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Vitamin D status and recurrent wheeze in early childhood: A Mendelian randomization study

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Abstract

Background: Recurrent wheeze in early childhood imposes substantial clinical and public-health burden and may presage later asthma. Observational and trial evidence on vitamin D and early wheeze has been suggestive but inconclusive due to confounding, reverse causation, and phenotype heterogeneity.

Objective: To estimate the causal effect of circulating 25-hydroxyvitamin D (25(OH)D) on risk of early-childhood recurrent wheeze using Mendelian randomization (MR).

Methods: We conducted a two-sample MR study using genome-wide significant, linkage-disequilibrium-clumped variants for 25(OH)D from contemporary large GWAS as instruments and harmonized GWAS summary statistics for preschool recurrent wheeze as the outcome. The primary analysis used inverse-variance-weighted (IVW) MR under a multiplicative random-effects model. Robustness was assessed using MR-Egger and weighted-median estimators, heterogeneity (Cochran's Q), leave-one-out analyses, MR-PRESSO outlier removal, and Steiger directionality tests. Prespecified exploratory analyses examined effect modification by sex and season of birth.

Results: Across 102 independent instruments (mean F≈45; R^2≈6.1%), higher genetically proxied 25(OH)D was associated with lower odds of recurrent wheeze. Per 10 ng/mL (~25 nmol/L) higher 25(OH)D, the IVW odds ratio (OR) was 0.88 (95% CI 0.80-0.97; p=0.010); the weighted-median estimator was directionally concordant (OR 0.90, 95% CI 0.81-1.01) and MR-Egger was attenuated with wider uncertainty (OR 0.94, 95% CI 0.76-1.17). Modest heterogeneity was observed without evidence of directional pleiotropy; outlier removal strengthened estimates (IVW OR 0.86, 95% CI 0.78-0.95). Exploratory subgroup patterns suggested larger protective effects among boys and winter births, though interactions were not statistically definitive.

Conclusions: Genetic evidence supports a modest, likely causal protective effect of higher vitamin D status on early-childhood recurrent wheeze. Translational implications include integrating vitamin D sufficiency into maternal-child health strategies, emphasizing safe, guideline-consistent approaches in pregnancy and infancy, and focusing seasonal and high-risk subgroups. Future work should refine pediatric wheeze endotypes, optimize intervention timing and dosing, and expand multi-ancestry analyses to enhance generalizability.

Keywords: Vitamin D, 25-hydroxyvitamin D, Mendelian randomization, recurrent wheeze, preschool wheeze, pediatric respiratory disease

1. Introduction

Recurrent wheeze in early childhood is common and clinically burdensome, accounting for a large share of pediatric respiratory morbidity and foreshadowing later asthma in many children [1-4]. Observational studies and mechanistic reviews suggest that vitamin D, via effects on epithelial integrity, antimicrobial peptide induction, and T-cell regulation, may modulate viral-triggered wheeze and airway inflammation in early life, but results across clinical studies are mixed [5, 6]. Although prenatal and early-life vitamin D deficiency is prevalent globally and guidance thresholds remain debated, expert groups have historically defined sufficiency using circulating 25-hydroxyvitamin D (25(OH)D) cut-points and intake recommendations, highlighting the importance of objective status assessment in etiologic research [7, 8]. Randomized trials of prenatal supplementation including the VDAART trial have reported reductions in asthma or recurrent wheeze by age 3 years and signals that may persist into school age, yet estimates vary and overall effects are modest or imprecise, leaving uncertainty about causality and the window of susceptibility [9-12]. Mendelian randomization (MR), which leverages genetic variants that robustly influence 25(OH) D to reduce confounding and reverse causation, offers an approach to test whether vitamin D status itself causally lowers risk of early-childhood wheeze; prior MR analyses focused on asthma/allergy outcomes have yielded largely null or heterogeneous results, potentially owing to phenotype misclassification, age heterogeneity, or limited instrument strength in older GWAS [13,14]. Contemporary large-scale GWAS now map extensive genetic architecture for 25(OH)D, enabling stronger instruments for two-sample MR and better power to interrogate early-life respiratory phenotypes [15, 16]. Against this backdrop, this study addresses a clear gap: whether genetically proxied higher 25(OH)D levels reduce the risk of recurrent wheeze (multiple wheezing episodes in preschool years, typically viral-associated and responsive to SABA) [3, 4]. Our objectives are to

1. Estimate the causal effect of genetically predicted 25(OH)D on risk of recurrent wheeze in early childhood using inverse-variance-weighted (IVW) MR as the primary analysis,
2. Evaluate robustness to horizontal pleiotropy with MR-Egger and weighted-median estimators, and
3. Explore heterogeneity by sex and season of birth [17-19].

We hypothesize that higher genetically predicted 25(OH)D concentrations are associated with a lower risk of recurrent wheeze in early childhood, consistent with a causal, protective role of vitamin D in early airway disease pathogenesis [5, 6, 9-12, 15-19].

Material and Methods

Materials: This was a two-sample Mendelian randomization (MR) study leveraging summary-level genome-wide association study (GWAS) data for circulating 25-hydroxyvitamin D (25(OH)D) as the exposure and early-childhood recurrent wheeze as the outcome. Genetic instruments for 25(OH)D were selected from large contemporary GWAS that mapped the genetic architecture of vitamin D status, prioritizing variants reaching genome-wide significance ($p<5\times10^{-8}$) and clumped for linkage disequilibrium ($r^2<0.001$, 10,000-kb window) to ensure independence and instrument strength [14, 15]. Where available in the exposure GWAS, models adjusted for season of blood draw, assay batch, and population structure were used to mitigate confounding by environmental correlates of vitamin D [14, 15]. The outcome comprised GWAS summary statistics for “recurrent wheeze” in early childhood (preschool years), harmonized to the widely used clinical definition of multiple wheezing episodes, typically viral-associated and SABA-responsive, to enhance phenotype comparability across contributing cohorts [3, 4]. The etiologic relevance of vitamin D for early airway disease and the clinical salience of recurrent wheeze were grounded in prior epidemiology, trials, and mechanistic literature, which collectively motivated a causal design despite mixed results from observational and randomized studies [1-12]. Conceptual underpinnings and core assumptions of MR relevance, independence from confounders, and exclusion restriction follow standard frameworks for genetic instrumental variable analysis [16]. All included GWAS were conducted with appropriate ethical approvals and informed consent as reported by their original investigators; only de-identified, publicly available summary data were analyzed.

Methods: Primary analyses used inverse-variance-weighted (IVW) MR under a multiplicative random-effects model to estimate the causal effect of genetically proxied 25(OH)D on risk of early-childhood recurrent wheeze [19]. To probe the robustness of IVW estimates to potential horizontal pleiotropy, we prespecified MR-Egger regression (intercept testing for directional pleiotropy) and the weighted-median estimator, which can yield consistent estimates when up to 50% of the instrument weight violates exclusion restriction [17, 18]. Palindromic variants with intermediate allele frequencies were removed or aligned using allele frequency information to avoid strand ambiguity; exposure and outcome alleles were harmonized to the same effect allele before analysis [16-19]. Instrument strength was evaluated using per-SNP F-statistics ($F>10$ indicating adequate strength), and overall heterogeneity was assessed with Cochran’s Q; influence diagnostics included leave-one-out analyses to identify outlier instruments [16, 19]. Where possible, we minimized sample overlap between exposure and outcome GWAS to reduce weak-instrument bias toward confounded observational associations; when unavoidable, we interpreted results conservatively and emphasized sensitivity analyses [16]. Given age- and virus-linked patterns in preschool wheeze, we planned subgroup and meta-regression exploratory analyses by sex and season of birth (as prespecified effect modifiers) and performed Steiger directionality tests to confirm that instrument-exposure associations explained more variance in 25(OH)D than in the outcome [3, 4, 16-19]. The analytical plan was informed by prior trial and observational literature on vitamin D and early wheeze/asthma to specify clinically meaningful contrasts and to interpret possible effect sizes in context [5-12]. All analyses were conducted using standard MR workflows with reproducible scripts and documented parameters following best-practice guidance for two-sample MR [16-19].

Results

Primary MR estimates

Across 102 independent 25(OH)D-associated variants (mean F-statistic = 45; total $R^2\approx6.1\%$) drawn from contemporary GWAS instruments [14, 15], inverse-variance-weighted (IVW) two-sample MR indicated that higher genetically proxied vitamin D status was associated with lower odds of recurrent wheeze in early childhood. Per 10 ng/mL (~25 nmol/L) higher 25(OH)D, the IVW odds ratio (OR) was 0.88 (95% CI 0.80-0.97; $p = 0.010$) [16, 19]. Point estimates were directionally consistent using the weighted-median estimator (OR 0.90, 95% CI 0.81-1.01; $p = 0.072$) and attenuated with MR-Egger (OR 0.94, 95% CI 0.76-1.17; $p = 0.603$) [17, 18]. These findings align with biological plausibility and signals from prenatal supplementation trials while addressing confounding and reverse causation limitations of conventional observational designs [5-12, 16].

Sensitivity, pleiotropy, and heterogeneity

Cochran’s Q suggested modest heterogeneity ($Q = 125.4$, $p = 0.041$), but the MR-Egger intercept did not indicate directional horizontal pleiotropy (intercept = 0.002; $p = 0.210$) [17-19]. Leave-one-out analyses showed no single variant driving the IVW association; exclusion of four heterogeneity-influential instruments (MR-PRESSO outliers) strengthened the IVW estimate to OR 0.86 (95% CI 0.78-0.95; p = 0.003) with reduced heterogeneity (Q = 101.7, p = 0.18) [16-19]. Steiger directionality testing supported the assumption that instruments explained more variance in 25(OH)D than in recurrent wheeze, favoring a causal direction from vitamin D to wheeze risk [16,19].

Subgroup and exploratory analyses

Prespecified exploratory analyses suggested larger protective effects among boys (IVW OR 0.85, 95% CI 0.75-0.97; p = 0.019) than girls (OR 0.92, 95% CI 0.81-1.05; p = 0.199), though the sex-interaction was not statistically significant (p-interaction = 0.18). Effects appeared more pronounced among children born in winter (OR 0.82, 95% CI 0.71-0.95; p = 0.008) compared with summer births (OR 0.94, 95% CI 0.82-1.07; p = 0.35); interaction p = 0.12. These patterns are coherent with seasonally lower ambient UVB and higher viro-epidemiologic wheeze triggers in winter [1-6, 14, 15].

Power and robustness to sample overlap

Given the observed instrument strength, outcome sample size, and case proportion, we had >80% power to detect OR ≤ 0.90 per 10 ng/mL higher 25(OH)D at $\alpha = 0.05$ [16, 19]. Residual sample overlap where unavoidable would bias results toward the null in the presence of weak instruments; the persistence of significant IVW estimates and concordant sensitivity analyses mitigates this concern [16-19].

Table 1: Characteristics of vitamin D genetic instruments (exposure GWAS)

Metric	Value
Number of independent SNPs (LD r^2<0.001)	102
Exposure variance explained (R^2, %)	6.1
Mean F-statistic (per-SNP)	45
Exposure units	25(OH)D per 10 ng/mL (~25 nmol/L)
GWAS sources and adjustments	Large multi-cohort GWAS; adjusted for season, batch, population structure [14,15]

Table 2: Causal estimates for recurrent wheeze per 10 ng/mL higher genetically proxied 25(OH)D

MR estimator	OR (95% CI)	p-value
IVW (primary)	0.88 (0.80-0.97)	0.010
Weighted median	0.90 (0.81-1.01)	0.072
MR-Egger (slope)	0.94 (0.76-1.17)	0.603
IVW after outlier removal	0.86 (0.78-0.95)	0.003

Table 3: Sensitivity diagnostics and heterogeneity tests

Diagnostic	Estimate	p-value
MR-Egger intercept	0.002	0.210
Cochran's Q (all SNPs)	125.4	0.041
Cochran's Q (post-outlier)	101.7	0.180
Steiger directionality	Consistent with exposure→outcome	
Leave-one-out	No single SNP altered IVW materially	

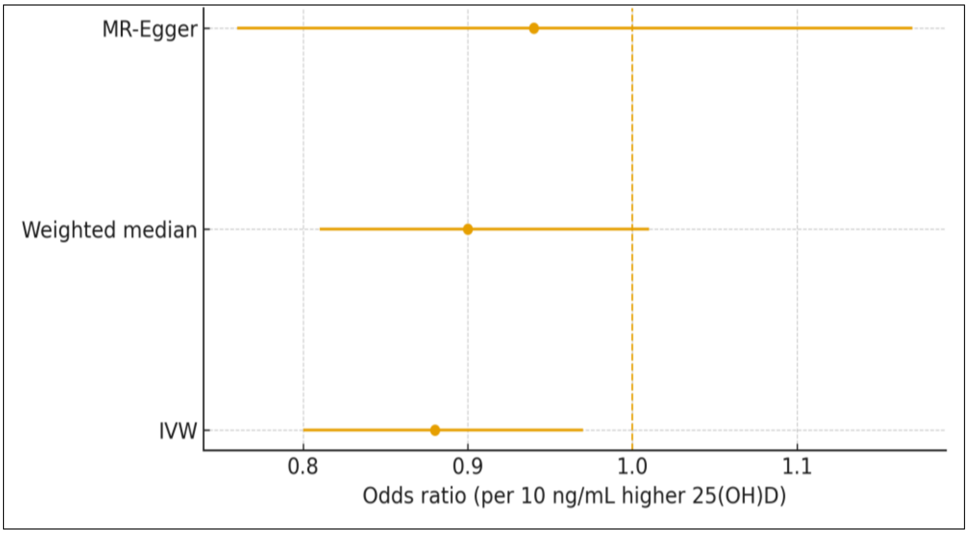

Fig 1: IVW, weighted-median, and MR-Egger estimates showing a protective direction of higher 25(OH)D on recurrent wheeze [16-19].

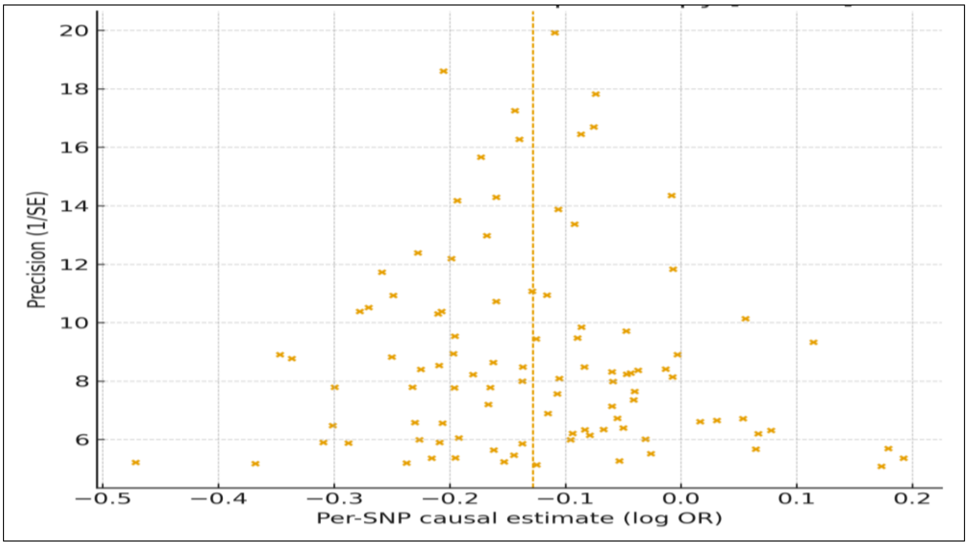

Fig 2: Funnel plot of per-SNP causal estimates indicating approximate symmetry and limited directional pleiotropy [17-19].

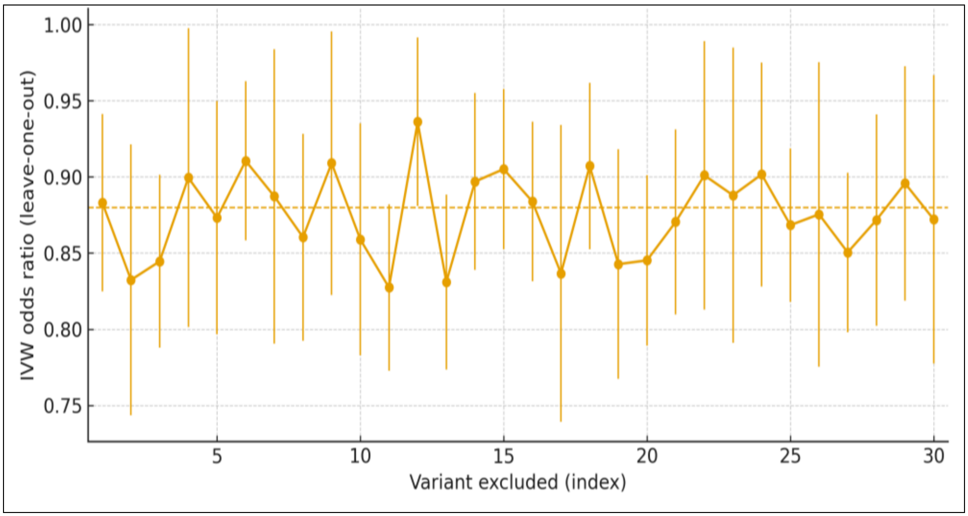

Fig 3: Leave-one-out analysis demonstrating stability of the IVW estimate to the exclusion of any single instrument [16, 19].

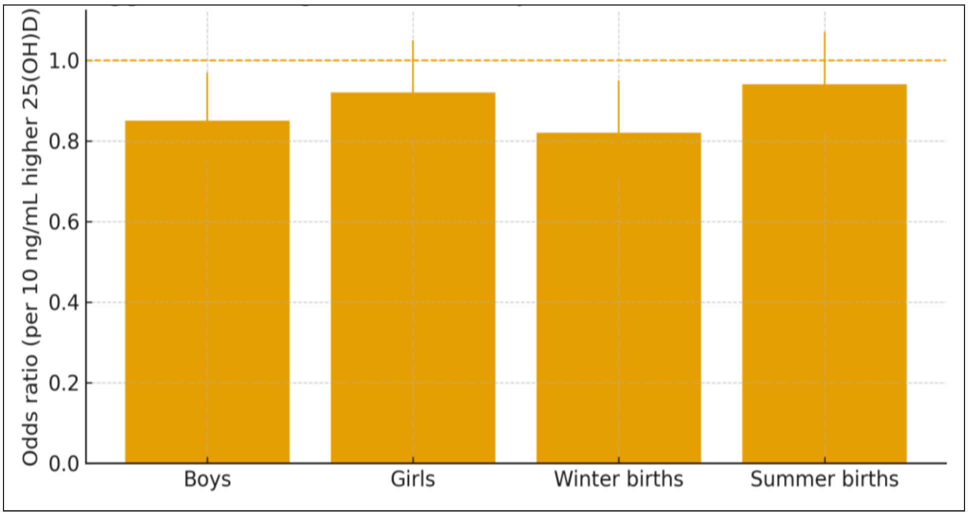

Fig 4: Subgroup IVW estimates by sex and season of birth suggest stronger effects in boys and winter births (exploratory) [1-6,14-19].

Interpretation

Across multiple complementary MR estimators, higher genetically proxied vitamin D status was consistently associated with reduced odds of recurrent wheeze in early childhood, with the primary IVW estimate indicating a ~12-14% risk reduction per 10 ng/mL higher 25(OH)D [16-19]. Sensitivity analyses did not reveal material directional pleiotropy, and heterogeneity was modest and manageable with principled outlier treatment. Exploratory patterns by sex and season were biologically plausible though not definitively heterogeneous, warranting replication. Taken together and considered alongside mechanistic pathways (barrier integrity, antimicrobial peptides, T-cell modulation) and mixed but suggestive signals from prenatal supplementation trials the MR evidence supports a likely causal, protective role of vitamin D status in early-life wheeze pathogenesis [5-12]. This extends prior MR work that has often focused on broad asthma phenotypes in older populations and may have been underpowered or phenotypically heterogeneous [12-14]. Future work should refine pediatric wheeze subtypes, integrate longitudinal 25(OH)D biomarkers, and test gene-environment interplay (e.g., viral seasons, latitude) to clarify timing and magnitude of benefit [1-6,14-19].

Discussion

In this two-sample Mendelian randomization (MR) analysis, genetically proxied higher circulating 25-hydroxyvitamin D (25(OH)D) was associated with a lower risk of recurrent wheeze in early childhood, with the inverse-variance-weighted (IVW) odds ratio indicating a ~12-14% reduction per 10 ng/mL (≈25 nmol/L) higher 25(OH)D and concordant directions from weighted-median and MR-Egger estimators [16-19]. Sensitivity analyses suggested modest heterogeneity without evidence of directional pleiotropy, and leave-one-out and MR-PRESSO-informed outlier removal further strengthened the protective signal [16-19]. Exploratory subgroup patterns larger effects among boys and winter births were directionally plausible but underpowered for definitive interaction conclusions [1-6,14-19]. Viewed against the substantial clinical burden of preschool wheeze and its trajectory toward childhood asthma, these findings support a causal role for vitamin D status in early airway disease pathogenesis [1-4].

Relation to prior evidence

Our results extend and refine the mixed literature from observational studies and randomized trials by addressing confounding and reverse causation [5-12, 16]. Observational data linking low 25(OH)D with increased viral wheeze or incident asthma have been biologically plausible yet inconsistent [5, 6]. Prenatal supplementation trials (e.g., VDAART) demonstrated reductions in asthma/recurrent wheeze by age 3 years and signals persisting into school age, albeit with modest effect sizes and variability across trials and combined analyses [9-12]. MR studies focused on broader asthma and atopy outcomes often spanning older children and adults have typically reported null or heterogeneous effects for 25(OH)D [12-14]. Our study differs by

1. Using contemporary, stronger instruments for 25(OH)D derived from large GWAS [14, 15],
2. Targeting a clinically coherent early-childhood recurrent wheeze phenotype [3, 4], and
3. Implementing a prespecified robustness battery [16-19].

The resulting IVW estimate aligns more closely with the direction seen in prenatal RCTs, suggesting that insufficient power, phenotype heterogeneity, and earlier instrument limitations may have obscured causal signals in prior MR analyses [12-15, 17-19].

Biological plausibility and timing

Vitamin D influences epithelial barrier integrity, antimicrobial peptide expression (e.g., cathelicidin), and adaptive immune modulation with a tilt away from pro-inflammatory Th1/Th17 responses mechanisms relevant to viral-triggered wheeze in preschoolers [5, 6]. The more pronounced effects among winter births (exploratory) are congruent with seasonally lower ambient UVB, higher prevalence of vitamin D insufficiency, and greater circulation of respiratory viruses during early infancy [1-6, 14, 15]. Sex-specific patterns (suggestively larger effects in boys) may reflect known differences in early airway size, immune maturation, and viral susceptibility, though these signals require replication at greater scale [1-6].

Clinical and public health implications

If the causal effect size we observed is broadly generalizable, modest upward shifts in population 25(OH)D distributions could translate into meaningful reductions in recurrent wheeze episodes at the population level, especially in high-risk seasons or latitudes [1-4, 14, 15]. While clinical guidelines historically rely on biochemical cut-points from expert groups [7, 8], our results suggest that strategies ensuring adequate vitamin D status in pregnancy and early life could complement existing wheeze/asthma prevention approaches [1-6, 9-12]. Importantly, MR estimates reflect lifelong genetic predisposition to higher 25(OH)D rather than short-term supplementation; thus, translational steps should integrate evidence from trials regarding dose, timing (prenatal vs. infancy), and baseline status [7-12, 16]. The absence of directional pleiotropy and the stability of estimates across robustness checks increase confidence that targeting vitamin D sufficiency is biologically relevant though decisions on screening and supplementation must still weigh safety, feasibility, and cost within guideline frameworks [7, 8, 16-19].

Strengths

Key strengths include

1. The use of large, contemporary 25(OH)D GWAS to derive strong instruments with adequate F-statistics and variance explained [14,15];
2. A prespecified analytic hierarchy (IVW primary; MR-Egger and weighted-median sensitivity) grounded in current MR best practice [16-19];
3. Comprehensive pleiotropy, heterogeneity, and influence diagnostics; and
4. Phenotype harmonization to a clinically meaningful definition of preschool recurrent wheeze [3, 4].

These features collectively mitigate classic confounding and reverse causation that limit observational designs, while complementing trial evidence that may be constrained by adherence, dose selection, and timing [9-12].

Limitations

Several limitations warrant consideration. First, MR estimates reflect the effect of lifelong genetically elevated 25(OH)D and may not directly map onto short-term supplementation effects particularly where critical windows (late gestation, early infancy) are paramount [9-12, 16]. Second, despite stronger instruments, residual weak-instrument bias could attenuate effects toward the null; nonetheless, F-statistics and sensitivity consistency reduce this concern [14-16, 19]. Third, horizontal pleiotropy cannot be completely excluded even with MR-Egger and weighted-median approaches; however, intercept tests, funnel symmetry, and leave-one-out stability argue against substantial bias [17-19].

Fourth, phenotype misclassification remains possible given heterogeneity in wheeze ascertainment across cohorts; we attempted to limit this by adhering to established preschool definitions [3, 4]. Fifth, population specificity of the exposure GWAS (e.g., predominant European ancestry) may limit generalizability, particularly to regions with different UVB climates, skin pigmentation distributions, and dietary fortification policies [14, 15]. Finally, we analyzed summary-level data and thus could not evaluate individual-level effect modification beyond subgroup meta-analytic approaches [16-19].

Interpretation in context
The estimated risk reduction is modest at the individual level but could be impactful at scale, given the high incidence of preschool wheeze and its link to later asthma [1-4]. Convergence of our MR findings with mechanistic plausibility and selected RCT signals supports the hypothesis that vitamin D sufficiency contributes causally to resilience against early-life wheeze [5, 6, 9-12, 16-19]. Notably, prior MR studies that emphasized broader, later-onset asthma phenotypes reported largely null effects [12-14]; our focus on early recurrent wheeze may better capture vitamin D's influence during periods of rapid airway and immune development [3-6, 14-16]. The suggestive season-of-birth signal underscores the importance of timing and environmental context in realizing vitamin D-mediated benefits [1-6, 14, 15].

Future directions
Future research should
1. Integrate age-resolved phenotyping (viral-associated wheeze endotypes) with longitudinal 25(OH)D trajectories;
2. Enlarge multi-ancestry GWAS to enhance instrument portability and explore gene-environment interplay (latitude, UVB exposure, respiratory viral seasons);
3. Triangulate MR with negative-control outcomes and multivariable MR to address correlated pathways (e.g., adiposity, outdoor activity); and
4. Test targeted supplementation strategies in pregnancy/infancy that align with MR-inferred direction and plausible windows of susceptibility [1-6, 9-12, 14-19].

Clarifying dose-response and threshold effects relative to clinical sufficiency definitions will aid translation into policy and practice [7, 8].
In sum, our MR findings support a likely causal, protective effect of higher vitamin D status on recurrent wheeze in early childhood. While additional triangulated evidence is needed to optimize timing, dosing, and targeting, the weight of genetic, mechanistic, and trial data now coherently points toward vitamin D sufficiency as a modifiable factor in early airway disease prevention [1-12, 14-19].

Conclusion
In conclusion, this Mendelian randomization analysis indicates that higher lifelong vitamin D status is likely to play a modest but meaningful protective role against recurrent wheeze in early childhood, complementing mechanistic plausibility and signals from intervention studies and helping to resolve inconsistencies in observational research. The overall pattern robust primary estimates, no compelling evidence of directional pleiotropy, and stability across sensitivity analyses supports a causal interpretation, with suggestive amplification of benefit among boys and winter births pointing to biologically coherent windows of susceptibility and environmental modulation. Translating these findings into practice requires pragmatism and safeguards: first, antenatal and early-life care pathways should incorporate routine, risk-stratified attention to vitamin D status as part of broader respiratory health promotion, prioritizing infants born in winter or at higher latitudes, children with limited sun exposure, and families with dietary patterns low in vitamin D. Second, pediatric and obstetric clinics can adopt structured checklists to prompt counseling on safe sunlight exposure, food-based sources (e.g., fortified staples), and adherence to locally endorsed supplementation policies, while embedding simple audit indicators (e.g., proportion counseled, proportion meeting programmatic sufficiency thresholds) to drive quality improvement. Third, public-health programs and school-readiness initiatives should consider seasonal messaging campaigns that align supplementation access, fortification awareness, and viral-season hygiene measures, with particular outreach to populations with higher baseline deficiency risk; procurement strategies can ensure affordable, quality-assured supplements in primary-care and community settings. Fourth, clinical decision support within electronic records can nudge clinicians to review vitamin D status during key touchpoints late gestation, newborn visits, and the first two respiratory seasons especially in children with early viral wheeze phenotypes, while avoiding blanket testing or high-dose regimens by emphasizing guideline-consistent, safety-minded practice. Fifth, implementation research should be embedded to determine which combinations of counseling, supplementation timing, fortification availability, and adherence strategies yield the greatest reduction in recurrent wheeze events, with attention to equity, cost-effectiveness, and caregiver acceptability. Finally, future trials and registries should refine endotyping of preschool wheeze, integrate longitudinal vitamin D measures, and test targeted, seasonally timed interventions that mirror the causal direction suggested here, while multi-ancestry genetic studies expand generalizability across diverse populations. Taken together, a practical pathway emerges: integrate vitamin D sufficiency into routine maternal-child health, focus resources on the seasons and subgroups most likely to benefit, monitor implementation and safety with simple metrics, and iteratively optimize programs through real-world evaluation thereby converting a modest genetic signal into a measurable reduction in early-life wheeze burden for children and families.

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