

Protective Effects of Vitamin D in Necrotizing Enterocolitis of Preterm Infants: From Basic Research to Clinical Translation

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Abstract

Necrotizing enterocolitis (NEC) is one of the most severe gastrointestinal emergencies in preterm infants, characterized by high morbidity, high mortality, and significant long-term sequelae, posing a major challenge to neonatal intensive care. Vitamin D (VitD), a pleiotropic steroid hormone precursor, exerts wide-ranging biological effects through its nuclear receptor (VDR). It plays crucial roles in maintaining intestinal barrier integrity, regulating immune homeostasis, modulating microbial balance, and mitigating oxidative stress. Increasing clinical evidence indicates that VitD deficiency in preterm infants is strongly associated with an elevated risk of NEC, whereas VitD supplementation reduces disease incidence and improves outcomes. This review systematically summarizes the protective roles and underlying molecular mechanisms of the VitD/VDR signaling axis in NEC, including reinforcement of epithelial tight junctions and mucosal barrier integrity, suppression of key inflammatory pathways, such as TLR4/NF- κ B, modulation of both innate and adaptive immune responses, optimization of gut microbial composition, and activation of antioxidative and anti-apoptotic signaling pathways. In addition, we discuss the influence of VDR gene polymorphisms on NEC susceptibility, the dose-response relationship and safety profile of VitD supplementation, and potential synergistic strategies involving combined interventions. Finally, we highlight future research directions based on multi-omics approaches and precision medicine, with the aim of facilitating the translational application of VitD from bench to bedside for the prevention and management of NEC in preterm infants.

Keywords

Vitamin D, Necrotizing Enterocolitis, Preterm Infants

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1. Introduction

Necrotizing enterocolitis (NEC) in preterm infants remains a major unresolved challenge in neonatal intensive care. Its pathogenesis is multifactorial, involving immaturity of the intestinal mucosal barrier, dysbiosis of the gut microbiota, ischemia-reperfusion injury, dysregulated immune and inflammatory responses, and genetic susceptibility [1]-[4]. Despite continuous improvements in neonatal intensive care, NEC-associated mortality remains high, and survivors often experience severe long-term complications, including short bowel syndrome and neurodevelopmental impairment [5] [6]. In recent years, the signaling axis formed by vitamin D (VitD) and its nuclear receptor (VDR) has gained increasing attention in pediatrics and perinatal medicine. Contrary to traditional understanding, VitD is not only a key regulator of calcium-phosphorus metabolism but also a “multi-functional guardian” of intestinal homeostasis. It strengthens the intestinal epithelial barrier, fine-tunes immune and inflammatory responses, and shapes a healthy gut microbiota composition [7]-[15]. VitD deficiency is highly prevalent among preterm infants and shows a significant inverse correlation with NEC risk; this finding provides a novel molecular target and intervention strategy for NEC prevention and management.

This review begins with the molecular basis of the VitD/VDR signaling axis, systematically elucidates its multi-pathway regulatory mechanisms in NEC, evaluates clinical epidemiological evidence, explores supplementation strategies and safety considerations, and discusses translational opportunities from bench to bedside. Our goal is to provide theoretical and practical guidance for the precision prevention of NEC in preterm infants through optimization of VitD-related interventions.

2. Clinical Evidence: The Epidemiological Association between VitD Deficiency and the Risk of NEC Onset

2.1. Prevalence of VitD Deficiency in Preterm Infants

Preterm infants are inherently at increased physiological risk of vitamin D deficiency after birth. Fetal VitD depends primarily on placental transfer, which reaches its peak during late pregnancy. Preterm delivery interrupts this process prematurely, resulting in insufficient fetal stores of 25-hydroxyvitamin D [25(OH)D] [16] [17]. In addition, the immaturity of hepatic and renal function in preterm infants impairs VitD hydroxylation and activation, further predisposing them to low serum VitD levels [9]. Multiple clinical studies have confirmed a significant inverse association between maternal and neonatal VitD levels and the risk of NEC [18] [19].

2.2. Influence of Maternal and Neonatal VitD Status on the Risk of NEC Onset

Prospective studies have demonstrated that serum 25(OH)D levels in preterm infants and their mothers are significantly lower than those in healthy control

groups (maternal group: OR = 0.92, $P < 0.001$; neonatal group: OR = 0.86, $P < 0.005$), indicating a significant association between neonatal vitamin D deficiency and NEC development [20]. Furthermore, for each 1 ng/mL increase in maternal and preterm infant serum 25(OH)D levels, the risk of NEC decreases by 0.751 and 0.582, respectively ($P < 0.001$), suggesting a clear dose-dependent protective effect of adequate vitamin D status against NEC [19].

2.3. Dose-Response Effects of Supplementation and Clinical Outcomes

Clinical research has explored how different VitD supplementation dosages influence NEC incidence. In a retrospective study, Öztaş *et al.* [21] compared NEC rates in preterm infants receiving various VitD dosages and found that high-dose VitD (800 IU/day) significantly reduced NEC incidence compared with the standard dose (400 IU/day) (7.7% vs. 12.6%, $P < 0.05$). These findings provide direct interventional evidence supporting the protective effect of sufficient VitD intake and suggest that higher supplementation dosages may be beneficial for achieving optimal serum 25(OH)D levels in preterm infants.

2.4. Biochemical Markers and Association with Long-Term Complications

Biochemically, VitD deficiency is closely associated with elevated inflammatory markers and intestinal barrier injury in preterm infants. Studies have shown that preterm infants with low VitD levels exhibit increased serum concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), along with elevated levels of intestinal-type fatty acid-binding protein (I-FABP). Studies have shown that low VitD status is associated with compromised epithelial tight junction integrity and increased enterocyte apoptosis, which in turn leads to elevated I-FABP release. Therefore, I-FABP is not merely an independent marker of intestinal injury but reflects, VitD-related impairment of mucosal barrier function and heightened susceptibility to NEC-associated epithelial damage which directly reflect the severity of intestinal epithelial barrier dysfunction [9] [22].

Additionally, a bidirectional relationship exists between NEC and metabolic bone disease. Evidence indicates that the risk of VitD-related bone metabolic abnormalities, such as rickets, is significantly increased in infants with NEC (OR = 2.65, 95% CI: 1.26 - 5.53, $P = 0.007$), suggesting that NEC-associated intestinal inflammation and malabsorption may severely impair VitD and calcium-phosphorus absorption, thereby exacerbating metabolic bone disease of prematurity (MBDP) [23]. Treatment with calcitriol, the active form of VitD, in MBDP infants with elevated parathyroid hormone (PTH) levels has been shown to improve bone metabolism and reduce PTH concentrations, indirectly highlighting the crucial role of adequate VitD status in maintaining overall metabolic stability and intestinal barrier integrity in preterm infants [24].

3. Molecular Mechanisms: Multi-Target Regulatory Network of the VitD/VDR Signaling Axis

3.1. Strengthening the Intestinal Epithelial Barrier: Regulation of Tight Junctions and Cytoskeletal Stability

The intestinal epithelial barrier is a critical structure for defending against bacterial invasion. In NEC infants, increased apoptosis of intestinal epithelial cells and reduced expression of tight junction proteins lead to enhanced intestinal permeability [4]. Experimental studies have indicated that 1,25(OH)₂D₃ significantly upregulates the expression of key tight junction proteins, including zonula occludens-1 (ZO-1) and occludin, in Caco-2 cells, thereby effectively counteracting lipopolysaccharide (LPS)-induced increases in epithelial permeability [25]-[27].

Experimental models have revealed that VitD enhances the expression of tight junction proteins through activation of the extracellular signal-regulated kinase signaling pathway, thereby improving intestinal barrier function and alleviating mucosal injury. VitD₃ administration significantly attenuates histopathological intestinal damage and reduces inflammatory cell infiltration, collectively indicating a protective effect on intestinal barrier integrity [18] [28].

3.2. Precision Anti-Inflammation: Suppression of the TLR4/NF-κB Pathway and Related Signaling Cascades

The pathogenesis of NEC is tightly linked to the exaggerated inflammatory response of the immature intestine to bacterial products. Among these mechanisms, aberrant activation of the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway constitutes a central driver of NEC-related inflammation [29]-[31]. TLR4, the primary receptor for LPS, induces downstream NF-κB activation, leading to robust production of pro-inflammatory cytokines. VitD supplementation markedly downregulates TLR4 expression in NEC-affected intestinal tissues, thereby inhibiting activation and nuclear translocation of NF-κB. This suppression substantially reduces levels of pro-inflammatory cytokines, including TNF-α and IL-6, ultimately attenuating intestinal inflammatory responses [31].

3.3. Immune Reprogramming: Rebalancing Innate and Adaptive Immunity

VitD exerts regulatory effects on both innate and adaptive immune cells. In dendritic cells, VitD inhibits LPS-induced inflammatory responses and reduces the production of IL-12 and IL-1β [9]. Additionally, VitD promotes the differentiation of regulatory T cells and suppresses Th17 activation, maintaining intestinal immune homeostasis and preventing excessive inflammation-induced mucosal injury [9]. In a study investigating maternal probiotic supplementation, Sharma *et al.* [32] found that early-life expression of intestinal VDR was closely associated with the establishment of immune tolerance, further supporting the central role of the VitD/VDR axis in regulating mucosal immune equilibrium.

3.4. Microbiota Modulation: Upregulation of Antimicrobial Peptides and Optimization of Microbial Community Structure

Gut dysbiosis is a critical contributor to the onset and progression of NEC. The VitD/VDR axis has emerged as an intrinsic regulator of gut microbiota homeostasis [32]. Activation of VDR enhances host innate defense mechanisms, notably through upregulation of antimicrobial peptides (AMPs).

Cathelicidin, a key AMP directly regulated by the VitD/VDR pathway, exhibits broad antibacterial activity against both Gram-positive and Gram-negative organisms. During NEC, intestinal expression of cathelicidin is decreased, promoting pathogenic bacterial colonization and translocation. By enhancing cathelicidin expression, the VitD/VDR pathway fosters the expansion of beneficial microbes such as *Lactobacillus* and *Bifidobacterium* while suppressing overgrowth of opportunistic pathogens, thereby reshaping microbial communities toward a protective composition and reducing NEC risk [33].

Fecal calprotectin, a marker of neutrophil migration into the intestinal lumen, is widely used as a noninvasive biomarker of intestinal inflammation. Jung *et al.* [34] reported a negative correlation between cord-blood VitD levels and fecal calprotectin concentrations in neonates ($P < 0.001$), suggesting that VitD deficiency is associated with a pro-inflammatory intestinal milieu, likely driven in part by dysbiosis and perpetuated through a vicious inflammatory cycle.

3.5. VDR Gene Polymorphisms: Genetic Basis for Individual Susceptibility

VDR mediates the biological activity of VitD, and its expression level and genetic polymorphisms significantly influence individual susceptibility to NEC [33] [35]. Using a VDR-knockout mouse model, Wang *et al.* [36] demonstrated that VDR deficiency renders the intestine more vulnerable to inflammatory insults, manifested as increased epithelial necrosis and heightened inflammatory responses. Functional polymorphisms of the VDR gene significantly influence receptor activity, transcriptional efficiency, and downstream signaling capacity. The FokI polymorphism alters the translation initiation site, producing a shorter VDR protein with enhanced transcriptional activity, thereby weakening epithelial defense and immune regulation. BsmI and ApaI polymorphisms, located in intronic regions near the 3' untranslated region, modulate VDR mRNA stability and expression levels, indirectly affecting receptor availability. The TaqI polymorphism, although synonymous, is linked to altered VDR protein folding and receptor-coactivator interactions. Collectively, these variants reduce VDR-mediated suppression of TLR4/NF- κ B signaling and impair tight junction maintenance, predisposing preterm infants carrying high-risk genotypes to exaggerated intestinal inflammation and increased NEC susceptibility [37] [38].

VDR signaling abnormalities affect not only immune responses but also calcium-phosphorus metabolic homeostasis [39] [40]. Preterm infants frequently de-

velop MBDP, which disrupts calcium/phosphorus balance, impairs skeletal development, and indirectly affects epithelial repair and inflammatory regulation. The VDR signaling pathway plays a crucial role in regulating the expression of proteins involved in cell junctions and signal transduction, including calmodulin and cadherins. Defective VDR function disrupts intracellular calcium homeostasis, further compromising both the integrity and reparative capacity of intestinal epithelial cells [38]. Furthermore, enzymes within the VitD metabolic pathway, particularly members of the CYP450 family, can modulate VDR function and the production of bioactive metabolites [41].

3.6. Antioxidant and Anti-Apoptotic Effects: Cellular Protection under Stress Conditions

Oxidative stress and apoptosis are prominent pathological features of NEC, contributing to widespread epithelial cell necrosis [4] [42]. VitD has been shown to exert both antioxidant and anti-apoptotic effects. VitD enhances the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, while reducing reactive oxygen species (ROS) production, thereby preserving mitochondrial function and maintaining redox balance [43]. In the context of NEC, ischemia-reperfusion-induced ROS generation is a major driver of cellular injury, and VitD's antioxidant capacity provides important protection against this process [44].

The p38 MAPK pathway is a pro-apoptotic signaling cascade activated under stress conditions. Animal studies have shown that VitD supplementation effectively suppresses p38 MAPK-mediated apoptosis, reducing mucosal necrosis and tissue injury [45]. Emerging evidence indicates that VitD directly regulates autophagy in intestinal epithelial cells through VDR-dependent transcriptional control of key autophagy-related genes.

Activation of the VitD/VDR axis upregulates Beclin-1 and LC3-II expression while suppressing mTOR signaling, thereby promoting autophagosome formation and autophagic flux. Concurrently, VitD enhances adenosine monophosphate-activated protein kinase (AMPK) activation, facilitating cellular energy sensing and mitochondrial quality control. In NEC models, these effects accelerate clearance of damaged organelles and attenuate apoptosis-autophagy imbalance, ultimately preserving epithelial cell viability and mucosal integrity [45] [46]. Thus, autophagy represents a direct mechanistic pathway, rather than a secondary phenomenon, by which vitamin D confers intestinal protection.

4. Clinical Translation: Challenges and Opportunities from Mechanistic Insights to Practical Application

4.1. Optimization of Supplementation Strategies: Dosage, Timing, and Monitoring

Although current evidence supports the potential benefits of VitD supplementation for NEC prevention, the optimal dosage, initiation timing, and duration of

supplementation remain subjects of ongoing debate. Preterm infants require higher VitD intake than term infants, and a core objective of supplementation is to rapidly establish adequate serum 25(OH)D levels to compensate for prematurely interrupted placental transfer. Studies suggest that higher supplementation doses (e.g., 800 IU/day) provide superior benefits compared with standard dosing (400 IU/day) [21]. Vestergaard *et al.* [47] further demonstrated that high-dose VitD improves placental VitD metabolism and enhances neonatal VitD stores, indicating that maternal supplementation during pregnancy combined with early postnatal supplementation may optimize VitD transfer and neonatal status. However, concerns remain that higher doses may increase the risk of hypercalcemia [17]. Moreover, differences in the efficacy of oral versus intravenous administration, the unique needs of preterm infants of varying gestational ages and birth weights, and appropriate monitoring intervals for serum 25(OH)D all require further clarification.

Preterm infants receiving human breast milk versus formula may also differ in VitD requirements. Even with high maternal VitD intake, infant serum VitD levels vary substantially, as shown in randomized controlled trials by Wagner *et al.* [48]. Given dynamic changes in growth rate, hepatic and renal maturation, and metabolic regulation, preterm infants exhibit considerable variability in VitD absorption and metabolism. Kołodziejczyk *et al.* [49] proposed a “dynamic monitoring” strategy, recommending stage-based measurement of serum 25(OH)D according to gestational age and postnatal days, allowing timely adjustment of dosing to avoid both deficiency and excess. Concurrent monitoring of serum calcium, phosphorus, and parathyroid hormone levels can further enhance safety, supporting prevention of MBDP and related complications [50].

From a safety perspective, serum 25(OH)D concentrations exceeding 100 ng/mL (250 nmol/L) are generally considered potentially toxic, with an increased risk of hypercalcemia, while sustained levels above 150 ng/mL are strongly associated with hypercalciuria and nephrocalcinosis. In preterm infants, most studies suggest maintaining serum 25(OH)D within a target range of 30-60 ng/mL, accompanied by regular monitoring of serum calcium, phosphorus, and parathyroid hormone levels to mitigate adverse effects [17] [48].

4.2. Combined Interventions: Synergistic Effects of VitD with Probiotics, Human Milk Fortifiers, and Other Nutritional Strategies

Vitamin D monotherapy enhances intestinal barrier integrity and immune homeostasis, yet combining VitD with other nutritional or microbiota-based interventions may yield more pronounced synergistic effects. Probiotics modify gut microbial composition and exhibit complementarity with VitD [34]. Prior research shows that probiotics increase small-intestinal VDR expression in neonatal mice and enhance mucosal barrier function, thereby facilitating more efficient utilization of VitD [32]. In a model of inflammatory bowel disease, Battistini *et al.* [11] found that VitD supplementation reshaped the gut microbiota toward a more

anti-inflammatory and stable configuration, while probiotics further amplified this remodeling effect.

VitD combined with human milk fortifiers (HMF) or antioxidants is also being explored as a strategy that may reduce NEC risk by targeting multiple pathways simultaneously. For the reason that preterm infants have fragile calcium–phosphorus metabolic balance from the earliest days after birth, maintaining mineral equilibrium requires multilayered support [50]. Khorana *et al.* [51] showed in a clinical trial that human milk supplemented with HMF significantly improved serum 25(OH)D and calcium-phosphorus levels in very-low-birth-weight infants compared with fortification using post-discharge preterm formula. Additional evidence suggests that combined interventions involving VitD, antioxidants, or prebiotics may relieve inflammation and enhance adenosine monophosphate (AMP) expression. Flores-Villalva *et al.* [52] reported that low VitD levels were associated with leukocytosis and inflammatory dysregulation, indicating that optimizing the inflammatory microenvironment through multiple pathways may help maintain proper VitD-VDR axis function.

4.3. Safety Assessment: Risks and Mitigation of High-Dose Supplementation

Although higher VitD doses may produce stronger biological effects, they may also increase the risk of adverse events such as hypercalcemia, hypercalciuria, and nephrocalcinosis [17]. Therefore, supplementation strategies must balance benefits and risks, and particular caution is needed for preterm infants with impaired renal function.

Previous studies have reported that high-dose VitD administered during pregnancy or early postnatal life may increase neonatal serum calcium levels, typically within controllable limits, but nevertheless warranting caution to avoid prolonged excessive exposure [48] [53]. Moreover, the immunological effects of high-dose VitD are not unidirectionally beneficial. Some studies indicate that excessive modulation of Th1/Th2 balance may lead to abnormal immune responses [53]. Thus, supplementation dosages should be individualized based on baseline neonatal status.

5. Future Aspiration: Integration of Multi-Omics Approaches and Precision Medicine

5.1. Multi-Omics Dissection of the VitD/VDR Signaling Network

The first 2 - 3 weeks after birth represent a critical window for the rapid establishment and reconstruction of the neonatal intestinal immune system. Application of multi-omics technologies, including genomics, transcriptomics, metabolomics, and metagenomics, enables comprehensive elucidation of VitD-mediated regulation of tight junction protein (TJP), AMPs, microbial remodeling, and related pathways during this pivotal period [11] [40]. Such approaches will deepen mechanistic understanding of VitD's protective effects in NEC.

At the genomic level, VDR polymorphisms have been proved closely linked with NEC susceptibility and the magnitude of inflammatory responses [37] [38], suggesting that genetic background may determine individual responsiveness to VitD-based interventions. Transcriptomic analyses have shown that VitD suppresses pro-inflammatory pathways such as TLR4/NF- κ B while upregulating protective genes including TJP and AMPs [27] [40], providing systematic insights into VDR-regulated gene networks. Chauss *et al.* [54], through transcriptomic analysis of autocrine VitD signaling in Th1 cells, demonstrated that VitD can “switch off” programmed inflammatory gene expression, offering valuable evidence for its immune reprogramming effects.

At the metabolomic level, VitD modulates key metabolic pathways such as AMPK and protein kinase B/glycogen synthase kinase 3 beta (AKT/GSK3 β) signaling [5] [8]. The role of VitD in maintaining epithelial energy homeostasis, regulating oxidative stress responses, and supporting mitochondrial stability in pre-term infants warrants further investigation. Metagenomic studies have demonstrated that the VitD/VDR axis reshapes the gut microbiota, increasing the abundance of commensal bacteria and reducing the expansion of opportunistic pathogens [11]. Conversely, microbial composition can influence VitD absorption and downstream metabolic activity, forming a bidirectional regulatory network. Future integration of multi-omics datasets with clinical phenotypes may allow construction of systems-biology models to identify critical targets of VitD intervention and provide a molecular basis for personalized supplementation strategies.

5.2. Development of Novel Targeted Therapeutics and Selective VDR Agonists

Although most selective VDR agonists have been investigated in extraintestinal disease models, emerging preclinical studies suggest growing interest in gut-targeted VDR modulation. Non-calcemic VDR agonists such as paricalcitol and maxacalcitol have demonstrated intestinal anti-inflammatory and barrier-protective effects in colitis models, indicating potential applicability to NEC. Furthermore, intestine-restricted delivery strategies, including nanoparticle-encapsulated VDR ligands, are under investigation to enhance mucosal specificity while minimizing systemic calcium-related adverse effects. While clinical trials in NEC are not yet available, these advances highlight a promising translational pathway toward intestine-specific VDR-based therapeutics [55].

VitD analogs with structural modifications have also shown superior anti-inflammatory, anti-apoptotic, and metabolic regulatory effects in various disease models [7] [8]. Coupled with advances in nanodelivery systems, these agents may achieve enhanced tissue specificity and improved targeting of the intestinal mucosa. Based on current evidence, selective VDR agonists may overcome the dose limitations associated with traditional VitD supplementation and offer a more precise and safer therapeutic option for NEC and other neonatal inflammatory disorders.

5.3. Construction of Risk Prediction Models and Individualized Intervention Strategies

The relationship between VitD and NEC is highly dependent on inter-individual variability, including maternal factors, gestational age, genetic polymorphisms, feeding patterns, and microbial composition. Developing multifactorial risk prediction models may be crucial for implementing precision interventions in the future. Incorporating intestinal inflammatory biomarkers (e.g., fecal calprotectin), dynamic 25(OH)D trajectories, and gut microbiota diversity features may improve predictive performance. For instance, the inverse association between low 25(OH)D levels and elevated cord-blood calprotectin [43] suggests a quantifiable link between VitD deficiency and early intestinal inflammation, an ideal parameter for model inclusion. Machine-learning approaches integrating genomic, metabolic, microbial, and clinical data may enable creation of NEC “risk fingerprints,” facilitating early identification of high-risk infants.

Based on prediction models, individualized VitD intervention plans could include stratified dosages, monitoring frequencies, and combined use of probiotics or nutritional fortifiers. The ultimate goal is to identify at-risk infants before NEC onset and intervene preemptively, thereby improving therapeutic effectiveness and reducing disease burden.

6. Conclusions and Perspectives: Toward a VitD-Driven Era of Precision NEC Prevention

VitD, a precursor of a pleiotropic steroid hormone, plays an indispensable role in both the prevention and pathophysiology of NEC in preterm infants. A substantial body of epidemiological evidence has established VitD deficiency as an independent risk factor for NEC [18]-[21]. At the molecular level, VitD activates the VDR signaling axis to enhance intestinal mucosal barrier integrity, suppress core inflammatory pathways, modulate immune balance, maintain gut microbiota homeostasis, and strengthen antioxidative and anti-apoptotic defenses [46] [47]. These coordinated mechanisms collectively outline a comprehensive and compelling protective framework by which VitD mitigates NEC pathogenesis.

Despite rapid progress and increasingly clear mechanistic insights, clinical translation still faces pivotal challenges, including determining optimal supplementation dosage, formulation, and timing, as well as designing individualized intervention strategies tailored to gestational age, genetic background, and microbial features. In the foreseeable future, the integration of multi-omics technologies with precision medicine principles offers promising pathways to refine VitD application in NEC prevention and management. Multi-layered data, from genomes and transcriptomes to metabolomes and microbiomes, will enable identification of key regulatory nodes within the VitD/VDR axis, guiding personalized supplementation strategies and therapeutic innovations.

From laboratory study to clinical implementation, the VitD/VDR signaling axis provides a novel and powerful framework. With continued research and transla-

tional efforts, VitD is poised to become a central and indispensable tool in the precision prevention of NEC, ultimately improving outcomes and safeguarding the health of vulnerable preterm infants.

Consent for Publication

All authors have given consent to publish.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All the authors made substantial contributions to the study. Jiping Luo wrote the original draft. Xiaofang Zhu: Conceived of and designed study, project supervision, reviewed and edited the article.

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Conflicts of Interest

The authors declare that they have no competing interests.

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