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The re-emerging role of linoleic acid in paediatric asthma

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Abstract

Asthma is the most common chronic disease within the paediatric population. Although it is multifactorial, its onset may be linked to early-life exposures with subsequent impact on immune system development. Microbial and dietary metabolic products have been implicated in the development and exacerbation of paediatric asthma. Linoleic acid is the most common omega-6 polyunsaturated fatty acid in the Western diet. In this review, we summarise the literature regarding the involvement of linoleic acid in the development of and its impact on existing paediatric asthma. First, we summarise the existing knowledge surrounding the relationship between human microbial metabolism and allergic diseases in children. Next, we examine cellular or animal model-based mechanistic studies that investigated the impact of dietary- and microbial-derived linoleic acid metabolites on asthma. Finally, we review the literature investigating the impact of linoleic acid metabolites on the development and exacerbation of childhood asthma. While there is conflicting evidence, there is growing support for a role of linoleic acid in the onset and pathophysiology of asthma. We recommend that additional cellular, animal, and longitudinal studies are performed that target linoleic acid and its metabolites.

Introduction

Asthma is a condition that results in inflammation of the lower airways and bronchoconstriction, and has been classified as the most common chronic condition within the paediatric population [1]. A variety of factors are associated with the development of childhood asthma [2–4]. However, recent studies have identified microbes associated with the gastrointestinal and respiratory tracts as covariates and possible causal factors of asthma development [1]. Many studies have suggested that disruption in early-life microbial exposure, and subsequent impact on immune system development, may be linked to the onset of paediatric asthma [5]. While many microbiome studies primarily focus on the taxonomic composition and proportional changes in the microbial species present in the gut or respiratory tract, recent studies have explored the expressed microbial metabolic products (metabolome) found in stool or serum. This includes specific metabolites such as γ-tocopherol/β-tocopheryl and 12,13-dihydroxy-9Z-octadecenoic acid (12,13-DiHOME), which are associated with the development of paediatric asthma [6, 7]. Short-chain fatty acids have also been investigated for a potential protective effect against the development of asthma as part of a "Mediterranean diet" [8].

For this review, we conducted a systematic PubMed literature search using the following search terms to identify studies that investigated the role of linoleic acid metabolites and the development of paediatric asthma: "linoleic acid", "12,13-DiHOME", "13-HODE", "CLA", "pediatric asthma" or "paediatric asthma", "polyunsaturated fatty acids", "n-6" and "n-3". There are multiple linoleic acid-derived lipid

mediators produced by the microbiome (*e.g.* 10-hydroxy-12(Z)-octadecenoic acid, also known as 12(Z)-10-HOME or HYA), but these compounds are excluded from this review due to sparse data in relation to asthma and atopic conditions. A review of the full complement of linoleic acid-derived mediators has recently been published [9].

Long-chain polyunsaturated fatty acids (PUFAs) consist of primarily two main groups: omega-3 (n-3) and omega-6 (n-6) PUFAs. The n-3 PUFAs are predominantly sourced from fish and seed oils consumed commonly in Mediterranean diets and include α-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The n-6 PUFAs are commonly found in plant oils [10, 11] and include linoleic acid, as well as dihomo-γ-linolenic acid (DHGLA) and arachidonic acid [12], which are formed from essential fatty acids.

Common dietary sources of n-3 and n-6 PUFAs are outlined in table 1. The consumption of ultra-processed foods is prevalent in the standard Western diet and has positively associated with the presence of asthma and wheeze in the paediatric population [13]. Accordingly, it is possible that removal of these foods from the diet may aid in mitigating asthma symptoms regardless of the putative effects of dietary linoleic acid. In addition, it is worth noting that some dietary sources of linoleic acid may carry important nutrients and can potentially promote paediatric health. As such, complete removal of some of these foods from the diet may result in a lack of essential nutrients [10].

The oxygenated lipid mediator products of 20-carbon arachidonic acid are collectively known as the eicosanoids and have been extensively demonstrated to exert profound roles in asthma and allergy [13]. Less well-known are the products of 18-carbon fatty acids collectively termed octadecanoids [9]. Among the octadecanoids, linoleic acid and its metabolites, *e.g.* 13-hydroxy-octadecadienoic acid (13-HODE), 13-hydroperoxy-octadecadienoic acid (13-HpODE) and 12,13-DiHOME, have been implicated in the development of asthma and exacerbation of existing asthma within the paediatric population [14, 15]. In addition, there have been multiple reports suggesting that n-3 PUFAs are beneficial for attenuating the onset of paediatric asthma [16–18]. While less investigated, n-3 PUFAs can also be converted to downstream oxygenated metabolites, including the octadecanoic acid from ALA, eicosanoids from EPA and docosanoids from DHA [19] (also known as specialised pro-resolving mediators). Figure 1 provides a summary of the sources and main octadecanoid metabolites of linoleic acid and ALA [10–12, 20].

The human microbiome in developing and existing asthma

The human microbiome is composed of bacterial, fungal, protist, archaeal and viral communities, and although microbial communities colonise every mucosal site within the human body, there are site-specific microbial signatures [20–23]. Our present understanding of the nature of the microbiome comes from the gastrointestinal tract [20, 23].

The timing of the acquisition of the microbiome in humans is a topic of active research. It is widely accepted that the first large-scale microbial acquisition and colonisation occurs during birth and is mainly derived from the maternal microbiota [24]. During the first 3 years of life, microbial colonisers undergo rapid compositional changes that often lead to a relatively stable adult-like microbial community structure; in the gut, this often occurs following the introduction of solid foods [25–27].

Although the human lung microbiome cannot be easily tracked longitudinally, studies reveal that lung and airway colonisation commences soon after birth, reaching maturity at ∼2–3 postnatal weeks in rodents [28] and 2–3 months postnatally in humans [29]. Thus, the likely sequence of ecological succession begins with microbes colonising the intestines early in life, and then appreciating within the airways later [30]. The

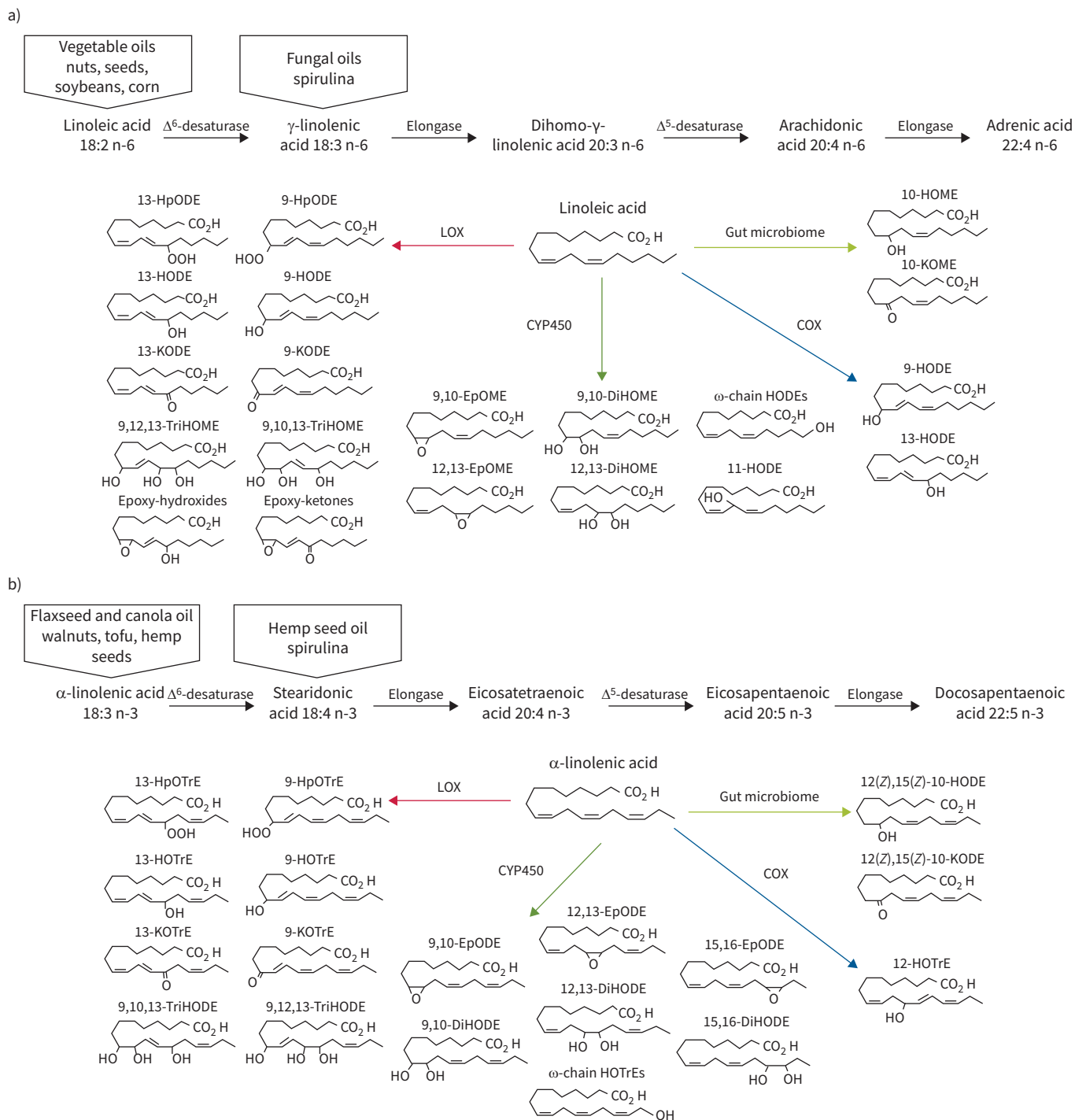| TABLE 1 Summary of dietary sources of polyunsaturated fatty acids (PUFAs)	
Dietary sources of n-3 PUFAs	**Dietary sources of n-6 PUFAs**
Fish oils: salmon, mackerel, sardines, anchovies, herring, rainbow trout	Plant oils and seeds: corn, soy, wheat germ, safflower, grape seed, rapeseed, poppy seed, sunflower, palm, hemp
Algae	Walnuts
Flaxseed	Grain-fed meats
Leafy vegetables	Eggs
Walnuts	

a)

b)

FIGURE 1 Pathway of linoleic and α-linolenic acid metabolism. a) Linoleic acid is an 18-carbon fatty acid (octadecanoid) and its dietary sources include plant oils along with other n-6 polyunsaturated fatty acids (PUFAs). Linoleic acid and its metabolites including 13-hydroxy-octadecadienoic acid (13-HODE), 13-HpODE (13-hydroperoxy-octadecadienoic acid) and 12,13-dihydroxy-9Z-octadecenoic acid (12,13-DiHOME) have been implicated in paediatric asthma. b) α-Linoleic acid (ALA) is also an octadecanoid. Its dietary sources include seed oils and fish along with other n-3 PUFAs. ALA and its metabolites along with other n-3 PUFAs may have a beneficial effect in preventing paediatric asthma. COX: cyclo-oxygenase; LOX: lipoxygenase.

microbial composition in adulthood is theorised to be at least partially attributed to early-life exposures, a theory supported by a recent study that suggests that the initial microbial occupants in infancy persist into adulthood [31].

An expanding body of work demonstrates that the microbial colonisation process occurs in tandem with and greatly influences immune development [20, 32–34]. For example, existing work using germ-free animal models has demonstrated that the absence of commensal microbes was correlated with pronounced intestinal defects or abnormalities of lymphoid tissue structure and function, suggesting a causal relationship between commensal microbiota and the development of the immune system [32, 33]. The microbiome's impact on immune system training is believed to operate within a limited developmental period in early life. Indeed, microbial colonisation of germ-free animals in early life restored normal immune function whereas conventionalisation in adulthood did not fully restore normal immune function [35]. This finding supports the so-called concept of a "critical window" of opportunity. Thus, proper training of the immune system by the gut microbiome can result in a potent local and systemic immune system response with long-lasting consequences for the host that may extend into adult life.

A growing body of evidence suggests a potential correlation between the gut microbiota and the lungs, conceptualised as the gut–lung axis, is a prominent contributor to respiratory health. The existence of active bidirectional crosstalk is supported by alterations in the gut and lung microbiota often manifested in several respiratory diseases [30, 36, 37]. For instance, inflammatory bowel disease can co-occur with asthma [38, 39], COPD [40] and other pulmonary disorders [41–43].

In addition, recent work shows that microbe–immune interactions throughout life can have profound impacts on lung health. For example, a recent study suggests that the lung microbiome (specifically lactobacilli) can reduce COPD [36, 37]. Another recent study that analysed data from two longitudinal birth cohorts in the United States (Vitamin D Antenatal Reduction Trial) and Denmark (Copenhagen Prospective Studies on Childhood Asthma 2010) determined that the 17q12-21 gene and microbial maturation were associated with an increased risk of asthma later in life [44]. Thus, early perturbations to microbial colonisation and their metabolic by-products in the gut and lung can lead to persistent, and sometimes irreversible alterations to specific immune features that have been linked to the risk of developing allergies, asthma and other immunological disorders later in life [36, 45–47].

Numerous large-scale independent birth cohort studies reveal that the early-life exposures and experiences that shape microbial development can also influence immune-microbiome parameters, which in turn impact an infant's risk of developing childhood asthma or atopy. Such early-life experiences or exposures include living in a microbial rich environment, consuming a diverse diet, method of delivery (vaginal delivery *versus* caesarean section) and gestational age at delivery [25, 48–56]. Due to the unique exposures of preterm infants' first few weeks to months of life in the neonatal intensive care unit (NICU), and subsequent alteration to their microbiome, these infants are at a higher risk of developing asthma later in life. Within the NICU, preterm infants have reduced contact with the external environment and are exposed, instead, to a sterile one. This isolation is hypothesised to impact both the development of their immune systems and the colonisation and succession of their microbial communities. Of particular concern is the successional development of the preterm infant gut microbiome in the NICU which can be dominated by a microbial community associated with an increased risk of childhood asthma [57]. For example, work done by STIEMSMA *et al*. [58] and ARRIETA *et al*. [50] indicated that alterations in microbial community composition and associated metabolites preceded the onset of childhood allergy and asthma. These alterations have consequences that persist into their school-aged years [6]. Infants with reduced proportions of the microbial genera *Bifidobacterium*, *Faecalibacterium* and *Akkermansia*, and increased proportions of the microbial genera *Candida* and *Rhodotorula* had the greatest risk for developing future asthma symptoms [50, 53, 54, 59]. These studies provide evidence for the involvement of the early-life gut microbiome in childhood asthma development, thus presenting opportunities for timely microbial interventions, particularly for high-risk infants.

Perturbations to the fungal microbiome may be an additional biomarker of asthma risk [50, 53, 60]. In two independent studies, early gut over-representation of the yeast *Pichia kudriavzevii* and later asthma development was reported in infants [50, 60]. Mechanistically, an overabundance of *P. kudriavzevii* in the neonatal mouse gut resulted in worsening of type-2 (immunoglobulin (Ig)E antibodies, T-helper (Th) type 2 cells and lung eosinophilia) and type-17 (Th17 cells and interleukin (IL)-17) inflammation in future allergic airway diseases. This example provides insights into one possible mechanism through which host–microbe interactions in the gut can lead to asthma.

Post-infancy, early-life respiratory viral infections, notably rhinoviruses, influenza and respiratory syncytial viruses are prominent in the development of asthma, worsening of asthma, and persistent immune system changes [22, 45, 61, 62]. A previous study that investigated the influence of gut microbiota manipulation on systemic immune and metabolic responses demonstrated that oral supplementation with *Lactobacillus*

johnsonii in adult mice previously infected with respiratory syncytial virus resulted in a decreased airway immunopathology [63]. The severity of viral infections can be modified by the microbial patterns of the upper airway microbiome. For example, colonisation with opportunistic pathobionts including *Haemophilus*, *Streptococcus* and *Moraxella* is associated with severe respiratory symptoms during viral illnesses in asthma [64–68]. In contrast, enrichment of *Corynebacterium*, *Staphylococcus* and *Dolosigranulum* is correlated with protection against severe respiratory symptoms [69–71].

Individuals with asthma have significantly different airway microbiota compared to healthy controls [72–75]. This could be used to discriminate T2-high (eosinophilic) and T2-low (neutrophilic/mixed-inflammation) asthma and atopy with 75% accuracy from bronchoalveolar lavage fluid samples and 80% accuracy from endobronchial brush samples [75, 76]. For example, the diversity of airway fungi has been shown to be significantly lower in patients with T2-high inflammation compared with T2-low inflammation. The question that remains is how a specific population of bacteria, fungi and/or viruses can increase the risk of developing paediatric asthma. One current hypothesis is that the metabolic products of microbial metabolism may be driving disease ethology.

The impact of faecal linoleates in developing and existing asthma

As discussed earlier, linoleic acid is the most highly consumed PUFA in the Western diet. Dietary sources of linoleic acid include vegetable oils, nuts, seeds, meats and eggs [10]. Developing fetuses obtain essential PUFAs from the maternal circulation [77], and the maternal diet may accordingly impact their risk of atopic disease. NWARU *et al.* [78] analysed data from the Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study and found that higher maternal consumption of total PUFA and ALA was associated with a decreased risk of allergic rhinitis in their offspring; however, these results may have mostly been driven by ALA and lost significance when adjusted for multiple comparisons. The study also found that maternal consumption of a higher ratio of n-6 PUFA to n-3 PUFA during pregnancy was associated with higher allergic rhinitis in their offspring. ROSA *et al.* [79] examined 1019 mother–child dyads in Memphis (TN, USA), who were recruited into the CANDLE (Conditions Affecting Neurocognitive Development and Learning in Early Childhood) study. They found that high maternal n-6 PUFA consumption was associated with an increased risk of past and current asthma diagnosis in children 4–6 years of age. Additionally, increased maternal n-6 PUFA consumption was associated with a higher risk of all measured respiratory outcomes (past asthma, current wheeze, current asthma and diagnosed current asthma) among children born to mothers with a self-reported history of asthma, but not in offspring of women without a history of asthma. To examine biochemical evidence of this phenomenon, BAI-TONG *et al.* [57] compared the microbiomes and metabolomes of two groups of preterm infants: infants born to mothers with or without a history of asthma. Milk and stool samples were analysed at three different time points in the NICU, from birth, 2 weeks postnatal age and 4–6 weeks postnatal age. Preterm infants of mothers with a history of asthma had a different stool metabolic profile to the infants born to mothers without a history of asthma. The main difference in the metabolite profiles of these two groups was the linoleic acid molecular spectral network, with the biggest difference at 4–6 weeks of life. Higher levels of multiple linoleic acid metabolites (*e.g.* monoolein or 1-(*cis*-9-octadecenoyl)-rac-glycerol, as well as compounds not annotated in the Global Natural Products Social Molecular Networking library) were detected in stool samples from preterm infants with a maternal history of asthma. These findings led to the hypothesis that an increase in specific linoleic acid metabolites may result in an increased pro-inflammatory process [57].

Other studies have also linked increased faecal content of linoleic acid metabolites in infants to an increased risk of childhood atopy and asthma [23, 48, 54]. In a ground-breaking study, LEVAN *et al.* [7] identified sources of 12,13-DiHOME in neonatal faeces by sequencing stool samples *via* shotgun metagenomic sequencing. They detected ∼1400 bacterial epoxide hydrolase genes that were more abundant in neonates who went on to develop atopy and/or asthma in childhood. Epoxide hydrolases, particularly the soluble epoxide hydrolases (EPHX2), convert fatty acid epoxides into the corresponding vicinal diols [80]. The 30 most abundant epoxide hydrolase genes were encoded by strains from *Enterococcus faecalis*, *Streptococcus*, *Bifidobacterium bifidum* and *Lactobacillus*. 11 of the most common bacterial epoxide hydrolases found were further evaluated to determine their capability of producing the 12,13-DiHOME. While all 11 epoxide hydrolases were capable of hydrolysing glycidol, a generic epoxide, only three specific strains (*E. faecalis* and two strains of *B. bifidum*) converted the epoxide precursor 12,13-EpOME to 12,13-DiHOME. An increase in these three epoxide hydrolase genes in 1-month-old infants significantly increased their probability of developing childhood allergies, eczema and asthma [7]. This firmly supported the interaction of the gut microbiome on pulmonary health *via* the gut–lung axis and suggests that inhibition of epoxide hydrolase activity is a potential therapeutic target (figure 2).
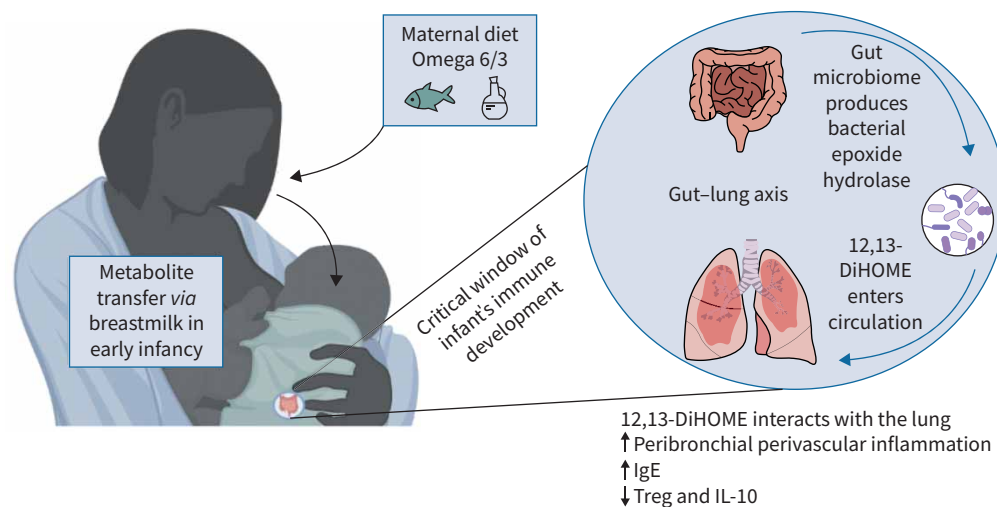
FIGURE 2 Impact of maternal diet on the infant microbiome. The human microbiome is thought to impact an infant's immune development during a critical period in early life. It is during this period when maternal dietary intake of n-3/n-6 polyunsaturated fatty acids (PUFAs), transferred in breastmilk, may affect asthma development. LEVAN et al. [7] demonstrated that neonates who produced specific bacterial epoxide hydrolases that convert 12,13-EpOME to 12,13-DiHOME demonstrated a significantly increased probability of developing childhood allergies, eczema and asthma. In a mouse model, intra-abdominal injection of 12,13-DiHOME led to increased peribronchial and perivascular inflammation. Administration of 12,13-DiHOME to human dendritic cells resulted in reduced anti-inflammatory cytokine secretion and reduction of the number of T-regulatory (Treg) cells. Ig: immunoglobulin; IL: interleukin. Figure created using BioRender.com.

It is not possible to determine whether the 12,13-DiHOME was derived from the human host (pulmonary tissue/microbiota) or gut microbiome. However, given that 12,13-DiHOME levels were elevated in the stool and gut bacteria were identified that could produce the 12,13-DiHOME in infants who subsequently developed atopy, there is strong evidence that this metabolite is coming from the gut. In order to confirm the synthetic source of the 12,13-DiHOME, labelling studies utilising a click chemistry based approach and bio-orthogonal chemistry could be employed.

The impact of nasopharyngeal linoleates in developing asthma

A study conducted by ZHU et al. [81] in 2022 investigated nasopharyngeal metabolomic signatures in infants with severe bronchiolitis and asthma development. It had been established previously that severe bronchiolitis in infants increased the risk of childhood asthma. Once the infants with a history of severe bronchiolitis reached the age of 3 years, 32% developed recurrent wheezing and by the age of 5 years, 27% developed asthma [81]. The investigators identified a metabotype (metabotype B) that was associated with a significantly higher risk of developing asthma (40.6%). The type B metabotype had high amounts of amino acid (e.g. methionine, histidine and glutathione) and HODE metabolites and low amounts of PUFAs and was characterised by a higher proportion of lifetime corticosteroid use, parental asthma and enriched linoleic acid metabolism pathways [81], suggesting a potential biomarker role.

Animal and in vitro models of linoleic acid metabolites and lung injury

Studies using animal and human in vitro models provide unique insight into the potential role of linoleic acid metabolites as a biomarker and also consider mechanistic impacts of linoleic acid on the development of asthma. The aforementioned LEVAN et al. [7] study examined the effect of 12,13-DiHOME on the development of atopy and asthma. The group injected mouse models intra-abdominally with 12,13-DiHOME and found it in the circulatory system where it interacted directly with the lung mucosa to exacerbate inflammation in the airways. It increased peribronchial and perivascular inflammation, increased IgE, decreased regulatory T (Treg) cells, and promoted pro-inflammatory cytokines [7]. The authors then went on to further examine the mechanism by which 12,13-DiHOME promotes inflammatory responses. Human dendritic cells were treated with 12,13-DiHOME, which activated the expression of peroxisome proliferator-activated receptor-γ regulated genes and reduced both the anti-inflammatory cytokine (IL-10, which protects against allergic inflammation) and the number of Treg cells in utero [7] (figure 2).

The octadecanoid 13-HODE can be formed from linoleic acid by 15-lipoxygenase activity and is a bioactive lipid mediator that regulates multiple signalling processes *in vivo*. Its role as a biomarker in asthma has been suggested by studies in both animal models and cultured lung epithelial cells. MABALIRAJAN *et al.* [15] administered 13-HODE to the lungs of naïve BALB/c and C57BL/6 mouse strains. The BALB/c mice exhibited signs of inflammatory foci and severe difficulty breathing, while the C57BL/6 mice exhibited pulmonary congestion and epithelial injury. Incubation of human bronchial epithelia cells with 13(S)-HODE led to increased levels of mitochondrial calcium and severe epithelial injury including mitochondrial structural alterations such as tubular swelling, cell shrinking and initiation of apoptosis. PANDA *et al.* [82] reported that administration of 13-HODE to allergic mice led to increased airway sensitivity and phenotypic features consistent with severe steroid unresponsive asthma. They found that 13-HODE administration resulted in decreased glucocorticoid receptor-α gene expression. Similar mitochondrial findings were seen in cellular model systems [15]. Figure 3a presents a hypothesised mechanism for the impact of 13-HODE in airway epithelial cells *via* the transient receptor potential cation channel subfamily V member 1 receptor. Suppression or inhibition of this receptor in mice blocked airway responses to 13-HODE [15].

Conjugated linoleic acid (CLA) is a mixture of ⩾28 different isomers with alternate double bond positioning and geometry relative to linoleic acid. It may be found in dairy products or formed from vaccenic acid in mammals *via* bacterial pathways.

Multiple studies have found an association between of *cis*-9, *trans*-11 CLA and allergic diseases [83, 84]. It is important to note that although *cis*-9, *trans*-11 CLA is a PUFA, it is not an omega-6 PUFA, but is a naturally occurring omega-7 isomer with potential anti-inflammatory effects [83].

JAUDSZUS *et al.* [83] found that administration of *cis*-9, *trans*-11 CLA to BALB/c mice correlated with a significant reduction in IgE production and *in vivo* airway hyperresponsiveness. Additionally, the authors found that mice fed with *cis*-9, *trans*-11 CLA were likely to have reduced mucus blocking their bronchial passages. HUANG *et al.* [84] examined the impact of *cis*-9, *trans*-11 CLA on human bronchial epithelial cells and found that *cis*-9, *trans*-11 CLA treatment reduced IL-6 levels and other pro-inflammatory
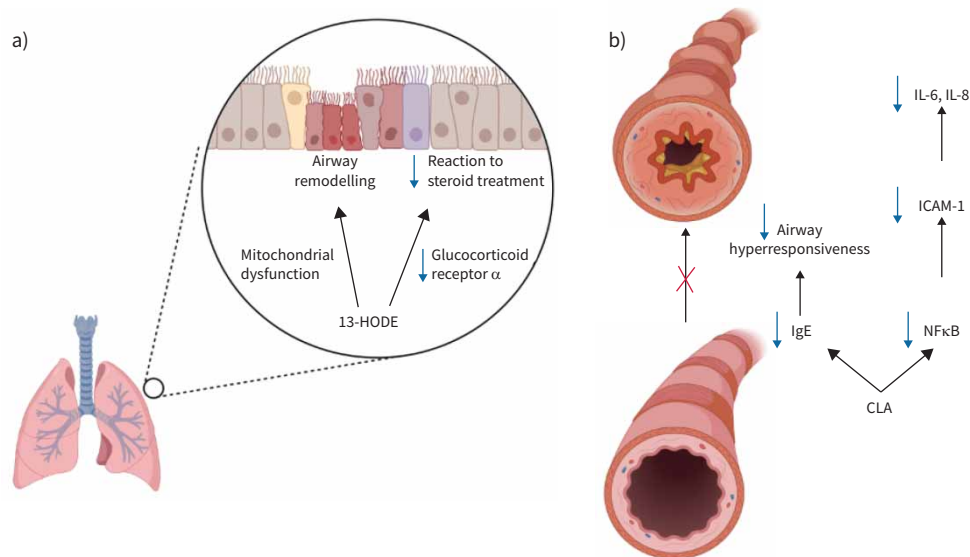

FIGURE 3 Allergic airway remodelling and sensitisation. a) The role of linoleic acid metabolite 13-hydroxy-octadecadienoic acid (13-HODE) in asthma has largely been based on animal and cell models. Hypothesised mechanisms include induction of airway remodelling due to mitochondrial dysfunction and decreased response to steroid treatment due to decreased expression of glucocorticoid receptor α. b) Administration of *cis*-9, *trans*-11, conjugated linoleic acid (c9,t11-CLA), found in dairy products and as a bacterial pathway product, led to a significant reduction of immunoglobulin (Ig)E levels and airway responsiveness in a mouse model and decreased interleukin (IL)-6 and IL-8 production when administered to human bronchial epithelial cells. ICAM: intercellular adhesion molecule 1. Figure created using BioRender.com.

cytokines and chemokines in a dose-dependent manner. From these studies, CLA has been suggested to have a protective effect against asthma mediators (figure 3b). Supplementary table S1 summarises studies using animal or *in vitro* model systems.

Early-life exposure to linoleic acid and childhood asthma

Numerous birth cohort studies have demonstrated that early-life exposures have the capacity to influence the development of allergic diseases. However, the studies that focus on the impact of PUFAs, including linoleic acid, are contradictory in their conclusions. Rucci *et al.* [85], through the Generation R Study, followed mothers and their children to examine the relationship between maternal fatty acid levels throughout pregnancy and the prevalence of allergic diseases (*e.g.* asthma and eczema) within their school-aged offspring. The mothers' fatty acid composition was determined during the second trimester; the children's lung and airway function were tested at 6 years of age along with a parental questionnaire about the children's asthma and eczema symptoms [85]. Surprisingly, higher levels of total PUFAs and total n-6 PUFAs during the second trimester of pregnancy correlated with a decreased risk of development of childhood asthma and an increased risk of development of childhood eczema. Interestingly, the associations were observed with γ-linolenic acid (C18:3n-6) and dihomo-γ-linolenic acid (C20:3n-6) levels, which are generally low relative to other n-6 PUFAs. This study had a number of limitations, including quantifying maternal PUFAs at only a single time point in pregnancy and not during the critical exposure window in infancy; a large population difference in maternal history of asthma or atopy (although this was adjusted for); and significant characteristic differences in the groups that completed the study and those that were lost to follow-up. While this study contradicts most of the existing literature on PUFA associations, it stresses the need for larger randomised control trials utilising PUFA supplementation at multiple time points in pregnancy and infancy.

Conversely, a 2012 study analysing the impact of fatty acid within breastmilk and colostrum found that high levels of n-6 PUFA in breastmilk increased an infant's risk of developing asthma-like symptoms [86]. Colostrum samples were analysed 2 days post-delivery while the breastmilk samples were analysed 2 weeks post-delivery. Confounders such as maternal history of eczema, asthma and/or rhinitis were accounted for. Asthma-like symptoms were analysed using a questionnaire at 6 and 12 months of age and atopy at 12 months of age. The authors concluded that high amounts of n-6 PUFAs in a mother's breastmilk is associated with an increase in asthma-like symptoms in infancy. The risk of atopy was lower in infants exposed to high levels of n-3 PUFAs [86]. The limitation in this study was that only one or two time points were tested for PUFAs in maternal breastmilk and infants were assessed for asthma-like symptoms up to 1 year of age and no further.

Similarly, another 2015 study also aimed to assess the relationship between the PUFA composition of breastmilk and child risk of developing asthma. Study participants consisted of 276 mothers, all of whom provided breastmilk samples when their children reached 3 months of age. The prevalence of asthma and allergy symptoms was determined *via* questionnaires (at 3 months of age, annually from 1 year to 8 years of age, at 11 years of age and 14 years of age) and IgE was measured at 4, 8 and 12 years of age. The authors concluded that, within allergic mothers (mothers who had a history of asthma or allergy), high levels of n-6 PUFA were correlated with an increased risk of asthma [87].

A few studies have looked at the interaction between n-3 and n-6 PUFAs. Miyake *et al.* [88] used data from the Ryukuys Child Health Study to investigate the relationship between PUFA intake and asthma. Teachers of 6–15-year-olds distributed questionnaires that were answered by the parents to determine asthma-like symptoms and dietary habits. Intake of both n-3 and n-6 PUFAs were independently associated with an increased prevalence of wheeze [88]. The authors reported multiple limitations, including the lack of dose–response relationships between diet and asthma, the inherent problem with surveys and participant recall and the inability to determine the longitudinal dietary impacts of asthma-like symptoms [88]. Conversely, a study by Magnusson *et al.* [89] used blood samples, IgE measures and symptom questionnaires to assess the relationship between n-3 and n-6 PUFA levels at 8 years of age and the prevalence of asthma and allergy at 16 years. Elevated n-3 and n-6 PUFA levels at 8 years were associated with decreased risk of developing asthma by 16 years. This is supported by Lee-Sarwar *et al.* [17], who followed study participants from birth, and determined that high levels of n-3 and n-6 PUFA were also correlated with a decreased risk of asthma.

To further determine causation in the relationship between linoleic acid and asthma, a 2016 study analysed the impact of dietary intake of *cis*-9, *trans*-11 CLA on children and adolescents with existing asthma. Throughout the course of the 12-week study, *cis*-9, *trans*-11 CLA or a placebo was administered to study participants. The placebo group had elevated pro-inflammatory cytokines and plasma eosinophil cationic

protein. The authors concluded that CLA may have protective effects on the level of cellular inflammation; however, the results produced provided no evidence that CLA helped relieve symptoms of asthma [90].

EKSTRÖM et al. [91] used data collected from food frequency questionnaires, blood samples and asthma prevalence questionnaires to investigate the role that dietary intake of PUFAs and the prevalence of PUFAs within a child's plasma had on both the development of asthma and overall lung function within the paediatric population. The authors determined that high levels of linoleic acid within an adolescent's plasma at 16 years was associated with a decreased risk of asthma at 24 years. Conversely, the authors also determined that high self-reports of dietary linoleic acid consumption at 8 years of age was associated with an increased risk of asthma at 24 years of age, suggesting that further investigation in the role of self-reported diet compared to plasma PUFA metabolite measurements is needed.

PAPAMICHAEL et al. [92] investigated the usefulness of PUFA metabolites as biomarkers of the mild-asthma phenotype within the paediatric population. This cross-sectional study compared spirometry with metabolomic profiling. 25 unique plasma PUFAs of various structure were identified. Linoleic acid was associated with impaired lung functions in obese children with asthma. The results suggested that plasma PUFA levels would be useful as a metabolic signature to assist in determining the need for patient-specific dietary modifications to achieve improved asthma control.

As seen from these summaries, population-based studies provide differing results depending on methodology, population characteristics and which metabolites are specifically measured. Although the linoleic acid metabolites (as well as arachidonic acid) were analysed in some of the population studies, the stool microbiome was not analysed in the older paediatric population, omitting an important source of linoleic acid metabolites. Large, prospective clinical studies with dietary interventions will be helpful to determine a causative role of PUFAs; specifically, linoleic acid and its metabolites, in asthma development and progression in children. Supplementary table S2 summarises the population studies investigating dietary linoleic metabolites, PUFA consumption and paediatric asthma.

Questions for further research
A primary question is whether the purported effects of linoleic acid metabolites occur *via* the parent PUFA and/or the downstream oxygenated products (*i.e.* octadecanoids) and when it occurs. While several studies indicate that linoleic acid metabolites impact the development and exacerbation of paediatric asthma and allergy, the mechanism and timing of this phenomenon remain unclear [15, 82, 90]. We have highlighted a few proposed mechanisms in our review; however, there are others that warrant further investigation. As an example, there has been work looking at G protein-coupled receptors (GPCRs) that recognise short-chain fatty acids (GPR43, GPR41) and long-chain fatty acids like n-3 PUFAs (GPR120), both prevalent in a Mediterranean diet. The n-3 fatty acids, through GPR120, have demonstrated downstream anti-inflammatory properties *via* inhibition of tumour necrosis factor and IL-6 [93]. While GPCRs have been investigated for their role in generalised mucosal immunity, this mechanism and others involving mucosal immunity and the gut–lung axis highlight some of the gaps in knowledge in the field of asthma development that should be further explored. Once we have greater understanding regarding the timing and mechanism of the role of octadecanoids in paediatric lung health, we can investigate whether dietary interventions result in protective metabolic patterns in those children at risk for developing asthma.

Conclusion
Linoleic acid is the most common n-6 PUFA in the standard Western diet [94]. Over the past century, the consumption of linoleic acid has risen substantially due to an increase in vegetable oils and food processing with a concomitant decrease in fish and fibre consumption [10, 12]. The health effects of the remodelling of dietary fat have been debated extensively in the literature [95–97] and recently, elevated linoleic acid has been associated with the development and exacerbation of paediatric asthma [85, 86, 88]. Several studies have established a link between levels of linoleic acid, its downstream octadecanoid metabolites and allergic inflammation [15, 82, 90]. However, it is unclear if linoleic acid metabolites directly activate inflammatory cascades leading to asthma-like symptoms or if they are simply biomarkers for asthma risk or severity. It is possible that oxidised linoleic acid products (*e.g.* HODEs, EpOMEs, TriHOMEs) are reflective of the increased systemic oxidative stress associated with obstructive lung disease [98]. Animal and clinical studies as well as *in vitro* models have reached contradictory conclusions in terms of the role of linoleic acid, necessitating the need for further investigation. However, mechanistic studies are increasingly suggesting that at the least, 12,13-DiHOME is a functional lipid mediator that directly impedes immune tolerance [7].

Population-based dietary studies have also reached conflicting conclusions in regard to the potential benefits of a Mediterranean diet [99], with the purported health benefits of the n-3 PUFAs including ALA. There is a requirement for additional rigorous prospective studies to determine the impact and timing of linoleic acid and its metabolites, as well as the ALA analogues, during infancy and the critical window of immune development [85, 86, 88]. While there is a plethora of data indicating that linoleic acid metabolites exert some bioactive effect on paediatric allergy and asthma, the timing and specific effects remain underexplored [82].

The gut microbiome clearly exerts a significant effect in immune development and there is a need to evaluate the interaction between microbiome speciation, dietary composition, and onset of atopy, particularly within the context of critical windows of susceptibility in those at risk for the development of atopy. Focused studies on the relationship between linoleic acid and the aetiology and pathophysiology of asthma and allergy have the potential to provide important indicators of the health effects of dietary fat, particularly in relation to the maternal and infant microbiome. It is our recommendation that further mechanistic and longitudinal prospective studies are performed in those individuals at risk for the development of asthma to determine the impact that linoleic acid and its downstream octadecanoid metabolic products have on the development and severity of asthma within the paediatric population.

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