Received: 26 September 2023 | Revised: 23 January 2024 | Accepted: 9 February 2024

DOI: 10.1111/all.16065

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW

Systematic review of the association between short chain fatty acids and allergic diseases

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Abstract

We performed a systematic review to investigate the current evidence on the association between allergic diseases and short chain fatty acids (SCFAs), which are microbially produced and suggested as one mechanism on how gut microbiome affects the risk of allergic diseases. Medline, Embase and Web of Science were searched from data inception until September 2022. We identified 37 papers, of which 17 investigated prenatal or early childhood SCFAs and the development of allergic diseases in childhood, and 20 assessed SCFAs in patients with pre-existing allergic diseases. Study design, study populations, outcome definition, analysis method and reporting of the results varied between papers. Overall, there was some evidence showing that the three main SCFAs (acetate, propionate and butyrate) in the first few years of life had a protective effect against allergic diseases, especially for atopic dermatitis, wheeze or asthma and IgE-mediated food allergy in childhood. The association between each SCFA and allergic disease appeared to be different by disease and the

Abbreviations: AD, atopic dermatitis; BCFAs, branched short chain fatty acids; NOS, Newcastle–Ottawa Scale; SCFAs, short chain fatty acids.

Remo Frei and Caroline Roduit share last authorship.

age of assessment. Further research that can determine the potentially timing specific effect of each SCFA will be useful to investigate how SCFAs can be used in treatment or in prevention against allergic diseases.

KEYWORDS
allergic diseases, butyrate, gut microbiome, propionate, short chain fatty acids

1 | INTRODUCTION

The imbalance in the interaction between the gut microbiome and the immune system has been suggested to play a role in the development of many immune-mediated diseases, including allergic diseases.[1,2] Alterations in the composition of gut microbiota have been widely reported in both children and adults with allergic diseases.[3–7] However, the mechanism of how this affects the risk of allergic diseases remains unclear. Microbiota can directly affect the immune system by interaction with microbe-associated molecular patterns (e.g., lipopolysaccharide) or indirectly by microbially produced metabolites, namely short chain fatty acids (SCFAs).[1,8,9]

SCFAs are volatile fatty acids produced by the gut microbiota through fermentation of food components and refers to those with up to five to six carbons in straight or branched-chain formation.[10] Acetate (C2), propionate (C3) and butyrate (C4) represent 90–95% of the total SCFAs in the colon and are mostly final metabolic products of carbohydrate fermentation.[11] The gut microbiota also produce low levels of valerate (C5), caproate (C6) and branched short chain fatty acids (BCFAs), mainly iso-valeric acid and iso-butyric acid, which are produced by the fermentation of amino acids.[10] It is well known that SCFAs, especially butyrate, are important substrates for maintaining the colonic epithelium.[12] SCFAs have anti-inflammatory properties and influence the immune cells through various pathways via G-protein-coupled receptors and histone deacetylase inhibition.[13,14] Their effects include inhibiting the production of pro-inflammatory cytokines by innate immune cells, promoting B-cell antibody production and accelerating differentiation of FOXP3+ regulatory T cells (Tregs).[8,9] The promotion of Tregs is mediated through several mechanisms, such as butyrate and propionate inducing the differentiation from naïve CD4+ T cells and butyrate enhancing Treg generation by its effect on macrophages and dendritic cells, also inducing IL-10 producing T cells.[15–17] Direct delivery of SCFAs to the gut by oral administration or an enema has undergone human trials for the treatment of inflammatory bowel disease or colitis.[18] Additionally, although only a minor proportion of microbially produced SCFAs (especially for butyrate) reach systemic circulation and other tissues, the immunomodulatory functions of SCFAs have also been shown outside the gut, such as in the lung, skin and brain, within animal models.[19–21] There is increasing interest in the role of SCFAs as one of the mechanisms for how gut microbiota can affect the risk of allergic disease and as a potential method of intervention.

Here, we conducted a systematic review of studies that investigated the association between SCFAs and (i) the development of allergic diseases in childhood and (ii) pre-existing allergic diseases, to have a comprehensive understanding of the current epidemiological evidence for the protective role of SCFAs against allergic diseases.

2 | METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[22]

The protocol of this systematic review was registered in PROSPERO (CRD42022324883) in May 2022.

2.1 | Eligibility criteria

We included observational studies and intervention studies that reported the association between the level of SCFAs in any human samples and allergic diseases in children and/or adults.

We included studies that identified or targeted one or more of the SCFAs- acetate, propionate, butyrate, valerate, caproate, iso-valeric and iso-butyric acid according to the level 1 and 2 annotation standards set forth.[23,24] Studies that (i) assessed SCFAs and future development of allergic diseases and (ii) assessed SCFAs in patients with pre-existing allergic diseases were included but reported separately. For the outcome of allergic diseases, studies on atopic dermatitis (AD), wheeze/asthma, allergic rhinitis, non-IgE-mediated and IgE-mediated food allergy and atopic sensitisation were included without limitation to their definitions (e.g., self-reported or physician diagnosis).

2.2 | Exclusion criteria

Animal studies, studies using untargeted metabolomics methods only, studies reported in a language other than English or conference abstracts were excluded. Intervention studies which compared short chain fatty acid (SCFA) levels only between the control and intervention group (and not between those with and without allergic diseases), studies that compared SCFAs by the response to a treatment or in which there was no healthy control group, were also excluded from this review.

2.3 | Search method

We searched Medline, Embase and Web of Science from database inception to September 2022. Search terms included, "allergy", "allergic disease", "atopic dermatitis", "eczema", "asthma", "wheeze", "allergic rhinitis", "hayfever", "SCFA", "short chain fatty acid", "acetate", "acetic acid", "propionate", "propionic acid", "butyrate", "butyric acid", "isobutyrate", "isobutyruc acid", "caproate", "hexanoic acid", "metabolomics" and "lipidomics". The full search terms are provided in supplementary material. The reference lists of eligible studies were also manually searched to identify additional literature. Two independent reviewers assessed the eligibility by screening the title and abstract, followed by the full text.

2.4 | Data extraction and risk of bias assessment

One reviewer (MS) completed data extractions, and data were confirmed with another reviewer (NS). Disagreements were resolved by consensus between the two reviewers. The risk of bias assessment was carried out using the Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies with some adjustments to the criteria.[25] A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories and maximum of two stars can be given for comparability. We classified studies having 0–33% of the highest possible total number of stars as high risk, 34%–67% as medium risk and 68%–100% as low risk.

2.5 | Data synthesis

Results from the studies were summarised separately for (i) studies that investigated the association between SCFAs and future development of allergic diseases and (ii) those that reported the association between SCFAs and pre-existing allergic diseases. Papers compared SCFAs between cases and controls either by their level/concentration using the observed value, relative abundance (proportion among the total SCFA) or proportion of individuals with high levels using a certain cut-off value (e.g., median, 75 or 95 percentile) or a combination of these, and the observed levels of SCFAs were not always reported. Thus, meta-analysis was not carried out and results were summarised based on direction of effect—disease had an association with the SCFAs in the negative direction (decreased level or concentration, relative abundance or proportion of individuals with high value in cases compared with controls), an association in the positive direction (increased level or concentration, relative abundance or proportion of individuals with high value in cases compared with controls) or no association. Due to differences in how studies interpret significant *p*-values, for the purposes of this review, *p*-value <.05 was considered as a significant association.

3 | RESULTS

A total of 6411 papers were identified, of which 241 full texts were assessed, and 36 papers met the eligibility criteria. One paper was identified by searching the references, and so a total of 37 papers were included in this review (Figure 1). Among the papers included, 17 papers reported the association between SCFAs measured prior to the allergy outcome, while 20 papers reported on the association between SCFAs and pre-existing allergic diseases.

3.1 | SCFAs and allergy development

3.1.1 | Study characteristics

A total of 17 papers used data from 13 studies, comprising 9 prospective cohort studies,[26–42] three interventional studies,[32,34,42] and one hospital-based case control study design with follow-up.[40] Sample size in terms of the number of individuals who had SCFAs compared in each paper was less than 50 in three,[27,30,32] between 50 and 100 in seven,[26,28,31,35,37–39] between 100 and 200 in four,[29,31,34,40,42] between 200 and 300 in two[36,41] and unclear for one paper.[33] SCFAs were mostly measured in faecal samples ($n=16$),[26–39,41,42] in urine[27] and in serum[40] in each one article. The largest number of papers used gas chromatography ($n=7$)[26,27,30,31,37,41,42] for sample analysis (Table S1). Details of each of the 17 papers, including the timing or definition of outcome, statistical analysis method and results are presented in Table 1.

3.1.2 | Quality assessment

Based on the NOS, the risk of bias was categorised as low for nine papers,[26,28,31,33–35,37–39] medium for seven papers[27,29,30,32,36,40,41] and high for one paper.[40] The details of the results of the assessments are presented in Table S2. The criterion for 'non-response rate' was the least fulfilled (four out of 17 papers) among all criteria.

3.1.3 | Synthesis of results

Results are summarised for each allergic disease in Tables 2 and 3.

3.2 | SCFAs and development of atopic dermatitis (Table 2, 10 papers)

Six papers assessed AD in early childhood (1–3 years),[32,33,35,38,39,42] while four papers assessed AD in later childhood (6, 8 or 13 years).[28,30,31,36] A significant decrease in the level (or proportion of children with high level) of any of the three main SCFAs

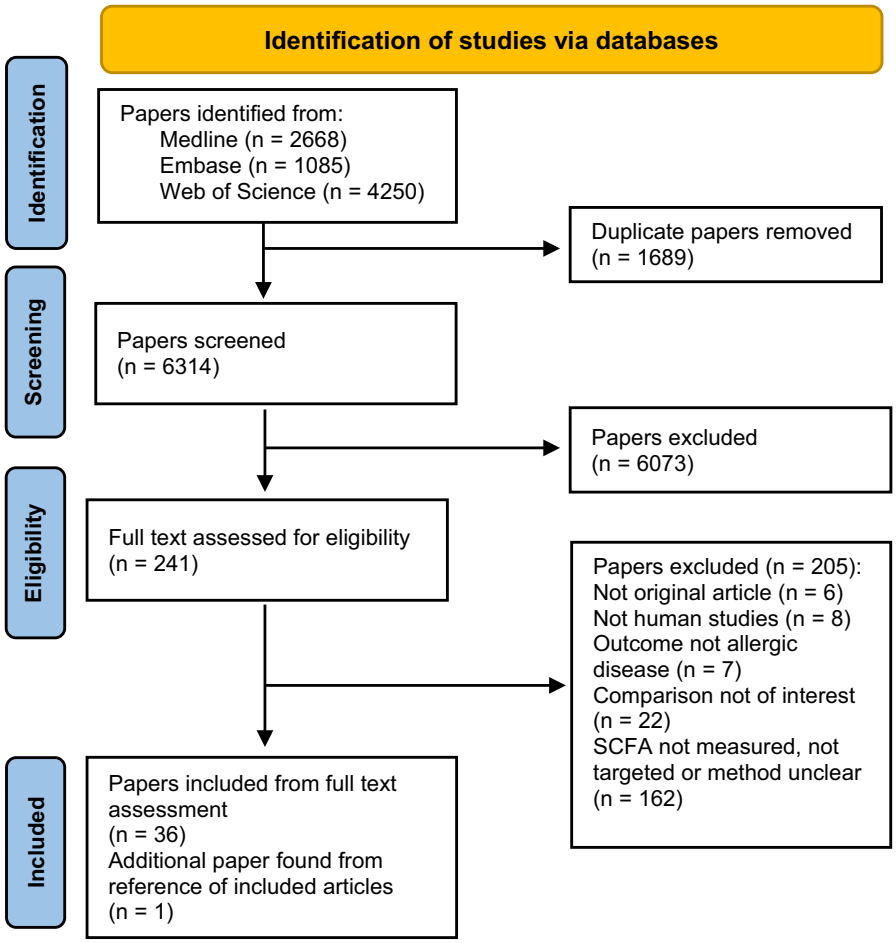

FIGURE 1 PRISMA flow chart showing the results of the literature search and the selection of studies. SCFA, short chain fatty acids.

(acetate, propionate or butyrate) among cases were reported in five of the six papers for early AD (acetate in one study, propionate in two studies and butyrate in four studies).[33,35,38,39,42] Among these papers, one birth cohort study only found a difference in SCFAs at 1 year when AD was assessed (Sasaki et al.).[38] Analysis from a Singaporean birth cohort study (GUSTO study) reported that butyrate and propionate were decreased in children with atopic AD but not in non-atopic AD compared with controls, using longitudinal analysis with SCFA measurements at 3 weeks, 3, 6 and 12 months and adjusting for confounders (Ta et al.).[39] Two other studies using longitudinal analysis reported that there was a reverse association between the SCFA profile (butyrate and propionate) and AD at 6 months in a study using data from a randomised controlled trial (Wopereis et al.)[42] and at 12 months in a Korean birth cohort study (Lee et al.).[33]

Among the four papers investigating the effect of SCFAs on late AD, decrease in acetate and butyrate in cases was reported only in the paper by Cheng et al., using the data from the GUSTO study. This paper reported that low faecal butyrate at 3 weeks, 3 and 6 months were longitudinally associated with AD (adjusted odds ratio: adjOR 13.2, 95% CI 1.1–158.3).[28] Decrease in valerate measured in early childhood among cases was shown with AD at 8 or 13 years in two different birth cohort studies conducted in rural Sweden.[30,31]

3.3 | SCFAs and development of wheeze/asthma (Table 3, nine papers)

Of the nine papers that investigated the outcome of wheeze/asthma,[26–31,34,36,40] six reported decrease in one or more of the three main SCFAs among children who developed the disease,[26–29,34,40] while there was no difference shown in the remaining three papers. Acetate was decreased among cases in all four studies that assessed prenatal or early infancy (6 months or before) samples and the development of wheeze/asthma at 6 years or earlier.[26,27,34,40] Of the two papers that reported the association between maternal acetate, one assessed faecal samples in a RCT on prenatal Vit D supplementation (Lee-Sarwar et al.)[34] and reported that the relative concentration of acetate was decreased in children with asthma/wheeze plus sensitisation (odds ratio: OR 0.46, 95% CI 0.33–0.94 by 10% increase in acetate). The other study reported an association of maternal serum acetate in a hospital-based case control study with follow up among pregnant women who have asthma (Thorburn et al.).[40] None of the studies which measured acetate at 1 year or later or those assessing wheeze/asthma at 8 years or later reported any difference in acetate ($n = 6$).[27–31,36]

Decrease in butyrate or propionate during infancy among cases was reported in two and three out of eight papers,[27–29] respectively, that investigated the outcome up to 8 years. Of these papers, the paper from Arrieta et al. using data from a Canadian birth cohort study

TABLE 1 Detailed description of the studies that investigated the association between short chain fatty acids and development of allergic diseases.

Author, Country, Year Study	Sample size of case/control	Sample type, analysis method	SCFAs measured[a]	Timing of outcome assessment and definition of outcome	Statistical method	Main results
Sandin et al, Sweden 2009 (BAS study)[37]	FA: 17/53, allergy: 10/19	Faeces at 1 and 4 years, GC	A, P, B, V, C, i-V, i-B, i-C	4 years, sensitisation: SPT positive, FA: doctor diagnosis, allergy: positive SPT and AD, BA or FA	Mann–Whitney *U*-test	No association between SCFA at 1 year and sensitisation at 4 years. Low levels of i-butyrate, i-valerate and valerate at 1 year were associated with FA at 4 years ($p = .01$, $p = .03$ and $p = .02$, respectively), which remained after excluding those with FA at 1 year. Allergic children had higher acetate but lower i-butyrate at 4 years compared with non-allergic children ($p = .02$ and $p = .04$), and a trend of lower i-valerate and valerate ($p = .06$ and $p = .06$) of which only valerate remained after excluding children with FA at 1 year.
Gio-Batta et al., Sweden 2022 (BAS study)[31]	AD: 28/33, FA: 28/33, BA: 19/33, RA: 28/33, sensitisation: 54/33	Faeces at 1 year, GC	A, P, B, V, C, i-V, i-B, i-C	13 years, AD: reported symptoms in the last 12 months, FA: reported symptoms, BA: report of diagnosis or medication use, symptoms in the last 12 months plus aeroallergen sensitisation (SPT ≥ 3 mm), ARC: symptoms in the last 12 months plus aeroallergen sensitisation, RA: BA or symptoms to aeroallergen exposure and sensitisation	Logistic regression (no adjustment)	The concentration of valerate at 1 year was inversely associated with AD at 13 year (OR 0.6, 95% CI: 0.4–1.0, $p = .049$) and a trend for FA (OR 0.6, 95% CI: 0.4–1.0, $p = .057$). The proportion of faecal valerate at 1 year was inversely associated with AD and FA (OR 0.6, 95% CI: 0.4–1.0, $p = .046$ and OR 0.5, 95% CI: 0.3–0.9, $p = .03$, respectively). No association between other SCFA and BA, ARC or RA.
Vuillermin et al., Australia 2020 (BIS study)[41]	57/240	Faeces at 36 weeks of gestation, GC	A, P, B, V, C, i-V, i-B	1 year, FA: sensitisation (SPT > 2 mm) and positive food challenge test	Unclear	No difference.
Sasaki et al., Switzerland 2022 (CARE study)[38]	27/39	Faeces at 3, 6 and 12 months, HPLC	A, P, B	Up to 1 year, AD: symptoms reported, diagnosis reported or made at clinical examination	Mann–Whitney *U*-test as continuous variable and chi-squared test as categorical variable	No difference in SCFAs as continuous variable. Children with AD were less likely to have high level of butyrate (>75 percentile cut-off at 18.86 μmol/g) at 12 months (11.5% vs 34.2%, $p = .04$). No difference in other SCFAs or at different time points.

(Continues)

TABLE 1 (Continued)

Author, Country, Year Study	Sample size of case/control	Sample type, analysis method	SCFAs measured[a]	Timing of outcome assessment and definition of outcome	Statistical method	Main results
Arrieta et al., Canada 2015 (CHILD study)[27]	13/13	Faeces and urine, 3 and 12 months, GC	A, P, B, V, C, i-V, i-B	Up to 1 year, atopic wheeze: SPT ≥2 mm and reported or clinician recorded wheeze at 1 year	Mann–Whitney *U*-test	Acetate higher in faeces of controls (14.13 ± 8.19 vs 7.77 ± 6.01 μmol/g faeces, $p = .03$), no difference in propionate (2.07 ± 2.08 vs 1.06 ± 0.91, $p = .38$) or butyrate (0.29 ± 0.51 vs 0.47 ± 0.56, $p = .15$) at 3 months. At 1 year, faecal propionate, iso-butyrate, butyrate, iso-valerate, valerate but not acetate was higher in controls. No difference in urine.
Lee et al., Korea 2022 (COCOA study)[33]	Number of samples: 110 (mild AD), 124 (moderate–severe AD)/112	Faeces at 3–36 months, GC–MS	A, P, B, V, i-V, i-B, methyl-valeric acid	Up to 3 year, AD: Hanifin and Rajka's criteria, every year from 6 months, SCORAD >25 as moderate–severe	SCFA-by-age z-score calculated using machine learning	Children with AD had highly matured SCFA profile before 12 months but delayed after 12 months compared with controls. Butyrate contributed more to the model than propionate.
Park et al, Korea 2020 (COCOA study)[35]	12 (transient AD), 12 (persistent AD)/33	Faeces at 6 months, GC–MS	A, P, B, V	Up to 2 years, AD: Hanifin and Rajka's criteria, transient AD: only 6 months, persistent AD: 6 months and 2 years	Kruskal–Wallis test and the Mann–Whitney *U*-test	Butyrate and valerate levels were lower in infants with transient AD than in healthy controls ($p = .011$ and $p = .004$, respectively) and than in the persistent AD group ($p = .020$ and $p = .008$, respectively). No difference in acetate or propionate.
Arrieta et al., Ecuador 2018 (ECUAVIDA study)[26]	27/70	Faeces at 3 months, GC	A, P, B, V, C, i-V, i-B	5 years, atopic wheeze: reported wheeze and sensitisation (SPT ≥3 mm)	Mann–Whitney *U*-test	Decrease in acetate (<0.05) and increase in caproate concentration (<0.01) in children who developed atopic wheeze. No difference in butyrate, propionate, iso-butyrate or valerate.
Gio-Batta et al., Sweden 2020 (FARMFLORA study)[30]	4 (AD), 2 (ARC), 3 (BA)/30	Faeces at 3 years, GC	A, P, B, V, C, i-V, i-B	8 years, AD: William's criteria or symptoms >6 months in the last 12 months, BA: reported symptoms with response to treatment, positive methacholine challenge or reversible bronchial obstruction by beta 2 agonist, FA: symptoms and reaction to exposure or at OFC, ARC: symptoms to exposure with sensitisation.	Mann–Whitney *U*-test	Children with AD had lower median concentration of valeric acid compared with controls (0.5 vs. 2.3 μmol/g, $p = .007$), which remained among only non-farm children. No other SCFA was associated with any of the outcomes.

TABLE 1 (Continued)

Author, Country, Year Study	Sample size of case/control	Sample type, analysis method	SCFAs measured[a]	Timing of outcome assessment and definition of outcome	Statistical method	Main results
Ta et al., Singapore 2020 (GUSTO study)[39]	14 (non-atopic AD), 19 (atopic AD)/30	Faeces at 3 weeks, 3, 6, and 12 months, LC–MS–MS	A, P, B, V, C, i-V, i-B, 2-methyl- and 4-methylbutyrate	Up to 3 years, AD: reported diagnosis, atopic: SPT ≥3 mm	Linear mixed-model and general linear model, adjusting for gender, birth order, mode of delivery, breastfeeding till 6 months, antibiotics at labour and family of atopic history	Lower concentrations of acetate, butyrate and propionate in atopic AD (adj $p < .05$), but not in non-atopic AD at all time points. Longitudinal analysis showed decreased butyrate and propionate associated with atopic AD (adj $p < .05$).
Cheng et al., Singapore 2022 (GUSTO study)[28]	AD: 35/32, wheeze: 19/43, recurrent wheeze: 9/53, inhalant sensitisation: 45/19, food sensitisation: 17/46, AD and wheeze: 16/30	Faeces at 3 weeks, 3, 6 and 12 months, LC–MS–MS	A, P, B, V, I, i-V, i-B, 2-methyl- and 4-methylbutyrate	Up to 8 years, AD: reported diagnosis, wheeze: reported wheeze and use of nebuliser, recurrent wheeze: wheeze more than once, sensitisation: SPT ≥3 mm	Logistic regression and Generalised Linear Mixed Models for longitudinal analysis, adjusting for gender, presence of siblings, mode of delivery, family history of atopic diseases and feeding pattern	Lower butyrate (≤25 percentile) at 3 and 6 months associated with increased risk of AD (adjOR (95% CI) = 58.3 (1.5–2315.7) and 41.9 (1.0–1678.9), respectively) compared to children with higher butyrate levels (≥75 percentile). A similar trend for lower acetate at 6 months [adjOR (95% CI) = 18.5 (1.0–336.2)] ($p < .05$). Lower caproate at 12 months increased the risk of wheeze compared with children with higher levels [adjOR (95% CI) =28.1 (1.2–650.3)]. Longitudinal analysis (3 weeks, 3 and 6 months) showed that lower butyrate levels increased the risk of wheezing (adjOR (95% CI) = 14.6 (1.2–189.7)), AD [adjOR (95% CI) = 13.2 (1.1–158.3)], food sensitisation [adjOR (95% CI) = 12.3 (1.3–115.0)] and combined outcomes of both wheezing and AD [adjOR (95% CI) = 22.6 (1.3–382.7)]. Low levels of propionate levels were associated with recurrent wheezing [adjOR (95% CI) = 7.4 (1.2–44.2)] for all 4 time points (Week 3, Months 3, 6 and 12).

(Continues)

TABLE 1 (Continued)

Author, Country, Year Study	Sample size of case/control	Sample type, analysis method	SCFAs measured[a]	Timing of outcome assessment and definition of outcome	Statistical method	Main results
Roduit et al., Austria, Switzerland, France, Germany and Finland, 2019 (PASTURE study)[36]	BA: 33/244, AR: 25/240, FA: 33/257, AD: 140/160, inhalant sensitisation: 11/166, food sensitisation: 102/174	Faeces at 1 years, HPLC	A, P, B	Up to 6 years, BA: reported diagnosis or at least 2 episodes of obstructive bronchitis in the year 4,5,6. FA: reported diagnosis, AD: reported diagnosis and/or SCORAD at 1 year, AR: reported diagnosis or symptoms, sensitisation: Serum sIgE measured at 6 years	Fisher's exact test (proportion) and logistic regression model (binary) adjusted for centre, farmer, sex, parent allergy, mode of delivery, breastfeeding and siblings	Proportion of children sensitised was lower among children with high levels of butyrate (26.7% vs 56.3% ≥95th percentile; >26.88 μmol/g) and propionate (20.0% vs 56.7%, >32.87 μmol/g), no association with acetate (14.3% vs 11.8%, >114.67 μmol/g). There was no association between the SCFAs and AD, AR, FA or BA. Children with SCFA in higher categories (>95th percentile vs lower) of butyrate or propionate had adjusted OR: 0.25 (95% CI, 0.08–0.82) and 0.20 (95% CI, 0.05–0.74), respectively for sensitisation.
Depner et al., Austria, Switzerland, France, Germany and Finland, 2020 (PASTURE study)[29]	44/94	Faeces at 1 years, HPLC	A, P, B	Up to 6 years, BA: reported diagnosis or at least 2 episodes of obstructive bronchitis in the year 4,5,6.	Logistic regression (no adjustment)	Children with butyrate in the upper quartiles, had OR 0.28 (95% CI 0.09–0.91, $p = .034$) of BA compared with those in the lowest quartile.
Wopereis et al., Australia, England, and Ireland, 2018 (PATCH trial, RCT among high-risk children)[42]	52/ 86	Faeces at 4, 12 and 26 weeks. GC	A, P, B, V, i-B	Up to 18 months, modified Hanifin and Rajka criteria	Principal response curves using ethnicity, feeding group, and siblings as covariates, with Monte Carlo permutation tests	Infants with AD had decreased lactate and increased propionate and butyrate at 12 weeks, which reversed at 26 weeks, where infants with AD had increased lactate and decreased propionate and butyrate.
Kim et al., the Netherlands 2015, (the PandA study, RCT among high-risk children)[32]	17/16	Faeces at 3 months, NMR	A, P, B	Up to 2 years, reported AD (with confirmation by a diagnosis in a number of cases)	ANOVA and orthogonal partial least squares-discriminant analysis (OPLD-DA)	No difference between case and control by ANOVA: Acetate 0.48 (0.42) versus 0.52 (0.39), Propionate 0.08 (0.09) versus 0.10 (0.08), *n*-butyrate 0.10 (0.10) versus 0.10 (0.11), total SCFA 0.65 (0.56) versus 0.72 (0.46), concentrations are in arbitrary units (standard deviation). But small difference in butyrate, acetate detected by OPLS-DA.

TABLE 1 (Continued)

Author, Country, Year Study	Sample size of case/control	Sample type, analysis method	SCFAs measured[a]	Timing of outcome assessment and definition of outcome	Statistical method	Main results
Lee-Sarwar et al., USA 2019, (VDAART study, RCT)[34]	BA: 70/80, sensitisation: 38/42, AR: 54/81, atopic BA: 17/63, BA and AR: 33/102	Faeces, third trimester, LC–MS–MS	A, P, B	Up to 6 years, BA: reported diagnosis, recurrent wheeze and medication use. Sensitisation: serum sIgE >0.35 kU/L, AR: reported diagnosis, asked every 3 months and at annual in person visits up to 6 years	Logistic regression, adjusted for early pregnancy BMI and breastfeeding.	None of the SCFAs were associated with BA, sensitisation or AR. Relative acetate inversely associated with atopic BA (OR 0.46, 95% CI 0.22–0.94, $p = .036$, for a 10% increase).
Thorburn et al., Australia 2015, hospital-based case control study with follow-up[40]	Total sample size 40	Serum, late phase pregnancy, NMR	A, P, B	Up to 1 year, two or more general practitioner visits for cough or wheeze, reported wheeze	Chi-squared test	Children born to mothers (without BA) with acetate lower than median (0.05315 mM) were more likely to require two or more general practitioner visits for cough or wheeze and a trend toward increased parent-reported wheeze. No association when mother had BA or for other SCFAs.

[a]Individual SCFAs are abbreviated as A: acetate, P: propionate, B: butyrate, V: valerate, C: caproate, i-B: iso-butyrate, i-V: iso-valerate, i-C, iso-caproate. BCFAs: branched short chain fatty acids.

Abbreviations: AD, atopic dermatitis/eczema; adjOR, adjusted odds ratio; AR, allergic rhinitis (including hay fever); ARC, allergic rhino-conjunctivitis; BA, asthma; FA, food allergy; GC, gas chromatography; GC–MS, gas chromatography mass spectroscopy; HPLC, high-performance liquid chromatography; LC–MS–MS, liquid chromatography tandem mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; OR, odds ratio; SPT, skin prick test.

TABLE 2 Summary of papers that reported the association between short chain fatty acids and atopic dermatitis later in life.

		Timing of outcome (atopic dermatitis) assessment						
		1 year	18 months	2–3 years			6–8 years	13 years
Timing of SCFA measurement	Newborn (<1 month)			Ta 2020[39] ▼ acetate, propionate, butyrate	Ta 2020[e,39] ▼ butyrate, propionate × acetate		Cheng2022[d,28] × all	Cheng2022[d,e,28] ▼ butyrate × others
	3–6 months	Sasaki 2022[38] × acetate, propionate, butyrate	Woperies 2018[e,38] propionate, butyrate △ at 12 weeks ▼ at 26 weeks × valerate, iso-butyrate	Park 2020[b,35] ▼ butyrate, valerate × acetate, propionate Ta 2020[39] ▼ acetate, propionate, butyrate Kim 2015[c,32] × acetate, propionate, butyrate		Lee 2022[e,33] mature pattern until 12 months and delayed after 12 months	Cheng2022[d,28] ▼ acetate, butyrate × others	
	12 months	Sasaki 2022[a,38] ▼ butyrate × acetate, propionate		Ta 2020[39] ▼ acetate, propionate, butyrate			Cheng2022[d,28] × all Roduit 2019 [36] × acetate, propionate, butyrate	Gio-Batta 2022[31] ▼ valerate × acetate, propionate, butyrate, iso-butyrate, iso-valerate, caproate, iso-caproate
	3 years old						Gio-Batta 2020[30] ▼ valerate × acetate, propionate, butyrate, iso-butyrate, iso-valerate, caproate, iso-caproate	

Note: Levels/concentrations, relative abundance or proportion of individuals with high levels observed in cases were ▼: decreased, △: increased or ×: not different compared with controls. For the purposes of this review, *p*-value <.05 was considered as a significant association. SCFAs were measured in faecal samples if not stated otherwise.

[a]SCFA measurement and outcome assessment are done at the same timing.

[b]Association was only found with transient AD and not with persistent AD.

[c]Small decrease in SCFA when analysed by orthogonal partial least squares-discriminant analysis.

[d]9 SCFAs (acetic, propionic, butyric, iso-butyric, valeric, isovaleric, 2-methylbutyric, caproic and 4-methylvaleric acids) were assessed in this study. No difference between case and control if not listed here.

[e]Results from longitudinal analysis using multiple time points during this period. Otherwise, results are from individual analyses between SCFAs measured at one or two timepoints in each cell.

TABLE 3 Summary of papers that reported the association between short chain fatty acids and wheeze/asthma, food allergy, allergic rhinitis and any allergy.

A. Wheeze/asthma	Timing of outcome assessment				
SCFA measurement	**1 year**	**5–6 years**	**8 years**		**13 years**
Prenatal (maternal)	Thorburn 2015 (serum)[40] ▼ acetate[a] × butyrate, propionate	Lee-Sarwar[34] ▼ acetate × butyrate, propionate			
Newborn (<1 month)			Cheng 2022[c,28] ▼ propionate × others	Cheng 2022[c,d,28] ▼ butyrate (3 weeks–6 months), ▼ propionate (3 weeks–12 months)	
3–6 months	Arrieta 2015[27] ▼ acetate × butyrate, propionate, iso-butyrate, valerate, iso-valerate, caproate	Arrieta 2018[26] ▼ acetate △ caproate × butyrate, iso-butyrate, propionate, valerate	Cheng 2022[c, 28] ▼ propionate × others		
12 months	Arrieta 2015[27 b] ▼ propionate, butyrate, iso-butyrate, valerate, iso-valerate × acetate	Roduit 2019[36] × acetate, propionate, butyrate Depner 2020[29] ▼ butyrate × acetate, propionate	Cheng 2022[c, 28] ▼ propionate, caproate × others		Gio-batta 2022[31] × acetate, propionate, butyrate, iso-butyrate, valerate, iso-valerate, caproate, iso-caproate
3 years	Gio-batta 2020[30] × acetate, propionate, butyrate, iso-butyrate, valerate, iso-valerate, caproate, iso-caproate				

B. Food allergy	Timing of outcome assessment			
SCFA measurement	**1 year**	**4 years**	**6 years**	**13 years**
Prenatal (maternal)	Vuillermin 2020[41] × acetate, propionate, butyrate, valerate, iso-butyrate, iso-valerate, caproate			
12 months		Sandin 2009[37] ▼ valerate, iso-valerate, iso-butyrate × acetate, propionate, butyrate	Roduit 2019[36] × acetate, propionate, butyrate	Gio-Batta 2022[31] ▼ valerate, propionate[e] △ butyrate[e] × acetate, iso-butyrate, iso-valerate, caproate, iso-caproate

C. Allergic rhinitis	Timing of outcome assessment		
SCFA measurement	**6 years**	**8 years**	**13 years**
Prenatal (maternal)	Lee-Sarwar 2019 [34] × acetate, propionate, butyrate		
12 months	Roduit 2019 [36] ×acetate, propionate, butyrate		Gio-Batta 2022[31] × acetate, propionate, butyrate, valerate, iso-butyrate, iso-valerate, caproate, iso-caproate
3 years		Gio-Batta 2020[30] × acetate, propionate, butyrate, valerate, iso-butyrate, iso-valerate, caproate, iso-caproate	

(Continues)

TABLE 3 (Continued)

D. Any allergy	Timing of outcome assessment				
SCFA measurement	**4 years**	**6 years**	**8 years**		**13 years**
Prenatal (maternal)		Lee-Sarwar 2019[34] × acetate, propionate, butyrate			
Newborns (<1 months)			Cheng 2022[c, 28] × all	Cheng 2022[c,d,28] ▼ butyrate (3 weeks–6 months, for food sensitisation or BA plus AD) × others	
3–6 months			Cheng 2022[c, 28] × all		
12 months	Sandin 2009[37] × acetate, propionate, butyrate, valerate, caproate, iso-butyrate, iso-valerate, iso-caproate	Roduit 2019[36] ▼ butyrate, propionate × acetate	Cheng 2022[c, 28] × all		Gio-Batta 2022[31] × acetate, propionate, butyrate, valerate, caproate, iso-butyrate, iso-valerate, iso-caproate (for respiratory allergy)
4 years	Sandin 2009[b,37] ▼ iso-butyrate, △ acetate× propionate, butyrate, valerate, caproate, iso-valerate, iso-caproate for sensitisation plus disease				

Note: Levels/concentrations, relative abundance or proportion of individuals with high levels observed in cases were ▼: decreased, △: increased or ×: not different compared with controls. For the purposes of this review, *p*-value <.05 was considered as a significant association. SCFAs were measured in faecal samples if not stated otherwise.

[a]Association was shown only when the mother had asthma.

[b]SCFA measurement and outcome assessment are done at the same timing.

[c]9 SCFAs (acetic, propionic, butyric, iso-butyric, valeric, isovaleric, 2-methylbutyric, caproic and 4-methylvaleric acids) were assessed in this paper. No difference between cases and controls if not listed here.

[d]Results from longitudinal analysis using multiple time points during this period. Otherwise, results are from individual analyses between SCFAs measured at one or two timepoints in each cell.

[e]These associations were shown only for some allergens when the stratified by allergens.

(CHILD study) only reported a decrease in cases when the measurement and outcome assessment was done at the same timepoint.[27] Roduit et al. analysed data from more than 300 children in a multinational European birth cohort study (PASTURE study) and reported that children with high level (>95th percentile) of butyrate or propionate at 1 year had lower proportion of asthma at 6 years, although these associations were not statistically significant.[36] However, Depner et al. reported a statistically significant decrease in butyrate among cases in a different analysis using a subset of the same data (upper quartiles vs lowest quartile, OR 0.28, 95% CI 0.09–0.91).[29] Analysis of the GUSTO study reported that propionate was associated with children with recurrent wheezing longitudinally (lowest vs highest quartile, adjOR 7.4, 95% CI 1.2–44.2) and at all time points (3 week, 3, 6 and 12 months).[26] This study also reported a decrease in caproate at 12 months to be associated with the development of wheeze/asthma up to 8 years (adjOR 28.1, 95% CI 1.2–650.3).[26]

3.4 | SCFAs and development of food allergy (Table 3, four papers)

None of the studies found association between food allergy (assessed between 1 and 13 years) and the three main SCFAs.[31,36,37,41] Two papers (Sandin et al. and Gio-batta et al.) using data from the same Swedish birth cohort study (BAS study) reported decreased level of valerate at 1 year in cases with food allergy at 4 years[37] and at 13 years.[31]

3.5 | SCFAs and development of allergic rhinitis (Table 3, four papers)

None of the four studies found association between allergic rhinitis and the three main or other SCFAs.[30,31,34,36]

3.6 | SCFAs and development of atopic sensitisation (Table 3, four papers)

Of the four papers,[28,34,36,37] analysis of the PASTURE study by Roduit et al. reported that children with high level of butyrate or propionate at 1 year were less likely to be sensitised at 6 years (>95th percentile vs lower, adjOR 0.25, 95% CI 0.08–0.82 for butyrate and 0.20, 95% CI 0.05–0.74 for propionate).[36] Decrease in butyrate was longitudinally (3 weeks, 3 and 6 months) associated with food sensitisation at 8 years (lowest vs. highest quartile adjOR 12.3, 95% CI 1.3–115.0) in the analysis by Cheng et al. using data from the GUSTO study.[28]

3.7 | SCFAs and development of any allergy (Table 3, three papers)

Three papers assessed the association between SCFAs and a combined outcome, each using a different definition.[28,31,37] A Swedish birth cohort study (BAS study) reported increase in acetate and decrease in iso-butyrate in children who were sensitised and had any allergic disease at 4 years, although only in samples assessed at 4 years and not at 1 year (Sandin et al.).[37] Cheng et al. reported decreased butyrate between 3 weeks and 6 months for children with both AD and asthma at 8 years (lowest vs highest quartile adjOR 22.6, 95% CI 1.3–382.7).[28]

3.8 | SCFAs and pre-existing allergic diseases

3.8.1 | Study characteristics

All articles in this category arose from unique studies, and of the total 20 studies,[43–62] most were case control studies ($n=15$).[43,46–51,53,55–61] The number of participants who had SCFAs measured and compared were less than 50 in seven studies,[44,47,48,52,53,60,62] between 50 and 100 in 10 studies,[43,45,50,51,55–59,61] and between 100 and 150 in three studies.[46,49,54] Most studies were carried out in children, with four studies in infants (1 year or younger),[44,45,55,57] and eight in children between 1 and 14 years.[43,46–50,56,58] SCFAs were measured in faecal samples in the majority of studies ($n=14$)[43–49,51–53,55,58,59,62] and gas chromatography ($n=7$, Table S1) was most often used for sample analysis.[43–45,47,49,52,55] The largest number of papers investigated the outcome of IgE-mediated food allergy ($n=9$). Details of each of the 20 papers are presented in Table 4.

3.8.2 | Quality assessment

Based on the NOS, 14 papers were assessed as having medium risk of bias,[43,46,47,49,50,52–54,57–62] five were low risk,[44,45,48,55,56] and one with high risk.[51] The details of the assessments are presented in Table S3. The criterion for "representativeness of the cases" was the least fulfilled (four out of 20 articles) among all criteria.

3.8.3 | Synthetisation of results (Table 5)

3.9 | SCFAs and pre-existing IgE-mediated food allergy (nine papers)

Of the eight studies in infants or children with IgE-mediated food allergy,[44,46,48–50,55,56,58] decrease in two or more of the three main SCFAs or total SCFA among cases were reported in five studies.[46,48–50,56] Salivary SCFAs were assessed in two studies of children with peanut allergy in the USA, (Ho et al. and Zhang et al.), of which one study reported decreased acetate, propionate and butyrate in cases (Ho et al)[50] and the other found a trend but not a statistically significant difference (Zhang et al).[58] One Chinese study (Tian et al.) reported decrease in all three main SCFAs measured in serum among children with IgE-mediated food allergy[56]

TABLE 4 Detailed description of the studies that investigated the association between short chain fatty acids and pre-existing allergic diseases.

Author, country, year, study design	Sample size of cases/controls	Sample type, analysis method	SCFA measured[a]	Outcome, definition of outcome	Statistical analysis method	Main results
Ivashkin et al., Russia 2019, case control study[51]	24 (atopic BA), 20 (non-atopic BA)/17	Faeces, gas–liquid chromatography	A, P, B	BA: unclear	Mann–Whitney *U*-test	Acetate, 5.87 ± 0.22 mg/g (healthy), 1.31 ± 0.59 (atopic asthma), 1.41 ± 0.59 (non-atopic asthma). Propionate 1.77 ± 0.08, 0.56 ± 0.33, 0.64 ± 0.36. Butyrate 1.73 ± 0.09, 0.39 ± 0.23, 0.57 ± 0.23, all $p < .001$.
Jung et al., Korea, 2013, case control study[61]	39/26	Serum, NMR	A	BA: specialist diagnosis based on history and evidence of reversible airway obstruction	Mann–Whitney *U*-test	Acetate was decreased in cases compared with controls ($p < .0001$).
Roessler et al., Germany 2012, within an RCT[52]	15/15	Faecal water, GC	A, P, B, V, C	AD: more than 10 points according to the atopy-score of Diepgen17, or flexural eczema or pruritis for at least 12 months, a SCORAD score of 5–30	Mann Whitney *U*-test	For samples taken after placebo: *n*-Caproate higher in healthy subjects 1.0 ± 0.7 vs AD 0.4 ± 0.6, no difference in acetate, propionate, iso-Butyrate, *n*-Butyrate, iso-Valerate, *n*-Valerate or total SCFA.
Wang et al., Taiwan 2022, hospital-based case control study[57]	47/47	Breastmilk, GC–MS	A, B	AD (of child): Hanifin and Rajka, objSCORAD for severity	independent *t*-test or Mann–Whitney *U*-test, Stepwise multiple regression analysis	Total SCFA and acetate were lower at each 716.0 ± 52.7 vs 1096.2 ± 122.5 μM and 468.3 ± 46.8 vs 857.3 ± 114.7 μM in the breastmilk of exclusively breastfeeding mothers whose child was AD compared with control ($p = .002, .005$) respectively. No difference in butyrate level (247.7 ± 18.1 vs 238.9 ± 23.0 μM; $p = .646$). When compared by lowest versus highest quartile, OR was 12, 95% CI 2.7–53.3, $p = .001$ for acetate and 10.52, 95% CI 2.27–48.76, $p = .003$ for SCFA. After adjustment for age, sex, parental allergy history, MUFA, palmitate and SCFA levels, acetate levels were correlated with AD, aOR 0.9980 (0.9964–0.9996), $p = .015$. Level of acetate and total SCFA negatively correlated with objective SCORAD score ($p = .013$ and 0.022).
Song et al., Korea 2016, hospital-based case control study[53]	12/12	Faeces, GC–MS	A, P, B	AD: SCORAD	Unclear	Butyrate and propionate increased in control compared with AD. No significant differences in acetate.

TABLE 4 (Continued)

Author, country, year, study design	Sample size of cases/controls	Sample type, analysis method	SCFA measured[a]	Outcome, definition of outcome	Statistical analysis method	Main results
Berni Canani et al., Italy 2016, within an intervention study[44]	19/20	Faeces, GC	B	IgE-mediated cow's milk FA: history, positive DBPCFC and positive sIgE	Nonparametric Kruskal–Wallis *H*-test (post hoc Tukey Kramer tests, Bonferroni multiple test correction)	No difference in butyrate between control vs cases at baseline. Among cases, children who became tolerant 6 months later had higher butyrate level than those who remained allergic at the time (12.52 ± 0.32 mmol/kg vs 10.32 ± 0.3 mmol/kg, $p = .0032$, Welch's *t*-test).
Thompson-Chagoyan et al., Spain 2011, hospital-based case control study[55]	46/46	Faeces, GC	A, P, B, BCFA, i-C	IgE-mediated cow's milk FA: history, positive SPT/sIgE and positive DBPCFC	Mann–Whitney *U*-test	Concentration of butyrate and BCFA were higher in cases compared with controls. The percentages of butyrate 6.7 (0.0–30.2) versus 1.8 (0.0–37.1); $p < .05$ and BCFA 3.1 (0.0–14.7) vs. 1.2 (0.0–7.4); $p < .01$ were also higher in cases compared with controls.
Dong et al., China 2018, hospital-based case control study[48]	6/4	Faeces, HPLC	A, P, B, i-B, lactate	IgE-mediated cow's milk FA: history, positive SPT/sIgE and positive OFC	Unclear	Total SCFA was increased in controls compared with cases (221.33 vs 255.95 mmol/kg), no difference in individual SCFAs
Goldberg et al., Israel 2020, hospital-based case control study[49]	84/31	Faeces, GC	A, P, B	IgE-mediated FA: history of reaction or positive OFC in the past year and positive SPT (milk, peanut, sesame and tree nuts)	ANOVA followed by pairwise *t*-test and FDR correction.	Lower concentrations in cases compared with controls for acetate ($q < 0.001$) butyrate ($q < 0.001$) and propionate ($q < 0.01$).
Ho et al., USA 2021, hospital-based case control study[50]	49/39 (atopic and non-atopic controls)	Saliva, LC–MS	A, B, P	IgE-mediated peanut allergy: positive OFC or reaction and sensitisation (SPT >3 mm and/or sIgE ≥0.35 kUA/L)	Mann–Whitney *U*-test	Subjects with peanut allergy had significantly reduced salivary acetate, butyrate, and propionate levels compared with the healthy controls (median acetate level = 153,000 ng/mL [IQR 95,950–218,000 ng/mL]vs 229,000 ng/mL [IQR = 129,000–32,000 ng/mL] [$p = .013$]; median butyrate level = 2930 ng/mL [IQR = 1540–5225 ng/mL] vs 5530 ng/mL [IQR = 3350–9290 ng/mL][$p = .001$]; and median propionate level 35,500 ng/mL[IQR 16,550–59,800 ng/mL] vs 49,900 ng/mL[32,900–75,600 ng/mL] [$p = .007$], respectively). No difference between atopic controls without FA vs healthy controls.

(Continues)

TABLE 4 (Continued)

Author, country, year, study design	Sample size of cases/controls	Sample type, analysis method	SCFA measured[a]	Outcome, definition of outcome	Statistical analysis method	Main results
De Filippis et al., Italy 2021, hospital-based case control study[46]	55 (FA), 30 (RA)/29	Faeces, GC–MS	B, P	IgE-mediated FA: sensitised and symptoms to food, RA: sensitised to one or more aeroallergens (pollens, house dust mite, dog)	Pairwise Wilcoxon test	Butyrate lower in FA versus control ($p < .001$) and RA versus control ($p < .001$) but not different between FA vs RA. Propionate lower in FA vs control ($p < .001$), RA vs control ($p < .01$) and RA vs FA ($p = .03$).
Tian et al., China 2022, hospital-based case control study[56]	40/40	Serum, HPLC	A, P, B	IgE-mediated FA: history, positive SPT and sIgE	Mann–Whitney *U*-test	Serum butyrate, acetate and propionate were lower in cases compared with controls (each $p < 0.001$).
Zhang et al., USA 2022, hospital-based case control study[58]	38 (high threshold), 13 (low threshold)/8	Saliva and faeces, LC–MS	A, P, B	IgE-mediated peanut allergy: positive DBPCFC	Unclear	The respective mean (SD) levels of acetate, butyrate and propionate were 4977.3 (2765.2), 33.6 (52.5), and 602.0 (349.0) in saliva and 425,249.8 (242,990.6), 158,865.5 (118,878.8), and 243,907.6 (128,934.9) in faeces. Salivary SCFAs trended highest in the controls compared with the cases, but the differences were not significant, and there were no significant differences between groups for faecal SCFA.
Bao et al., USA 2021, observational study[62]	23/13	Faeces, GC–MS	A, B, P, V, C, i-B, i-V, 2-methylbutyric acid	IgE-mediated FA: positive OFC	Wilcoxon's rank-sum tests with multiple testing adjustment	No difference in any of the SCFAs between FA and non-FA.
Diaz et al, Spain 2018, hospital-based case control study[47]	17/10	Faeces, GC	A, P, B, i-B, i-V	Non-IgE cow's milk allergy: history, negative SPT and/or IgE and positive OFC	Mann–Whitney *U*-test	There were no significant differences in acetate, butyrate, propionate levels between cases and controls, but a trend of increase in butyrate in cases (17.59 (12.74–21.41) versus 12.88 (6.14–14.3), $p = .06$). BCFAs (Iso-butyric acid and iso-valeric acid) was higher in cases than in control ($p = .03$), 5.13 (3.08–6.52) versus 2.59 (1.94–3.37) μmol/g.
Berni Canani et al., Italy 2018, hospital-based case control study[43]	46/23	Faeces, GC	B	Non-IgE mediated cow's milk allergy: clinical history, SPT and/or sIgE and DBPCFC	Non-parametric Kruskal–Wallis and pairwise Wilcoxon tests	Cases had lower butyrate concentration than controls. Butyrate highest in extensively hydrolysed casein formula (EHCF) plus *Lactobacillus rhamnosus* GG treated > healthy control or EHCF treated > untreated (at diagnosis).

TABLE 4 (Continued)

Author, country, year, study design	Sample size of cases/controls	Sample type, analysis method	SCFA measured[a]	Outcome, definition of outcome	Statistical analysis method	Main results
Zhou et al., China 2021, hospital-based case control study[60]	18/17	Faeces, GC–MS	A, P, B, V, i-B, i-V	AR: History of reaction in the past year, sensitisation by positive SPT or sIgE >3.5Ku/L	SCFA levels compared individually by ANOVA followed by pairwise *t*-test and FDR correction	Acetate, propionate and butyrate concentrations were lower in cases compared with controls.
Zhou et al., China 2021, hospital-based case control study[59]	36/36	Serum, HPLC	A, P, B	AR: International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis	Student *t*-test or Mann–Whitney *U*-test	Acetate, propionate and butyrate concentrations were lower in cases compared with controls.
Böttcher et al., Sweden 2000 (BAS study)[45]	25/47	Faeces, GC	A, P, B, V, C, i-B, i-V, i-C	Allergy: positive SPT to at least one allergen and allergic symptoms	Mann–Whitney *U*-test	Controls had higher levels of propionate, butyrate, iso-butyrate, iso-valerate and valerate levels compared with cases ($p < .01$ for propionate, the rest <0.05). Iso-caproate higher in cases but very small number of samples. Relative distribution of propionate and valerate was higher in controls ($p < .001$ and $p < .05$) and similar trends were seen for i-butyrate i-valerate ($p = .08$ and $p < .1$). Relative distribution of i-caproate and acetate were higher in cases ($p < .01$ and $p < .001$).
Stinson et al., Australia, Japan, USA, Norway and South Africa, 2020 cohort studies[54]	47/62	Human milk 1 month after birth, NMR	A, P, B, V, i-V, i-B, formate	Atopy or not: either sensitisation measured by serum IgE or SPT, BA, AD, pet/environmental allergy, FA (either history or diagnosis)	Linear mixed models	Human milk from atopic women had significantly lower acetate ($p = .02$) and butyrate ($p = .001$), median levels were 57% and 62% lower, respectively. There was difference in countries.

Abbreviations: AD, atopic dermatitis/eczema; adjOR, adjusted odds ratio; AR, allergic rhinitis (including hay fever); ARC, allergic rhino-conjunctivitis; BA, asthma; DBPCFC, double blind placebo control food challenge test; FA, food allergy; GC, gas chromatography; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; LC–MS, liquid chromatography mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; OFC, oral food challenge test; OR, odds ratio; RA, respiratory allergy; SPT, skin prick test.

[a]Individual SCFAs are abbreviated as A: acetate, P: propionate, B: butyrate, V: valerate, C: caproate, i-B: iso-butyrate, i-V: iso-valerate, i-C, iso-caproate, BCFAs: branched short chain fatty acids.

TABLE 5 Summary of studies that investigated the association between short chain fatty acids and pre-existing allergic diseases.

Disease	Population group	Author, year	Results
IgE food allergy	Infant	Berni Canani 2016[44]	× butyrate
	Children	Dong 2018[48]	▼ total SCFA × acetate, propionate, butyrate, iso-butyrate
		Thompson-Chagoyan 2011[55]	△ butyrate, BCFA × acetate, propionate, iso-caproate
		Goldberg 2020[49]	▼ acetate, propionate, butyrate
		Ho 2021 (saliva)[50]	▼ acetate, propionate, butyrate
		De Filippis 2021[46]	▼ propionate, butyrate
		Tian 2022 (serum)[56]	▼ acetate, propionate, butyrate
		Zhang 2022 (saliva and faeces)[58]	× acetate, propionate, butyrate
	All ages	Bao 2021[62]	× acetate, propionate, butyrate
Atopic dermatitis	Adults[a] (exposure) infants (outcome)	Wang 2022 (breastmilk)[57]	▼ acetate, total SCFA × butyrate
	Adults	Roesller 2012[52]	▼ caproate × acetate, butyrate, propionate, valerate, iso-butyrate, iso-valerate
	Unclear	Song 2016[53]	▼ propionate, butyrate × acetate
Non-IgE- cow's milk allergy	Infants	Berni Canani 2018[43]	▼ butyrate
		Diaz 2018[47]	△ BCFA (iso-butyrate, iso-valerate) × acetate, propionate, butyrate
Allergic rhino-conjunctivitis	Adults	Zhou 2021 (serum)[59]	▼ acetate, propionate, butyrate
		Zhou 2021[60]	▼ acetate, propionate, butyrate × iso-butyrate, iso-valerate
Asthma	Adults	Jung 2013 (serum)[61]	▼ acetate
		Ivashkin 2019[51]	▼ acetate, propionate, butyrate
Sensitisation (aeroallergen)	Children	De Filippis 2021[46]	▼ propionate, butyrate
Combination of sensitisation and any allergic disease	Infants	Böttcher 2000[45]	▼ propionate, butyrate, valerate, iso-butyrate, iso-valerate △ acetate, caproate, iso-caproate
	Adults	Stinson 2020 (breastmilk)[54]	▼acetate, butyrate × formate, propionate, valerate, iso-butyrate, iso-valerate

Note: Levels/concentrations, relative abundance or proportion of individuals with high levels observed in cases were, ▼: decreased, △: increased or ×: not different compared with controls. For the purposes of this review, p-value <.05 was considered as a significant association. SCFAs were measured in faecal samples if not stated otherwise.

Abbreviations: BCFA, branched short chain fatty acid; SCFA, short chain fatty acid.

[a]This study measured SCFA levels of breastmilk from mothers of children with and without atopic dermatitis.

Increase, rather than decrease in faecal butyrate and BCFA among cases compared with controls was reported in one Spanish study of infants with IgE-mediated cow's milk allergy (Thompson-Chagoyan et al.).[55]

3.10 | SCFAs and pre-existing atopic dermatitis (three papers)

Two studies assessed SCFAs and pre-existing AD in the same individual.[52,53] Song et al. reported decrease in propionate and butyrate among cases compared with healthy controls,[53] while Roesller et al. reported decrease in caproate in cases.[52] A hospital-based case control study (Wang et al.) in Taiwan reported that acetate and total SCFA in the breastmilk from mothers of exclusively breastfed children was negatively associated with the presence of the children's AD (lowest vs highest quartile, OR 12, 95% CI 2.7–53.3 for acetate and 10.52, 95% CI 2.27–48.76 for total SCFA), and the association with acetate level remained after adjusting for potential confounders including total SCFA (adjOR 0.998, 95% CI 0.9964–0.9996).[57] This study also reported that breastmilk acetate level negatively correlated with objective SCORAD scores of the children's AD.[57]

3.11 | SCFAs and pre-existing non-IgE-mediated cow's milk allergy (two papers)

One Italian study reported decrease in butyrate among infants with non-IgE-mediated cow's milk allergy compared with healthy controls

(Berni Canani et al.),[43] and another Spanish study (Díaz et al.) reported increase in BCFAs and tendency of an increase in butyrate among cases.[47]

3.12 | SCFAs and pre-existing allergic rhinitis (two papers)

Two separate Chinese hospital-based case control studies, one using faeces,[60] another using serum,[59] reported decrease in all three main SCFAs among adult patients with allergic rhinitis.

3.13 | SCFAs and pre-existing asthma (two papers)

Ivashkin et al. assessed the three main SCFAs in the faeces of adult asthma patients and reported decrease in all three compared with healthy controls,[51] and a Korean study using NMR (Jung et al.) reported decrease in serum acetate among cases.[61]

3.14 | SCFAs and pre-existing aeroallergen sensitisation (one paper)

Children who were sensitised to aeroallergens were reported to have decreased levels of propionate and butyrate in one Italian hospital-based case control study (De Filippis et al.).[46]

3.15 | SCFAs and pre-existing any allergy (two papers)

A paper using data from six birth cohort studies (Stinson et al.) conducted in different countries reported that human milk from mothers who have any allergic disease have decreased level of acetate and butyrate compared to those without.[54] Another Swedish birth cohort study (Böttcher et al.) reported that 1-year-old children who had any allergic disease with sensitisation had decreased level of propionate, butyrate, valerate, iso-butyrate and iso-valerate compared with controls.[45]

4 | DISCUSSION

This systematic review summarised the current evidence on the association between SCFAs and allergic diseases. Due to the large variability in methodologies of the included papers, meta-analysis to estimate the effect size of SCFAs for allergic diseases was not possible and we conducted a narrative synthesis of the results. Overall, there was some epidemiological evidence for the association between decrease in the three main SCFAs measured early in life and AD, wheeze/asthma and IgE-mediated food allergy in childhood.

The gut microbiome develops from a relatively simple composition to a more complex adult-like pattern in the first few years of life.[63,64] A shift from the *Bifidobacterium* dominant microbiota to a more diverse microbiota with species of the phyla Bacteroidetes or Firmicutes occurs around the time of solid-food introduction.[63,64] This leads to increase in microbial functionality to break down complex dietary and endogenous carbohydrates, which results in the increase in the production of SCFAs that continues over the first few years of life.[28,65,66] Our results suggest a protective role of SCFAs during this period against childhood allergic diseases and support the hypothesis that disordered functional development of the gut microbiome plays a role in allergic diseases.[29,39]

SCFAs that showed decrease in cases appeared to be different by allergic diseases and by the timing of measurement or disease assessment. This may be due to the difference in the methodologies or study population of the studies included for each disease. However, it may also be due to the difference in the characteristics of these diseases (e.g., organ and onset) and suggest the possibility that there is a timing or disease-specific effect for each SCFA. For studies investigating the association between SCFAs and the development of AD, an association with decreased butyrate was most often reported, as compared to the other SCFAs. In an experimental model of AD-like skin inflammation, it was shown that although supplementation of either acetate, propionate or butyrate led to improvement of clinical outcomes, the effect was the largest for butyrate.[67] Both butyrate and propionate (but not acetate) are known to induce differentiation of naïve T cells into Tregs.[16,68] Butyrate has also been reported to enhance Treg generation by affecting macrophages and dendritic cells.[15] Although our results may suggest a clearer association between AD and butyrate compared with other SCFAs, possibly due to these immunological properties, it is difficult to conclude from the small number of observational studies. The association between the three major SCFAs investigating AD at 6 years old or later was less clear than in studies assessing AD at a younger age. This may suggest that there is a lower protective effect by SCFAs against late-onset AD or persistent AD.

The association between SCFAs and childhood wheeze or asthma appeared to be clearer for acetate when measured in the prenatal period or in early infancy as compared to later time point measurements. This might be partly explained by the differences in the metabolism and production of the SCFAs. Among the three main SCFAs, acetate has the highest concentration in the systemic circulation, since butyrate is mostly absorbed the colonic epithelium and propionate is mainly taken up by the liver.[11] Maternal acetate in systemic circulation can cross the placenta and affect the immune system in the mice foetus, which has also been suggested in human studies.[40,69] Additionally, while the production of butyrate and propionate increase over the first few years of life, the increase in the level of acetate is relatively small.[28,65,66] Thus, the rather unclear protective effect of acetate measured at later time points might be due to the increasing influence of the other SCFAs, such as propionate or butyrate.

Only one out of four studies that investigated the association between the three major SCFAs and development of food allergy

later reported any difference between cases and controls,[31] in which there was only a difference in a small subgroup of children with allergy to specific foods. On the other hand, five out of eight studies on pre-existing childhood IgE-mediated food allergy[46,48–50,56] reported decrease in one or more of the three main SCFAs among cases. This discrepancy might be because studies of pre-existing disease had higher proportions of cases among the total study population due to the study design (case control design) compared with studies of food allergy development (prospective cohort design), and thus had more statistical power to detect a difference. Additionally, only one paper that investigated the development of food allergy diagnosed cases by oral food challenge tests,[41] and otherwise self-reported symptoms or diagnosis was used. Conversely, all studies that investigated children with pre-existing food allergy had their diagnosis clinically confirmed by either sensitisation with a history and/or oral food challenge tests, which may have reduced the possibility of misclassification bias.

None of the studies showed any association between early-life SCFAs and the development of allergic rhinitis. This may suggest that the protective effect of early-life SCFAs are not applicable in the long term for the prevention of allergic rhinitis, which has a later onset than the other allergic diseases. However, two studies assessed the outcome at 6 years, which may have been too early to capture all cases.[34,36] Two case control studies among adult allergic rhinitis patients showed decrease in the three major SCFAs, which suggests that they may have some role in the disease.[59,60]

Compared with acetate, butyrate and propionate, less research is conducted on valerate, caproate and BCFAs, such as iso-butyric acid and iso-valeric acid, which are detected at considerably lower amounts than the major three SCFAs.[10] Five studies investigated valerate and the development AD later in life.[28,30,31,35,42] Decreased level of valerate, but no other SCFA among children who developed AD was reported in two papers,[30,31] and one paper reported a decrease in valerate and butyrate among cases.[35] Some animal studies have demonstrated that valerate upregulates tight junction proteins and keratin,[70,71] which promotes barrier function and plays a role in AD.[72] The association between valerate and the development of food allergy was assessed in three studies,[31,37,41] of which two reported decreased level in cases,[31,37] compared with controls. One of these studies additionally reported decrease in BCFAs among cases,[37] while an increase in BCFA levels among cases was reported in two studies investigating the association with pre-existing IgE-mediated food allergy or non-IgE-mediated cow's milk allergy.[47,55] BCFAs are fermentation products of amino acids and have been shown to correlate negatively with fibre consumption and positively with protein consumption.[10] Since little is known about the molecular mechanisms of BCFAs, it is unclear whether our result suggests a role in the disease, or it is reflecting some difference in the dietary pattern between the comparison groups in these studies.

There are several considerations for the interpretation of these results. Since most SCFAs are rapidly absorbed by the epithelium, faecal concentrations measured at one time point may not accurately capture the dynamic production of SCFAs and be biased due to the individual characteristics such as intestinal transit or permeability,[73] as well as sample handling methods.[74] Nevertheless, most studies use faecal samples as a proxy for SCFA production in the colon, which is considered a valid approach. Targeting genes in the synthesis pathways, such as butyryl-CoA in butyrate production,[75,76] or quantifying the abundance of known SCFA producers has also been used as an alternative method to investigate SCFA production. However, these methods are also limited since SCFA production is influenced by other factors including the type or abundance of substrates and the characteristics of the gut environment such as pH or oxygen concentration.[76,77] Secondly, the temporal association between SCFAs and disease development was unclear in studies that have assessed SCFAs and the outcome at the same timepoint, and also for studies that assessed SCFAs in infancy and AD, since the onset of disease may have been before SCFAs were measured. Additionally, no clinical trials using SCFAs as intervention have been conducted for allergic diseases up this date. Thus, the decrease in SCFAs among cases in these studies may not be a cause but a consequence of the disease (reverse causation) or that of a risk factor of the disease.

Papers varied in how they reported details of methods such as participant selection, sample analysis method, sensitivity of their method and their results. How participants were selected was often unclear in case control studies and nested case control studies, raising a concern for selection bias. For sample analysis methods, the column or machine used for chromatography-based analysis, or whether standards were used in mass spectroscopy-based methods were not always stated, which may be an issue in terms of the reliability and reproducibility of the results for these studies. Detection limit was only stated in four papers, of which three were from the same study.[31,37,45,54] In general, mass spectrometry in combination with gas chromatography or liquid chromatography are considered as highly sensitive in detecting SCFAs, while nuclear magnetic resonance is less sensitive.[78] However, this can also be affected by sample preparation methods and the type of matrix.[74,79] A small number of studies used serum, breastmilk and saliva, in which SCFA levels were in a considerably lower range compared with faecal samples in line with previous reports.[80,81] Meaningful comparison of SCFA levels between papers were not possible since many papers did not report the observed value or reported different parameters or comparison groups. Standardised reporting of sample analysis method and the results may allow better understanding of the preferred method by each matrix and exploring factors that affect SCFA levels across different populations.

Only 9 out of the total 37 papers (24%) had a sample size of over 100, which may have reduced the statistical power to detect a difference in SCFAs between cases and controls. In fact, some studies showed a tendency of a difference in SCFAs between groups, however, this was not considered as a significant association for the purpose of this review. The relatively small sample size has also limited the possibility of accounting for potential confounders for

the association between SCFAs and allergic disease in these studies, suggesting the possibility of residual confounding. Only five of the 17 studies in the SCFAs and development of allergy category,[28,30,33,35,39] and one study in the pre-existing allergic diseases category,[57] accounted for factors besides sex and age in their design or analysis. Finally, the possible influence of publication bias, where studies with statistically significant positive results were more likely to be published and thus included in this review, needs to be taken into consideration.

The association between dietary factors and SCFA levels were evaluated in a few studies. Breastfeeding was negatively correlated with propionate,[36,42] butyrate[36,42] or BCFAs.[42] Higher butyrate level at 1 year was associated with early introduction or longer duration of consumption of yogurt, fish,[36,38] or vegetables and fruit.[36] Dietary fibre intake at 1 year was negatively associated with faecal iso-butyric and iso-valeric acid at 3 years in a Swedish rural cohort.[30] One study showed that fibre intake of the mother was positively correlated with faecal SCFA levels, but not with the offspring outcome.[34] Several studies in animal models have shown results supporting the potential link between dietary fibre, which is the major substrate for SCFA production, SCFAs and allergic diseases. High fibre diet increased the production of SCFAs in mice and was shown to be protective against food allergy,[82] allergic inflammation in the lung[21,40] and AD-like skin inflammation, although[67] this link is less clearly described in studies among humans.[83–85] A recent systematic review has reported that there is some evidence on the protective effect of higher intake of dietary fibre against asthma or respiratory symptoms in humans, while the association was unclear for atopic dermatitis, allergic rhinitis and food allergy, with only small number of studies.[86] An effective and feasible dietary intervention using dietary fibre that can increase SCFA levels as well as affect the immune system is an important topic for future research.

In conclusion, this systematic review showed that there was some evidence for the protective effect of early life SCFA against childhood allergic diseases. The evidence was clearer for the role of early life SCFAs in the development of atopic dermatitis or wheeze/asthma later in childhood, and for pre-existing IgE-mediated food allergy in childhood. Further research that would determine the timing specific effect of each SCFA and uncover the mechanisms by which SCFA levels in the human body can be modified, will be useful to identify how SCFAs can be used in treatment or in prevention against allergic diseases.

AUTHOR CONTRIBUTIONS

MS, RF, LO, CV, RL and CR were involved in the conception of the study. MS, NS, JA, KH, RF and CR performed the article search and screening, MS and NS extracted and summarised the data. MS wrote the manuscript and all authors provided critical feedback.

ACKNOWLEDGEMENTS

We thank Martina Gosteli for her support in constructing the search terms. Open access funding provided by Universitat Zurich.

FUNDING INFORMATION

No funding was obtained for this study.

CONFLICT OF INTEREST STATEMENT

All authors have nothing to declare within the scope of this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sasaki M, Suaini NHA, Afghani J, et al. Systematic review of the association between short chain fatty acids and allergic diseases. *Allergy*. 2024;00:1-23. doi:10.1111/all.16065