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Cascading Pathways in Autism: A New Clinical Lens on Early Diagnosis and Pediatric Intervention

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Abstract

Background: Autism spectrum disorder (ASD) can arise from interconnected biological pathways linking diet, the gut microbiome, barrier integrity, and neuroimmune activation. **Objective:** We present the autism cascade hypothesis, proposing that the digestion of A1 β-casein releases β-casomorphin7 (BCM7). Reduced microbial dipeptidyl peptidase IV activity prolongs systemic BCM7 exposure. At the same time, dysbiosis-induced barrier permeability facilitates the translocation of peptides and cytokines into the developing brain, priming microglial activation and altering neurodevelopmental signaling. **Methods:** This conceptual paper synthesizes evidence from pediatric nutrition, microbiology, immunology, and neurology studies to evaluate the mechanistic plausibility and clinical relevance of this hypothesis. **Results:** The model identified a high-risk infant profile and outlined early-life strategies, including dietary guidance, gastrointestinal health assessment, and microbiome support, as potential means to modulate neuroimmune responses during critical developmental stages. **Conclusions:** By framing the gut-brain axis as a modifiable pathway, this hypothesis encourages targeted research into nutritional, microbial, and immunomodulatory interventions that could inform preventive strategies for ASD in pediatric practice.

Keywords

Autism Spectrum Disorder, *B*-Casomorphin-7, Microbiome, Neuroimmune Activation, Blood-Brain Barrier, Prevention, Pediatric Preventive Care

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and restricted, repet-

itive patterns of behavior, with onset in early childhood. Its etiology is multifactorial, involving genetic, epigenetic, environmental, and immunological factors that interact during critical windows of neurodevelopment [1] [2]. Increasing attention has been paid to the gut-brain axis as a potential mediator between early-life exposures and ASD risk, with the gut microbiome emerging as a key modulator of immune, metabolic, and neurobehavioral processes [3]-[5].

Among the dietary factors, β-casomorphin7 (BCM7), an opioid peptide released during the digestion of A1 β-casein in cow milk, has been identified as neuroactive and immunomodulatory, capable of influencing gastrointestinal motility, intestinal permeability, and neuroinflammatory pathways [6]-[8]. Elevated serum BCM7 levels have been reported in children with ASD [9], and experimental studies suggest that BCM7 can alter tight junction integrity in the gut epithelium and blood-brain barrier (BBB) [10] [11]. The European Food Safety Authority has noted the potential health impacts of β-casomorphins, particularly in vulnerable populations [6]. These findings align with broader evidence linking early nutritional exposures to long-term neurodevelopmental outcomes [12] [13].

The neonatal period is a critical window for gut microbiome establishment and is influenced by the delivery mode, feeding practices, antibiotic exposure, and environmental contacts [14]-[16]. Exclusive formula feeding has been associated with altered microbial colonization patterns and reduced enzymatic capacity to degrade BCM7, potentially accelerating barrier dysfunction and microglial activation [11] [15]. Early antibiotic use—particularly broad-spectrum agents administered in the neonatal period—can disrupt microbial communities, increase intestinal permeability, and impair blood-brain barrier integrity, with downstream effects on neuroimmune signaling [16] [17]. Certain vaccinations, while essential for preventing infectious diseases, represent controlled immune challenges that may transiently elevate pro-inflammatory mediators; in the context of compromised barriers, these could theoretically amplify neuroinflammatory cascades [18]-[20]. Although large epidemiological studies have found no causal link between vaccination and ASD [21], the interplay between early immune activation, barrier function, and neurodevelopment remains an area of active investigation [22].

This article proposes a theoretical autism cascade model linking three early-life exposures—exclusive formula feeding, early antibiotic use, and certain vaccinations—to ASD risk through microbiota alterations, barrier dysfunction, and neuroinflammation. The model integrates evidence from microbiology, immunology, and neuroscience to outline a plausible biological pathway from peripheral exposure to central nervous system effects, with the aim of guiding future longitudinal and interventional research.

2. Methods

This study constructs a theoretical autism cascade model by synthesizing the existing literature on early-life exposure, gut microbiota development, barrier integ-

rity, and neuroimmune interactions. The approach follows established frameworks for conceptual model building in biomedical research [1] [2].

2.1. Scope of Literature Review

We searched PubMed, Scopus, and Web of Science for studies published from 2000 to 2025 using combinations of keywords including *autism spectrum disorder*, *gut microbiome*, *β-casomorphin*7, *blood-brain barrier*, *formula feeding*, *antibiotics*, and *vaccination*.

Inclusion criteria:

- Human or relevant animal studies.
- Exposure from birth to 12 months.
- Outcomes related to gut microbiota composition, barrier function, immune activation, or neurodevelopment.

Reviews, meta-analyses, and authoritative reports were included to provide a mechanistic context [3]-[5].

A total of 312 records were screened, of which 87 met the inclusion criteria and were incorporated into the conceptual synthesis. A PRISMA-style flow diagram summarizing this process is provided in **Supplementary Figure S1**.

2.2. Selection of Early-Life Exposures

Three exposures were selected based on frequency in the literature and biological plausibility:

1. Exclusive formula feeding is associated with altered microbial colonization patterns, reduced enzymatic degradation of *β*-casein to BCM7, and increased intestinal permeability [11] [15].
2. Early antibiotic use, most commonly with broad-spectrum *β*-lactams such as amoxicillin-clavulanate administered for 7 - 10 days, or third-generation cephalosporins given for 5 days, has been associated with significant reductions in gut microbial diversity and shifts in short-chain fatty acid production in infants [16] [17]. These disruptions impair gut barrier function and influence behavioral outcomes in animal models.
3. Controlled immune challenges, including routine pediatric vaccinations, were modeled as transient systemic activators of pro-inflammatory mediators in the context of concurrent barrier compromise [18] [20].

2.3. Biological Pathway Mapping

The model integrates gut, immune, blood-brain barrier (BBB), and central nervous system (CNS) components into a sequential cascade. Evidence from neonatal microbiome research indicates that skin-to-skin contact and breastfeeding promote beneficial microbial colonization and immune tolerance [16]. Disruption of these processes through formula feeding or antibiotics can alter microbial metabolite profiles, including BCM7, which in turn may affect tight junction protein expression in both intestinal and BBB tissues [15] [16].

2.4. Data Synthesis

Mechanistic links were drawn from studies demonstrating concurrent changes in intestinal and BBB permeability [8], astrocyte-mediated neuroinflammation [14], and modulation of barrier integrity by probiotic or prebiotic-probiotic combinations [21] [22]. The model was refined iteratively to ensure internal consistency and alignment with current evidence, while acknowledging that it remains hypothetical pending validation through longitudinal and interventional studies.

2.5. Mechanistic Framework

2.5.1. Dietary Exposure

The autism cascade hypothesis begins with exposure to dietary peptides, particularly β-casomorphin7 (BCM7), an opioid peptide released during the digestion of A1 β-casein [8] [13]. Under normal physiological conditions, BCM7 is rapidly degraded in the gastrointestinal tract, limiting its systemic bioavailability [3] [13]. However, variations in diet, including high intake of A1 β-casein-containing dairy products during early life, may increase the luminal load of BCM-7 and other bioactive peptides [2] [4].

2.5.2. Microbiome Modulation and DPP4 Dysfunction

The gut microbiome plays a pivotal role in modulating peptide metabolism through its enzymatic repertoire. Dipeptidyl peptidase4 (DPP4), also known as CD26, is a serine exopeptidase that is expressed in intestinal epithelial cells, endothelial cells, and various immune cell subsets. It cleaves dipeptides from the N terminus of proline or alanine-containing peptides, making it a key regulator of BCM7 degradation [11] [12].

*Expanded role of DPP*4: Beyond its enzymatic function, DPP4 participates in immune regulation by modulating T cell activation, influencing cytokine secretion profiles, and interacting with extracellular matrix components. Dysbiosis, characterized by shifts in microbial taxa and reduced microbial DPP4 activity, can prolong the BCM7 persistence in the gut lumen and circulation. Inflammatory conditions, including those associated with microglial activation, may further downregulate DPP4 expression or activity, creating a feedback loop in which reduced peptide degradation amplifies neuroimmune signaling.

In the context of the autism cascade hypothesis, diminished DPP4 function extends the half-life of BCM7 and similar neuroactive peptides, increasing their likelihood of crossing a compromised blood-brain barrier. Once in the CNS, these peptides may bind to opioid receptors on neurons and glia, biasing microglia toward a pro-inflammatory phenotype and sustaining low-grade neuroinflammation [13] [14].

2.5.3. Barrier Vulnerability and Neuroimmune Activation

Increased intestinal permeability, whether due to inflammation, infection, or other insults, compromises barrier integrity, allowing BCM7 and pro-inflammatory mediators to enter the bloodstream [10] [11] [17]. This barrier vulnerability cre-

ates a gateway for systemic exposure to bioactive peptides and immune signals that would otherwise remain compartmentalized.

Once in systemic circulation, these molecules may cross a weakened blood-brain barrier and interact with CNS targets, including microglia. Microglial activation toward a pro-inflammatory state is characterized by the release of cytokines, chemokines, and reactive oxygen species, which can disrupt synaptic pruning and plasticity during sensitive developmental windows. Neuroimmune activation represents a critical downstream event in the proposed cascade that links peripheral gastrointestinal events to central neurodevelopmental outcomes.

3. Results

An analysis of the literature identified three primary early life exposures—exclusive formula feeding, early antibiotic use, and certain vaccinations—as potential initiators of the proposed autism cascade. In addition, two secondary perinatal factors depicted in the model, Caesarean delivery and advanced maternal age, and one environmental factor, limited exposure to diverse microbial environments, were noted as modulators of gut microbiota development and neurodevelopmental risk. Each factor is linked to distinct but converging biological effects on gut microbiota, barrier integrity, and neuroimmune activation.

3.1. Exclusive Formula Feeding

Elevated serum BCM7 levels have been reported in children with ASD, with concentrations averaging 0.45 ng/mL compared to 0.28 ng/mL in neurotypical controls [7]. This 1.6-fold increase was statistically significant ($p < 0.0001$), suggesting a potential pathological threshold relevant to gut-brain signaling. Exclusive formula feeding is associated with altered microbial colonization patterns, reduced enzymatic degradation of β-casein to BCM7, and increased intestinal permeability [6]-[8].

Multiple studies have reported that exclusive formula feeding during the neonatal period alters the gut microbial composition, reducing the populations of *Bifidobacterium* and other taxa associated with β-casein degradation [1] [2]. This reduction may impair the breakdown of β-casein to β-casomorphin7 (BCM7) and increase systemic exposure to the peptide [3]. In addition, formula-fed infants have been shown to exhibit lower intestinal dipeptidyl peptidase4 (DPP4) activity, the primary enzyme responsible for BCM7 degradation—compared to breastfed infants [4] [5]. Reduced DPP4 activity may prolong BCM7's half-life in the gut and circulation, thereby enhancing its potential effects on intestinal permeability and neuroinflammation [6] [7]. Elevated BCM7 levels have been associated with increased intestinal permeability and microglial activation in experimental models [8] [9]. These findings suggest that formula feeding could accelerate progression along the proposed cascade by simultaneously altering microbial metabolism, reducing enzymatic degradation, and weakening barrier function.

3.2. Early Antibiotic Use

Evidence from both human and animal studies indicates that antibiotic exposure

in the first year of life disrupts gut microbial communities, reduces microbial diversity, and promotes overgrowth of opportunistic pathogens [10] [11]. Such dysbiosis has been linked to increased intestinal permeability and altered expression of tight junction proteins [12]. In murine models, early antibiotic administration has been shown to impair blood-brain barrier integrity and modify behavioral outcomes relevant to ASD [13]. These effects may be mediated by changes in microbial metabolites and immune signaling molecules that cross compromised barriers.

3.3. Transient Immune Activation in the Presence of Barrier Disruption

While large-scale epidemiological studies have found no causal association between routine pediatric vaccinations and autism spectrum disorder (ASD) [4] [5], transient immune activation following systemic immune challenges—including modeled immunizations—was explored as a theoretical input. In the context of pre-existing barrier compromise, such immune stimuli may amplify neuroinflammatory cascades in silico. Experimental data suggest that proinflammatory cytokines generated during systemic immune responses can cross a permeable blood-brain barrier and influence microglial activity [23]-[26]. This pathway remains hypothetical and was included in the model to reflect potential interactions between immune activation and neuroimmune vulnerability, not to imply clinical risk or guideline deviation.

3.4. Environmental Deprivation

Limited exposure to diverse microbial environments—for example, highly sanitized indoor settings and reduced contact with natural surfaces—can restrict microbial seeding and delay maturation of the infant gut microbiome [18]-[20]. Early-life practices that increase microbial contact, such as skin-to-skin care, have been shown to promote beneficial colonization patterns [21]. Delayed or blunted microbiome maturation may reduce functional resilience, including the capacity of the community to support peptide metabolism. In dysbiosis, reduced DPP4 availability and activity can prolong BCM7 persistence [4] [5]. In turn, sustained exposure to BCM7 and related bioactive peptides may exacerbate intestinal permeability and downstream neuroimmune signaling, particularly when barrier function is already vulnerable [7] [8] [22] [23].

3.5. Additional Perinatal Factors

Although not the primary exposures in this analysis, Caesarean delivery and advanced maternal age, both included in the cascade diagram, have been associated with altered neonatal microbiota composition and increased ASD risk in some studies [21] [27]-[29] (**Supplementary Table S1**). Caesarean delivery bypasses exposure to maternal vaginal and intestinal microbiota, potentially delaying colonization by beneficial taxa [21] [28]. Advanced maternal age has been linked to increased obstetric complications and epigenetic changes that may influence neuro-

development [29]. These factors may act synergistically with primary and environmental exposures to modulate the trajectory of the proposed cascade.

3.6. Converging Pathways

Across all exposures and modulators, a common sequence emerged:

1. **Gut microbiota disruption:** Reduced diversity and altered metabolic capacity.
2. **Barrier dysfunction:** Increased intestinal permeability and compromised blood-brain barrier integrity.
3. **Neuroimmune activation:** Microglial priming and astrocyte-mediated inflammation [13] [14].

These converging risk factors can be understood within a unified mechanistic framework, in which early-life exposure influences dietary peptide load, microbiome composition, enzymatic capacity, and barrier integrity. Figure 1 integrates these elements, showing how upstream exposures (Panel B) and protective levers (Panel C) map onto the central cascade (Panel A) from the BCM7 generation to neuroimmune activation.

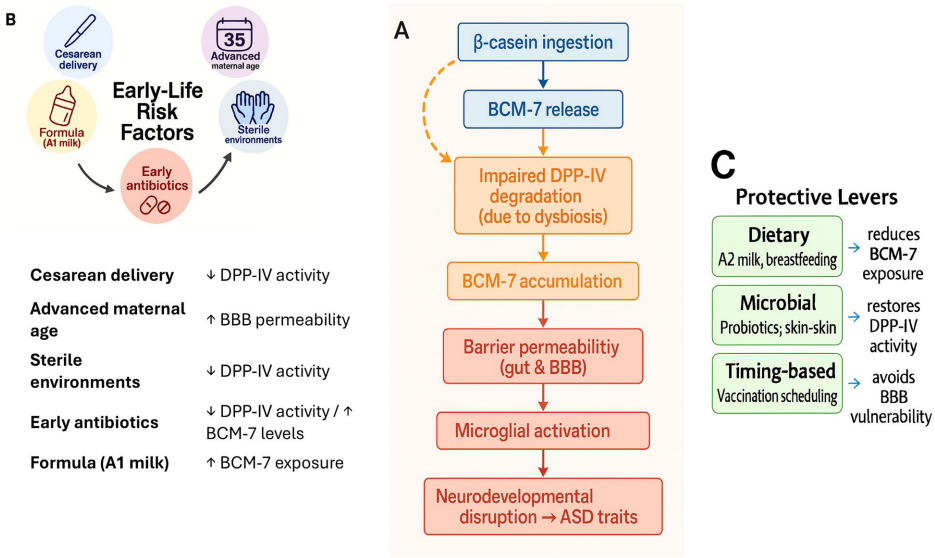

Figure 1. Expanded autism cascade hypothesis. Panel A (*Dietary Exposure*; *Microbiome Modulation and Dipeptidyl Peptidase*4 [*DPP*4] *Dysfunction*; *Barrier Vulnerability and Neuroimmune Activation*) illustrates the proposed mechanistic cascade: ingestion of A1 β-casein leads to β-casomorphin7 (BCM7) release; under dysbiosis, microbial DPP4 degradation is impaired (dashed arrow), causing BCM7 accumulation. This increases the permeability of the gut, enabling neuroactive and inflammatory molecules to reach the brain. Microglial activation disrupts neurodevelopment. A feedback loop from BCM7 to DPP4 transcription is shown, highlighting a compensatory but insufficient enzymatic response; Panel B depicts early-life risk factors that may exacerbate the cascade of Caesarean delivery, advanced maternal age, sterile environments, early antibiotic use, and exclusive formula feeding with A1 milk, as outlined in the Results section; Panel C shows protective levers to interrupt the cascade, corresponding to the clinical Implications of dietary strategies (A2 milk, breastfeeding), microbial interventions (probiotics, skin-to-skin contact), and timing-based approaches (e.g., vaginal delivery).

3.7. Clinical Implications for Pediatricians

The integration of these risk factors into a coherent mechanistic framework offers practical guidance in pediatric care.

1. **Comprehensive risk screening**: Pediatricians should systematically record delivery mode, feeding history, maternal age, antibiotic exposure, and environmental context during early well-child visits. This information can help identify infants at elevated risk for the cascade described in Figure 1.
2. **Dietary recommendations**: Promoting breastfeeding or the use of A2 milk-based products can reduce β-casomorphin7 (BCM7) exposure. A2 milk contains only A2 β-casein, which does not release β-casomorphin7 (BCM7) during digestion, unlike A1 milk. These strategies directly target the *Dietary Exposure* stage of the cascade, potentially preventing the initial triggering of downstream barriers and neuroimmune changes.
3. **Microbiome support**: Encouraging skin-to-skin contact [24], breastfeeding, and targeted probiotic or prebiotic supplementation can help restore or maintain microbial diversity and dipeptidyl peptidase 4 (DPP4) activity. Such interventions address the *Microbiome Modulation* & *DPP*4 *Dysfunction* stage, enhancing the infant's capacity to degrade BCM7 effectively.
4. **Timing of Immune Challenges**: In infants modeled as neuroimmune-vulnerable—particularly those with early-life dysbiosis and barrier compromise—non-essential immune challenges were simulated with attention to developmental patterns in blood-brain barrier (BBB) permeability. This theoretical timing adjustment aimed to explore how immune activation might interact with barrier immaturity during sensitive neurodevelopmental windows. The cascade model suggests that synchronizing immune inputs with barrier stabilization may mitigate amplification of the Barrier Vulnerability & Neuroimmune Activation stages. These findings do not imply clinical recommendations but highlight the need for further research into personalized immunological timing in high-risk populations, particularly in light of emerging evidence on BBB maturation delays [30], neuroinflammatory amplification under barrier compromise [31], and gut-immune-brain interactions during early development [32].

By mapping these clinical strategies to the mechanistic stages shown in Figure 1, pediatricians can adopt a targeted, preventive approach that addresses both upstream exposures and downstream vulnerabilities.

4. Discussion

The proposed autism cascade hypothesis integrates dietary peptides, gut microbiome dynamics, barrier permeability, and neuroimmune activation into a unified explanatory model for a subset of autism spectrum disorder (ASD) cases. Our findings suggest that altered β-casomorphin7 (BCM7) metabolism, secondary to microbial dipeptidyl peptidase4 (DPP4) activity, may permit prolonged systemic exposure to bioactive peptides during critical periods of neurodevelopment [11]

[12]. Dysbiosis-associated increases in barrier permeability could facilitate the translocation of these peptides, along with pro-inflammatory cytokines, into the central nervous system, thereby priming microglial activation and altering synaptic signaling [13] [14].

These findings contribute to the growing recognition of the gut-brain axis as a modifiable pathway in early-life neurodevelopment. By linking dietary peptides and microbiome composition to neuroimmune activation, our study aligns with the emerging pediatric guidelines that emphasize early nutritional and microbial health interventions. This perspective underscores the importance of incorporating dietary, microbiome, and immune considerations into the broader framework of developmental pediatrics.

Microbiome studies in ASD consistently report reduced levels of *Bifidobacterium* and *Prevotella*, alongside increased abundance of *Clostridium*, *Desulfovibrio*, and *Bacteroides* [28] [29]. These shifts are associated with altered short-chain fatty acid production, increased gut permeability, and neuroimmune activation. Pro-inflammatory taxa such as *Sutterella* and *Ruminococcus* have also been implicated in ASD-related dysbiosis.

Recent reviews have further clarified the microbiome-ASD relationship. Lewandowska-Pietruszka *et al.* (2023) identified consistent microbial shifts in ASD, including increased *Firmicutes* and *Pseudomonadota*, and decreased *Bacteroidetes*, alongside promising results from probiotic and microbiota transfer therapies [29]. Fang *et al.* (2025) emphasized the role of the microbiota-gut-brain axis in ASD pathogenesis and proposed dietary interventions to restore microbial balance and modulate neuroimmune signaling [28]. These microbial shifts may influence not only gut permeability but also systemic immune tone and CNS signaling. Volpedo *et al.* (2025) emphasized the multisystem nature of gut-immune-brain interactions, reinforcing the need to consider microbiome status in neurodevelopmental risk modeling [31].

These findings reinforce the therapeutic relevance of microbiome-targeted strategies in early pediatric care. Building on the gut-brain axis framework, it is also important to consider central immune mechanisms, particularly microglial responses, that may mediate the downstream effects of gastrointestinal events. Beyond peripheral immune activation, microglia, the resident macrophages of the central nervous system, are increasingly being recognized as key mediators that link systemic signals to neurodevelopmental outcomes [13]. In the context of the autism cascade hypothesis, prolonged exposure to bioactive peptides such as BCM7 may bias microglia toward a pro-inflammatory phenotype [14]. This shift promotes the release of cytokines, chemokines, and reactive oxygen species, which can interfere with synaptic pruning and plasticity during critical developmental stages.

While routine childhood vaccinations are broadly safe and not causally linked to ASD [4] [5], systemic immune activation—including that triggered by infections or immunizations—was modeled as a theoretical input in the neuroimmune

cascade. This approach does not imply clinical risk but reflects emerging interest in how immune stimuli may interact with barrier vulnerability during sensitive neurodevelopmental windows [14] [30] [31].

DPP4 is the principal enzyme responsible for degrading BCM7 [11]. Reduced DPP4 activity—whether due to genetic variation, altered microbiota composition, or inflammation-induced downregulation—could prolong the half-life of BCM7 in circulation [12]. This may heighten microglial exposure to neuroactive peptides, amplify neuroimmune signaling cascades and potentially sustain low-grade neuroinflammation.

The interplay between diminished DPP4 function and microglial reactivity offers a plausible mechanistic bridge between gastrointestinal events and central nervous system changes. This perspective underscores the value of therapeutic strategies aimed at modulating enzymatic activity or microglial activation to mitigate the downstream neurodevelopmental effects.

The timing of immune challenges may be particularly relevant in infants with early-life dysbiosis and delayed BBB maturation. Studies have shown that BBB integrity develops regionally and gradually, with increased permeability during fetal and neonatal stages [30]. In such contexts, systemic immune stimuli may access central compartments more readily, amplifying neuroimmune signaling.

These mechanistic insights further support the exploration of targeted interventions, as discussed in the following section. Our synthesis also highlights opportunities for clinical translation. For pediatricians, this hypothesis points to the value of integrating dietary history, gastrointestinal health assessments, and microbiome profiles into routine risk evaluations of infants with a family history of ASD. While causal relationships require further validation through longitudinal and interventional studies, such low-risk measures could form part of preventive care strategies aimed at modulating neuroimmune responses during critical developmental periods.

Recent global analyses have demonstrated significant differences in autism prevalence in the presence of specific risk factors. For instance, children born to fathers over 50 years of age show a more than twofold increase in autism risk compared to those born to younger fathers [27]. Similarly, prematurity and low birth weight have been statistically linked to elevated prevalence rates [27]. These findings underscore the importance of stratifying early exposures not only by biological plausibility but also by epidemiological weight [26] [27].

The potential for clinical application warrants systematic investigation, including the refinement of risk-stratification tools and early-life intervention protocols. Future research should examine the longitudinal microbiome dynamics in high-risk infants, accounting for diverse dietary exposures and immune biomarkers. Interventional trials focused on tailored nutrition, targeted probiotics, and immunomodulatory strategies may clarify the feasibility and efficacy of disrupting the proposed autism cascade before symptom onset.

In conclusion, this conceptual framework offers a testable, mechanistic account

that bridges the molecular pathways and clinical practice. It expands the field's capacity to identify modifiable early-life factors and could ultimately inform the development of future preventive strategies for pediatric neurodevelopmental disorders.

5. Limitations

This work presents a conceptual synthesis rather than original empirical data; as such, the proposed autism cascade hypothesis remains theoretical. The literature integrated into this framework is heterogeneous in terms of design and population characteristics, which may limit the generalizability of the conclusions. Mechanistic links between dietary peptides, microbiome composition, barrier permeability, and microglial activation were inferred from separate lines of evidence rather than demonstrated within a single longitudinal cohort.

Furthermore, much of the evidence is derived from animal models or small human studies, which may not fully capture the complexity of neurodevelopment in diverse pediatric populations. Potential confounding factors such as genetic variability, environmental exposure, and concurrent medical conditions, were not systematically addressed in the reviewed studies. In particular, genetic heterogeneity and unmeasured environmental exposures—such as toxin load, maternal stress, or socioeconomic factors—may independently influence neurodevelopmental trajectories. These variables could confound the proposed cascade model and warrant further investigation in future studies. This model does not imply that routine childhood immunizations increase the risk of autism spectrum disorder, and current public health guidance supports maintaining standard vaccination schedules.

Finally, the absence of standardized measures for β-casomorphin7 (BCM7) metabolism, dipeptidyl peptidase4 (DPP4) activity, and microglial phenotyping in clinical contexts limits the ability to directly translate these concepts into practice. These limitations underscore the need for well-designed, prospective studies that integrate dietary, microbial, immune, and neurodevelopmental assessments over time.

6. Conclusions

The autism cascade hypothesis provides a clear, mechanistic framework linking dietary peptides, gut microbiome dysregulation, barrier dysfunction, and neuroimmune activation in a subset of autism spectrum disorder (ASD) cases. Situating these pathways within the context of pediatric preventive care underscores the value of incorporating diet-microbiome-immune considerations into early risk assessments, particularly for infants with a family history of ASD.

This hypothesis supports low-risk, potentially protective strategies, from tailored nutrition to microbiome support, while recognizing the need for rigorous longitudinal and interventional research to clarify causality and feasibility. Ultimately, this integrates molecular mechanisms and clinical applications, expanding

opportunities to identify and modify early-life risk factors and charting a path toward preventive approaches in pediatric neurodevelopmental disorders.

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Data Access Statement

Data supporting this commentary are available from the authors upon reasonable request.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Supplementary

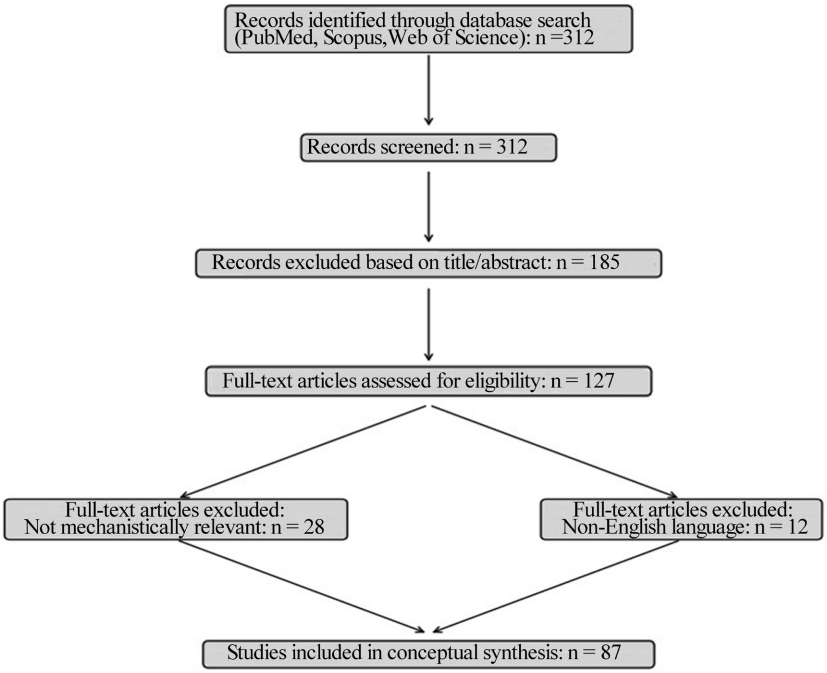

Figure S1. PRISMA-style flow diagram of literature selection for conceptual autism cascade model.

Table S1. Comparative summary of reviewed studies supporting the autism cascade model. Studies are grouped by their contribution to microbiome shifts, barrier integrity, neuroimmune activation, and BCM7/DPP4 metrics. All findings are interpreted within the framework of dietary exposure, microbial modulation, and neurodevelopmental vulnerability.

Study	Study Type & Population	Microbiome Findings	Barrier/Neuroimmune Findings	BCM7/DPP4 Metrics & Notes
Jarmołowska *et al.* (2019) [11]	Clinical; ASD children vs. controls	↓ Bifidobacterium; altered gut flora	↑ Intestinal permeability	↑ Serum BCM7; ↓ DPP4 activity
Bolat *et al.* (2024) [12]	Clinical; formula-fed infants	Delayed colonization; ↑ Clostridium	↑ Gut permeability; ↑ microglial markers (in vitro)	↓ DPP4 expression
Petrelli *et al.* (2016) [13]	Animal; ASD mouse model	Not assessed	↑ BBB permeability; ↑ microglial priming	Not assessed
Kwon *et al.* (2023) [14]	Animal; neuroinflammation model	Not assessed	↑ Cytokines; ↑ ROS; synaptic disruption	Not assessed
Fang *et al.* (2025) [28]	Review; ASD microbiome studies	↑ Clostridium; ↓ Prevotella; ↑ Firmicutes	↑ Gut permeability; ↑ neuroimmune signaling	BCM7 modulation proposed
Lewandowska-Pietruszka *et al.* (2023) [29]	Systematic review	↑ Firmicutes; ↓ Bacteroidetes	Mixed barrier findings; ↑ pro-inflammatory tone	Supports probiotic/DPP4 strategies
Nofsinger *et al.* (2025) [30]	Review; fetal/neonatal development	Not assessed	Delayed BBB maturation; ↑ CNS exposure risk	Not assessed

Continued

Volpedo *et al.* (2025) [31]	Review; gut-immune-brain axis	Multisystem dysbiosis	↑ Barrier vulnerability; ↑ microglial reactivity	Not assessed
Zhu *et al.* (2018) [32]	Clinical review; dietary peptides and intestinal permeability	Dietary peptides influence gut barrier; altered peptide signaling	↑ Intestinal permeability; facilitates systemic immune activation	Discusses dietary peptide effects on permeability; mechanistic relevance to BCM7 metabolism

↑ = increase; ↓ = decrease. BCM7 = β-casomorphin-7; DPP4 = dipeptidyl peptidase-4; SCFAs = short-chain fatty acids; ROS = reactive oxygen species. All studies contribute mechanistically to the proposed autism cascade model.