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Serum 25(OH)D concentrations are differentially associated with innate and adaptive immune cell markers, with threshold effects near 40 ng/mL: A cross-sectional study

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Highlights

- Nonlinear associations between vitamin D and immune cell subsets in healthy adults.
- Threshold effects at ~40 ng/mL for T cells and natural killer (NK) cells.
- High vitamin D (>40 ng/mL) suppresses T cells but boosts NK cells.
- Associations stronger in males and middle-aged (40-59 years) individuals.
- Higher vitamin D concentrations associated with distinct innate and adaptive immune profiles.

Abstract

The nonlinear relationship and threshold effects of vitamin D on immune function in healthy adults remain unclear. This cross-sectional study of 316 healthy adults (January 2022 to June 2023)



natural killer [NK] cells) quantified by flow cytometry. Restricted cubic spline and piecewise regression models evaluated nonlinear relationships and inflection points. Compared to the low 25(OH)D group (<28.45 ng/mL), the high group (>28.45 ng/mL) had higher NK cell counts (306.00 vs 272.50, $P < .01$) and percentages (15.52% vs 14.21%, $P < .01$), but lower CD3+ T cell percentage (69.99% vs 73.20%, $P < .01$). Multivariate regression confirmed that 25(OH)D was negatively associated with CD3+ T cell percentage ($\beta = -0.16$, $P < .001$), and positively with NK cell count ($\beta = 3.62$, $P = .002$) and NK cell percentage ($\beta = 0.16$, $P < .001$). Restricted cubic spline analyses revealed significant threshold effects, with inflection points at 40.94 ng/mL for CD3+ T cell percentage ($P = .003$), 37.86 ng/mL for NK cell count ($P = .005$), and 40.94 ng/mL for NK cell percentage ($P = .022$). Subgroup analyses showed stronger correlations in males and individuals 40 to 59 years of age ($P < .05$). Our findings suggest that vitamin D may exert threshold-dependent dual immunomodulatory effects—enhancing innate immunity (NK cells) while suppressing adaptive immune activation (CD3+ T cells). Higher 25(OH)D concentrations (around 40 ng/mL) were associated with distinct immune profiles in this healthy cohort. These associations may provide preliminary insights for future studies, although causal relationships cannot be inferred from this cross-sectional design.

Graphical abstract

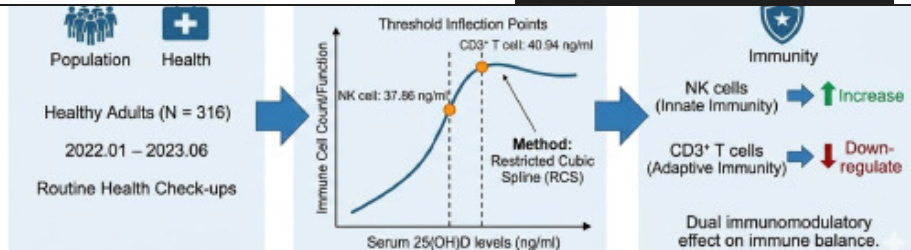
The graphical abstract illustrates the nonlinear associations between serum 25-hydroxyvitamin D (25(OH)D) concentrations and immune cell parameters in healthy adults ($N = 316$). It highlights the dual immunomodulatory effects of 25(OH)D: enhanced innate immunity (NK cells) and suppressed adaptive immunity (CD3+ T cells), with identified threshold inflection points at 37.86 and 40.94 ng/mL, respectively. These findings challenge traditional linear perspectives on vitamin D's immune effects. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; NK cells,



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Keywords

Vitamin D; Immune function; Threshold effects; NK cells; Adaptive immunity

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Introduction

Traditionally recognized as a fat-soluble secosteroid hormone, vitamin D (VitD) plays a pivotal role in calcium-phosphate homeostasis and skeletal mineralization [[1], [2], [3]]. Beyond its classical functions, emerging evidence has highlighted its critical immunomodulatory role. Epidemiological studies have repeatedly shown an association between VitD deficiency and an increased risk of cardiovascular disease, cancer, and autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and type 1 diabetes [2,4]. Furthermore, VitD supplementation appears to confer benefits by reducing the risk of tumors and autoimmune diseases [4].

Vitamin D modulates immune responses through a dual mechanism: it enhances innate immune system's rapid defense capabilities while simultaneously restraining the overactivation of adaptive immunity [5]. These effects are primarily mediated via the VitD receptor (VDR), which regulates multiple genes related to the immune system, including those involved in T-cell



deficiency and elevated concentrations of circulating inflammatory markers [7,8].

Whilst serum or plasma concentrations of 25-hydroxyvitamin D (25(OH)D) are commonly utilized to evaluate VitD status, with earlier guidelines from the National Academy of Medicine [9] and the Endocrine Society [10] categorizing concentrations as deficiency, insufficiency, and sufficiency, the most recent guidelines no longer advocate these fixed thresholds or their direct associations with specific health outcomes such as immune function [11].

In view of the heterogeneity observed within healthy populations, there is an increasing necessity for more individualized VitD management strategies. For instance, specific groups, including obese individuals and pregnant women, may necessitate elevated 25(OH)D concentrations to achieve a favorable reduction in the risk of adverse outcomes [[12], [13], [14]]. It is important to note that the immunomodulatory effects of VitD demonstrate a concentration-dependent threshold effect, and its association with various immune function indices appears to differ by cell type [15].

Despite advances in elucidating the mechanisms through which VitD influences both adaptive and innate immunity, high-quality evidence remains lacking regarding the clinical value of VitD monitoring and the optimal strategies for immune regulation in healthy individuals. In particular, further research is required to fully clarify the specific relationships and threshold effects between VitD concentrations and distinct immune cell subsets (e.g., those mediating adaptive vs innate responses).

The present study collected data on VitD concentrations and peripheral blood immune function from health check-up participants in order to investigate the associations, nonlinear relationships, and threshold effects between VitD and various immune indicators. The subsequent phase of the study involved the investigation of the potential modification of these associations by factors such as age and sex, with the objective of



formulated that serum 25(OH)D concentrations are nonlinearly associated with immune cell subsets, with distinct thresholds for innate and adaptive immunity. However, due to the cross-sectional design, it is not possible to draw causal inferences, and the observed associations should be interpreted as hypothesis-generating.

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Study participants

This cross-sectional study was conducted at the Medical Examination Centre of The First Affiliated Hospital of Chongqing Medical University. Data were retrospectively collected from 316 adults who underwent routine health check-ups between January 2022 and June 2023. To ensure the “healthy” status of the cohort, the following inclusion criteria were applied: (1) no self-reported history of chronic systemic diseases; (2) no history of malignant tumors; (3) no evidence of acute infections or ...



ng/mL), the high VitD group (>28.45 ng/mL) exhibited a significantly older age (48.50 vs 44.50 years), a higher proportion of males (65% vs 47%), and a higher body mass index (BMI) (24.50 vs 22.79). In addition, several immune function indicators differed significantly between the groups: participants in the high VitD group had higher NK cell counts (306.00 vs 272.50) ...

Threshold-dependent enhancement of innate immunity and suppression of adaptive immunity

This cross-sectional study of 316 healthy individuals revealed nonlinear relationships and threshold effects between serum 25(OH)D concentrations and distinct immune function parameters. Elevated 25(OH)D concentrations were found to be associated with increased NK cells percentages, as well as reduced CD3+ T lymphocyte percentages. The present findings are consistent with prior research indicating that VitD enhances innate immunity while suppressing adaptive immune overactivation [16]. ...

Conclusion

In summary, the present study demonstrates differential associations between 25(OH)D concentrations and innate (NK cells) vs adaptive (CD3+ T lymphocytes) immune markers, with threshold effects identified near 40 ng/mL. These cross-sectional findings suggest that higher VitD concentrations above this level were associated with enhanced innate immunity and reduced adaptive immune activation. Nevertheless, it is not possible to establish causal relationships. Future research may benefit from ...

Sources of support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. ...

Ethics approval and consent to participate



University (March 20, 2025/No. 2025-185-01). The requirement for obtaining informed consent from participants was waived because: (1) the study posed no more than minimal risk to participants; (2) the research could not practically be carried out without the waiver; and (3) the privacy and confidentiality of ...

Data availability

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

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT-3.5 for language editing and grammar improvement to enhance the manuscript's readability, and for assistance in designing the graphical abstract. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. ...

CRediT authorship contribution statement

Peng Lei: Writing – review & editing, Supervision, Methodology, Conceptualization. **Shaoyan Wu:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Rong Luo:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Binyang Tang:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Sicen Wu:** Validation, Resources, Investigation. ...

Author declarations

The authors declare no competing interests. ...

Acknowledgment

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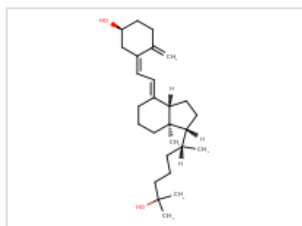
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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CYP27B1, cytochrome P450 family 27 subfamily B member 1; G1a, early G1 phase; G1b, late G1 phase; IL-13, interleukin-13; IL-17, interleukin-17; IL-2, interleukin-2; IL-21, interleukin-21; IL-4, interleukin-4; IL-5, interleukin-5; IL-9, interleukin-9; NK cells, natural killer cells; RCS, restricted cubic spline; Th1, T helper 1 cells; Th17, T helper 17 cells; Th2, T helper 2 cells; Tregs, regulatory T cells; VDR, vitamin D receptor; VitD, vitamin D.

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