Optimising vitamin D status in children with pre-school wheeze or asthma: a pilot study (OptiVit)

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What is wheeze?

A high-pitched continuous sound produced during expiration due to narrowing of the smaller airways.

Narrowed small airway

Normal small airway
## Wheezing illness in children

### Pre-school wheeze vs. Asthma

<table>
<thead>
<tr>
<th></th>
<th>Pre-school wheeze</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>≤ 5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td><strong>Prevalence, %</strong></td>
<td>25 – 38</td>
<td>21 – 27</td>
</tr>
<tr>
<td><strong>Precipitant of acute symptoms</strong></td>
<td>Respiratory syncytial virus (41.5 %)</td>
<td>Human rhinovirus (73 %)</td>
</tr>
</tbody>
</table>

Vitamin D for the management of asthma (Review)


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castro 2014</td>
<td>-1.194</td>
<td>0.5806</td>
<td>201</td>
<td>207</td>
<td>38.6%</td>
<td>0.30 [0.10, 0.95]</td>
</tr>
<tr>
<td>Jensen 2016</td>
<td>0</td>
<td>0.8864</td>
<td>11</td>
<td>11</td>
<td>16.8%</td>
<td>1.00 [0.18, 5.68]</td>
</tr>
<tr>
<td>Majak 2009 (1)</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>18</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Majak 2011 (2)</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>24</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Martineau 2015</td>
<td>-0.9671</td>
<td>0.6058</td>
<td>125</td>
<td>125</td>
<td>35.4%</td>
<td>0.38 [0.12, 1.25]</td>
</tr>
<tr>
<td>Tachimoto 2016</td>
<td>-1.6032</td>
<td>1.1762</td>
<td>54</td>
<td>35</td>
<td>9.4%</td>
<td>0.20 [0.02, 2.02]</td>
</tr>
<tr>
<td>Urashima 2010 (3)</td>
<td>0</td>
<td>1.1787</td>
<td>51</td>
<td>59</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>484</td>
<td>479</td>
<td>100.0%</td>
<td><strong>0.39 [0.19, 0.78]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 1.63, df = 3 (P = 0.65); I² = 0%

Test for overall effect: Z = 2.65 (P = 0.008)

Footnotes:
(1) No events in either arm
(2) No events in either arm
(3) No events in either arm
7-dehydrocholesterol → Vitamin D

Vitamin D → 25(OH)D

25(OH)D → CYP27B1

CYP27B1 → 1,25(OH)₂D

1,25(OH)₂D → inflammatory responses

1,25(OH)₂D → ↑ antiviral responses
Research gaps

- Limited number of trials in children
- Missing data on plasma 25(OH)D in some paediatric studies (Yadav and Mittal 2014, Indian J Pediatr)
- Failure to attain optimal 25(OH)D in others (Majak et al. 2011, J Allergy Clin Immunol; Lewis et al. 2012, Ann Allergy Asthma Immunol)
- Most effective dosing regimen in optimising 25(OH)D in children with wheezing illness is unknown
- 400 IU/day recommended by Department of Health may not be sufficient to attain 25(OH)D >75 nmol/L
The OptiVit study design

**Visit 1 – Screening:** 40 children with recent attacks of pre-school wheeze or asthma

Assessment of 25(OH)D and concentration of inflammatory mediators in nasal epithelial lining fluid

Exclude if 25(OH)D > 75nmol/L

**Visit 2:** 400 IU vitamin D₃ p.o. for 3 months

**Visit 3:** Assessment of 25(OH)D and concentration of inflammatory mediators in nasal epithelial lining fluid

1,000 IU vitamin D₃ p.o. for further 3 months if 25(OH)D concentration <150 nmol/L

**Visit 4 – Final study:** Assessment of 25(OH)D and concentration of inflammatory mediators in nasal epithelial lining fluid
25(OH)D results by study visit to date

25(OH)D by study visit in pre-school wheezers

25(OH)D by study visit in children with asthma

Target 25(OH)D
Why didn’t 25(OH)D levels go up?

- Poor adherence
- Alternative explanation: dysregulated vitamin D metabolism associated with chronic airway inflammation
- Asthma associated with airway inflammation \(^{(Pelaia \text{ et al.} \ 2015, \ Mediators \ Inflamm.)}\)
- In other clinical contexts, inflammation is associated with increased activity of enzymes responsible for synthesis and degradation of 1,25(OH)\(_2\)D \(^{(Wobke \text{ et al.} \ 2014, \ Front \ Physiol.)}\)
7-dehydrocholesterol $\rightarrow$ Vitamin D $\leftarrow$ 24R,25(OH)$_2$D

$\downarrow$ 25(OH)D $\rightarrow$ 1,25(OH)$_2$D $\rightarrow$ CYP24A1 activity

↓ CYP27B1 $\rightarrow$ 24R,25(OH)$_2$D

Airway Inflammation
Hypothesis

Cholecalciferol

24R,25(OH)₂D

Asthma

25(OH)D

4β,25(OH)₂D₃

1,25(OH)₂D₃

Asthma
Post-supplementation 25(OH)D by disease status

- **Asthma**: 108 participants
- **COPD**: 98 participants
- **Healthy controls**: 21 participants

Statistical significance:
- p = 0.002 (between Asthma and COPD)
- p < 0.0001 (between Asthma and Healthy controls)
Adjusted post-supplementation 25(OH)D by disease status

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
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<tr>
<td><strong>Mean 25(OH)D nmol/L</strong></td>
<td><strong>SD</strong></td>
<td><strong>Mean difference</strong></td>
</tr>
<tr>
<td>86.4</td>
<td>28.0</td>
<td>-16.9</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, BMI, smoking status, vitamin D supplementation, ethnicity, and baseline 25(OH)D concentration
Vitamin D metabolite: parent ratios by disease status

A

B

C

D

P = 0.001
P < 0.001
P = 0.004
P = 0.001
P = 0.001
P = 0.001
P = 0.001
P = 0.001
P = 0.26
P = 0.48
P = 0.14
P = 0.93
Summary

- Neither dose investigated was effective in elevating 25(OH)D concentration into the optimal range
- Patients with asthma have blunted 25(OH)D response to vitamin D supplementation, as compared with healthy controls
- This is associated with decreased 25-hydroxylase activity, and increased 1-alpha hydroxylase activity
- No difference in activity of 24-hydroxylase and 4β-hydroxylase by disease status
- **Implication**: patients with inflammatory airway disease may need more generous doses of vitamin D supplements than healthy controls in order to achieve optimal vitamin D status
Acknowledgments

All study participants and their parents!

Professor Adrian Martineau
Professor Chris Griffiths
Professor Andy Bush
Dr. David Jolliffe
Parent vitamin D and hydroxylated metabolites by disease status

A

\[ \text{P} = 0.74 \]

\[ \text{P} = 0.74 \]

B

\[ \text{P} = 0.83 \]

\[ \text{P} = 0.008 \]

C

\[ \text{P} = 0.002 \]

\[ \text{P} = 0.004 \]