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Prenatal alcohol exposure and childhood atopic disease: A Mendelian randomisation approach

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Background: Few epidemiological studies have investigated whether alcohol consumption during pregnancy increases the risk of childhood atopic disease. A

difficulty with using reported alcohol intake to measure exposure is that under-reporting is common and associations are likely to be confounded. In contrast, a Mendelian randomisation approach should produce unbiased and unconfounded effect estimates and can strengthen causal inference.
Methods: In a UK population based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC), we have analysed whether the maternal alcohol dehydrogenase (ADH)1B gene variant is associated with childhood atopic outcomes at 7 years of age. Carriers of the minor A allele drink less in pregnancy and metabolise alcohol faster, thus reducing adverse effects of alcohol on the fetus. We also analysed associations with reported alcohol consumption in pregnancy.
Results: Maternal ADH1B genotype was strongly associated with childhood asthma. Mothers carrying the minor A allele were half as likely to have children with asthma as mothers who were homozygous for the G allele (odds ratio 0.50 (95% CI: 0.33 to 0.75), P=0.001, N=6,701). There were no significant associations with other atopic outcomes. In contrast, mothers who reported drinking once a week or more in the last two months of pregnancy were less likely to have children with asthma and hayfever than mothers who reported never drinking (OR 0.81 (0.65 to 0.99) and 0.75 (0.59 to 0.95), respectively).
Conclusions: The genetic results suggest that prenatal alcohol exposure increases the risk of childhood asthma. The contradictory associations with reported alcohol intake are likely to be confounded.

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Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood
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Background: Recent findings suggest that the natural history of asthma and atopy begins in foetal life. However, studies investigating the influence of foetal exposure to stressful life events (SLE) on asthma and atopic diseases are lacking.
Aim: To test whether the children of mothers who had experienced SLE during pregnancy are at an increased risk for asthma, atopic eczema and allergic rhinitis.
Methods: The association between maternal SLE (at least one among: divorce, mourning or loss of the job) during pregnancy and the occurrence of asthma and atopic diseases in childhood was studied in a population (n=3854) of children, aged 3-14 years, living in Northern Italy. The parents filled in a standardized questionnaire about the children's health and the events occurred to their mothers during pregnancy.
Results: 337 (9%) of the mothers experienced at least one SLE during pregnancy. After adjusting for potential confounders (including risk factors of the children and their families, birth complications or drug use during pregnancy and children's characteristics at birth), the foetal exposure to SLE was positively associated with wheezing (OR: 1.45, 95%CI: 1.07-1.97), asthma (OR: 1.68, 95%CI: 1.02-2.77), allergic rhinitis (OR: 1.69, 95%CI: 1.06-2.68) and atopic eczema (OR: 1.47, 95%CI: 1.08-2.00).
Conclusion: The children of mothers who had experienced SLE during pregnancy were at a moderately increased risk of having wheezing, asthma, eczema and allergic rhinitis during their childhood. Maternal stress during pregnancy may enhance the expression of asthma and atopic phenotypes in children, strengthening the hypothesis that proneness to atopy begins in utero.

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Clinical index to evaluate the risk of primary ciliary dyskinesia in children
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Introduction: Primary ciliary dyskinesia (PCD) is a rare genetic disorder causing a variety of symptoms. The diagnostics of PCD is challenging as the clinical presentation can differ in particular patients. Also the methods (as high-speed videomicroscopy or electron microscopy) to diagnose PCD are usually available only in specialized centres.
Aim & objective: To find out if a simple clinical index can be used to differentiate the patients with high risk of PCD.
Methods: All patients with PCD diagnosed in our clinic (n=31) and all patients sent to the diagnostic centre as suspected of PCD in 2009-2011 (n=352) were included into the study. We randomly divided the study group into 2 subgroups. The analysis subgroup was used for model preparation and hold-out group was used for subsequent cross-validization of the model. We measured quality of the test (model) by computing area under ROC curve (AUC) and discriminant validity by comparing total scores for group with or without PCD diagnosis.
Results: The clinical index included 7 yes/no questions concerning the history and clinical symptoms. One point was assigned to each yes answer. AUC for analysis subsample was 0.94, AUC for hold-out subsample 0.89. Discriminant validity was measured in whole study group by non-parametric Mann-Whitney U-test: (U=555.5, Z=-7.08, $p<0.0001$).
Conclusions: A simple clinical 7-item questionnaire can be used to evaluate the risk of PCD and to discriminate the patients that should be referred to diagnostic centre.

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PCD with normal ultrastructure is not rare
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Introduction: The presence of ultrastructural abnormalities (UA) on transmission electron microscopy (TEM) is proposed as gold standard for the diagnosis of Primary Ciliary Dyskinesia (PCD). Functional evaluation after ciliogenesis in culture (CC) is only proposed if the diagnosis is doubted. Because secondary changes are frequent, all samples are evaluated by CC at our centre. Since the detection of a *DNAH11* mutation, the existence of the subtype normal ultrastructure but abnormal motility (NU) is proven. Using CC, we show that this subtype is not as rare as thought.
Methods: Over 22 years, the CC procedure was used in 3077 subjects, of which 200 were diagnosed as PCD. Epithelial cells are isolated from nasal biopsies and cultured as a monolayer. After losing all the cilia they are brought into suspension, to gain cilia *de novo*.
Results: UA was found in 133 subjects, NU in 67. In only 35 of the NU, ciliary beat frequency (CBF) could be measured before CC. It was abnormal in 22 and normal in 13, with absent ciliary coordination in 7 of these 13. After CC, all the samples lacked coordination, pathognomonic for PCD. CBF was abnormal in 50 and normal in 17 subjects. Repeat biopsy in 18 patients was identical. CC was the only technique to make the diagnosis of PCD in 39 subjects.
nNO did not significantly differ from the UA group. There was familial occurrence of NU in 4 sibling pairs, consanguinity in 13.6%, situs inversus in 34%. The clinical characteristics (bronchiectasis, nasal secretions, hearing loss, draining ears, polyposis nasi, infertility) were similar in UA and NA.
Conclusion: CC is the most reliable tool to diagnose PCD and unambigouously detect patients with PCD and NA who might be missed when using other diagnostic methods.

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Development of postnatal lung function in very low birth weight infants with or without BPD
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Background: Very low birth weight (VLBW) infants (<1500g) with bronchopulmonary dysplasia (BPD) may suffer lung damage through mechanical ventilation and maturational arrest. Functional lung development was compared between VLBW infants with and without BPD.
Patients and methods: Sequentially lung function tests (LFT) were performed at 50, 70 and 100 weeks postmenstrual age in 55 VLBW infants (29 with BPD (O2 supplementation at 36 weeks gestational age) and 26 VLBW infants without BPD (controls)). Mean gestational age (26 vs 29 weeks), birth weight (815 g vs 1125 g), and rates of mechanical ventilation ≥7d (55% vs 8%) differed significantly between BPD and controls.
Main results: Body weight and length were persistently lower in BPD infants, as compared to controls, no significant differences were seen for respiratory rate, respiratory and airway resistance, functional residual capacity (FRC), maximal expiratory flow at FRC and blood gas values. Tidal volume, minute ventilation, respiratory compliance and FRC determined by SF6 multiple breath washout were significantly lower in BPD infants compared to controls, but the differences vanished after normalization to body weight.
Conclusions: While somatic growth and some lung function parameter were delayed in BPD infants, their lung function appeared to develop along trajectories of non-BPD infants when actual body weight is being considered. Longitudinal LFT of preterm infants after discharge may help to identify BPD infants at risk of incomplete recovery of respiratory function, which can lead to respiratory problems later on.

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Multiple trigger and episodic viral wheeze in early childhood: Are these phenotypes stable over time?
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Aim: In young children with wheeze it is common to distinguish between those who wheeze only during respiratory tract infections (episodic viral wheeze, EVW) and those who also wheeze due to other factors (multiple trigger wheeze, MTW). The stability of this classification has recently been questioned. In two population based cohort studies, we compared the prevalence and stability of these phenotypes in early childhood.

Methods: We included 14062 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) and 4300 from the Leicester Respiratory Cohorts (LRC). Mothers received postal questionnaires including questions on wheeze and triggers of episodes in past 12 months when children were aged 2, 4 and 6yrs.
Results: Between ages 2 and 6yrs, prevalence of current wheeze decreased from 18 to 10% in ALSPAC and from 23 to 16% in LRC. Among children with wheeze the proportion of those with MTW as opposed to EVW increased from 55% (both cohorts) to 70% (ALSPAC) and 74% (LRC). Among children with EVW who wheezed again 2yrs later, a considerable proportion were reclassified as MTW in both cohorts (Tables). There was less reclassification from MTW to EVW.

Table 1

		EVW 4yrs [%]	MTW 4yrs [%]
EVW 2yrs	ALSPAC	50	50
	LRC	44	56
MTW 2yrs	ALSPAC	19	81
	LRC	20	80

Table 2

		EVW 6yrs [%]	MTW 6yrs [%]
EVW 4yrs	ALSPAC	61	39
	LRC	53	47
MTW 4yrs	ALSPAC	16	84
	LRC	11	89

Conclusion: The phenotypes EVW and MTW show limited stability through early childhood suggesting that triggers of wheeze alone are not sufficient to distinguish underlying disease processes, or that the disease processes change in some children throughout this period.
Funding: BDS is recipient of a ERS/Marie Curie Joint Research Fellowship (MC 1614-2010).

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Increased risk of preschool wheeze both with higher BMI in infancy and at age 4 years

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Background: Overweight has been associated with wheezing and asthma both in children and adults. It is debated whether overweight early in life predisposes for later wheeze or if the association is due to asthmatic children being less active. The aim of this study was to explore the relationship between body mass index, BMI, and recurrent wheeze ($\geq$ 3 episodes during the last 12 months) at preschool age.
Methods: Data were obtained from a prospective, longitudinal study of a cohort of children born in Western Sweden in 2003. 8176 families (50% of the birth cohort) were randomly selected. The parents answered questionnaires at 6 and 12 months and at 4.5 years of age. The response rate at 4.5 years was 4496, i.e. 83% of the 5398 questionnaires distributed at 4.5 years. Odds ratios were calculated with BMI as a continuous variable.
Results: In multivariate analyses, the risk of recurrent wheeze at preschool age was increased both by a higher BMI at age 12 months (OR 1.2, 95% CI 1.03-1.4) and by a higher BMI at age 4 years (OR 1.2, 1.04-1.4).
Adjusting for recurrent wheeze during infancy or excluding children with recurrent wheeze during infancy had no major influence on the ORs.
In addition, recurrent wheeze in infancy did not increase the risk of overweight at 4 years.
The analyses controlled for preterm birth, smoking during pregnancy, family history of atopy, own allergic disease in infancy, parental education, short breast-feeding, small for gestational age, gender and maternal overweight before pregnancy.
Conclusion: A higher BMI at 12 months or at 4 years both increased the risk of recurrent wheeze at preschool age. Wheezing during infancy did not explain the associations seen.

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Interactions between exposure to cigarette smoke and variations in the GSTM genotype for asthma quality of life

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Background: Asthma is a heterogeneous condition and our hypothesis is that gene environment interactions explain some of the variation within the asthmatic population. Here we report on an interaction between exposure to second hand smoke (SHS, an oxidant stress) and variation in the gene coding for antioxidant protein GST-M for asthma outcomes.
Methods: Children with asthma were recruited from primary and secondary care across Scotland. A respiratory questionnaire and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) were completed and DNA collected. A subset underwent an assessment including spirometry and exhaled nitric oxide. Saliva was collected for cotinine analysis.
Results: From 894 children recruited, PAQLQ and DNA were obtained in 499 (56%). There were 88 children exposed to SHS. Compared to children null for GSTM who were not exposed to SHS, the overall PAQLQ score for exposed children null for GSTM was reduced (meaning worse quality of life) by a mean of -0.7 [95% CI -0.1, -1.3] p=0.020. Similar associations were present for domains of symptoms (mean difference -0.7 [-0.1, -1.3]) and emotions (mean difference -0.7 [-0.1, -1.2]) but not activities (mean difference -0.3 [95% CI -0.9, +0.3]). There were no differences in spirometry or exhaled nitric oxide between GSTM null children who were and were not exposed to SHS.
Conclusion: Our findings support the hypothesis that gene environment interactions are important to some of the heterogeneity of asthma. Whilst all children with asthma should avoid SHS exposure, parents of children null for GTSM (50% of all asthmatics) might be considered for specific intervention.