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ORIGINAL RESEARCH

# The Hidden Pathway: Membrane Vitamin D Receptor Deficiency and T-Cell Senescence in Pediatric Atopic Dermatitis – A Retrospective and Cross-Sectional Investigation

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**Background:** Pediatric Atopic dermatitis (AD) is a common, relapsing inflammatory skin disease in children. While linked to vitamin D deficiency, the roles of T-cell senescence and vitamin D receptor (VDR) signaling remain unclear.

**Objective:** To explore vitamin D status, VDR expression (soluble/sVDR, membrane/mVDR, nuclear/nVDR), and T-cell senescence in pediatric AD.

**Methods:** Serum 25-hydroxyvitamin D (25(OH)D) levels were analyzed in 408 pediatric AD patients and matched controls. In a subset (89 patients, 35 controls), plasma sVDR was measured by ELISA. T-cell immunophenotyping, senescence markers ($CD27^{-}CD28^{-}$), and mVDR/nVDR expression were assessed via flow cytometry.

**Results:** Children with AD had significantly lower serum 25(OH)D ($p$<0.05) and sVDR ($p$<0.05). Although major T-cell subset proportions were similar, children with AD showed expanded senescent populations within $CD3^{+}$ ($p$<0.01), $CD8^{+}$ ($p$<0.05), $CD4^{+}$ ($p$<0.05), and Regulatory T (Treg) cells ($p$<0.01). mVDR expression was pervasively reduced across all immune cells in pediatric AD (for CD3-, CD3+ and CD8+: p<0.0001; for CD4+, T follicular helper (Tfh) cells: $p$<0.001; for Treg: $p$<0.01). Senescent cells expressed higher mVDR than non-senescent cells in both groups (NC: CD3-, $p$<0.0001; CD3+ and CD8+, $p$<0.01; CD4+, $p$<0.001. AD: CD3-, CD3+, CD8+ and CD4+, $p$<0.0001), yet overall children with AD exhibited lower mVDR levels both in non-senescent and senescent cells (non-senescent cells: CD3-, $p$<0.001; CD3+ and CD4-, $p$<0.0001; CD4+, $p$<0.01. senescent cells:CD3-, CD3+ and CD8+, $p$<0.0001; CD4+, $p$<0.01). nVDR alterations were more limited, with elevation only in Tfh cells ($p$<0.05) of children with AD.

**Conclusion:** Pediatric AD is characterized by accelerated T-cell senescence and a widespread mVDR pathway deficiency. This receptor defect, coupled with vitamin D deficiency, may drive immune dysregulation and premature T-cell aging, highlighting potential therapeutic targets in both ligand and receptor pathways.

**Keywords:** 25-hydroxyvitamin D, vitamin D receptor, T cell, senescence, pediatric atopic dermatitis

## Introduction

Atopic dermatitis (AD) is a common, chronic, and relapsing inflammatory skin disease with a complex pathophysiology and diverse clinical manifestations. It imposes a significant burden on the physical and mental health of affected children and their families.[1] Approximately 80% of patients with atopic dermatitis experience disease onset during infancy or childhood, with symptoms often persisting into adulthood.[1] The pathogenesis of AD is driven by three major pathological

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factors: skin barrier disruption, immune system alterations, and pruritus; these factors interact, making the pathogenesis of AD highly complex.[2–5]

Recent studies have identified aging as a critical factor in the development and progression of AD in the elderly.[6,7] A hallmark of aging is chronic, low-grade inflammation, which is associated with a significant decline in immune system function, a state known as immunosenescence.[8] Both innate and adaptive immunity are affected during the process of immunosenescence.[9,10] T-cell senescence is characterized by phenotypic and functional alterations, including changes in T-cell numbers and properties, leading to functional exhaustion and decreased activity.[11] The aging organism exists in a state of systemic, low-grade chronic inflammation,[11] and conversely, inflammation can accelerate immunosenescence.[12] CD27 and CD28 are key costimulatory molecules constitutively expressed on naïve and central memory T cells, playing essential roles in T-cell activation, proliferation, and survival.[13] The progressive loss of CD28 and CD27 expression occurs during repeated antigen-driven T-cell differentiation and is widely recognized as a hallmark of immunosenescence and replicative senescence.[14] Intriguingly, a recent study indicated that in immunosenescence, $CD8^+$ T cells undergo particularly notable changes, exhibiting a more senescent ($CD27^-CD28^-$) phenotype, and surprisingly, this phenomenon appears to be age-independent and may be accelerated by chronic inflammation.[14]

Researches have demonstrated that the activation of various $CD4^+$ and $CD8^+$ T-cell subsets are extensively involved in the initiation and progression of pediatric AD.[2,15–17] Based on the chronic inflammatory nature of pediatric AD, we hypothesize that immunosenescence, particularly T cell senescence, may contribute to its pathogenesis. Given the central role of T cell dysregulation in AD, the senescence of these cells could be critically involved. Highly differentiated $CD8^+$ T cells demonstrating downregulation of CD27 and CD28 surface markers exhibit senescence-like characteristics.[18] Importantly, these senescent $CD8^+$ T cells are not terminally defective but retain capacity for functional reprogramming during differentiation.[18] Modulating the state of senescent T cells may therefore represent a promising therapeutic strategy for mitigating tissue damage caused by senescent cell accumulation. This raises key questions about whether $CD4^+$ T cells possess similar plasticity, whether differential senescence states between $CD4^+$ and $CD8^+$ T cell populations contribute to the altered $CD4^+$/$CD8^+$ ratio observed in AD patients, and whether targeting immunosenescence could ameliorate pediatric AD progression.

Vitamin D has emerged as a critical immunomodulator, influencing the activation, proliferation, and apoptosis of T cells.[19–22] The presence of the VDR in almost all immune cells underscores its importance in immune regulation.[23] Notably, VDR expression is indispensable for optimal T-cell activation, with levels significantly upregulated upon stimulation.[24] Furthermore, interesting disparities exist: $CD8^+$ T cells exhibit the highest VDR levels among major immune cells,[25] yet the functional outcomes of vitamin D signaling appear to differ between $CD4^+$ and $CD8^+$ T cells.[26,27] While some evidence suggests a potential link between vitamin D and the aging of $CD8^+$ T cells,[25] the role of vitamin D and its receptor pathways in regulating T-cell senescence, especially in the context of pediatric AD, remains poorly defined. Current clinical studies on vitamin D supplementation in AD have yielded inconsistent results,[28–31] highlighting the need to move beyond serum level correlations and investigate the cellular mechanisms, particularly VDR-mediated signaling.

Based on this background, we hypothesize that children with AD exhibit a distinct profile of T-cell senescence compared to healthy controls, and that vitamin D may ameliorate AD progression by modulating this process. This study aims to: 1) evaluate the serum vitamin D and soluble VDR levels in AD children; 2) comprehensively characterize the senescence status of various T-cell subsets in peripheral blood; and 3) investigate the expression patterns of both mVDR and nuclear nVDR across immune cell populations and their relationship with cellular senescence. Our work seeks to provide novel insights into pediatric AD pathogenesis from an immunosenescence perspective and to elucidate vitamin D's potential mechanisms, thereby offering a theoretical foundation for its therapeutic application in AD management.

## Materials and Methods

### Study Population and Ethical Approval

All children with AD in the acute flare phase were recruited from the Department of Dermatology at Hunan Children's Hospital between May 2023 and January 2025. Normal control (NC) subjects were selected from children undergoing health check-ups at the same institution during the corresponding period. The retrospective analysis of serum 25(OH)D levels was conducted in 408 children with AD and an equal number of age- and sex-matched healthy controls (mean age:

7.09±3.53 years for controls; 7.09±3.75 years for children with AD). A total of 89 children with AD and 35 age-matched healthy controls were recruited for the sVDR and flow cytometry assay (mean age: 4.64±3.59 years for controls; 4.59 ±3.73 years for children with AD). The diagnosis of AD was confirmed according to the Hanifin and Rajka criteria. Patients who had received systemic corticosteroids, immunosuppressive agents, or vitamin D supplements, or had concomitant other immunological diseases within the past 3 months were excluded. This study was approved by the Institutional Review Board of Hunan Children's Hospital (Approval No: HCHLL-2024-264), and written informed consent was obtained from the parents or guardians of all participants.

## Blood Sample Collection and Processing

Anticoagulated blood samples remaining after complete blood count testing were collected from the patients, and then centrifuged at 1500 × g for 10 minutes to separate plasma and cellular components. The upper plasma layer was carefully aliquoted and stored at −80°C until subsequent ELISA analysis. The remaining cell pellet was subjected to red blood cell lysis, followed by staining with fluorescently labeled antibodies for flow cytometry.

## Measurement of Serum 25-Hydroxyvitamin D and Soluble VDR

The concentration of plasma 25(OH)D was measured on AutoLumo A6200 (Autobio Experimental Instruments Co., Ltd., China) – a chemiluminescence immunoassay clinic detection platform using 25-OH Vitamin D CLLA Microparticles Kit (Global Trade Item Number: 06970150901233, Autobio Experimental Instruments Co., Ltd., China) according to the manufacturer's instructions. The level of sVDR in plasma was determined by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human Vitamin D Receptor ELISA Kit, CSB-E05136h, CUSABIO TECHNOLOGY LLC., China). All samples were tested in duplicate.

## Flow Cytometry

All flow cytometry antibodies were purchased from BD Biosciences (USA), except for the VDR-specific antibody, which was obtained from Invitrogen (Thermo Fisher Scientific, USA). Leukocytes were isolated by lysing red blood cells with a lysis buffer. To analyze T-cell subsets, T-cell senescence markers, and vitamin D receptor (VDR) expression. Leukocytes were stained with fluorescently labeled antibodies against surface markers (zombie, CD45, CD3, CD4, CD8, CD27, CD28, CD25, CD127, PD1, CXCR5, mVDR) and, for intracellular nVDR staining, cells were fixed and permeabilized prior to intracellular VDR antibody incubation. The $CD8^+$ T cell population was defined as $CD3^+CD4^-$ cells within the $CD45^+$ $CD3^+$ lymphocyte gate. Data were acquired on BD LSRFortessa$^{TM}$ Cell Analyzer (BD Biosciences, USA).

## Statistical Analysis

All statistical analyses were performed using SPSS Statistics software (version 20). Data visualization was chosen based on distribution – box plots (depicting quartiles) for non-normally distributed data and bar graphs (showing mean ± standard deviation (*SD*)) for normally distributed data. Differences between groups were analyzed by Mann–Whitney *U*-test or Student's *t*-test. Given the unequal sample sizes for the sVDR and flow cytometry analyses, comparisons between the AD and control groups were performed using the Mann–Whitney *U*-test. Correlations were assessed by Pearson's or Spearman correlation coefficient. A two-tailed $p$ value of less than 0.05 was considered statistically significant.

# Results

The harvested peripheral blood nucleated cells were stained for flow cytometry to analyze the frequency of distinct T-cell subsets, as well as senescent cells of different subsets. The multistep gating strategy is depicted in Supplementary Figure 1.

## Profiling of Leukocyte Subsets in AD

The peripheral blood leukocyte subsets in 89 cases of pediatric AD patients and 35 cases NC were analyzed by flow cytometry. The analysis revealed that no significant differences were observed in the proportions of peripheral blood


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$CD3^-$, $CD3^+$, $CD4^-$, or $CD4^+$ cells between NC and pediatric AD patients. Similarly, the frequencies of Treg and Tfh cells were comparable between the two groups (Supplementary Figure 2).

## Immune Senescent Condition of Leukocytes ($CD45^+$) in Peripheral Blood

To investigate differences in immunosenescent cells between pediatric AD patients and NC, we performed flow cytometric analysis of peripheral blood $CD45^+$ leukocytes. Senescent immune cells were identified based on the absence of CD27 and CD28 surface markers ($CD27^-CD28^-$), allowing us to characterize the senescence status across various immune cell subsets.

We performed viSNE (t-distributed stochastic neighbor embedding–based visualization) analysis to evaluate the distribution of senescent leukocyte subsets (Figure 1A). As shown in the figure, notable differences were observed in the populations of senescent and non-senescent $CD4^-$ cells, as well as senescent and non-senescent $CD4^+$ T cells between the NC and pediatric AD groups.

We further quantified the proportions of individual senescent cell subsets showed in t-SNE. The results revealed significant differences between the pediatric AD and NC groups in the frequencies of senescent $CD3^-$ leukocytes ($p<0.001$), senescent $CD3^+$ T cells ($p<0.01$), senescent $CD8^+$ T cells (identified as $CD3^+CD4^-$, $p<0.05$), senescent $CD4^+$ T cells ($p<0.05$), as well as senescent Treg cells ($p<0.01$). Notably, with the exception of senescent $CD3^-$ cells, which were significantly higher in the NC group, all other senescent cell populations were significantly elevated in the pediatric AD group (Figure 1B–K).

## Reduced Serum 25(OH)D in Pediatric Atopic Dermatitis

We retrospectively analyzed serum 25-hydroxyvitamin D [25(OH)D] levels in 408 pediatric AD patients, with a control group comprising age- and sex-matched healthy children. A significant reduction in serum 25-hydroxyvitamin D [25 (OH)D] levels was observed in the pediatric AD group as compared to the control group ($p<0.05$, Figure 2A).

## Decreased Serum Soluble Vitamin D Receptor (sVDR) in Children with Atopic Dermatitis

Consistent with the observed alterations in serum 25-hydroxyvitamin D, ELISA-based quantification demonstrated that serum levels of soluble VDR (sVDR) were significantly lower in the pediatric AD group than in the NC group ($p<0.05$, Figure 2B).

## Expression of mVDR and nVDR in Immune Cells

To further investigate the VDR pathway, we used flow cytometry to evaluate the expression levels of membrane and nuclear VDR across various leukocyte subsets in the peripheral blood of both populations from children in the pediatric AD and NC groups.

Notably, the mean fluorescence intensity (MFI) of mVDR was significantly lower in children with pediatric AD compared to NCs within the $CD45^+CD3^-$ leukocyte ($p<0.0001$), $CD45^+CD3^+$ T-cell ($p<0.0001$), $CD8^+$ T-cell ($p<0.0001$), $CD4^+$ T-cell ($p<0.001$), Treg ($p<0.01$), as well as Tfh populations ($p<0.001$). Moreover, the expression of mVDR was significantly higher on $CD45^+CD3^-$ leukocytes than on $CD45^+CD3^+$ T cells (NC, $p<0.0001$; AD, $p<0.0001$), and significantly higher on $CD8^+$ T cells compared to $CD4^+$ T cells (NC, $p<0.05$; AD, $p<0.001$) in both pediatric AD and NC groups. However, this expression pattern was not observed between Treg and Tfh cells, as no significant difference in mVDR expression levels was found between these two subsets (Figure 3A–F).

In contrast to the expression pattern of mVDR, the protein levels of nVDR in peripheral blood $CD45^+CD3^-$ leukocytes, $CD45^+CD3^+$ T cells, $CD8^+$ T cells, and $CD4^+$ T cells did not differ significantly between pediatric AD and normal controls. Additionally, it was noted that, unlike in healthy controls, children with AD exhibited significantly higher nVDR expression in $CD8^+$ T cells compared to $CD4^+$ T cells ($p<0.001$). In both pediatric AD and NC, nVDR expression was significantly higher in Tfh cells than in Treg cells (AD and NC, $p<0.01$). Furthermore, the protein level of nVDR in Tfh cells was significantly elevated in children with AD compared to NC subjects ($p<0.05$) (Figure 3G–L).

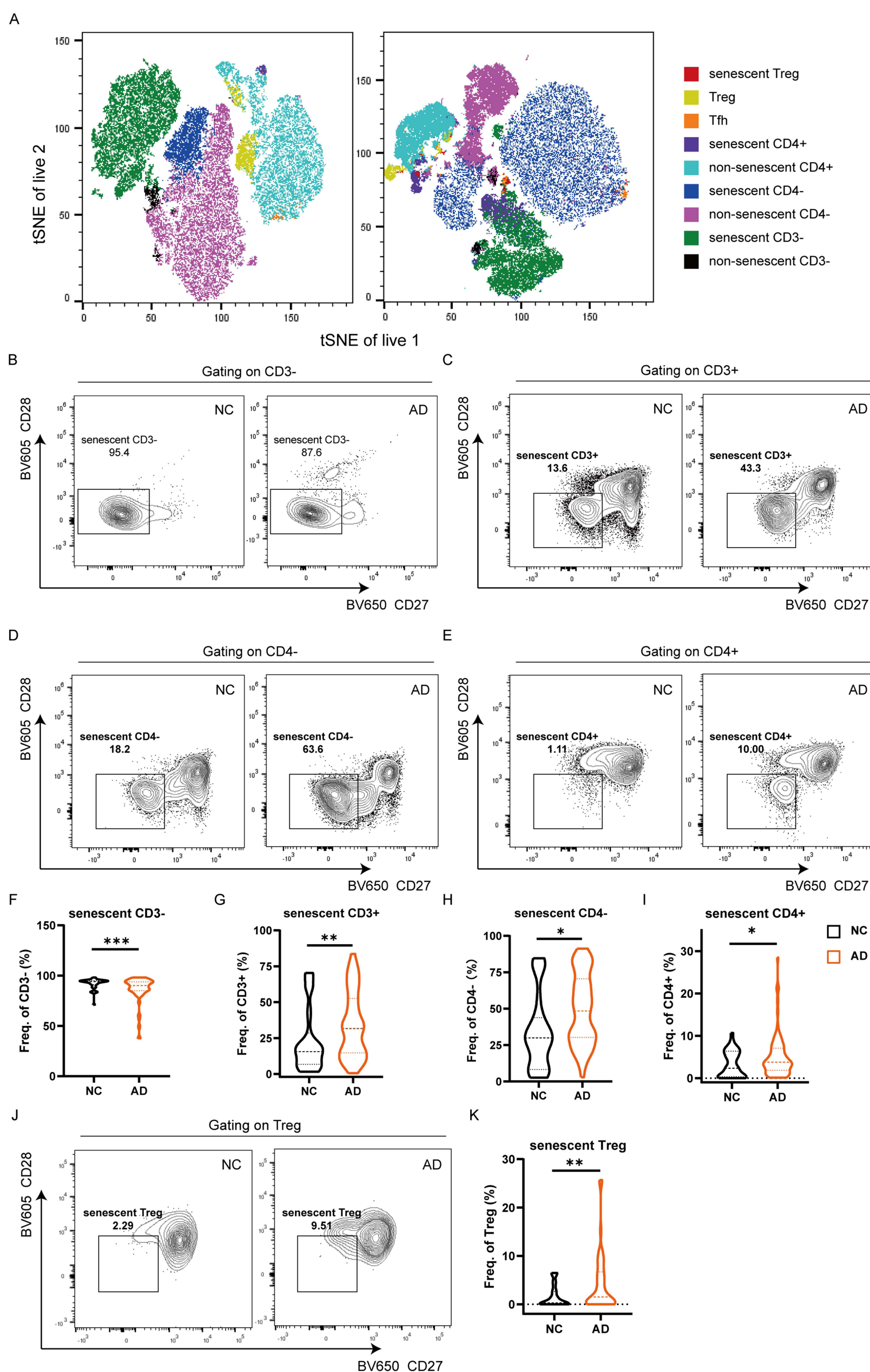


**Figure 1** Peripheral blood T-cell senescence is elevated in children with AD. (**A**) viSNE plot depicting senescent immune cells in AD and NC groups. (**B**–**K**) Flow cytometric analysis confirms a significant increase in the frequency of CD27⁻CD28⁻ senescent cells in AD patients across multiple T-cell subsets, including $CD3^+$ T cells **(C** and **G)**, $CD8^+$ T cells (identified as $CD3^+CD4^-$) (**D** and **H**), $CD4^+$ T cells (**E** and **I**), and Tregs (**J** and **K**), compared to NCs. (NC, n=35; AD, n=89; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).


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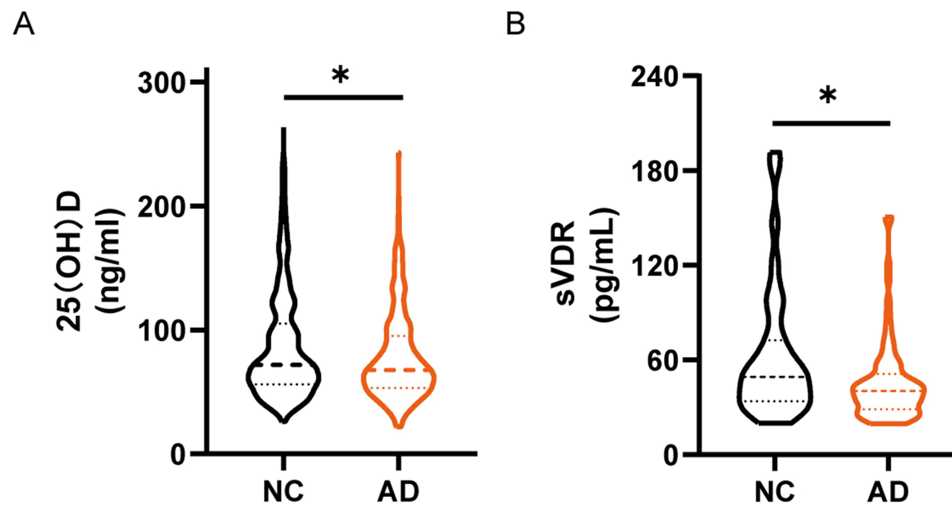


**Figure 2** Reduced plasma levels of 25-hydroxyvitamin D and soluble VDR in children with AD. (**A**) Concentration of plasma 25-hydroxyvitamin D [25(OH)D]. (**B**) Concentration of plasma soluble VDR (sVDR). (NC, n=35; AD, n=89; $^{*}p < 0.05$).

## mVDR and nVDR Expression Profiles in Senescent Immune Cells

We evaluated the MFI of mVDR and nVDR across immune cell populations to explore their potential relationship with immunosenescence. Strikingly, significantly elevated mVDR expression on senescent cells compared to non-senescent cells was a universal feature of $CD45^{+}CD3^{-}$ leukocytes (both AD and NC, $p$<0.0001), $CD45^{+}CD3^{+}$ T cells (NC, $p$<0.01; AD, $p$<0.0001), $CD8^{+}$ T cells (NC, $p$<0.01; AD, $p$<0.0001), and $CD4^{+}$ T cells (NC, $p$<0.001; AD, $p$<0.0001), a phenomenon evident in both NC and children with AD. Moreover, the expression of mVDR was consistently and significantly higher in the NC group compared to the pediatric AD group across both senescent and non-senescent populations of the same cell subsets (non-senescent cells: $CD3^{-}$, $p$<0.001; $CD3^{+}$ and $CD4^{-}$, $p$<0.0001; $CD4^{+}$, $p$<0.01. senescent cells:$CD3^{-}$, $CD3^{+}$ and $CD8^{+}$, $p$<0.0001; $CD4^{+}$, $p$<0.01) (Figure 4A–H).

Analysis of nVDR revealed a more restricted pattern: its expression was elevated in senescent cells only within the $CD3^{+}$ ($p$<0.0001) and $CD8^{+}$ ($p$<0.01) T cell compartments of children with AD, and no significant inter-group differences (pediatric AD vs NC) were detected in any subset, regardless of senescence status (Figure 4I–P).

Furthermore, we analyzed the expression of both VDR forms in Treg cells. For mVDR, senescent Tregs in the NC group exhibited significantly higher expression than their non-senescent counterparts ($p$<0.001), a difference that was absent in the pediatric AD group. Moreover, mVDR expression was significantly higher in the NC group than in the pediatric AD group for both non-senescent ($p$<0.01) and senescent ($p$<0.001) Tregs (Figure 5A and B).

Analysis of nVDR in Treg cells failed to reveal any significant differences, either between senescent and non-senescent states within each group, or between the pediatric AD and NC groups for either Treg population. The nVDR expression levels remained similar across all comparisons (Figure 5C and D).

# Discussion

This study provides significant advancements in understanding pediatric AD pathogenesis by systematically investigating the relationships between vitamin D status, VDR expression patterns, and T-cell senescence. Our findings reveal a complex immunological landscape characterized by accelerated immunosenescence and distinct alterations in VDR signaling pathways in children with AD in the acute flare phase.

## Immunosenescence in Pediatric AD: Beyond Chronological Aging

Traditionally considered a feature of aging, immunosenescence has recently been recognized as a process that can occur independently of chronological age, particularly in chronic inflammatory conditions.[17] Our study demonstrates that children with AD in the flare phase exhibit significant expansion of senescent T cells across multiple subsets, including

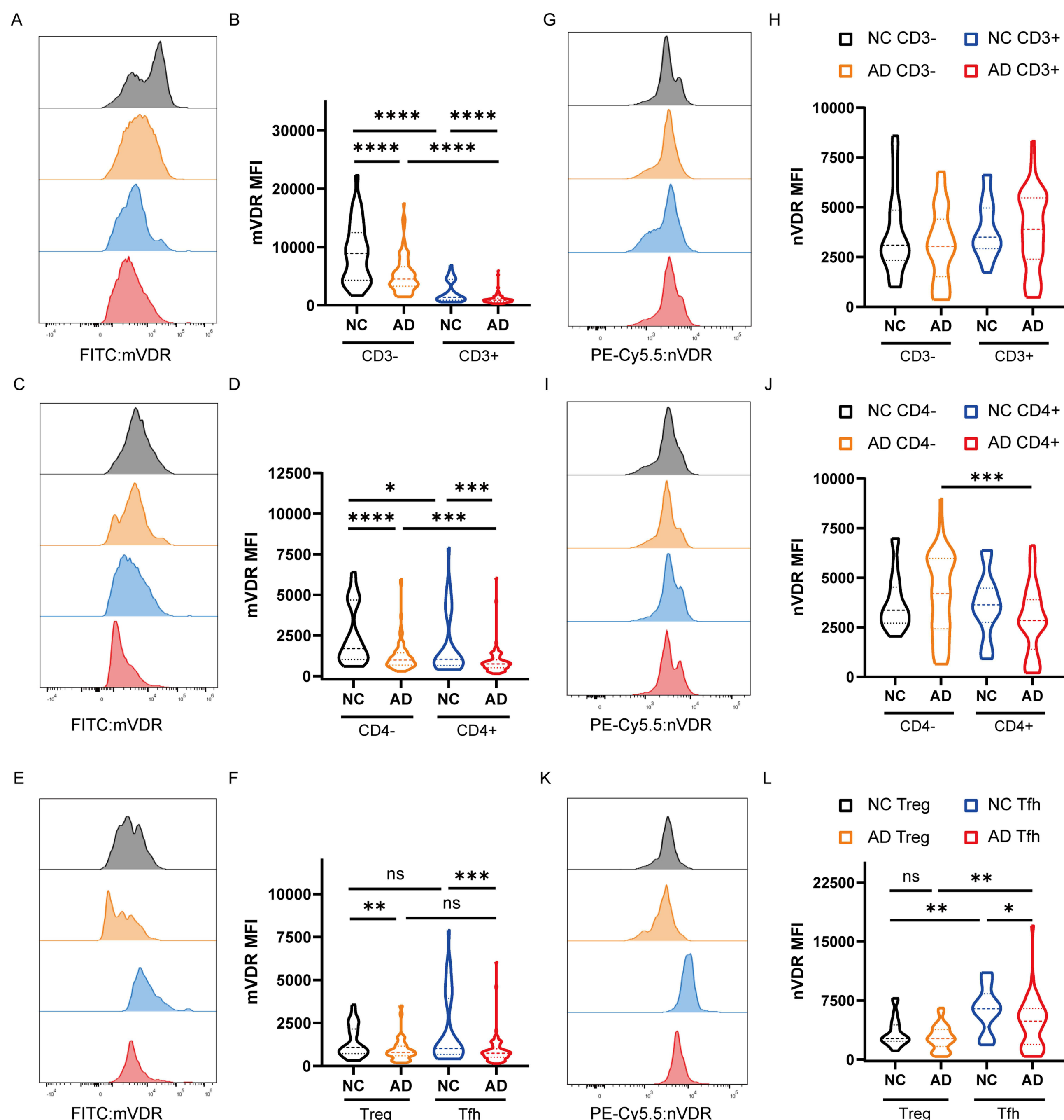


**Figure 3** Pervasive deficiency in mVDR but not nVDR in AD immune cells. (**A–F**) mVDR expression (MFI) was significantly lower in AD children than in NCs within all immune subsets analyzed, including CD45⁺CD3⁻ leukocytes, CD45⁺CD3⁺ T cells, CD8⁺ T cells, CD4⁺ T cells, Treg, and Tfh cells. (**G–L**) nVDR protein levels, however, were largely comparable between AD and NC groups, with exceptions noted in the CD8⁺ vs CD4⁺ T cell comparison and elevated Tfh cell expression in AD. (NC, n=35; AD, n=89; ns, not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

CD3⁺ T cells, CD8⁺ T cells, CD4⁺ T cells, and Tregs. This finding challenges the conventional view that immunosenescence is exclusively an age-related phenomenon and suggests that chronic inflammation in AD may drive premature immune aging. The preservation of overall T-cell subset proportions alongside dramatic expansion of their senescent fractions indicates that AD immunopathology may be driven more by qualitative defects in T-cell homeostasis than by simple quantitative imbalances.


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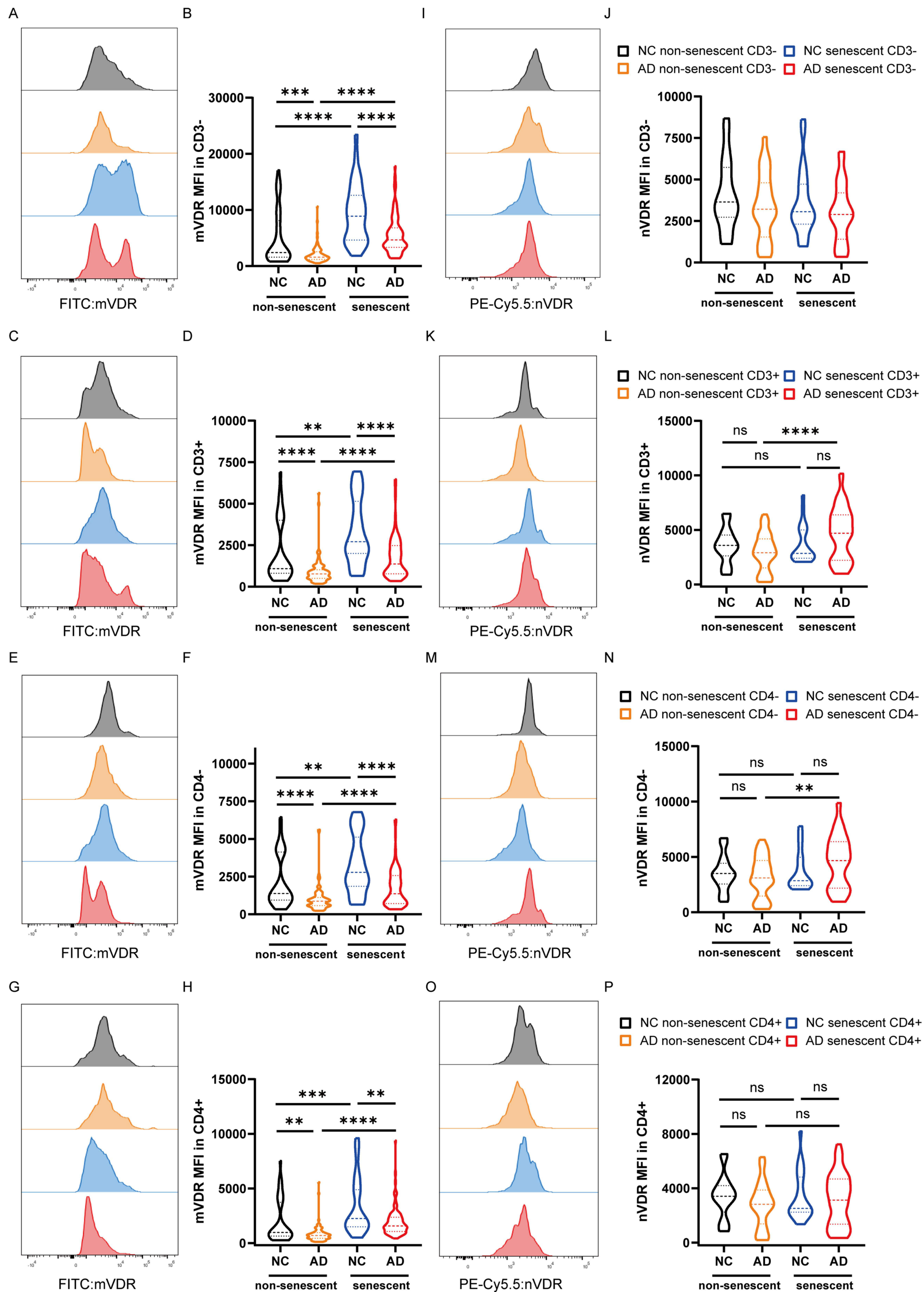


**Figure 4** mVDR is universally associated with cellular senescence while nVDR shows a restricted pattern. (**A**–**H**) mVDR expression (MFI) is significantly elevated on senescent cells within all immune subsets analyzed. Despite this, NC subjects maintain higher overall mVDR levels than AD patients across all cellular states. (**I**–**P**) nVDR demonstrates a limited association with senescence, showing elevated expression only in senescent CD3$^{+}$ and CD8$^{+}$ T cells of AD patients, with no overall difference between AD and NC groups. (NC, n=35; AD, n=89; ns, not significant, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

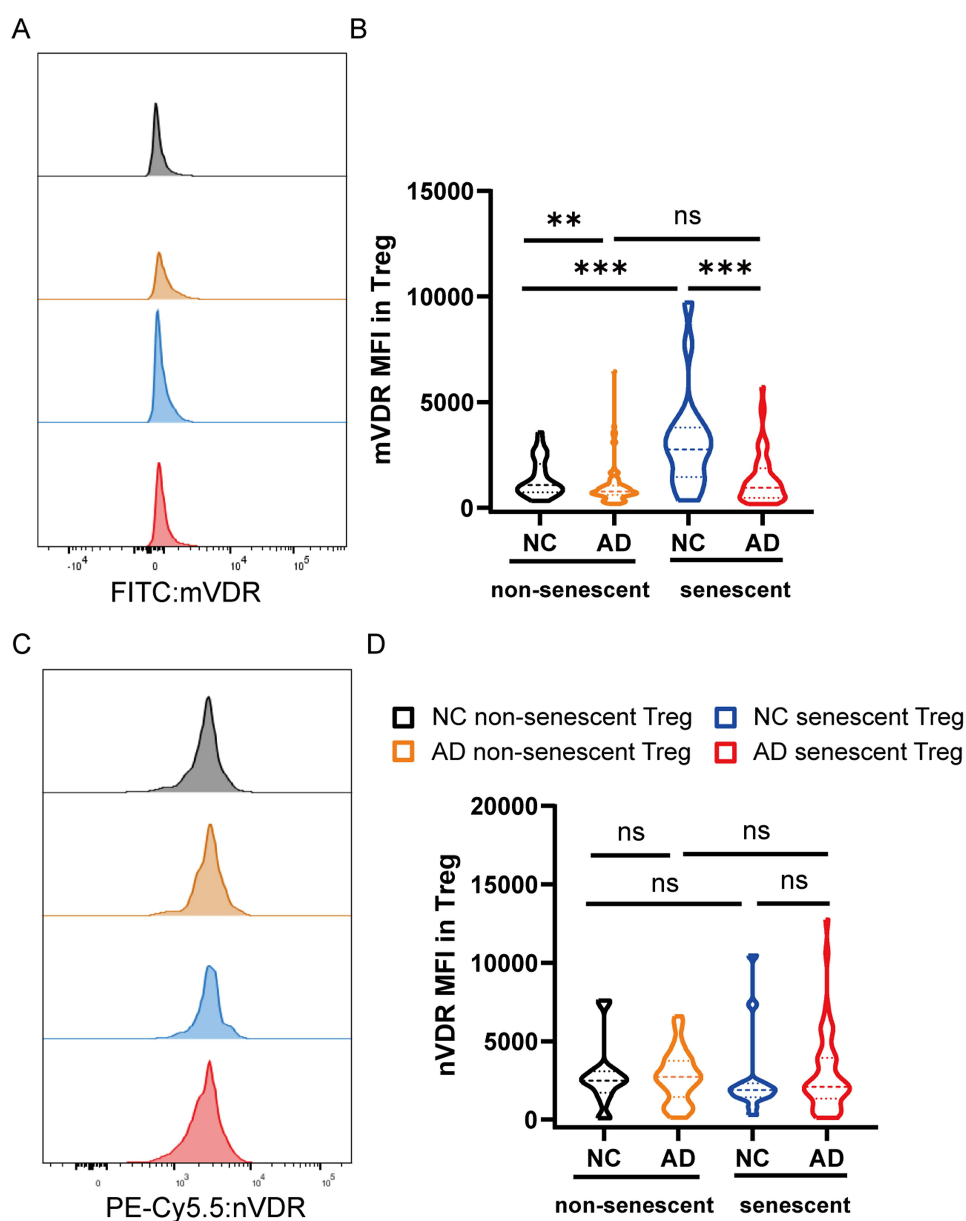


**Figure 5** Contrasting VDR isoform profiles in Treg cells. mVDR expression was elevated on senescent Tregs in NCs and was globally higher in NCs versus AD subjects (**A** and **B**), whereas nVDR expression remained stable across all comparisons, showing no association with senescence or disease status (**C** and **D**). (NC, n=35; AD, n=89; ns, not significant, $^{**}p < 0.01$, $^{***}p < 0.001$).

The senescent T-cell phenotype observed in our pediatric AD cohort, characterized by $CD27^{-}CD28^{-}$ expression,[18] represents a state of functional compromise rather than terminal differentiation. Interestingly, emerging evidence suggests that senescent $CD8^{+}$ T cells maintain capacity for functional reprogramming,[18] raising important questions about the plasticity of senescent T cells in AD and their potential for therapeutic modulation.

## Vitamin D and VDR Dysregulation in AD Pathogenesis

Our findings confirm previous reports of reduced serum 25(OH)D levels in children with AD,[32,33] consistent with the known epidemiological association between vitamin D status and AD severity. However, the therapeutic implications of this association remain unclear, as vitamin D supplementation trials have yielded inconsistent results.[32,34] This paradox suggests that serum vitamin D levels alone may not fully capture the complexity of vitamin D signaling in AD.


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The novel aspect of our work lies in the comprehensive analysis of cellular VDR expression. We identified a pervasive deficiency in mVDR expression across all major immune cell subsets in AD children in the flare stage, coupled with reduced levels of sVDR in serum. This dual deficiency in both membrane-associated and circulating VDR isoforms suggests fundamental impairment in vitamin D signaling capacity in AD.

## mVDR Deficiency: A Novel Mechanism in AD Immunopathology

The most significant finding of our study is the identification of mVDR deficiency as a potential central mechanism in AD pathogenesis. While previous research has primarily focused on the nuclear VDR pathway,[23–27] our data highlight the importance of the non-genomic, rapid-response signaling pathway mediated by mVDR. The universally lower mVDR levels in AD patients, even in non-senescent cells, indicate a fundamental impairment that may render T-cells more susceptible to senescence and dysfunction.

Interestingly, we observed that mVDR expression was consistently elevated on senescent cells compared to their non-senescent counterparts in both pediatric AD and control groups, suggesting that high mVDR expression might serve as a biomarker of T-cell senescence. However, the overall deficiency of mVDR in children with AD in the flare phase creates a paradoxical situation where cells may be primed for senescence but lack adequate mVDR-mediated signaling for proper cellular regulation.

This mVDR deficiency model provides a plausible explanation for the mixed results of vitamin D supplementation trials.[31,33] If the primary receptor apparatus for rapid-response signaling is deficient, simply increasing the ligand (vitamin D) may yield limited clinical efficacy. This insight suggests that future therapeutic strategies should consider both vitamin D status and mVDR expression levels.

## Differential Roles of VDR Isoforms in Immune Regulation

Our comparative analysis of VDR isoforms reveals distinct patterns of dysregulation. While mVDR demonstrated consistent deficiency across all immune cell subsets, the nVDR pathway showed a more restricted and context-dependent pattern of alteration. The general preservation of nVDR protein levels between AD and NC groups in most cell subsets suggests that the classic genomic signaling pathway remains relatively intact, while specific alterations in subsets like $CD8^+$ T cells and Tfh cells indicate cell-type-specific dysregulation.

The finding that $CD8^+$ T cells possess the highest levels of VDR among major immune cells is particularly relevant given their prominent role in immunosenescence.[27] Our data extend this understanding by demonstrating subset-specific alterations in both mVDR and nVDR expression that may contribute to the immune dysregulation characteristic of AD.

The theoretical contribution of this work is the proposal of a "mVDR Deficiency and Accelerated Immunosenescence" model in AD. This model integrates the known epidemiological link with vitamin D deficiency while providing a novel cellular mechanism centered on receptor expression and T-cell aging. From a practical perspective, measuring mVDR expression on specific immune cells could emerge as a valuable biomarker for assessing immunological aging and disease severity, potentially identifying patients who may not respond to conventional vitamin D supplementation.

## Limitations and Future Directions

We acknowledge that no formal a priori sample size calculation was performed in this study. Given its exploratory nature, the sample size was primarily determined by the availability of eligible participants and residual clinical specimens during the study period. This reflects a pragmatic approach aimed at maximizing the use of clinically obtained samples while minimizing additional blood collection from pediatric individuals—an important ethical consideration in research involving children.

Nevertheless, the absence of a pre-specified sample size calculation represents a limitation. Although the statistical tests employed Mann–Whitney *U*-test are robust to unequal group sizes, the smaller control cohort may have reduced statistical power to detect smaller effect sizes. Moreover, the findings should be considered hypothesis-generating rather than confirmatory. To address this limitation, future prospective studies with pre-determined sample size calculations are warranted.

The absence of uniformly documented disease severity scores for some of the enrolled participants limited our ability to perform a comprehensive correlation analysis between laboratory findings and clinical status, an aspect that should be prioritized in subsequent investigations.

In this study, we unable to analyze the senescence status of T follicular helper (Tfh) cells or the VDR expression profiles in their senescent subsets due to the low frequency of Tfh cells in peripheral blood, which did not allow for a reliable assessment.

Several other limitations of our study should be acknowledged. The correlative nature of our findings necessitates functional validation through in vitro and in vivo models. The exclusive focus on peripheral blood cells may not fully reflect pathological processes in cutaneous lesions, and the functional consequences of reduced mVDR expression on T-cell signaling, cytokine production, and proliferative capacity remain to be elucidated.

Future research should prioritize: (1) prospective studies incorporating standardized, longitudinal assessments of disease severity (eg, SCORAD) to clarify how mVDR expression and T-cell senescence fluctuate with flare intensity and treatment response; (2) functional studies to determine how mVDR downregulation directly promotes T-cell senescence and dysfunction; (3) investigation of the molecular mechanisms responsible for transcriptional and post-transcriptional suppression of mVDR in AD; and (4) exploration of therapeutic strategies that combine vitamin D metabolites with approaches aimed at upregulating or stabilizing mVDR expression.

## Conclusion

Our study demonstrates that children with AD in the acute flare phase exhibit accelerated T-cell senescence and pervasive deficiency in mVDR expression across immune cell subsets. These findings provide new insights into AD pathogenesis and suggest that mVDR deficiency may represent a previously underappreciated factor contributing to immune dysregulation in this condition. The dissociation between mVDR and nVDR expression patterns indicates that vitamin D's immunomodulatory effects are mediated through distinct and dissociable pathways, advocating for therapeutic strategies that concurrently target ligand availability and receptor expression.

## Highlights

- We identify a deficiency in membrane VDR (mVDR) in pediatric atopic dermatitis (AD).
- Our study reveals accelerated T-cell senescence as a hallmark of pediatric AD, indicating its relevance beyond aging.
- mVDR deficiency may link low vitamin D status to T-cell senescence and explain inconsistent outcomes in vitamin D supplementation trials.
- Therapeutic strategies targeting mVDR function, rather than vitamin D alone, may offer improved clinical potential.

## Abbreviations

25(OH)D, 25-hydroxyvitamin D; AD, Atopic dermatitis; NC, normal controls; VDR, vitamin D receptor; sVDR, soluble VDR; mVDR, membrane-bound VDR; nVDR, nuclear VDR; MFI, mean fluorescence intensity.

## Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Hunan Children's Hospital (approval code HCHLL-2024-264). Written informed consent was obtained from the parent/legal guardian of the patient before enrollment.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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