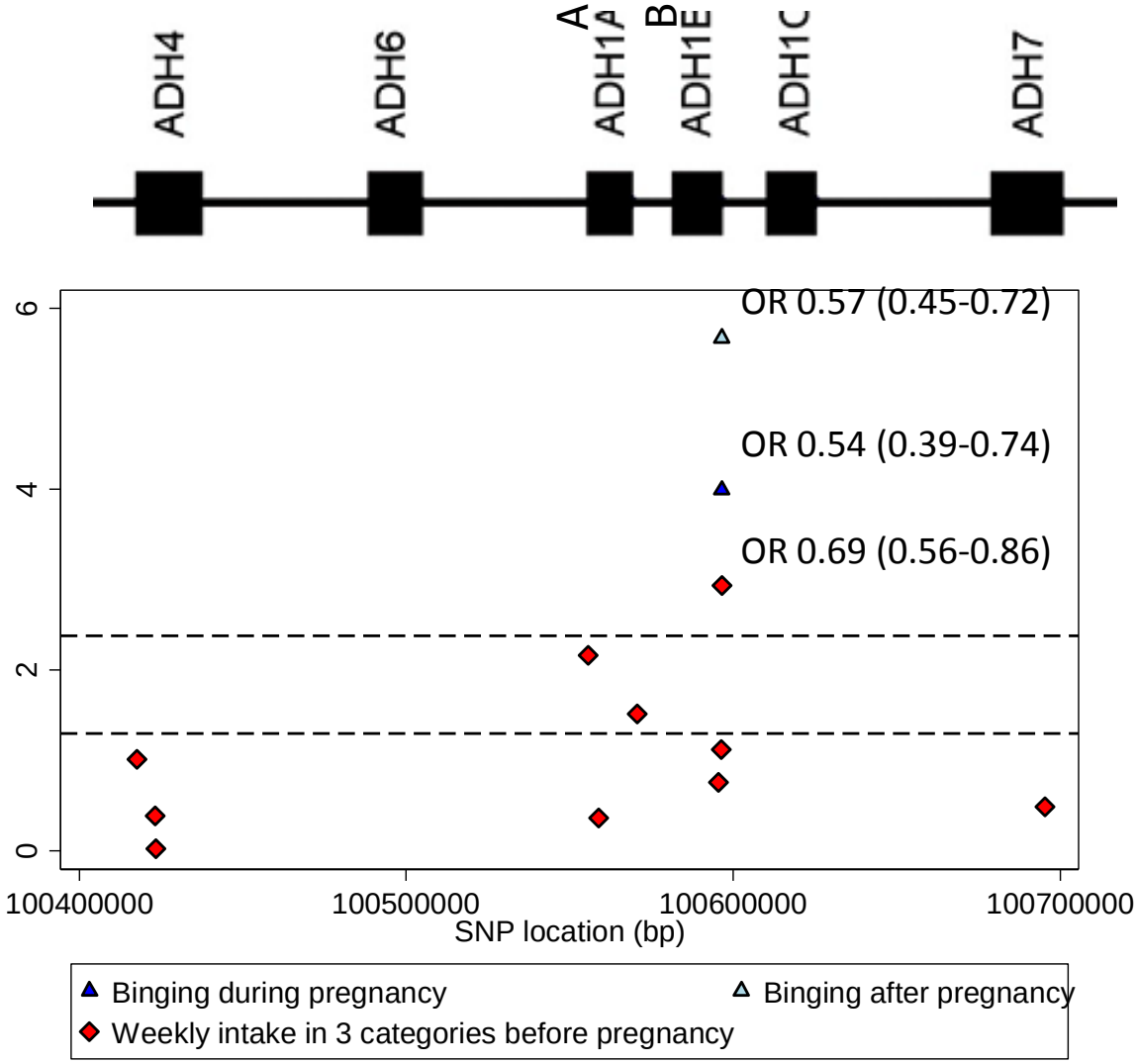
Gene	SNP
ADH4	rs4699714
ADH4	rs3762894
ADH4	rs4148884
ADH1A	rs2866151
ADH1A	rs975833
ADH1A	rs1229966
ADH1B	rs2066701
ADH1B	rs4147536
ADH1B	rs1229984
ADH7	rs 284779



Main Outcomes

- IQ at age 8 years: WISC-III (Wechsler, Golombok and Rust, 1992), age-adjusted

- SATS test results at age 11


ADH4
ADH6
ADH1A
ADH1B
ADH1C
ADH7
OR 0.57 (0.45-0.72)
OR 0.54 (0.39-0.74)
OR 0.69 (0.56-0.86)
0
2
4
6
100400000
100500000
100600000
100700000
SNP location (bp)
Binging during pregnancy
Binging after pregnancy
Weekly intake in 3 categories before pregnancy

Association between ADH1B genotype and alcohol intake

Time period		Absolute number	Proportion carrying rare allele - %	Chi-square test for trend	P-value
Maternal alcohol consumption levels					
Before pregnancy	never	511	6.5	13.15/1df	0.0003
	<1 drink/wk	2,693	5.7		
	1-6 drinks/wk	3,084	4.2		
	7+ drinks/wk	837	3.2		
First trimester	never	3,242	5.8	14.81/1df	0.0001
	<1 drink/wk	2,833	4.2		
	1-6 drinks/wk	1,030	3.3		
	7+ drinks/wk	138	2.9		

Association of confounding variables with maternal ADH1B genotype and maternal alcohol intake

	rare allele carrier (n=361)	rare allele non-carrier (n=7265)	P*	Drink < 1 unit per wk (n=5568)	Drink ≥ 1 unit per wk (n=6753)	P*
Mother's age (mean, SD)	28.5 (4.7)	28.2 (4.8)	0.248	27.6 (4.9)	28.5 (4.9)	<0.0001
Parity (1st baby)	157 (45.9%)	3137 (45.6%)	0.945	3538 (64.3%)	3209 (48.0%)	<0.0001
Higher than O-level education	131 (39.2%)	2386 (35.6%)	0.189	1424 (28.0%)	2632 (41.8%)	<0.0001
Manual social class	173 (59.9%)	3435 (62.7%)	0.344	2419 (54.1%)	2336 (39.2%)	<0.0001
Mother smoked during 1st trimester	70 (20.1%)	1678 (24.2%)	0.094	1372 (24.7%)	1734 (25.7%)	0.19
Calcium mg per week (mean, sd)	6741 (2010)	6555 (1945)	0.106	6432 (1990)	6731 (1945)	<0.0001
Vitamin C mg per week (mean, sd)	582 (247)	561 (240)	0.132	533 (237)	585 (241)	<0.0001
Iron mg per week (mean, sd)	74.6 (23.3)	72.6 (22.7)	0.126	71.1 (23.1)	74.7 (22.7)	<0.0001
Folate mg per week (mean, sd)	1786 (513)	1741 (501)	0.128	1712 (512)	1781 (498)	<0.0001
High EPDS score	57 (17.2%)	1076 (19.9%)	0.841	925 (18.3%)	1046 (16.7%)	0.05

Association between maternal ADH1B and children's cognitive outcomes

Outcome	Sample	Number	Average difference in score (SE)	P-value
Key Stage 2 Score	Original sample	6,637	1.99(0.57)	0.00045
	Original sample adjusted for pre-pregnancy alcohol	6,342	2.25(0.56)	0.00006
	UK born only	5,579	1.92(0.60)	0.0014
	UK born & adjusted for ASPM, MCPH1 & lactase persistence	5,410	2.83(1.31)	0.031
IQ score	Original sample	4,175	0.72(1.16)	0.54
	Original sample adjusted for pre-pregnancy alcohol	4,103	0.98(1.17)	0.40
	UK born only	3,704	0.41(1.22)	0.74
	UK born & adjusted for ASPM, MCPH1 & lactase persistence	3,588	-1.02(2.77)	0.71

Other genotypes

Gene	SNP	Mother (coef, 95% CI, p-value)	Child (coef, 95% CI, p-value)
ADH4	rs4148884	-2.23 (-4.13 to -0.33) p=0.022	1.86 (-0.11 to 3.82) p=0.064
ADH1A	rs2866151	1.01 (-0.70 to 2.71) p=0.247	-2.81 (-4.51 to -1.10) p=0.001
ADH1A	rs975833	1.14 (-0.68 to 2.96) p=0.219	-2.39 (-4.24 to -0.54) p=0.011
ADH1B	rs414736	0.62 (-1.17 to 2.41) p=0.498	-2.26 (-4.11 to -0.42) p=0.016
ADH7	rs284779	0.11 (-0.93 to 1.16) p=0.829	-1.20 (-2.22 to -0.175) p=0.022

Per allele effects - Model selected by AIC (Akaike's information criterion) - best model based on data

Conclusions and Future work

- Maternal ADH1B genotype is associated with maternal alcohol intake during pregnancy and offspring school performance at age 11.
- Child's genotype at the ADH1A, ADH1B, ADH4 and ADH7 locus is associated with IQ score at age 8.
- Results need to be replicated in other cohorts, but suggest that mothers' alcohol intake affects offspring cognition and school performance.

Prenatal alcohol exposure, childhood development and teenage drinking :a study of trans-generational effects

4-year project funded by UK Medical Research Council, start October 2010

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Cohorts moba CHILDREN OF THE 90s (ALSPAC)

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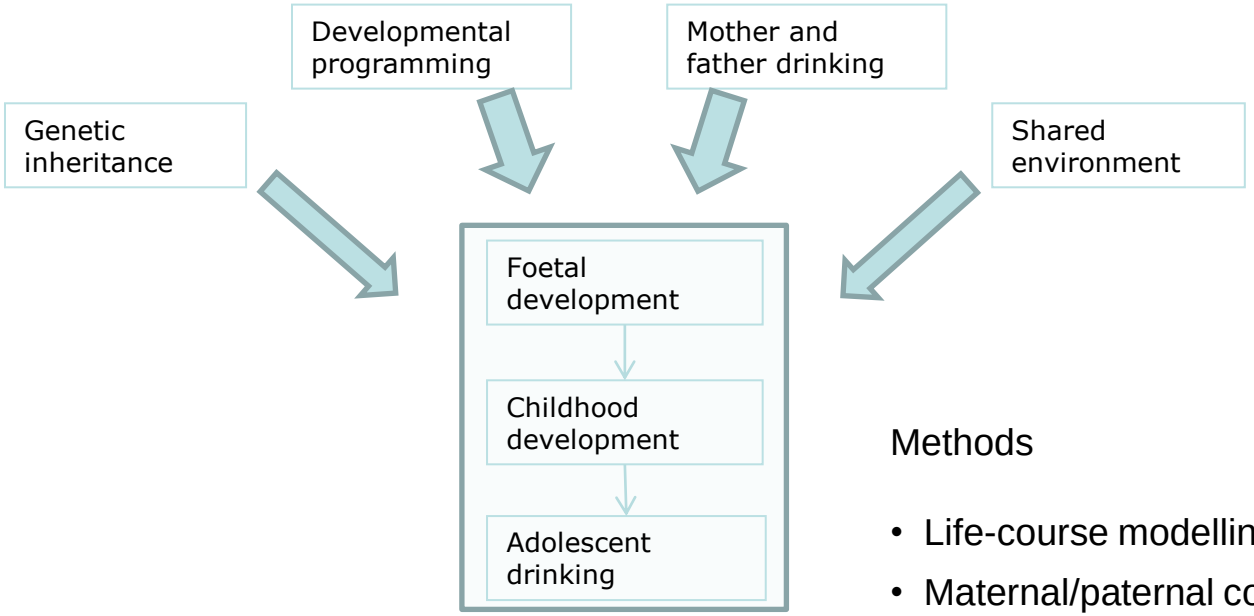
Prenatal alcohol exposure, childhood development and teenage drinking : a study of trans-generational effects



Methods

- Life-course modelling
- Maternal/paternal comparisons
- Within-siblings comparisons (MoBa)
- Epigenetic effects – candidate genes DNA methylation
- Mendelian Randomization
- Instrumental variable analyses

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