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Infant lung function and wheeze in later childhood within the Southampton Women's Survey

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To the Editor:

We were interested to read van der Gugten *et al.*'s study reporting associations between increased neonatal respiratory resistance and wheezing illnesses during infancy, and between reduced neonatal respiratory compliance and wheezing illnesses during the first 5 years of life and late-onset and persistent wheeze phenotypes. Reduced respiratory compliance was also associated with asthma, defined both according to primary care consultations, prescriptions or referral for wheezing illnesses, and according to patient reported symptoms and lung function at the age of 5 years.[1] The authors proposed that compliance and resistance might reflect different lung characteristics which are associated with symptoms in different age periods. Our data from normal-term infants within the Southampton Women's Survey birth cohort provide further evidence that impaired physiological measurements soon after birth are associated with specific wheeze phenotypes. We previously reported an association between lower forced expiratory flow at functional residual capacity ($V'max_{FRC}$) in early infancy and later transient wheeze.[2] The paper by Gugten *et al.* has led us to analyse our data further with regards to respiratory compliance (Crs) and we have found that lower Crs is associated with asthma in our cohort also. Using the raised volume thoracoabdominal compression technique we also measured forced expiratory flow in the first 0.4 seconds of expiration ($FEV_{0.4}$); lower $FEV_{0.4}$ measurements were associated with increased childhood asthma risk.

We have previously described our methods.[3] In brief, lung function was measured between 5 and 14 weeks of age in 147 term infants. Infants were tested lying supine in quiet sleep, augmented by oral chloral hydrate (75-100mg/kg). $V'max_{FRC}$ and $FEV_{0.4}$ were calculated from partial and raised volume expiratory flow volume curves respectively. Crs was calculated from passive flow-volume curves following single occlusions. Wheeze data were collected at 6, 12, 24 and 36 months and 6 years using questions from the ISAAC core questionnaire wheezing module. Ninety five children provided questionnaire data and spirometry at age 6 years. Associations between infant lung function measurements and binary outcomes were assessed using

poisson regression; linear regression was used for continuous outcomes. Significant confounders were included within multivariable models.[2] Table 1 shows an association between lower early infancy Crs and childhood asthma together with an association between lower $V'max_{FRC,}$ and transient wheeze. The former confirms van der Gugten's finding of reduced early life Crs in children later diagnosed with asthma and the latter, although not identical to van der Gugten's findings, is, however, consistent with their proposal that low airway calibre is a likely contributor to wheeze symptoms in infancy. In contrast to van der Gugten we did not find an association between Crs and persistent wheeze.

Van der Gugten's study employed the minimally invasive single breath occlusion technique to measure lung function, follow-up data included spirometry and information collected from general practitioners' electronic patient files. Strengths of this approach are large sample size (549 infants) and availability of data describing symptom frequency. Our study included additional measurements of forced expiratory flows but respiratory resistance and wheeze frequency data were not available. Our asthma outcome was not directly comparable to van der Gugten's since it was based upon a doctor's diagnosis irrespective of primary care contacts, current symptoms or medications.

Impaired neonatal lung function, characterised by reduced values for the fraction of expiratory time to peak tidal expiratory flow to total expiratory time ($t_{tpef:te}$), has previously been found to be associated with childhood asthma.[4] Our approach is unique, however, in employing the raised volume thoracoabdominal compression technique to consider the relationship between timed expiratory flows measured soon after birth and asthma later in childhood. We found that reduced $FEV_{0.4}$ was associated with asthma but not with other wheeze phenotypes.

Van der Gugten found higher neonatal Rrs and lower neonatal Crs to be associated with lower childhood FEV_1 and $FEF_{25-75\%}$. Within our cohort both $V'max_{FRC}$ and $FEV_{0.4}$ were positively associated with childhood FEV_1 and

$FEF_{25-75\%}$ (V,max_{FRC} p=0.001 and p<0.001 respectively and $FEV_{0.4}$ p=0.049 and p=0.041 respectively), Crs soon after birth was not significantly associated with these spirometric measurements. This difference between the two studies may reflect a lack of power in our smaller study, since a closer relationship could be expected between forced expiratory flows in infancy and childhood given that airway calibre is a significant determinant of each of these measurements.

Tracking of lung function suggests relative impairment of lung function persists from early infancy to childhood, yet investigation of the relationship between infant lung function and phenotypes of wheezing illness, as noted by van der Gugten, has produced conflicting results. Analysis of 125 infants enrolled in the Tucson Children's Respiratory Study found reduced $V'max_{FRC}$ during early infancy in individuals wheezing transiently at or before age 3 years, but no association was found with wheezing beyond 3 years of age.[5] In contrast, a study from Perth found reduced $V'max_{FRC}$ in infancy to be associated with persistent but not transient wheeze.[6] These differences may reflect variation in infant lung function techniques, correction for body size, age of outcome or the genetic pre-disposition of the population. Importantly, where invasive techniques have been used this has limited study size. Broad wheeze phenotypes are likely to be heterogeneous and variable contributions from separate sub-phenotypes across relatively low powered studies may give rise to conflicting results. In support of this heterogeneity we have we have previously presented data suggesting that the traditional persistent wheeze category contains a mix of individuals only some of whom those with onset of persistent wheeze before one year of age have relative lung function impairment from birth.[2]

We are grateful to Van der Gugten *et al.* for the opportunity to compare our findings with those from a larger cohort. Whilst previous studies have demonstrated reduced lung function soon after birth in individuals who wheeze in infancy,[7, 8] the relationship between infant lung function and wheezing disorders beyond infancy is less clear.[5, 6] van der Gugten's findings in conjunction with those from the Southampton Women's Survey

provide evidence that structural airway impairments in infancy may differentially predict asthma and wheeze in childhood.

Table 1. Mean infant lung function values according to wheeze phenotype determined at 6-year follow-up (Relationship between $V'max_{FRC}$ and $FEV_{0.4}$ and Tucson phenotypes previously published in Collins et al)

Phenotype	$V'max_{FRC}$		$FEV_{0.4}$		Crs^3	
	Ratio geometric mean	(95% CI)	Ratio geometric mean	(95% CI)	Ratio geometric mean	(95% CI)
No asthma	1 (reference)		1 (reference)		1 (reference)	
Asthma	0.76	(0.54, 1.07)	**0.83**	**(0.71, 0.97)***	**0.86**	**(0.74, 0.99)***
Never wheeze	1 (reference)		1 (reference)		1 (reference)	
Transient wheeze	**0.71**	**(0.58, 0.88)***	0.96	(0.87, 1.00)	0.96	(0.88, 1.05)
Late wheeze	0.84	(0.32, 2.22)	1.11	(0.76, 1.62)	1.01	(0.71, 1.42)
Persistent wheeze	0.67	(0.43, 1.05)	0.93	(0.76, 1.12)	0.97	(0.83, 1.15)

Measures of infant lung function were adjusted for age and sex where necessary and logarithmically transformed to achieve normality. Those who never wheezed formed the reference group for transient late and persistent wheeze, whilst never asthma was the reference for asthma. Linear regression adjusted for significant confounders (as described in Collins *et al*.), significant associations shown in bold.

*P < 0.05

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