Fetal growth restriction and asthma; is the damage done?

Kimberley C. W. Wang[1,2]*, Alan L. James[3,4] and Peter B. Noble[1]

Running Head: IUGR on asthma development

[1]School of Human Sciences, The University of Western Australia, Crawley 6009, Western Australia, Australia

[2]Telethon Kids Institute, The University of Western Australia, Nedlands 6009, Western Australia, Australia

[3]Department of Pulmonary Physiology and Sleep Medicine, West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Nedlands 6009, Western Australia, Australia

[4]Medical School, The University of Western Australia, Nedlands 6009, Western Australia, Australia

***Corresponding Author:**

Kimberley C. W. Wang, PhD.

School of Human Sciences,

The University of Western Australia

35 Stirling Highway,

Crawley 6009,

Western Australia, Australia

Email: kimberley.wang@uwa.edu.au

Abstract

Trajectories of airway remodelling and functional impairment in asthma are consistent with the notion that airway pathology precedes or coincides with the onset of asthma symptoms and may be present at birth. An association between intrauterine growth restriction (IUGR) and asthma development has also been established and there is value in understanding the underlying mechanism. This review considers airway pathophysiology as a consequence of IUGR that increases susceptibility to asthma.

Context – defining and understanding asthma

Asthma is a condition of variable and transient symptoms of breathlessness, wheeze, chest tightness and cough, triggered by exposures such as viral infections, allergens, cold air or exercise. Contraction of the airway smooth muscle (ASM) layer around the wall reduces lumen diameter, increases resistance to airflow and the work of breathing. Reduced airflow is most often measured as the forced expiratory volume in one second (FEV_1), which falls proportionally more than forced vital capacity (FVC), the total volume of air exhaled out of the lung. Some degree of airway narrowing can be induced in most people, but is excessive in those with asthma, a condition referred to as 'airway hyperresponsiveness'.

Pathology in asthma lies principally at the level of the bronchial tree, affecting both large and small airways, but to varying degrees across patients (20). The transient, excessive airway narrowing in asthma is determined by increased ASM thickness within an inflamed wall (21, 61). Excess secretion of mucus also plays a part in airway narrowing, especially in severe cases (42), and there is more recent interest on the adverse consequences of ventilation inhomogeneity (19) and/or heterogeneously distributed airway remodelling (20, 72).

A fundamental and unanswered question in asthma is how airway pathology, particularly increased ASM thickness, evolves to produce respiratory impairment. The conventional hypothesis is that inflammation drives remodelling in asthma (91). However, histological studies in children have failed to identify inflammation prior to airway remodelling (15). There is instead reason to suggest that airway remodelling is an independent developmental disorder (outlined below), a concept that may explain the known association between intrauterine growth restriction (IUGR) and asthma.

Asthma – why should it be considered a disease of development?

The answer to this question in many ways is addressed in other comprehensive reviews (25, 53) describing a disease that first presents in childhood and the vast data demonstrating immunological priming by prenatal or early postnatal inflammatory events. While it serves no purpose to replicate the information contained within the above reviews, we wish to set the scene by presenting evidence from a structural-functional (physiological) perspective that implicates disrupted developmental processes in the onset of asthma.

Let us first consider the trajectory of one of the primary structural abnormalities in asthma; the ASM layer. Children diagnosed with asthma have increased thickness of the ASM layer (75) indicating that the principal effector for bronchoconstriction is abnormal early in the clinical course of the disease. It can even be argued that ASM thickening precedes diagnosis of asthma since children presenting with ASM remodelling at pre-school age go on to develop asthma (66). When further examining changes in ASM thickness in adult life, there seems to be little to no impact of age, age of diagnosis or duration of disease on ASM thickening (33). The damage may well be done; the ASM layer is thickened early in life (prior to or shortly after birth) with little or no meaningful progression in remodelling thereafter.

Temporal changes in airway structure in asthma mirror the trajectory of function. Measures of airway function soon after birth (69) have shown functional impairments that likely reflect the airway geometry (16). For example, the Perth Infant Asthma Follow-up study assessed airway responsiveness from 1 month to 24 years of age. Data from this longitudinal cohort demonstrate that: (i) airflow capacity is partially established in infancy (70) as low lung function at birth correlates with poorer lung function in adulthood (69), and; (ii) reduced lung function at 1 month of age is predictive of persistent asthma and wheeze at 24 years of age (69,

70). Another study of the same cohort showed that increased airway responsiveness to histamine in infancy is associated with childhood wheeze (88). These data are consistent with the idea that abnormal lung development and growth that occur *in utero* or very early in life will alter respiratory function from the beginning of the postnatal period and subsequently increase risk to diagnosed asthma and other respiratory illness.

Historical perspective of the 'fetal origins of adult disease hypothesis'

In 1986, Barker and Osmond observed that poorer parts of the United Kingdom with high infant mortality also had elevated rates of adults with ischaemic heart disease, and implicated poor nutrition in early life as a cause of disease (9). Barker identified a similar association between poor nutrition and obstructive lung disease and introduced the concept of 'programming', wherein an adverse *in utero* environment retards fetal weight gain and constrains irrecoverably the growth of the airways (7). Several years later, Lucas refined the definition of 'programming' as the *"induction, deletion, or impaired development of a permanent somatic structure or the 'setting' of a physiological system by which an early stimulus or insult, operating at a 'sensitive' period, results in long-term consequences for function"* (50). In 1992, Hales and Barker proposed the *'thrifty phenotype'* hypothesis in the context of type 2 diabetes, whereby the fetus and infant was considered nutritionally thrifty in an environment of scarce nutrition, resulting in impaired development of the pancreas (29). It was argued that the negative health consequences to the infant would be minimised if similar nutritional conditions were maintained in postnatal life, whereas risk of type 2 diabetes would increase if extrauterine conditions abruptly shifted from low to high nutrition (29). In ensuing years, Gluckman *et al.* dubbed this nutritional mismatch the 'Predictive Adaptive Response' theory (27).

The seminal studies described above provided the grounding for Barker to coin the overarching paradigm; the 'fetal origins of adult disease (FOAD)' hypothesis which states that environmental factors, particularly nutrition, act in early life to programme the risks for the early onset of cardiovascular and metabolic disease in adult life and premature death (6). The hypothesis described a framework to identify why fetal undernutrition occurring at different trimesters leads to the development of cardiovascular disease in later life. Although there is now an overwhelming body of evidence from population studies supporting the FOAD, the hypothesis was not initially universally accepted. Critics pointed to the limitations of Barker's epidemiology studies, such as a lack of data to show nutrition as the underlying factor for the associations and any specific correlation between fetal growth and adult disease (71). Several of these sceptics become converts after their own data collection supported Barker's hypothesis (26). An interview with David Barker about the legacy of his findings, published in The New Yorker, discussed the opposition he faced throughout his career, and his strong belief in his data (30).

Association between IUGR, low birth weight and asthma

Intrauterine growth restriction is a condition of pregnancy where the developing fetus undergoes a range of neuroendocrine and cardiovascular adaptations in response to reduced nutrient and oxygen supply (including placental insufficiency) that affects normal growth and development (54). Given that fetal lung development is controlled by numerous humoral, mechanical and genetic signals that are susceptible to deviations from homeostatic conditions, the FOAD hypothesis fittingly extends to the respiratory system. Indeed a relationship between IUGR and chronic obstructive pulmonary disease has been proposed for several decades (8). A similar association between IUGR and asthma has now also been realised (39), and there is

an intriguing correlation between reduced fetal size and incidence of wheeze and asthma at 5, 10 and 15 years of age (85-87).

The clinical definition of IUGR is a birth weight less than 2 standard deviation below normal weight (or less than the 10^{th} percentile). In a study of 763,666 children from the Swedish Medical Birth Register, the odds ratio for asthma was 1.24 in IUGR affected children compared with those born at a healthy weight (38). Other studies demonstrate that IUGR is associated with reduced lung function ($FEV_{0.4}$, FEV_1, FVC, FEV%, forced expiratory $flow_{25-75}$) (18, 40, 60) and increased airway resistance (81). The definition of IUGR is distinct from low birth weight (<2.5 kg), though there is a clear and intuitive relationship between these conditions. Epidemiological studies around the globe have repeatedly shown that babies with low birth weight have an increased risk of respiratory disease in adult life, including asthma (8, 10, 68, 90). Two meta-analyses concluded that low birth weight is associated with increased risk of asthma both in children and adults (59, 102), suggesting adverse intrauterine conditions and impaired fetal growth as a determinant of obstructive airway disease.

Onset of airway pathology after IUGR

There is mounting evidence that IUGR causes airway pathology in the postnatal period and we will separately consider direct effects on structure-function (a particular focus) as well as inflammation. Notwithstanding the postulated interrelationship between airway structure-function and inflammation, it is reasonable to assume that any developmental insult (e.g., undernutrition has already been highlighted) which modifies airway structure-function or inflammation will increase susceptibility to disease, but these disorders do not have to originate from the same pathway. In a mouse model where airway remodelling and inflammation were independently induced, both abnormalities caused exaggerated constriction of the airway

lumen alone and was further exacerbated when remodelling and inflammation occurred simultaneously (93). The findings of this biological simulation emphasised that airway pathologies acquired through different pathways will combine to worsen function and disease outcomes. An effect of IUGR on airway structure-function and/or inflammation may therefore tip the scales in favour of airway disease.

Animal models of IUGR have been employed to better understand the implications to postnatal health, including rats, mice and sheep. The general approach to induce IUGR is to reduce the availability of nutrients or oxygen through maternal undernutrition or hypoxia, or placental restriction after surgical intervention (36, 58, 83). Using maternal hypoxia-induced IUGR in rodents as an example, a decrease in birth weight of at least 22% was observed, corresponding to the 10^{th} percentile of the normal population, comparing well with what is observed clinically (36). A decrease in body weight alone is of course unlikely to explain any association with asthma, however, can be considered a marker of a perturbed system.

There are a variety of animal studies that have examined changes in airway structure-function and/or inflammation after IUGR, findings of which will be discussed below. In addition to the acknowledged differences in species and methodological approach to IUGR induction, the duration and timing of prenatal intervention is an important variable that will affect study findings. Airway development begins relatively early in gestation (pseudoglandular phase), compared with alveoli that appear later in gestation (saccular phase) and continue to populate into the postnatal period (79). Due to these temporal differences in airway and lung (alveolar) development, the phenotypic response to IUGR may theoretically differ if the exposure occurs early or later in gestation. That is, an airway disorder with early disruption and/or a lung parenchymal disorder with later exposure. This observation is

demonstrated nicely using data from the Dutch famine cohort; individuals that were exposed to restricted nutrients in early and mid-gestation, but not late gestation, had an increased prevalence of obstructive airway disease (49).

Airway structure-function

A first consideration is whether lung (and/or airway) size is reduced after IUGR and can account for lower exhaled volumes and flow. There is a clear and consistent decrease in absolute lung weight after IUGR (46, 48, 73, 82, 95), but importantly, not relative to body weight (2, 48, 73, 97). That lung size remains proportional to body mass is significant because lung function is always normalised to anthropometric parameters, as was the case in the Perth Infant Asthma Follow-up study, where maximal flow was standardised to infant body length (70). Direct measurements of lung volume (by plethysmography or stereology) have been performed in rodents, and are not affected by IUGR at juvenile (92) or adult timepoints (92, 94). Assuming that basement membrane perimeter is an appropriate index of airway size (35), there is also no evidence of an effect of IUGR on airway size in mice, rats or sheep. Respiratory consequences after IUGR may therefore be more complicated than a simple reduction in organ growth.

Any physiological change after IUGR that favours narrowing of the airway lumen is expected to increase susceptibility to airflow limitation in asthma. There is a well-established relationship between airway structure and function (57) that describes a balance between forces produced by the ASM layer and opposing mechanical after-loads. Activation of the ASM is regulated by the effectiveness of physical barriers such as the airway epithelium (67), while the extent of lumen narrowing is determined by wall compliance and encroachment of the

folded mucosa (64, 65). Many of these morphological properties have been shown to be susceptible to IUGR.

Controversy endures regarding the physiological role of the ASM layer under conditions of health (56), with most recent data strengthening support for the idea that contraction of ASM minimises anatomical deadspace (24). To the contrary, there is little doubt about the adverse consequences of a thickened ASM layer in asthma severity (33), and with this in mind, several studies have examined changes in ASM thickness after IUGR. In a mouse model of IUGR produced by maternal exposure to hypoxia during mid gestation (specifically the pseudoglandular-canalicular phase), there was an increase in the thickness of the ASM layer (95). Thickness of the ASM layer was also inversely correlated with body weight (Figure 1). The mechanism of ASM thickening was initially thought to reflect increased proliferation of ASM cells in view of studies demonstrating hyper-proliferation of fetal ASM cells from human subjects that were cultured under hypoxic conditions (31). However, proliferation of fetal ASM after maternal hypoxia was not different from the Control group, nor was there evidence of differential apoptosis (in fact apoptosis of fetal ASM cells was not observed in either group) (95). Alternative explanations for the increased thickness of the ASM layer seen in the IUGR group is cell hypertrophy or increased deposition of extracellular matrix (ECM) within the layer, changes which have been observed respectively in patients with asthma (34) and fixed airflow obstruction (37).

Thickening of the ASM layer after IUGR, as proposed above, could certainly contribute to increased susceptibility to asthma, requiring only a broncho-constricting stimulus (inflammation in response to allergen) to promote airway narrowing. The mouse study was nonetheless preliminary observations and it is important to appreciate that ASM remodelling

does not persist after the pregnant mice are returned to normoxic conditions 3-4 days prior to birth (95) and was not detectable in juvenile and adult mice after IUGR (92). There were similarly no changes in ASM thickness in a sheep model of late gestation placental restriction (97). Changes in mRNA expression of α-smooth muscle actin has however been observed after IUGR (45). Caffeine exposure from gestational days 7-20 produced IUGR and was associated with increased α-smooth muscle actin (45) and may contribute to airway and/or vascular remodelling.

In addition to potential changes in ASM structure, the reactivity of the airway wall to a contractile stimulus is altered by IUGR. In a rodent model of isocaloric protein restriction, respiratory system resistance was increased after methacholine inhalation challenge in young male offspring, and before and after methacholine in adult male offspring (1). The study did not assess female offspring, which do not necessarily respond to IUGR in the same manner as male counterparts. Male offspring from maternal hypoxia-induced IUGR mice are hyperresponsive to methacholine in early life and hyporesponsive in later life (92). The latter is accounted for by reduced ASM contractility, as was demonstrated in tracheal segments *in vitro*, where force per muscle cross-sectional area was reduced (62). In comparison, female offspring are normo-responsive in early life and hyperresponsive in later life (92) (Figure 2). Observations of sexual dimorphism in the response to IUGR are not inconsistent with asthma trajectories where there is a higher prevalence of asthma in males during early life but a higher prevalence in females in later life (78). An effect of IUGR which favours airway hyperresponsiveness in females and hyporesponsiveness in males with age would be expected to shift asthma towards a female dominated disease. Sex differences in the response to IUGR logically point to hormonal influences, a research area that warrants attention, as it may have relevance to asthma prevalence in males and females (43).

The extent of bronchoconstriction produced by ASM contraction is dependent on opposing mechanical afterloads (57). Wignarajah *et al*. proposed that a likely consequence of IUGR is increased airway compliance, based on findings of reduced cartilage area in sheep airways after placental restriction (97). In pigs, cartilage abundance is inversely related to both compliance and airway narrowing induced by parasympathetic nerve stimulation (65). A change in airway wall compliance has been noted in infants with wheezing disorders (23). Direct measurements of airway compliance (stiffness) after IUGR do not support the proposal of an increase in airway compliance. Tracheal segments from adult mice who were exposed to hypoxia-induced IUGR were notably stiffer compared with Control mice, and in this instance the effect was independent of sex (62). An increase in airway stiffness has also been demonstrated in asthma (14), though its significance to airway function is disputed. Stiffening could certainly be protective in providing a mechanical opposition to ASM shortening (55). The counter-argument is that airway stiffness adversely effects airway function. Airway stiffness regulates the response to dynamic stresses and strains produced by breathing movements (4, 63). Stiffening of the airway wall attenuates mechanically mediated bronchodilation, particularly in response to deep inspiration (63), which in turn facilitates a more pronounced narrowing response. There is also evidence that when in contact with a more rigid substrate, contractile performance of ASM cells is enhanced (3). Together, there is an argument to be made that airway wall stiffening after IUGR contributes to asthma by blunting inhibitory control of ASM or upregulating a contractile phenotype of ASM.

Non-uniform ventilation (heterogeneity) has been implicated in asthma pathogenesis. Using nitrogen washout protocols, ventilation heterogeneity was correlated with airway hyperresponsiveness in asthma, independent of inflammation (19). Ventilation heterogeneities

are related to both poor asthma control and more frequent exacerbations (13) and increase with bronchoconstriction (89). Given that ventilation heterogeneities in patients with asthma remain relatively fixed over time (six months apart) (17), changes may reflect an underlying structural or mechanical mechanism. In a rat model of maternal hypoxia-induced IUGR, male offspring exhibited increased variability of lumen calibre in histological sections (94). It was suggested that the most likely explanation was a variation in airway compliance, particularly as lungs were fixed at a distending pressure of 20 cmH_2O, raising the possibility of variable inflation between airways. Subsequent modelling assessed potential consequences for human lung function based on variable lumen calibre driven by changes in compliance (94) (Figure 3). The results of this mathematical simulation suggested that bronchoconstrictor response would be enhanced in an IUGR individual.

The airway epithelial barrier is abnormal in asthma, a defect which presents early in life. Most notably, there is a dysregulation of epithelial tight junctions in children with asthma (47), contributing to a 'leaky' membrane and by extension reduced protection against inhaled allergens. There is very little evidence to suggest that the epithelial barrier is compromised after IUGR. Maternal-hypoxia induced IUGR in mice does not affect epithelial expression of claudin-1, claudin-18, occludin and zonula occluden-1 (48). In growth-restricted sheep, the airway epithelial area is reduced at eight weeks postnatal age (97), however, it is not clear how such changes in epithelial area would affect epithelial barrier function. Percentage epithelial loss of epithelium is positively correlated to contractile response to acetylcholine (67), suggesting that gross morphology of the epithelium does somewhat influence functional response. The same study did not observe any correlation between epithelial area and permeability.

A variety of other respiratory changes after IUGR have been documented that are not necessarily characteristic of an asthmatic phenotype. In the aforementioned late gestation sheep model of IUGR, there was a thicker alveolar blood-air barrier due to expansion of the basement membrane, reduced number of alveoli and a thicker septum following increased ECM deposition (51, 52). The rat model of IUGR induced via caffeine exposure (introduced during periods of both airway and lung parenchymal development) showed similar findings to the sheep model of IUGR, where there was a thickened alveoli septum with increased pulmonary interstitium in the IUGR offspring (45). Somewhat surprising, structural differences in sheep were not accompanied by changes in lung compliance (52), in contrast to IUGR rats where there was a reduction in lung compliance and a concomitant profibrotic remodelling of the ECM (1). A modification in the amount and type of ECM is a feature of asthma (5), including changes within the lung parenchyma (96). Mechanical changes to the lung in asthma are reflected by reduction in lung elastic recoil pressure (increased compliance) (84) and therefore do not mirror changes observed in animals after IUGR. Changes to lung parenchyma after IUGR may therefore reflect the effects of late gestation exposure. Finally, there is a subtle change in diaphragmatic function after IUGR, characterised by delayed relaxation following electrical field stimulation (22). In asthma, impaired respiratory skeletal muscle function (80) may be expected due to a reduced sarcomere length following lung hyperinflation (76). To the best of our knowledge, intrinsic physiological abnormalities of respiratory skeletal muscles have not been identified in asthma.

Inflammation

A shift in inflammatory profile after IUGR is expected to modify susceptibility to diseases of immunity, including asthma. In the maternal hypoxia-induced IUGR rodent model, total inflammatory cells are increased in the bronchoalveolar lavage fluid in juvenile and adult

mice (48) (Figure 4), with a predominance towards neutrophils in adult rats (94). Various cytokines in the bronchoalveolar lavage fluid are also modified; IUGR in mice is associated with an increase in interleukin (IL)-2, IL-13 and eotaxin, but only in male offspring (48), again highlighting the potential differential effect of sex on the response to developmental disorders. In a rat model of IUGR following caffeine exposure, there was increased expression of transforming growth factor β, IL-1β, and IL-8 in the lungs of female offspring (45). Collectively these data suggest that the inflammatory profile of IUGR offspring is abnormal and may play a role in the inflammatory cascade present in asthma. The inflammatory changes may be specific to the lungs, as was proposed in the IUGR mouse study, where changes within bronchoalveolar lavage fluid were not replicated in fluid obtained after peritoneal gavage, an index of systemic inflammation (48) (Figure 4). Shorter term systemic inflammation is probable, as was the case after single umbilical artery ligation in sheep, which increased pro-inflammatory cytokines in IUGR fetuses 1 week after ligation (11).

It is important to appreciate that the above studies reflect the naïve state of an unchallenged immune system. Symptoms of asthma are however brought on through exposure to various environmental triggers, particularly allergens, but also cold air, exercise or respiratory tract viral infection. Although wheezing in infancy is associated with reduced lung function, the development of sensitivity to aeroallergens remains the biggest postnatal risk factor for persistent wheezing and diagnosed asthma in childhood (32). The question is then whether the response to environmental triggers differs in an individual subject to growth restriction *in utero*.

Numerous studies have examined the effect of exposing IUGR offspring to environmental stimuli. Following ovalbumin (allergic) sensitisation and challenge, the

offspring of mice with protein restriction-induced IUGR showed , increased concentrations of IL-13, IL-14, tumour necrosis factor-α (TNF-α) and number of eosinophils, neutrophils and macrophages in the bronchoalveolar lavage fluid, as well as immunoglobulin E in the serum (Xing *et al.*, 2020). Of significance, this inflammatory response to ovalbumin was greater in IUGR offspring, the mechanism of which was attributed to epigenetic modifications of the vascular non-inflammatory molecule 1 (Vnn-1) gene (100). Methylation of the Vnn-1 promoter is apparent in asthmatic children who respond poorly to corticosteroid treatment (99). In a rat model of IUGR induced by undernutrition, offspring exposed to ovalbumin exhibited increased lung infiltration of eosinophils and greater plasma immunoglobulin E, compared with age-matched animals that were not growth restricted (101). The mechanism was again attributed to epigenetics, specifically histone acetylation of the endothelin-1 gene promoter. Response to other non-allergic stimuli has also been reported to change in IUGR-affected animals. In the offspring of IUGR rats exposed to lipopolysaccharide, there were increased inflammatory cell infiltration, lung injury scores and levels of IL-6 and TNF-α in the lungs compared with Control offspring (45). Exposure to lipopolysaccharide is implicated in the resistance to corticosteroid therapy and more severe asthma (28). Overall, it appears that the inflammatory response to environmental triggers is excessive after IUGR and likely contributes to its association with asthma. Not to be discounted, this 'second hit' scenario could certainly interact with remodelling processes and further increase ASM thickness.

Future avenues for study

The remit of this review was to challenge convention and present a controversial viewpoint that, right or wrong, would stimulate new discussion on the pathogenesis of asthma. With this in mind, we are proposing that developmental interruptions such as IUGR give 'birth' to an abnormal airway wall that predisposes to asthma. Changes in airway compliance are

noted, as well as changes in lung immunity that appear to involve epigenetic phenomenon, an area of research that should continue. Sex-dependent effects of IUGR are also of interest and may provide important information on hormonal influences in disease development. A particularly intriguing question is whether the ASM is abnormal at birth? This speculation is raised with knowledge of the trajectory of airway structure-function and preliminary evidence from animal studies which together provides only circumstantial evidence. The underlying assumption of all animal models is that the methodological approach used to simulate IUGR (undernutrition, hypoxia and placental restriction induced during early or late gestation for variable durations) is relevant to the human condition. The good news is that this should in theory be a testable hypothesis; directly assess airway structure at birth and track its association with future disease. Concrete data on the kinetics of ASM remodelling should inform strategies for disease mitigation and possibly pharmacological ablation of the ASM layer, proposed in our recent review (91).

Computed tomography (CT) has been used to assess lung growth and airway dimensions from healthy individuals from birth to adulthood (41, 74). A parameter of particular interest includes lumen cross sectional area across airway generations, as has been assessed in infants with chronic lung disease (77). Studies could be designed to examine how airway dimensions (mean and variability i.e., heterogeneity) is impacted by IUGR. The limitation of CT (in addition to concerns relating to dose of radiation) is that resolution of the airway wall is low, and it is not possible to discern the ASM layer. Other imaging approaches can be considered, particularly polarised-sensitive optical coherence tomography (44) that extracts quantitative images of the ASM layer based on tissue orientation and organisation. Probes are however delivered bronchoscopically (98), and therefore more invasive compared with the CT-based approach. If these logistical constraints can be overcome, polarised-sensitive optical

coherence tomography could be used to determine if the ASM layer is thickened in IUGR individuals who go on to develop asthma.

One last suggestion for future study is the assessment of airway reactivity in individuals who were identified as having been affected by IUGR. It would be interesting to establish whether these subjects have an innately different bronchoconstrictor response, as has been suggested in part by animal studies. This scenario is akin to asymptomatic hyperresponders (12) who have more reactive airways despite no overt burden of disease. Individuals who exhibit increased responsiveness to contractile stimuli are potentially at greatest risk of asthma development, if they also acquire an inflammatory disorder, particularly allergy.

Conclusion

There is good reason to suggest that asthma is a disease of development. Identifying the mechanism for any association between IUGR and asthma serves to advance our broader knowledge of airway disease. With solid scientific evidence demonstrating an effect of IUGR on airway pathophysiology (altered structure-function and inflammation), strategies for intervention prior to and after birth can therefore be designed, possibly through manipulation of specific developmental processes.

Funding

K.C.W.W. is supported by a Thoracic Society of Australia and New Zealand/National Asthma Council of Australia - Asthma and Airways Career Development Fellowship, and a National Health & Medical Research Council of Australia Early Career Research Fellowship (1090888) and Project Grant (1120128).

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Authors' contribution

All authors drafted the manuscript, critically revised the manuscript and approved the manuscript.

436 **References**

437 1. **Alejandre Alcazar MA, Ostreicher I, Appel S, Rother E, Vohlen C, Plank C, and**
438 **Dötsch J**. Developmental regulation of inflammatory cytokine-mediated Stat3 signaling: the
439 missing link between intrauterine growth restriction and pulmonary dysfunction? *J Mol Med*
440 *(Berl)* 90: 945-957, 2012.

441 2. **Allison BJ, Hooper SB, Coia E, Zahra VA, Jenkin G, Malhotra A, Sehgal A,**
442 **Kluckow M, Gill AW, Sozo F, Miller SL, and Polglase GR**. Ventilation-induced lung injury
443 is not exacerbated by growth restriction in preterm lambs. *Am J Physiol Lung Cell Mol Physiol*
444 310: L213-223, 2016.

445 3. **An SS, Kim J, Ahn K, Trepat X, Drake KJ, Kumar S, Ling G, Purington C,**
446 **Rangasamy T, Kensler TW, Mitzner W, Fredberg JJ, and Biswal S**. Cell stiffness,
447 contractile stress and the role of extracellular matrix. *Biochem Biophys Res Commun* 382: 697-
448 703, 2009.

449 4. **Ansell TK, McFawn PK, Mitchell HW, and Noble PB**. Bronchodilatory response to
450 deep inspiration in bronchial segments: the effects of stress vs. strain. *J Appl Physiol (1985)*
451 115: 505-513, 2013.

452 5. **Araujo BB, Dolhnikoff M, Silva LF, Elliot J, Lindeman JH, Ferreira DS, Mulder**
453 **A, Gomes HA, Fernezlian SM, James A, and Mauad T**. Extracellular matrix components
454 and regulators in the airway smooth muscle in asthma. *Eur Respir J* 32: 61-69, 2008.

455 6. **Barker DJ**. Fetal origins of coronary heart disease. *BMJ* 311: 171-174, 1995.

456 7. **Barker DJ**. The intrauterine origins of cardiovascular and obstructive lung disease in
457 adult life. The Marc Daniels Lecture 1990. *J R Coll Physicians Lond* 25: 129-133, 1991.

458 8. **Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, and Shaheen SO**. Relation
459 of birth weight and childhood respiratory infection to adult lung function and death from
460 chronic obstructive airways disease. *BMJ* 303: 671-675, 1991.

9. **Barker DJ, and Osmond C**. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 327: 1077-1081, 1986.

10. **Barker DJ, Osmond C, Forsén TJ, Thornburg KL, Kajantie E, and Eriksson JG**. Foetal and childhood growth and asthma in adult life. *Acta Paediatr* 102: 732-738, 2013.

11. **Bertucci MC, Loose JM, Wallace EM, Jenkin G, and Miller SL**. Anti-inflammatory therapy in an ovine model of fetal hypoxia induced by single umbilical artery ligation. *Reprod Fertil Dev* 23: 346-352, 2011.

12. **Boulet LP**. Asymptomatic airway hyperresponsiveness: a curiosity or an opportunity to prevent asthma? *Am J Respir Crit Care Med* 167: 371-378, 2003.

13. **Bourdin A, Paganin F, Préfaut C, Kieseler D, Godard P, and Chanez P**. Nitrogen washout slope in poorly controlled asthma. *Allergy* 61: 85-89, 2006.

14. **Brackel HJ, Pedersen OF, Mulder PG, Overbeek SE, Kerrebijn KF, and Bogaard JM**. Central airways behave more stiffly during forced expiration in patients with asthma. *Am J Respir Crit Care Med* 162: 896-904, 2000.

15. **Castro-Rodriguez JA, Saglani S, Rodriguez-Martinez CE, Oyarzun MA, Fleming L, and Bush A**. The relationship between inflammation and remodeling in childhood asthma: A systematic review. *Pediatr Pulmonol* 53: 824-835, 2018.

16. **Cox DW, Mullane D, Zhang GC, Turner SW, Hayden CM, Goldblatt J, Landau LI, and Le Souëf PN**. Longitudinal assessment of airway responsiveness from 1 month to 18 years in the PIAF birth cohort. *Eur Respir J* 46: 1654-1661, 2015.

17. **de Lange EE, Altes TA, Patrie JT, Parmar J, Brookeman JR, Mugler 3rd JP, and Platts-Mills TA**. The variability of regional airflow obstruction within the lungs of patients with asthma: assessment with hyperpolarized helium-3 magnetic resonance imaging. *J Allergy Clin Immunol* 119: 1072-1078, 2007.

18. **Dezateux C, Lum S, Hoo AF, Hawdon J, Costeloe K, and Stocks J**. Low birth weight for gestation and airway function in infancy: exploring the fetal origins hypothesis. *Thorax* 59: 60-66, 2004.

19. **Downie SR, Salome CM, Verbanck S, Thompson B, Berend N, and King GG**. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. *Thorax* 62: 684-689, 2007.

20. **Elliot JG, Jones RL, Abramson MJ, Green FH, Mauad T, McKay KO, Bai TR, and James AL**. Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. *Respirology* 20: 66-72, 2015.

21. **Elliot JG, Noble PB, Mauad T, Bai TR, Abramson MJ, McKay KO, Green FHY, and James AL**. Inflammation-dependent and independent airway remodelling in asthma. *Respirology* 23: 1138-1145, 2018.

22. **Francis MR, Pinniger GJ, Noble PB, and Wang KCW**. Intrauterine growth restriction affects diaphragm function in adult female and male mice. *Pediatr Pulmonol* 55: 229-235, 2020.

23. **Frey U, Makkonen K, Wellman T, Beardsmore C, and Silverman M**. Alterations in airway wall properties in infants with a history of wheezing disorders. *Am J Respir Crit Care Med* 161: 1825-1829, 2000.

24. **Gazzola M, Henry C, Couture C, Marsolais D, King GG, Fredberg JJ, and Bossé Y**. Smooth muscle in human bronchi is disposed to resist airway distension. *Respir Physiol Neurobiol* 229: 51-58, 2016.

25. **Gern JE, Lemanske Jr RF, and Busse WW**. Early life origins of asthma. *J Clin Invest* 104: 837-843, 1999.

26. **Gillman MW, and Rich-Edwards JW**. The fetal origin of adult disease: from sceptic to convert. *Paediatr Perinat Epidemiol* 14: 192-193, 2000.

27. **Gluckman PD, Hanson MA, and Spencer HG**. Predictive adaptive responses and human evolution. *Trends Ecol Evol* 20: 527-533, 2005.

28. **Hadjigol S, Netto KG, Maltby S, Tay HL, Nguyen TH, Hansbro NG, Eyers F, Hansbro PM, Yang M, and Foster PS**. Lipopolysaccharide induces steroid-resistant exacerbations in a mouse model of allergic airway disease collectively through IL-13 and pulmonary macrophage activation. *Clin Exp Allergy* 50: 82-94, 2020.

29. **Hales CN, and Barker DJ**. Type 2 (non-insulindependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35: 595–601, 1992.

30. **Hall SS**. Small and Thin: The controversy over the fetal origins of adult health. In: *The New Yorker*2007.

31. **Hartman WR, Smelter DF, Sathish V, Karass M, Kim S, Aravamudan B, Thompson MA, Amrani Y, Pandya HC, Martin RJ, Prakash YS, and Pabelick CM**. Oxygen dose responsiveness of human fetal airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 303: L711-719, 2012.

32. **Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U, and Multicentre Allergy Study (MAS) group**. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 368: 763-770, 2006.

33. **James AL, Bai TR, Mauad T, Abramson MJ, Dolhnikoff M, McKay KO, Maxwell PS, Elliot JG, and Green FH**. Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. *Eur Respir J* 34: 1040-1045, 2009.

34. **James AL, Elliot JG, Jones RL, Carroll ML, Mauad T, Bai TR, Abramson MJ, McKay KO, and Green FH**. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med* 185: 1058-1064, 2012.

35. **James AL, Hogg JC, Dunn LA, and Paré PD**. The use of the internal perimeter to compare airway size and to calculate smooth muscle shortening. *Am Rev Respir Dis* 138: 136-139, 1988.

36. **Jang EA, Longo LD, and Goyal R**. Antenatal maternal hypoxia: criterion for fetal growth restriction in rodents. *Front Physiol* 6: 176, 2015.

37. **Jones RL, Noble PB, Elliot JG, Mitchell HW, McFawn PK, Hogg JC, and James AL**. Airflow obstruction is associated with increased smooth muscle extracellular matrix. *Eur Respir J* 47: 1855-1857, 2016.

38. **Källén B, Finnström O, Nygren KG, and Otterblad Olausson P**. Association between preterm birth and intrauterine growth retardation and child asthma. *Eur Respir J* 41: 671-676, 2013.

39. **Kindlund K, Thomsen SF, Stensballe LG, Skytthe A, Kyvik KO, Backer V, and Bisgaard H**. Birth weight and risk of asthma in 3-9-year-old twins: exploring the fetal origins hypothesis. *Thorax* 65: 146-149, 2010.

40. **Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, and Kotecha S**. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. *Am J Respir Crit Care Med* 181: 969-974, 2010.

41. **Kuo W, Ciet P, Andrinopoulou ER, Chen Y, Pullens B, Garcia-Peña P, Fleck RJ, Paoletti M, McCartin M, Vermeulen F, Morana G, Lee EY, Tiddens HAWM, and Group. NCCS**. Reference values for central airway dimensions on CT Images of children and adolescents. *AJR Am J Roentgenol* 210: 423-430, 2018.

42. **Kuyper LM, Paré PD, Hogg JC, Lambert RK, Ionescu D, Woods R, and Bai TR**. Characterization of airway plugging in fatal asthma. *Am J Med* 115: 6-11, 2003.

556 43. **Lauzon-Joset JF, Mincham KT, Abad AP, Short BP, Holt PG, Strickland DH, and**
557 **Leffler J**. Oestrogen amplifies pre-existing atopy-associated Th2 bias in an experimental
558 asthma model. *Clin Exp Allergy* 50: 391-400, 2020.
559 44. **Li Q, Karnowski K, Noble PB, Cairncross A, James A, Villiger M, and Sampson**
560 **DD**. Robust reconstruction of local optic axis orientation with fiber-based polarization-
561 sensitive optical coherence tomography. *Biomed Opt Express* 9: 5437-5455, 2018.
562 45. **Liu HX, Hou LF, Chen T, Qu W, Liu S, Yan HY, Wen X, and Ping J**. Prenatal
563 caffeine ingestion increases susceptibility to pulmonary inflammation in adult female rat
564 offspring. *Reprod Toxicol* 74: 212-218, 2017.
565 46. **Liu X, Lin Y, Tian B, Miao J, Xi C, and Liu C**. Maternal protein restriction alters
566 VEGF signaling and decreases pulmonary alveolar in fetal rats. *Int J Clin Exp Pathol* 7: 3101-
567 3111, 2014.
568 47. **Looi K, Buckley AG, Rigby PJ, Garratt LW, Iosifidis T, Zosky GR, Larcombe**
569 **AN, Lannigan FJ, Ling KM, Martinovich KM, Kicic-Starcevich E, Shaw NC, Sutanto**
570 **EN, Knight DA, Kicic A, and Stick SM**. Effects of human rhinovirus on epithelial barrier
571 integrity and function in children with asthma. *Clin Exp Allergy* 48: 513-524, 2018.
572 48. **Looi K, Kicic A, Noble PB, and Wang KCW**. Intrauterine growth restriction
573 predisposes to airway inflammation without disruption of epithelial integrity in postnatal male
574 mice. *J Dev Orig Health Dis* 2020.
575 49. **Lopuhaä CE, Roseboom TJ, Osmond C, Barker DJ, Ravelli AC, Bleker OP, van**
576 **der Zee JS, and van der Meulen JH**. Atopy, lung function, and obstructive airways disease
577 after prenatal exposure to famine. *Thorax* 55: 555-561, 2000.
578 50. **Lucas A**. Programming by early nutrition in man. *Ciba Found Symp* 156: 38–50, 1991.

51. **Maritz GS, Cock ML, Louey S, Joyce BJ, Albuquerque CA, and Harding R**. Effects of fetal growth restriction on lung development before and after birth: a morphometric analysis. *Pediatr Pulmonol* 32: 201-210, 2001.

52. **Maritz GS, Cock ML, Louey S, Suzuki K, and Harding R**. Fetal growth restriction has long-term effects on postnatal lung structure in sheep. *Pediatr Res* 55: 287-295, 2004.

53. **Martinez FD**. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 6: 272-277, 2009.

54. **McMillen IC, Adams MB, Ross JT, Coulter CL, Simonetta G, Owens JA, Robinson JS, and Edwards JL**. Fetal growth restriction: Adaptations and consequences. *Reproduction* 122: 195–204, 2001.

55. **McParland BE, Macklem PT, and Pare PD**. Airway wall remodeling: friend or foe? *J Appl Physiol (1985)* 95: 426-434, 2003.

56. **Mitzner W**. Airway smooth muscle: the appendix of the lung. *Am J Respir Crit Care Med* 169: 787-790, 2004.

57. **Moreno RH, Hogg JC, and Paré PD**. Mechanics of airway narrowing. *Am Rev Respir Dis* 133: 1171-1180, 1986.

58. **Morrison JL**. Sheep models of intrauterine growth restriction: fetal adaptations and consequences. *Clin Exp Pharmacol Physiol* 35: 730-743, 2008.

59. **Mu M, Ye S, Bai MJ, Liu GL, Tong Y, Wang SF, and Sheng J**. Birth weight and subsequent risk of asthma: A systematic review and meta-analysis. *Heart Lung Circ* 23: 511-519, 2014.

60. **Nikolajev K, Koskela H, and Korppi M**. Birth weight and adult lung function: a within-pair analysis of twins followed up from birth. *World J Pediatr* 4: 222-226, 2008.

61. **Noble PB, Jones RL, Cairncross A, Elliot JG, Mitchell HW, James AL, and McFawn PK**. Airway narrowing and bronchodilation to deep inspiration in bronchial segments from subjects with and without reported asthma. *J Appl Physiol (1985)* 114: 1460-1471, 2013.

62. **Noble PB, Kowlessur D, Larcombe AN, Donovan GM, and Wang KCW**. Mechanical abnormalities of the airway wall in adult mice after intrauterine growth restriction. *Front Physiol* 10: 1073, 2019.

63. **Noble PB, McFawn PK, and Mitchell HW**. Responsiveness of the isolated airway during simulated deep inspirations: effect of airway smooth muscle stiffness and strain. *J Appl Physiol (1985)* 103: 787-795, 2007.

64. **Noble PB, Sharma A, McFawn PK, and Mitchell HW**. Elastic properties of the bronchial mucosa: epithelial unfolding and stretch in response to airway inflation. *J Appl Physiol (1985)* 99: 2061-2066, 2005.

65. **Noble PB, Turner DJ, and Mitchell HW**. Relationship of airway narrowing, compliance, and cartilage in isolated bronchial segments. *J Appl Physiol (1985)* 92: 1119-1124, 2002.

66. **O'Reilly R, Ullmann N, Irving S, Bossley CJ, Sonnappa S, Zhu J, Oates T, Banya W, Jeffery PK, Bush A, and Saglani S**. Increased airway smooth muscle in preschool wheezers who have asthma at school age. *J Allergy Clin Immunol* 131: 1024-1032, 2013.

67. **Omari TI, Sparrow MP, and Mitchell HW**. Responsiveness of human isolated bronchial segments and its relationship to epithelial loss. *Br J Clin Pharmacol* 35: 357-365, 1993.

68. **Ortqvist AK, Lundholm C, Carlström E, Lichtenstein P, Cnattingius S, and Almqvist C**. Familial factors do not confound the association between birth weight and childhood asthma. *Pediatrics* 124: e737-743, 2009.

69. **Owens L, Laing IA, Zhang G, and Le Souëf PN**. Infant lung function predicts asthma persistence and remission in young adults. *Respirology* 22: 289-294, 2017.

70. **Owens L, Laing IA, Zhang G, Turner S, and Le Souëf PN**. Airway function in infancy is linked to airflow measurements and respiratory symptoms from childhood into adulthood. *Pediatr Pulmonol* 53: 1082-1088, 2018.

71. **Paneth N, and Susser M**. Early origin of coronary heart disease (the "Barker hypothesis"). *BMJ* 310: 411-412, 1995.

72. **Pascoe CD, Seow CY, Hackett TL, Paré PD, and Donovan GM**. Heterogeneity of airway dimensions in humans: a critical determinant of lung function in asthmatics and non-asthmatics. *Am J Physiol Lung Cell Mol Physiol* 312: L425-L431, 2017.

73. **Poudel R, McMillen IC, Dunn SL, Zhang S, and Morrison JL**. Impact of chronic hypoxemia on blood flow to the brain, heart and adrenal gland in the late gestation IUGR sheep fetus. *Am J Physiol Regul Integr Comp Physiol* 308: R151-162, 2015.

74. **Rao L, Tiller C, Coates C, Kimmel R, Applegate KE, Granroth-Cook J, Denski C, Nguyen J, Yu Z, Hoffman E, and Tepper RS**. Lung growth in infants and toddlers assessed by multi-slice computed tomography. *Acad Radiol* 17: 1128-1135, 2010.

75. **Regamey N, Ochs M, Hilliard TN, Mühlfeld C, Cornish N, Fleming L, Saglani S, Alton EW, Bush A, Jeffery PK, and Davies JC**. Increased airway smooth muscle mass in children with asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 177: 837-843, 2008.

76. **Roussos C, and Macklem PT**. The respiratory muscles. *N Engl J Med* 307: 786-797, 1982.

77. **Sarria EE, Mattiello R, Rao L, Tiller CJ, Poindexter B, Applegate KE, Granroth-Cook J, Denski C, Nguyen J, Yu Z, Hoffman E, and Tepper RS**. Quantitative assessment

650 of chronic lung disease of infancy using computed tomography. *Eur Respir J* 39: 992-999,
651 2012.
652 78. **Schatz M, and Camargo Jr CA**. The relationship of sex to asthma prevalence, health
653 care utilization, and medications in a large managed care organization. *Ann Allergy Asthma*
654 *Immunol* 91: 553-558, 2003.
655 79. **Schittny JC**. Development of the lung. *Cell Tissue Res* 367: 427-444, 2017.
656 80. **Soares AAA, Barros CM, Santos CGC, Dos Santos MRA, Silva JRS, Silva Junior**
657 **WMD, and Simões SM**. Respiratory muscle strength and pulmonary function in children with
658 rhinitis and asthma after a six-minute walk test. *J Asthma* 55: 259-265, 2018.
659 81. **Sonnenschein-van der Voort AM, Gaillard R, de Jongste JC, Hofman A, Jaddoe**
660 **VW, and Duijts L**. Foetal and infant growth patterns, airway resistance and school-age asthma.
661 *Respirology* 21: 674-682, 2016.
662 82. **Sutherland AE, Crossley KJ, Allison BJ, Jenkin G, Wallace EM, and Miller SL**.
663 The effects of intrauterine growth restriction and antenatal glucocorticoids on ovine fetal lung
664 development. *Pediatr Res* 71: 689-696, 2012.
665 83. **Swanson AM, and David AL**. Animal models of fetal growth restriction:
666 Considerations for translational medicine. *Placenta* 36: 623-630, 2015.
667 84. **Tonga KO, Chapman DG, Farah CS, Oliver BG, Zimmermann SC, Milne S, Sanai**
668 **F, Jetmalani K, Berend N, Thamrin C, and King GG**. Reduced lung elastic recoil and fixed
669 airflow obstruction in asthma. *Respirology* 25: 613-619, 2020.
670 85. **Turner S, Fielding S, and Devereux G**. First trimester fetal size and prescribed asthma
671 medication at 15 years of age. *Eur Respir J* 51: 1701509, 2018.
672 86. **Turner S, Prabhu N, Danielan P, McNeill G, Craig L, Allan K, Cutts R, Helms P,**
673 **Seaton A, and Devereux G**. First- and second-trimester fetal size and asthma outcomes at age
674 10 years. *Am J Respir Crit Care Med* 184: 407-413, 2011.

87. **Turner SW, Campbell D, Smith N, Craig LC, McNeill G, Forbes SH, Harbour PJ, Seaton A, Helms PJ, and Devereux GS**. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. *Thorax* 65: 391-397, 2010.

88. **Turner SW, Young S, Goldblatt J, Landau LI, and Le Souëf PN**. Childhood asthma and increased airway responsiveness: a relationship that begins in infancy. *Am J Respir Crit Care Med* 179: 98-104, 2009.

89. **Tzeng YS, Lutchen K, and Albert M**. The difference in ventilation heterogeneity between asthmatic and healthy subjects quantified using hyperpolarized 3He MRI. *J Appl Physiol (1985)* 106: 813-822, 2009.

90. **Villamor E, Iliadou A, and Cnattingius S**. Is the association between low birth weight and asthma independent of genetic and shared environmental factors? *Am J Epidemiol* 169: 1337-1343, 2009.

91. **Wang KCW, Donovan GM, James AL, and Noble PB**. Asthma: Pharmacological degradation of the airway smooth muscle layer. *Int J Biochem Cell Biol* 126: 105818, 2020.

92. **Wang KCW, Larcombe AN, Berry LJ, Morton JS, Davidge ST, James AL, and Noble PB**. Foetal growth restriction in mice modifies postnatal airway responsiveness in an age and sex-dependent manner. *Clin Sci (Lond)* 132: 273-284, 2018.

93. **Wang KCW, Le Cras TD, Larcombe AN, Zosky GR, Elliot JG, James AL, and Noble PB**. Independent and combined effects of airway remodelling and allergy on airway responsiveness. *Clin Sci (Lond)* 132: 327-338, 2018.

94. **Wang KCW, Morton JS, Davidge ST, Larcombe AN, James AL, Donovan GM, and Noble PB**. Increased heterogeneity of airway calibre in adult rats after hypoxia-induced intrauterine growth restriction. *Respirology* 22: 1329-1335, 2017.

95. **Wang KCW, and Noble PB**. Foetal growth restriction and asthma: Airway smooth muscle thickness rather than just lung size? *Respirology* 25: 889–891, 2020.

96. **Weitoft M, Andersson C, Andersson-Sjöland A, Tufvesson E, Bjermer L, Erjefält J, and Westergren-Thorsson G**. Controlled and uncontrolled asthma display distinct alveolar tissue matrix compositions. *Respir Res* 15: 67, 2014.

97. **Wignarajah D, Cock ML, Pinkerton KE, and Harding R**. Influence of intrauterine growth restriction on airway development in fetal and postnatal sheep. *Pediatr Res* 51: 681-688, 2002.

98. **Williamson JP, McLaughlin RA, Noffsinger WJ, James AL, Baker VA, Curatolo A, Armstrong JJ, Regli A, Shepherd KL, Marks GB, Sampson DD, Hillman DR, and Eastwood PR**. Elastic properties of the central airways in obstructive lung diseases measured using anatomical optical coherence tomography. *Am J Respir Crit Care Med* 183: 612-619, 2011.

99. **Xiao C, Biagini Myers JM, Ji H, Metz K, Martin LJ, Lindsey M, He H, Powers R, Ulm A, Ruff B, Ericksen MB, Somineni HK, Simmons J, Strait RT, Kercsmar CM, and Khurana Hershey GK**. Vanin-1 expression and methylation discriminate pediatric asthma corticosteroid treatment response. *J Allergy Clin Immunol* 136: 923-931.e923, 2015.

100. **Xing Y, Wei H, Xiao X, Chen Z, Liu H, Tong X, and Zhou W**. Methylated Vnn1 at promoter regions induces asthma occurrence via the PI3K/Akt/NFκB-mediated inflammation in IUGR mice. *Biol Open* 9: bio049106, 2020.

101. **Xu XF, Hu QY, Liang LF, Wu L, Gu WZ, Tang LL, Fu LC, and Du LZ**. Epigenetics of hyper-responsiveness to allergen challenge following intrauterine growth retardation rat. *Respir Res* 15: 137, 2014.

102. **Xu XF, Li YJ, Sheng YJ, Liu JL, Tang LF, and Chen ZM**. Effect of low birth weight on childhood asthma: a meta-analysis. *BMC Pediatr* 14: 275, 2014.

Figure Legend

Figure 1. Why is IUGR associated with asthma development? The figure illustrates a working paradigm where IUGR (A) is accompanied by changes in airway structure-function, and potentially the airway smooth muscle layer (B). The thickness of the ASM was inversely related to fetal body weight in growth restricted mice. Functional dysfunction of the airway will contribute to asthma pathogenesis when combined with other environmental triggers that drive a potentially enhanced inflammatory response in IUGR affected individuals (C). The end point is a physiologically abnormal airway that is also inflamed (D), giving rise to symptoms of wheeze, chest tightness and cough. Control (open circles); IUGR, intrauterine growth restriction (closed circles); ASM, airway smooth muscle; ECM, extracellular matrix; P_{bm}, perimeter of basement membrane. Data (B) are from mice, originally published in 10.1111/resp.13851, (95).

Figure 2. Bronchial challenge to methacholine in female mice (8 weeks) after IUGR. Animals from IUGR-affected pregnancies exhibited a greater bronchoconstrictor response compared with the Control group. Values are mean ± SEM. *Significantly different from Control ($P<0.05$). Control (open circles); IUGR, intrauterine growth restriction (filled circles); MCh, methacholine. Data originally published in 10.1042/CS20171554, (92).

Figure 3. A mathematical simulation of human lung resistance based on the observed variation in lumen calibre in IUGR male rats (7 weeks). The underlying mechanism was purported to arise from a variable distribution of airway compliance. The model simulates bronchoconstriction to increasing log concentrations (Log agonist) of a contractile agonist. Control (open circles); IUGR, intrauterine growth restriction (closed circles). Data originally published in 10.1111/resp.13071, (94).

Figure 4. Total inflammatory cells in BAL fluid (A) and the peritoneal cavity (B) from male and female mice at 8 weeks of age. In IUGR offspring, there was an increase in inflammation, which appeared to be specific to the lungs, as there was no change in fluid obtained from the peritoneal cavity (and index of systemic inflammation). Data are mean ± SEM. *Significantly different from Control (P<0.05). Male, open bars; Female, closed bars. IUGR, intrauterine growth restriction; BAL, bronchoalveolar lavage. Data originally published in 10.1017/S2040174420000744, (48).