

Perspective

Interpreting Divergent Short-Chain Fatty Acid Effects in Alzheimer's Disease: A Seven-Axis Framework

Shuo Liu¹, Danrui Han¹, Tao Bai², He Chen¹, Jian-Ping Li^{3*}

¹The Fourth People's Hospital of Shenyang, Shenyang, Liaoning Province, China. ²Department of Neurology, Shengjing Hospital of China Medical University, China Medical University, Shenyang, China. ³HLA Laboratory, Liaoning Blood Center, Shenyang, Liaoning Province, China

[Received June 19, 2026; Revised July 30, 2026; Accepted August 2, 2026]

ABSTRACT: Studies of short-chain fatty acids (SCFAs) in Alzheimer's disease (AD) report protective, neutral, and adverse findings, but the same class label often conceals non-equivalent exposures and endpoints. We propose an AD-specific interpretive framework that organizes this heterogeneity as a causal sequence: source or intervention → SCFA species, dose, and route → absorption and metabolic filtering → target-compartment exposure → host and disease state → responding cell type → endpoint. Seven interdependent axes—SCFA species, dose, route, compartment, exposure context, disease stage, and responding cell type—identify the coordinates needed to compare studies. This organization separates administered dose from achieved exposure, direct entry into the central nervous system from blood–brain barrier or peripheral gut–brain signaling, and stage-related disease biology from evidence of stage-specific treatment efficacy. It also requires symmetric interpretation of null findings according to exposure verification, target engagement, power, cellular resolution, and endpoint specificity. The framework integrates rather than replaces established microbiome, pharmacological, and neuroimmune principles and has not been validated as a predictor of effect direction. Its explanatory value can be tested by prespecified meta-regression, variance partitioning, interaction analysis, matched-exposure replication, and causal mediation. Persistent opposite effects under matched coordinates would indicate missing dimensions or failure of the framework. This Perspective therefore supports mechanism-linked, biomarker-informed research rather than nonspecific SCFA supplementation in unselected patients.

Keywords: Alzheimer's disease; short-chain fatty acids; microbiota–gut–brain axis; biological compartment; disease stage; causal framework

1. The interpretive problem and the framework's contribution

Short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate, connect microbial fermentation with epithelial metabolism, immune signaling, receptor activation, and chromatin regulation [1,2]. In Alzheimer's disease (AD), this broad biology has encouraged a simple narrative in which loss of SCFA-producing microbes is harmful and restoration of SCFAs is protective. The evidence is less uniform. Human studies report lower fecal SCFAs in mild cognitive impairment, sex- and amyloid-dependent associations with longitudinal biomarkers, and amyloid-associated shifts in SCFA-

related microbial pathways in cognitively unimpaired adults [3,4,5]. Experimental studies include beneficial barrier, inflammatory, cellular, pathological, and behavioral endpoints, but mixed-SCFA exposure has also increased amyloid- β (A β) plaque deposition in an amyloid model [6].

The individual sources of this heterogeneity are not new: microbiome research recognizes ecological context, pharmacology distinguishes administered dose from exposure, and neuroimmunology emphasizes cell state. Existing discussions, however, do not consistently require every AD-related SCFA claim to be located within one causal chain, nor do they always separate target-compartment exposure from a proxy measurement or

*Correspondence should be addressed to: Dr. Jian-Ping Li, HLA Laboratory, Liaoning Blood Center, Shenyang, Liaoning Province, China. Email: jianpinglilnbc@163.com.

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name the endpoint to which “protective” or “adverse” refers. The contribution of this Perspective is therefore integrative and organizational rather than the discovery of seven new variables.

We selected seven axes because they are mechanistically proximal to effect direction, are usually recoverable or prospectively measurable, and lead to concrete reporting or design decisions. They are SCFA species, dose, route, biological compartment, exposure

context, disease stage, and responding cell type. The list is deliberately parsimonious rather than exhaustive. Sex, diet, bowel transit, medication, comorbidity, and analytical conditions are prespecified host or measurement modifiers within exposure context, and they may also influence disease and cell state. Source or intervention and endpoint bookend the causal sequence but are not additional axes. The axes are interdependent and should not be treated as seven parallel votes.

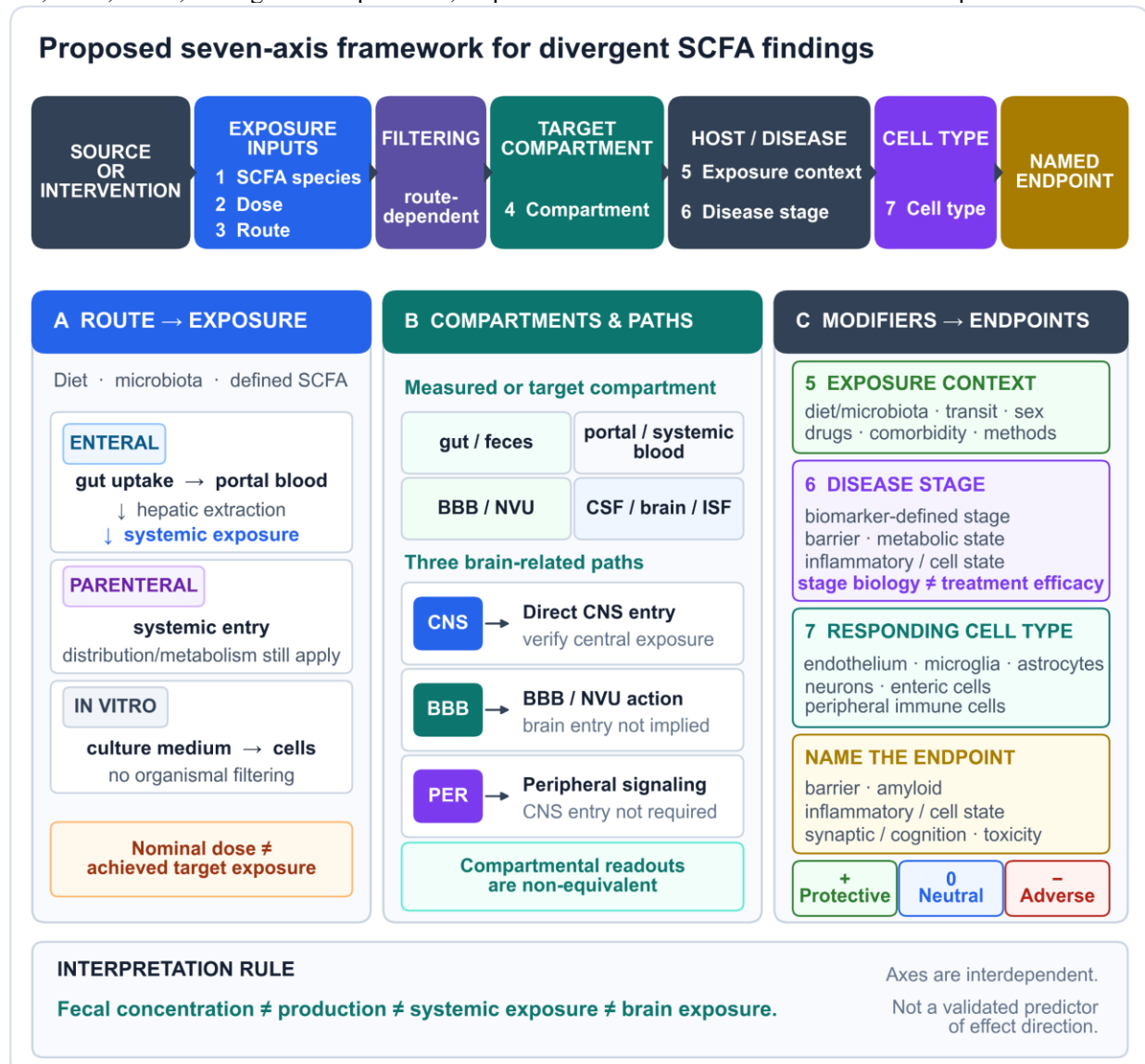


Figure 1. A proposed seven-axis causal framework for interpreting divergent short-chain fatty acid effects in Alzheimer’s disease. A source or intervention generates a defined or mixed short-chain fatty acid input. Species, dose, and route establish the initial exposure, which is then shaped by intestinal uptake, portal and hepatic metabolism, systemic distribution, and other route-dependent filtering. The compartment axis distinguishes gut, portal/systemic, barrier, and central sites. Target-compartment exposure is modified by exposure context and disease stage before producing cell-specific responses and named endpoints. Direct central nervous system entry, blood–brain barrier or neurovascular action, and indirect peripheral signaling are distinct paths and require different measurements. Protective, neutral, and adverse directions refer to the specified endpoint and may coexist within one study. The framework is conceptual and has not been validated as a predictor of effect direction. Aβ, amyloid-β; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; ISF, interstitial fluid; NVU, neurovascular unit; SCFA, short-chain fatty acid.

Table 1. Causal organization of the seven axes and corresponding reporting and design requirements.

Causal position	Axis	Interpretive role	Minimum reporting requirement	Preferred design recommendation
Exposure input	SCFA species	Acetate, propionate, butyrate, and mixtures differ in metabolism, potency, and tissue access.	Report each molecule and counter-ion separately; give mixture composition.	Compare defined species or justify a mixture; include molecule-specific exposure measures.
Exposure input	Dose	Administered dose and achieved concentration can recruit different mechanisms.	Report nominal dose, concentration, frequency, duration, intake, and timing.	Measure achieved concentration–time profiles and test non-linear dose responses.
Exposure input	Route	Diet, microbes, oral salts, injection, and culture produce different kinetics and co-exposures.	Report formulation, route, vehicle, pH/osmolality controls, and feeding or sampling timing.	Match route to the causal question and include route-matched controls.
Filtering and target exposure	Compartment	Lumen, feces, epithelium, portal blood, peripheral blood, BBB, CSF, and brain tissue are non-equivalent.	Name the sampled matrix and analytical method; avoid extrapolating beyond it.	Pair source and target compartments; measure barrier or tissue exposure when central action is claimed.
Host modifier	Exposure context	Diet, microbial function, transit, stool water, sex, medications, comorbidity, and methods alter production and response.	Report prespecified biological and analytical covariates and handling conditions.	Use repeated sampling, functional microbiome measures, sex-stratified analyses, and causal-inference plans.
Disease modifier	Disease stage	Stage may alter barriers and cell states but does not itself prove differential efficacy.	Define cognition and AD biomarkers; separate biological and clinical stage.	Compare matched exposures across biomarker-defined stages and test stage-by-exposure interactions.
Response	Cell type	Endothelium, microglia, astrocytes, neurons, enteric cells, and peripheral immune cells can diverge.	Name the responding cell and resolution of the assay; do not infer from bulk tissue alone.	Use suitable cell sorting, imaging, flow, reporter, genetic, single-cell, or spatial methods.

Note: Source/intervention precedes the seven axes and the named endpoint follows them; neither is counted as an additional axis. The axes are interdependent. BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; SCFA, short-chain fatty acid.

The resulting framework is: source or intervention → species, dose, and route → absorption and metabolic filtering → target-compartment exposure → host and disease state → responding cell type → endpoint (Fig. 1 and Table 1). It is a hypothesis-generating interpretive model, not an established explanation for every discordant result, a clinical algorithm, or a validated predictor of treatment response.

2. From source to endpoint: a causal seven-axis framework

2.1 Exposure inputs: species, dose, and route

Dietary fiber, a live microbial intervention, a postbiotic, an oral SCFA salt, systemic administration, and direct cell-culture exposure are different starting conditions. Fiber changes substrate supply, microbial competition, cross-feeding, and multiple metabolites over time; an oral salt produces a defined luminal bolus that is filtered by epithelial and hepatic metabolism; injection bypasses part of that filtering; and cell culture removes it altogether

[7,8]. A benefit after fiber exposure is therefore not evidence of an SCFA mechanism unless a defined SCFA pathway is measured and linked to the endpoint. In male 5xFAD mice, for example, a fiber-plus diet improved several AD-related endpoints while canonical fecal SCFAs changed little, supporting mechanisms beyond classical SCFA production [9].

Acetate, propionate, and butyrate should likewise not be pooled as interchangeable “SCFAs.” They differ in production pathways, colonocyte use, hepatic extraction, systemic availability, receptor potency, and intracellular metabolism [1,2]. Dose and route jointly determine the concentration–time profile. An administered drinking-water concentration or oral dose is not the achieved exposure in plasma, cerebrospinal fluid (CSF), brain tissue, or a specific cell. Reporting both the formulation and measured concentrations is therefore essential.

2.2 Metabolic filtering and target-compartment exposure

SCFA concentration, production, amount, and exposure describe different quantities. Concentration is an amount per unit volume or mass; production is generation over time; amount or output is the recovered quantity, ideally time-normalized; and exposure is the concentration–time profile at a defined biological site. A single fecal concentration integrates production, microbial and host utilization, transit, stool water, and excretion and cannot, by itself, identify any one of them [10,11]. Low fecal butyrate may reflect low production or efficient colonocyte uptake, whereas a high concentration may reflect increased production, rapid transit, reduced absorption, or low utilization.

Metabolic filtering produces marked cross-compartment decoupling. Stable-isotope delivery in healthy adults estimated systemic availability of colonic acetate, propionate, and butyrate at approximately 36%, 9%, and 2%, respectively [12]. Human portal, hepatic, and peripheral sampling likewise shows substantial epithelial and hepatic extraction, especially for butyrate and propionate [13,14]. Thus, fecal concentration is not peripheral immune exposure, and peripheral concentration is not brain exposure.

Three routes to a brain-related endpoint must be distinguished. First, an SCFA may enter the central nervous system (CNS), in which case brain tissue, interstitial fluid, or appropriately interpreted CSF measurements are needed. Second, it may act on blood–brain barrier (BBB) endothelium or the neurovascular unit without requiring substantial parenchymal entry. Third, it may signal indirectly through peripheral immune, enteroendocrine, metabolic, autonomic, or vagal pathways. CSF concentration, brain-tissue concentration, and a BBB endothelial response are not equivalent measures. In an APPPS1-21 study, 150 mM sodium propionate in drinking water reduced reactive astrogliosis and A β plaque area, but cortical propionate was detectable in only 1 of 11 treated samples; the accompanying Th17/IL-17 data support a predominantly peripheral route [15]. By contrast, a physiological 1 μ M propionate exposure protected a human BBB endothelial model from inflammatory and oxidative stress [16], illustrating a barrier-local mechanism rather than proof of brain entry.

2.3 Host and disease state: exposure context and disease stage

AD progression is accompanied by changes in BBB integrity and temporally and spatially heterogeneous neuroinflammatory states [17,18]. Human single-nucleus and chromatin studies further demonstrate cell-type-specific AD-associated molecular programs, although their largely cross-sectional designs do not directly establish within-person stage transitions [19,20]. These disease-associated biological differences are established

more securely than stage-specific SCFA efficacy. Here, “preclinical AD” denotes biomarker-defined AD in a cognitively unimpaired person, “prodromal AD” denotes biomarker-supported mild cognitive impairment, and “advanced symptomatic AD” denotes moderate-to-severe AD dementia; these shorthand clinical terms do not map one-to-one onto a single pathological stage [21].

It is plausible, but not established, that an early disease state may retain greater reversibility. The same exposure could also produce greater central access after late-stage barrier disruption, or a qualitatively different rather than merely weaker response in advanced disease. A 12-week probiotic trial dominated by severe AD showed no cognitive or serum inflammatory benefit, but did not measure SCFAs or target engagement; it therefore cannot demonstrate stage-specific failure of an SCFA intervention [22]. Stage-specific efficacy requires the same species, dose, route, duration, and exposure verification to be compared across biomarker-defined stages.

Exposure context modifies both production and response. Habitual diet, fermentable substrate, microbial functional genes, cross-feeding, transit time, constipation, stool water, intestinal permeability, frailty, diabetes, kidney or liver function, medications, and analytical procedures can alter the observed association. Sex is a biological variable within this layer, not a post hoc covariate. Sex-linked differences in microbial ecology and fermentation, hormonal and immune signaling, vascular or endothelial function, body composition, and AD risk can modify both achieved exposure and host response, although direct evidence assigning any one of these mechanisms to sex-specific SCFA effects in AD remains limited. Human fecal SCFA associations with amyloid and longitudinal biomarkers have differed by sex [4], and microbiome perturbation altered amyloidosis and microglial phenotypes differently in male and female AD-model mice [23]. Both sexes should be included where feasible, sex-by-exposure interactions should be prespecified, and male-only experiments should not be generalized without qualification.

2.4 Responding cell type and named endpoint

Microglia, astrocytes, endothelial cells, neurons, enteric cells, and peripheral immune cells differ in receptor expression, substrate use, chromatin state, and inflammatory history. Microbiota-derived metabolites can support microglial maturation under one condition yet alter plaque-associated microglial programs under another [6,24]. Propionate can modify peripheral Th17/IL-17 signaling with downstream astrocyte changes [15], whereas butyrate can affect BBB transporters, tight-junction proteins, and intraendothelial A β 42

accumulation [25]. Whole-tissue cytokines or histone acetylation may conceal opposing cell-specific responses. Effect direction is therefore endpoint-dependent. Plaque area, soluble A β 40 or A β 42, endothelial A β accumulation, clearance, total amyloid burden, tau phosphorylation, inflammatory markers, synaptic function, and cognition are not interchangeable. A lower plaque burden does not automatically imply improved cognition or reduced neurotoxicity, and a barrier benefit does not establish a microglial or neuronal benefit. Each conclusion should name the endpoint, direction, compartment, and time point.

3. Mechanistic plausibility depends on concentration and context

SCFAs can act through free fatty acid receptor 2 (FFAR2; GPR43), free fatty acid receptor 3 (FFAR3; GPR41), other metabolite-sensing receptors, cellular metabolism, and histone deacetylase (HDAC)-related mechanisms [1,26,27]. Receptor expression and coupling vary by cell type, species, developmental or disease state, and assay. Ligand potency is also receptor- and assay-dependent; evidence that a receptor is expressed is not evidence that it was engaged at the achieved concentration. Genetic or pharmacological perturbation, proximal signaling, and exposure measurement provide stronger support.

Table 2. Representative physiological concentrations and experimental SCFA exposures.

Setting	Acetate	Propionate	Butyrate	Interpretation and limitations
Human large-intestinal contents	Approximately 44–69 mmol/kg	Approximately 14–27 mmol/kg	Approximately 15–26 mmol/kg	Rounded directly from regional values reported across the large intestine in a historical postmortem study (13); region, diet, transit, and postmortem conditions limit generalization.
Human feces, contemporary healthy cohort	29.56 $\pm$ 8.73 nmol/mg	8.56 $\pm$ 3.57 nmol/mg	9.49 $\pm$ 5.31 nmol/mg	Cohort means on the reported sample-weight basis; 313 fecal samples (11). Feces are residual output, not production rate or absorbed exposure.
Human portal blood	258 $\pm$ 98 μ M	88 $\pm$ 68 μ M	29 $\pm$ 19 μ M	Mean $\pm$ SD calculated from the six individual portal-vein values in a historical postmortem study (13); these are not universal reference intervals.
Human peripheral blood	Approximately 70–173 μ M	Approximately 4–5 μ M	Approximately 4–8 μ M	Representative values spanning postmortem peripheral venous sampling and intraoperative radial arterial sampling (13,14). Collection, matrix, fasting, and assay effects are substantial.
Human CNS/CSF	No standardized physiological reference range	No standardized physiological reference range	No standardized physiological reference range	Sparse, assay-dependent data do not support treating CSF, brain tissue, interstitial fluid, and BBB endothelial exposure as equivalent.
Human BBB endothelial model	NR	1 μ M	NR	Propionate protected a human BBB endothelial model at a physiologically motivated concentration (16); an in vitro barrier response does not establish CNS entry.
Direct-CNS adverse-exposure model	NR	0.26 M solution, 4 μ L per intracerebroventricular injection	NR	Repeated direct ventricular administration in adult male rats bypassed intestinal and hepatic filtering (34). The achieved brain concentration was not reported, and this exposure is not comparable with oral or peripheral physiological exposure.
Receptor and whole-cell mechanistic studies	FFAR responses reported from tens of μ M to low-mM concentrations	FFAR responses can occur from low- to high- μ M concentrations	FFAR responses generally in the tens- to hundreds-of- μ M range; 0.1–2 mM in macrophage HDAC-linked experiments	These are assay-dependent response ranges, not target-tissue reference concentrations. FFAR potency varies by ligand, receptor, species, and readout (26,27). Whole-cell HDAC-related exposures can exceed peripheral physiology (28,29).
Representative AD-model drinking-water studies	67.5 mM in a mixed-SCFA solution (6)	25.9 mM in a mixture (6); 150 mM sodium propionate (15)	40 mM in a mixture (6); 4.4 g/L sodium butyrate (approximately 40 mM) (32)	These are administered solution concentrations, not achieved brain or cell exposure; duration, intake, sodium, metabolic filtering, and model stage differ.

Note: Values are representative, not clinical reference intervals. Unit conversion and comparison across wet weight, dry weight, plasma, serum, culture medium, and administered drinking water require caution. NR, not reported for that setting; FFAR, free fatty acid receptor; HDAC, histone deacetylase.

The concentration gap is particularly important for HDAC-related claims. Peripheral human propionate and butyrate are generally in the low-micromolar range, whereas whole-cell studies commonly use hundreds of micromolar to millimolar butyrate. Intestinal macrophage experiments, for example, used approximately 0.1–2 mM butyrate to link anti-inflammatory effects to HDAC inhibition [28]. Biochemical potency does not translate directly into intact-cell target engagement because uptake and rapid metabolism can reduce intracellular free SCFA; SCFAs may also increase histone acetylation through acetyl-CoA metabolism and p300 activation rather than simple direct HDAC inhibition [29]. Table 2 therefore presents representative physiological concentrations beside commonly used experimental exposures without implying equivalence.

Formulation introduces further causal variables. Sodium acetate, sodium propionate, and sodium butyrate add sodium and can change palatability, water intake, ionic strength, pH, and osmolality. Free acids can acidify culture medium or the intestinal lumen. In vitro experiments should include pH- and osmolality-matched vehicle controls; in vivo studies should report counter-ion, solution pH, consumption, body weight, and an appropriate sodium control when relevant. Chandra and colleagues, for example, compared 150 mM sodium propionate with 150 mM NaCl [15]. These controls do not eliminate every formulation effect, but they make a metabolite-specific interpretation more credible.

4. Reading positive, neutral, and adverse evidence symmetrically

Human observational studies establish association and heterogeneity, not target-organ exposure. Kuehn and colleagues measured fecal SCFAs in 287 participants, predominantly cognitively unimpaired adults in AD-risk-enriched cohorts and identified sex- and amyloid-dependent cross-sectional associations together with longitudinal plasma phosphorylated tau 217 (pTau217) and cognitive associations [4]. The findings support stratification, but mediation based on fecal concentration does not demonstrate that propionate reached or acted directly in the CNS. A small crossover diet study in 17 older adults showed diet-related fecal SCFA changes associated with CSF AD biomarkers, yet circulating or central SCFA exposure was not measured [30].

Interventional null results require the same biological scrutiny as positive results. We propose five categories. A confirmed biological null requires adequate exposure, relevant target engagement, sufficient power, and no effect on the prespecified endpoint. An inconclusive null lacks exposure or target-engagement evidence. An underpowered null has intervals compatible with a

meaningful effect. An endpoint-specific null shows engagement but no change in one endpoint, without negating effects elsewhere. A mixed-cell null may arise when opposing cell responses cancel in bulk tissue. This classification prevents positive results from being accepted biologically while every neutral result is dismissed as exposure failure. In 69 healthy men, extruded wheat bran increased serum acetate and butyrate but did not alter prespecified psychobiological endpoints; this is an endpoint-specific human null, not evidence of universal SCFA inactivity and not an AD efficacy trial [31].

Animal studies demonstrate perturbational plausibility but are highly coordinate-dependent. In germ-free and specific-pathogen-free APPPS1 mice, a drinking-water mixture of 67.5 mM acetate, 25.9 mM propionate, and 40 mM butyrate increased plasma SCFAs and A β plaque load while changing plaque-associated microglia [6]. In SAMP8 mice, 4.4 g/L sodium butyrate from weaning for five months reduced several gut, plasma, and hippocampal A β measures and improved selected memory outcomes [32]. SAMP8 is an accelerated-aging model with endogenous murine amyloid biology and differs conceptually from APP-overexpressing models such as APPPS1 or 5xFAD; these studies should not be read as matched replications. The Brossaud study also showed endpoint specificity: memory improved, whereas disinhibition and hyperactivity did not [32].

Adverse evidence outside AD is relevant to safety and biological range, but requires equally cautious transfer. In a randomized crossover experiment, 1 g calcium propionate consumed with a mixed meal increased postprandial counter-regulatory signals and reduced insulin sensitivity in healthy adults [33]. A different hazard boundary was observed after direct central exposure: in adult male Long-Evans rats, three or five total intracerebroventricular injections of 4 μ L 0.26 M propionic acid impaired spatial reversal learning and beam performance and produced reactive astroglial and microglial changes [34]. Sodium acetate produced overlapping behavioral abnormalities in that study, and direct ventricular dosing bypassed intestinal and hepatic filtering; the experiment therefore does not establish a propionate-specific mechanism, oral-dose neurotoxicity, or harm in AD. Together, these studies argue against treating “more propionate” as uniformly beneficial while also showing why metabolic and direct-CNS hazards must not be conflated. Table 3 compares selected positive, neutral, adverse, and mechanistically non-specific findings using the same fields; NR indicates information not reported or not verified from the source.

Table 3. Selected positive, neutral, adverse, and mechanistically non-specific findings interpreted with matched fields.

Study/system; sex and stage	Exposure or measurement	Dose, route, duration	Measured compartments or achieved exposure	Target-engagement evidence	Primary endpoint and direction	Key limitation or null classification
Kuehn et al., 2025 (4); humans, both sexes, predominantly cognitively unimpaired; n=287	Fecal acetate, propionate, butyrate, and related SCFAs; observational	No intervention	Feces; PET and CSF biomarkers were analyzed cross-sectionally, whereas plasma pTau217 and cognition were analyzed longitudinally; circulating and central SCFAs were not measured	Not applicable to an intervention	Sex- and amyloid-dependent associations; SCFAs associated with slower plasma pTau217 accumulation or cognitive decline in specified analyses	Observational and fecal-compartment limited; mediation does not establish direct CNS action.
Nagpal et al., 2019 (30); humans, 12 women and 5 men; 11 MCI and 6 cognitively normal, age 64.6 ± 6.4 years	Modified Mediterranean-an-ketogenic diet versus American Heart Association diet	Randomized crossover; each diet 6 weeks with 6-week washout	Fecal SCFAs and CSF AD biomarkers; no plasma or CSF SCFAs	Diet altered microbiota and fecal SCFA pattern	Diet-related fecal changes associated with CSF biomarker changes	Pilot n=17; association, multiple co-exposures, and no target-compartment SCFA measurement.
Agahi et al., 2018 (22); humans, 31 women and 17 men; 83.5% severe AD; n=48	Two multispecies probiotic capsules versus placebo	Oral, 12 weeks; one capsule of each formulation every other day; each formulation contained three strains totaling 3 × 10 ⁹ CFU	Serum inflammatory/oxidative markers and cognition; SCFAs not measured	None for an SCFA pathway	No between-group cognitive or serum biomarker benefit	Inconclusive null for an SCFA mechanism; cannot establish stage-specific SCFA inefficacy.
Colombo et al., 2021 (6); APPPS1 mice, both sexes; early plaque deposition	Sodium acetate + propionate + butyrate	Drinking water; 67.5/25.9/40 mM; 8 weeks in germ-free mice or 4 weeks in SPF mice	Plasma SCFAs increased toward or above SPF levels; brain plaque and microglia endpoints	Achieved plasma exposure; microglial transcriptomic and phagocytic changes	Aβ plaque load increased; plaque-associated microglia changed	Mixed exposure; small groups; plaque endpoint does not establish cognition or global neurotoxicity.
Brossaud et al., 2026 (32); SAMP8 accelerated-aging model, sex-mixed (numbers by sex NR); treatment from weaning	Sodium butyrate	Drinking water, 4.4 g/L (approximately 40 mM), ad libitum, 5 months	Fecal butyrate decreased, interpreted by the authors as increased uptake; Aβ was measured in colon, plasma, and hippocampus; achieved plasma/ brain butyrate concentration NR	Colon HDAC-related and APP-processing readouts; multi-compartment Aβ changes	Selected memory, gut function, Aβ, and inflammatory endpoints improved; disinhibition/hyperactivity unchanged	SAMP8 is not an APP-transgenic model; early prevention paradigm; achieved systemic or brain butyrate exposure was not quantified.
Chandra et al., 2025 (15); APPPS1-21, male and female, 1–3 months	Sodium propionate	Drinking water, 150 mM; NaCl concentration-matched control; 2 months	Plasma pathways measured; cortical propionate detectable in 1/11 treated samples	Reduced peripheral Th17/IL-17; astrocyte-specific transcriptomics; IL-17 antibody epistasis	GFAP+ astrocytosis and Aβ plaque area reduced	Supports an indirect immune-astrocyte route, not substantial brain propionate entry; ABX effect was male-specific.
Veerareddy et al., 2026 (25); human BBB endothelial models and colonized mice; sex NR	Butyrate or butyrate-producing bacterial colonization	In vitro dose/duration NR here; microbial colonization in vivo	BBB endothelial cultures; mouse brain tissue readouts	AKT/ERK activation and inhibitor reversal; P-gp, claudin-5, and TIMP-2 changes	Intraendothelial Aβ42 accumulation decreased and barrier-related readouts improved	Barrier-cell endpoint; does not establish equivalent microglial, neuronal, cognitive, or human clinical effects.
Zhao et al., 2025 (9); male 5xFAD and WT mice; 1–6 months	Fiber-plus diet (1% cellulose, 2% pectin,	Dietary, 5 months	Fecal SCFAs and lipidomics; no circulating or brain SCFA measurement	Canonical fecal SCFAs showed only modest,	Aβ, microglia, neurogenesis, barrier, and cognitive	Protective phenotype without demonstrated canonical SCFA mediation; multiple

	2% inulin) versus fiber- free diet			taxa-specific changes	endpoints improved	lipid and ecological pathways changed.
Dalile et al., 2022 (31); 69 healthy men	Extruded wheat-bran cereal versus placebo	55 g/day orally, 28 days	Serum and fecal SCFAs; serum acetate and butyrate increased	Systemic exposure change demonstrated	No effect on primary or secondary psychobiologic al endpoints	Endpoint-specific null with modest exposure change; non-AD population and endpoints.
Tirosh et al., 2019 (33); 14 healthy adults, sex NR in the main report; mouse experiments also reported	Calcium propionate with mixed meal versus placebo	Double-blind randomized crossover; 1 g orally with a 500-kcal meal; acute 4-hour assessment	Plasma propionate and postprandial hormonal/metabolic measures	Increased glucagon, FABP4, and norepinephrine; reduced insulin sensitivity	Adverse metabolic direction: insulin resistance and compensatory hyperinsulinemi a	Small, acute, non-AD food-preservative challenge with no neurological endpoint; relevant to dose/context and metabolic safety, not proof of AD harm.
Shultz et al., 2009 (34); adult male Long– Evans rats; non- AD neurobehavioral model	Propionic acid; sodium acetate, propanol, and PBS controls	Direct right- lateral-ventricle injection; 4 µL of 0.26 M solution per injection; three or five total propionic-acid injections	Direct CNS administration; achieved brain concentration NR	Reactive astrogliosis and activated microglial changes after propionic acid	Adverse central- exposure direction: impaired spatial reversal learning and beam-task performance	Artificial high local CNS exposure in a model developed for autism; sodium acetate caused overlapping behavioral effects. It does not establish propionate-specific, oral-dose, physiological-exposure, or AD toxicity.

Note: “NR” means not reported in the source or not verified from the accessible source; it is not an inferred negative. Aβ, amyloid-β; ABX, antibiotics; AD, Alzheimer’s disease; AKT, protein kinase B; APP, amyloid precursor protein; BBB, blood–brain barrier; CFU, colony-forming units; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinase; FABP4, fatty acid-binding protein 4; GFAP, glial fibrillary acidic protein; HDAC, histone deacetylase; IL-17, interleukin-17; MCI, mild cognitive impairment; PBS, phosphate-buffered saline; PET, positron emission tomography; P-gp, P-glycoprotein; pTau217, phosphorylated tau 217; SCFA, short-chain fatty acid; SPF, specific pathogen-free; Th17, T helper 17; TIMP-2, tissue inhibitor of metalloproteinases 2; WT, wild type.

5. Quantitative tests and conditions that would weaken the framework

The framework should be evaluated prospectively rather than used to explain every result after the fact. First, a systematic evidence map can code species, administered dose, route, duration, model or clinical stage, sex, sampled compartments, achieved concentrations, target engagement, cell-resolution method, and named endpoint. Hierarchical meta-regression can then test whether these variables and prespecified interactions—such as species × compartment, route × achieved exposure, or stage × cell type—predict standardized effect direction or magnitude while accounting for study and model clustering.

Second, variance partitioning can compare a baseline model containing study quality and model class with an expanded seven-axis model. Incremental explained variance, prediction error in held-out studies, and calibration should be reported rather than only within-sample significance. Sparse cells and collinearity will limit current analyses, so the primary value may initially be to identify combinations for which evidence is absent. Third, matched-exposure replication should hold species, achieved concentration, route, timing, model stage, sex, and endpoint constant across laboratories. Factorial experiments can vary one coordinate at a time. Within a causal chain, mediation analysis should test whether an

intervention changes target-compartment exposure, whether that exposure changes a proximal cellular pathway, and whether the pathway mediates a named endpoint. Temporal ordering and sensitivity analyses for unmeasured confounding are required; a statistical indirect effect alone does not prove molecular mediation. The framework would be weakened if the seven axes add little reproducible explanatory or predictive value, if prespecified interactions fail repeatedly, or if opposite effects persist under adequately powered and closely matched coordinates. Such findings would indicate omitted dimensions—such as microbial co-metabolites, genetic background, circadian timing, or unmeasured cell states—or that the proposed organization is insufficient. Context should never become a post hoc device that makes the model unfalsifiable.

6. Measurement and translational priorities

Longitudinal human studies should use repeated, time-aligned sampling rather than a single stool specimen. At minimum, reports should document recent and habitual diet, bowel frequency and transit or Bristol stool form, constipation and laxative use, antibiotics, metformin, proton-pump inhibitors, probiotics, major comorbidities, fasting status, collection-to-freezing interval, storage temperature, freeze–thaw history, extraction method, and

analytical platform. Fecal concentration should be normalized or accompanied by wet and dry weight, stool water, and—where feasible—total fecal output over a defined interval. Concentration and total output answer different questions. Paired fecal and plasma sampling is a practical minimum when systemic exposure is claimed, but direct CNS, BBB, and indirect peripheral hypotheses require different measurements. Prospective analysis plans should use an explicit causal diagram to distinguish confounders, mediators, and consequences; repeated-measures models and sensitivity analyses should address time-varying exposure and residual confounding.

Cell specificity is necessary, but single-cell and spatial multi-omics are not mandatory. Targeted cell sorting, flow cytometry, immunohistochemistry, reporter systems, cell-specific genetic perturbation, and validated cell-enrichment methods can provide adequate resolution when aligned with the causal question. The goal is to connect exposure with the responding cell and pathway, not to maximize technology.

Proposed responder groups remain research hypotheses. Low fermentable substrate intake, low microbial functional capacity, altered barrier function, systemic inflammation, or an early AD stage have not been validated as predictors of benefit from SCFA-directed treatment. Biomarkers should be separated into four levels: exposure biomarkers (for example, a defined plasma SCFA concentration), pathway-activity biomarkers (FFAR signaling or HDAC-related target engagement), biological-response biomarkers (barrier, immune, or cell-state change), and benefit biomarkers (cognition, function, or clinical progression). Low fecal butyrate alone does not define a “deficient” pathway because efficient uptake can produce the same observation.

Current evidence therefore does not justify nonspecific SCFA supplementation as a disease-modifying treatment for AD. A credible trial should specify the molecule and formulation, establish dose–exposure relationships, stratify or adjust for stage and host context, include both sexes where feasible, verify the intended pathway, and prespecify endpoint-specific benefits and harms. The near-term objective is to determine when an SCFA-linked pathway is actionable, not to classify SCFAs globally as protective or harmful.

7. Boundaries and conclusion

The framework does not assume that all published findings are mutually compatible. Analytical error, limited power, selective reporting, model fidelity, and uncontrolled co-interventions may also generate discordance. Nor does it establish that altered SCFAs initiate human AD or that manipulating them changes

clinical progression. Most human evidence remains observational, and many mechanistic experiments use exposures that are not directly comparable with systemic physiology.

Divergent SCFA findings become more interpretable when they are placed in a causal sequence from source to named endpoint. Fecal concentration is not production or brain exposure; acetate, propionate, and butyrate are not interchangeable; disease-stage biology is not evidence of stage-specific efficacy; CNS entry, BBB action, and indirect peripheral signaling are distinct; and one cellular or amyloid endpoint cannot stand in for cognition or toxicity. The seven-axis framework offers a testable way to expose these differences. Its value will be determined by whether prospectively measured coordinates improve explanation and out-of-sample prediction—and by whether it can identify genuine contradictions when they remain.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

S.L. conceived the Perspective, designed the conceptual framework, and drafted the manuscript. D.H. contributed to literature collection, reference organization, and manuscript formatting. T.B. contributed to the neuroinflammation and Alzheimer's disease sections and critically reviewed the manuscript. H.C. contributed to the gut microbiota, short-chain fatty acid, and epigenetic regulation sections and assisted with figure and table preparation. J.P.L. supervised the work, refined the manuscript structure, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Use of generative artificial intelligence-assisted technologies

During manuscript preparation and revision, the authors used ChatGPT and OpenAI Codex to assist with language editing, structural organization, consistency checking, literature organization, and document formatting. The authors independently verified all scientific content, source articles, references, interpretations, and final wording, and take full responsibility for the manuscript.

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