

# A good wheeze: the story of Cochrane Airways asthma reviews

**A presentation to:**  
**Population Health Research Institute**  
09 May 2017

**Trusted evidence.**  
**Informed decisions.**  
**Better health.**



# Topic selection

2010 Asthma Partnership project

BTS/SIGN guidelines

Speak to people

Patient workshop



# PPI

18 attendees

Professional facilitators

1. What do you do when you have an asthma attack
2. Problems/issues with regular inhaler
3. Asthma control

Survey online

“Asthma can take over your life but having the right support makes that easier to deal with.” Informing research priorities by exploring the barriers and facilitators to asthma control: a qualitative analysis of survey data, Normansell R, Welsh E, Asthma Research and Practice 2015;11, DOI: 10.1186/s40733-015-0011-5



# Asthma management

**Asthma education for school staff**

**Cognitive behavioural therapy (CBT) for adults and adolescents with asthma**

Home telemonitoring and remote feedback between clinic visits for asthma

Interventions to improve adherence to inhaled steroids for asthma

Interventions to improve inhaler technique for people with asthma

**Lay-led and peer support interventions for adolescents with asthma**

**Patient- and parent-initiated oral steroids for asthma exacerbations**

**Personalised asthma action plans for adults with asthma**

**Pulse oximeters to self monitor oxygen saturation levels as part of a personalised asthma action plan for people with asthma**

**Remote versus face-to-face check-ups for asthma**

**Shared decision-making for people with asthma**

# Asthma therapies

Different oral corticosteroid regimens for acute asthma

Gastro-oesophageal reflux treatment for asthma in adults and children

Increased versus stable doses of ICS for exacerbations of chronic asthma in adults and children

LAMA added to LABA/ICS versus LABA/ICS for adults with asthma

LAMA added to ICS versus addition of LABA for adults with asthma

LAMA added to ICS versus higher dose ICS for adults with asthma

LAMA added to ICS versus the same dose of ICS alone for adults with asthma

## **Stepping down the dose of inhaled corticosteroids for adults with asthma**

Stopping LABA for adults with asthma well controlled by LABA and ICS

Stopping LABA for children with asthma well controlled on LABA and ICS

Sublingual immunotherapy for asthma

Vitamin D for the management of asthma

# Asthma monitoring

Exhaled nitric oxide levels to guide treatment for adults with asthma

Exhaled nitric oxide levels to guide treatment for children with asthma



# Vital statistics

1 patient workshop

25 reviews

48 authors

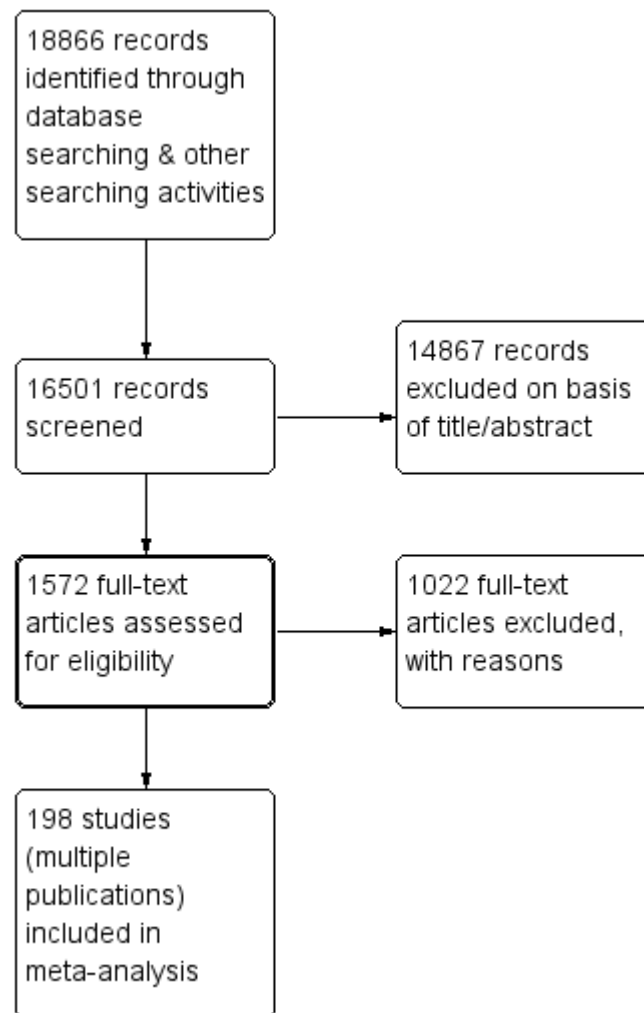
72 peer reviewers

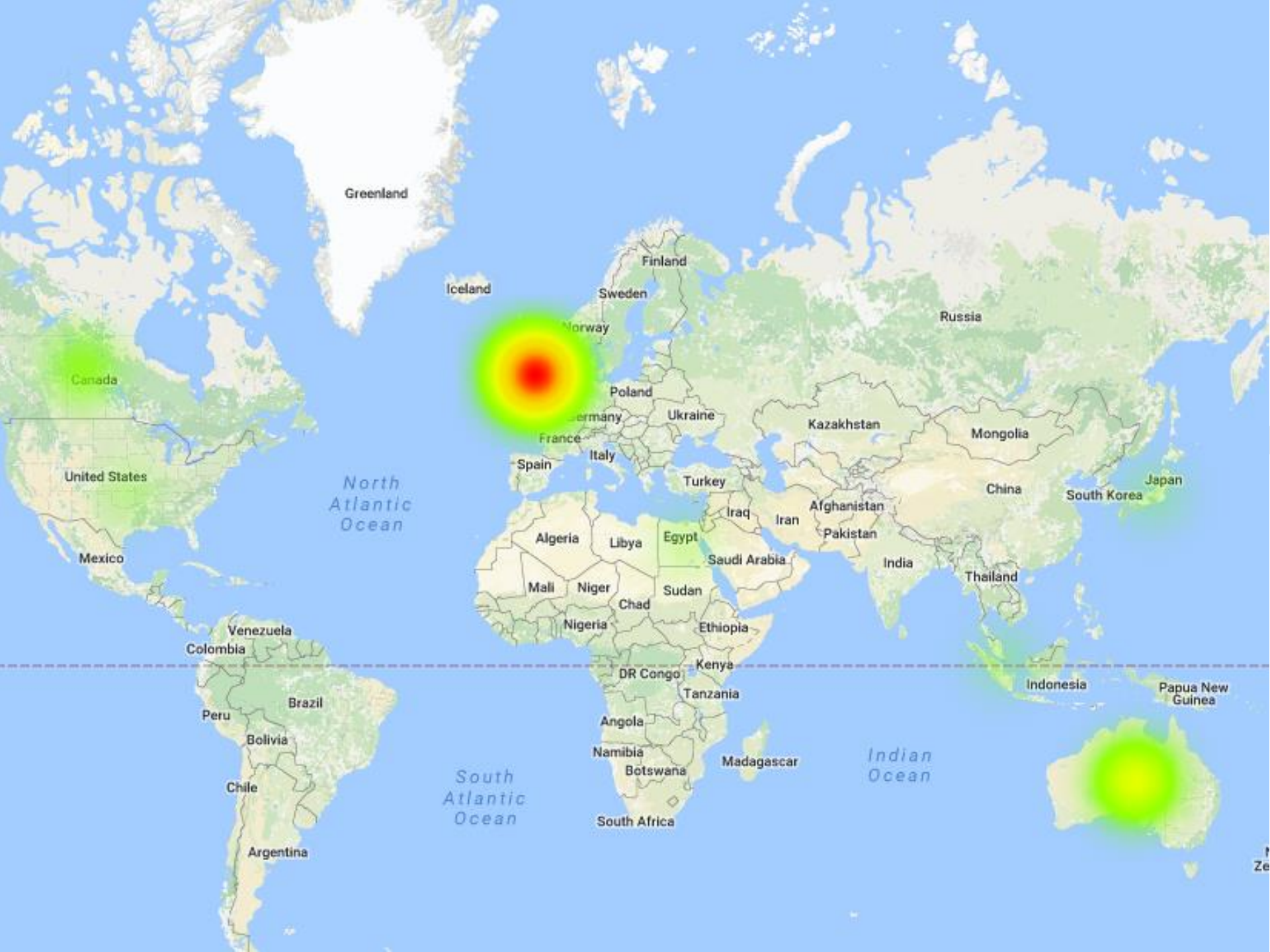
285 included studies

16 translations of 11 papers

334 meta-analyses

557,983 words







# Timescale

Draft protocol: 2.0 months

Publish protocol: 3.2 months

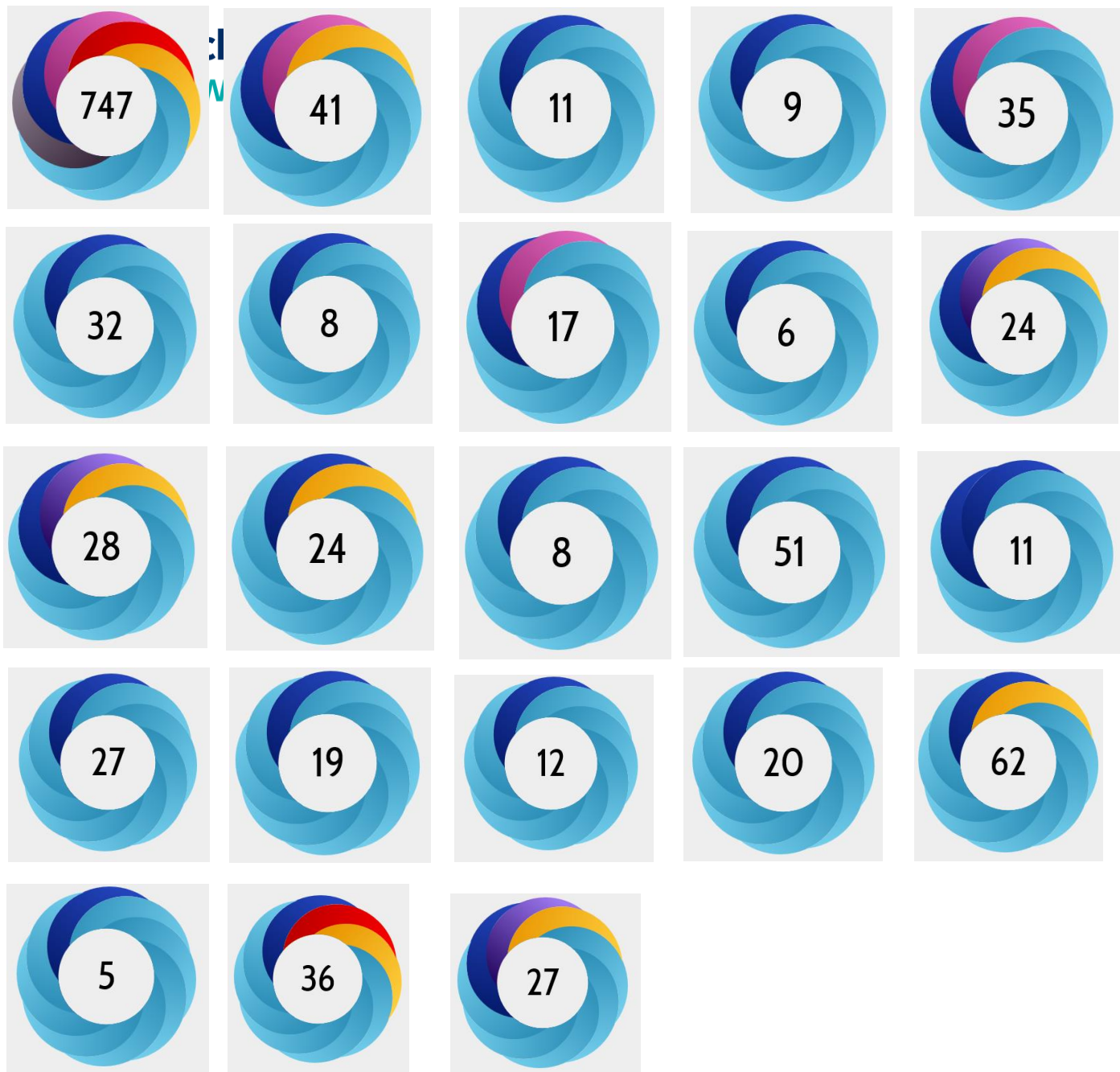
Draft Review: 7.3 months

Publish review: 4.2 months

Title registered to review published: 14.6 months







# Vitamin D for asthma:

**Funding:** This study was supported by a grant from the National Institute for Health Research (NIHR) under its Health Technology Assessment programme (reference No 13/03/25, to ARM). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. See the supplementary material for details of sources of support for individual investigators and trials. The NIHR was not involved in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.



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**NHS NIHR** **NIHR Dissemination** @NIHR\_DC · Mar 10

Half as many people attended hospital for [#asthma](#) treatment each year when taking [#vitaminD](#)



**Vitamin D supplements can reduce risk of asthm...**

People with mild to moderate asthma experience fewer severe asthma attacks if they take vitamin D supplements. This review found that the average n...

[discover.dc.nihr.ac.uk](https://discover.dc.nihr.ac.uk)

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**Cochrane UK** @CochraneUK · Mar 30

Listen up!

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Podcast: Do injectable pneumococcal vaccines prevent pneumonia in people with COPD? [#CochraneEvidence](#) [#COPD](#)

**CochraneAirways** @CochraneAirways · Apr 18

What can your school do to prepare teachers to help in an asthma attack? [bit.ly/2oa7TTN](#) @TeacherToolkit @lookwhatjendid @tomwhitby



**Could teaching teachers about asthma save lives? - Evidently Co...**

GP Dr Robin Carr discusses Cochrane evidence on whether asthma education for school staff could improve the care of children with asthma...

[evidentlycochrane.net](https://evidentlycochrane.net)

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**MathioudakisAG** @MathioudakisAG · Apr 1

Interventions to improve inhaler technique for people with [#asthma](#) [@CochraneAirways](#). [bit.ly/2mOiesB](https://bit.ly/2mOiesB)



**CochraneAirways** @CochraneAirways · Apr 18

39 RCTs involving over 16,000 adults&children w/asthma. F-up median 6 months Most studies reported adherence to ICS

**Interventions to improve adherence to inhaled s...**

**CochraneAirways** @CochraneAirways · Mar 20

Guidelines recommend clinicians check patients' inhaler technique regularly - what is not clear is how to help & what impact will be achieved

6 4

**CochraneAirways** @CochraneAirways · Apr 19

Weak evidence suggests lay-led&peer support interventions could lead to small improvement in asthma-related quality of life for teens...1/2

6 4





*In this blog, GP Dr Robin Carr discusses the latest Cochrane evidence on whether teaching staff could improve the care of children with asthma in schools and reduce asthma deaths.*

“You can’t be serious, kids still die of asthma in your country?” my shocked friend said.

I remember as a GP when I first arrived in Somerset that they were still talking about asthma deaths some years earlier. At that stage, the number of asthma deaths was about 2000 per year.

## Preventing asthma deaths

The overall deaths from asthma have come down in the last 30 years but it still remains a real alarm that we all read [The National Review of Asthma Deaths \(NRAD\) report](#) on as it highlights the added risks in low-income, minority and ethnic groups for increased asthma mortality.

The most shocking of all were the numbers of children who had died from asthma. Many of these, if they had been helped, could have prevented their deaths. Most of them had not received an asthma action plan.

There were a number of simple contributions that could have been made by the primary and secondary care. The simplest of these was a Personalised Asthma Action Plan. Primary care and schools had a significant part to play in this great responsibility and an opportunity.

Having witnessed many asthma attacks in adults and children, I can promise you that if a child was as this would inevitably be spotted by the parents or child and make the situation exactly what to do and had the kit to do it, it was still alarming. I can only imagine the panic of a parent, as a teacher of an asthmatic child, when faced with a possible life threatening situation to avoid this position and may even have considered their role as a teacher, if they

## Finding out if teaching staff about asthma

## Asthma in schools: Could teaching teachers save lives?



Are long-acting muscarinic antagonists (LAMAs) effective in adults with poorly controlled asthma?

BY LYNDIA WARE MARCH 24, 2016 // 0 COMMENTS

TWEET SHARE

# Evidently Cochrane

Sharing health evidence you can trust

*A blog for clinicians written by Lynda Ware, giving an overview of care.*

In the UK 5.4 million people are receiving treatment for asthma, or, put another way, about 3 people every day. In addition, the NHS is around £1 billion pounds per year. All this is happening

Long-acting muscarinic antagonists (LAMAs) are known to be effective in obstructive pulmonary disease and this suite of four Cochrane reviews considers whether they have a role in asthma management. LAMAs are an add-on therapy in the BTS/SIGN October 2014 guidelines for the management of asthma in adults, despite Spiriva (tiotropium) not having a licence for the treatment of severe asthma in September 2014.

## What did the Cochrane review

The reviews looked at trials in which LAMAs were added to existing

The comparisons were:

- LAMA + ICS *versus* same dose ICS
- LAMA + ICS *versus* higher dose ICS
- LAMA + ICS *versus* LABA + ICS
- LAMA + LABA/ICS *versus* LABA/ICS

where LAMA = long-acting muscarinic antagonist; ICS = inhaled

## What were the outcomes?

The primary outcomes across all the reviews were:

- exacerbations requiring oral corticosteroids
- asthma-related quality of life



# Preventing and treating asthma attacks

Four reviews:

- Sublingual immunotherapy
- Improve adherence to inhaled steroids
- Improving inhaler technique
- Finding the right dose of oral steroids



# Sublingual immunotherapy for asthma



# Sublingual immunotherapy for asthma

52 studies included, randomly assigning 5,077 participants to SLIT or control

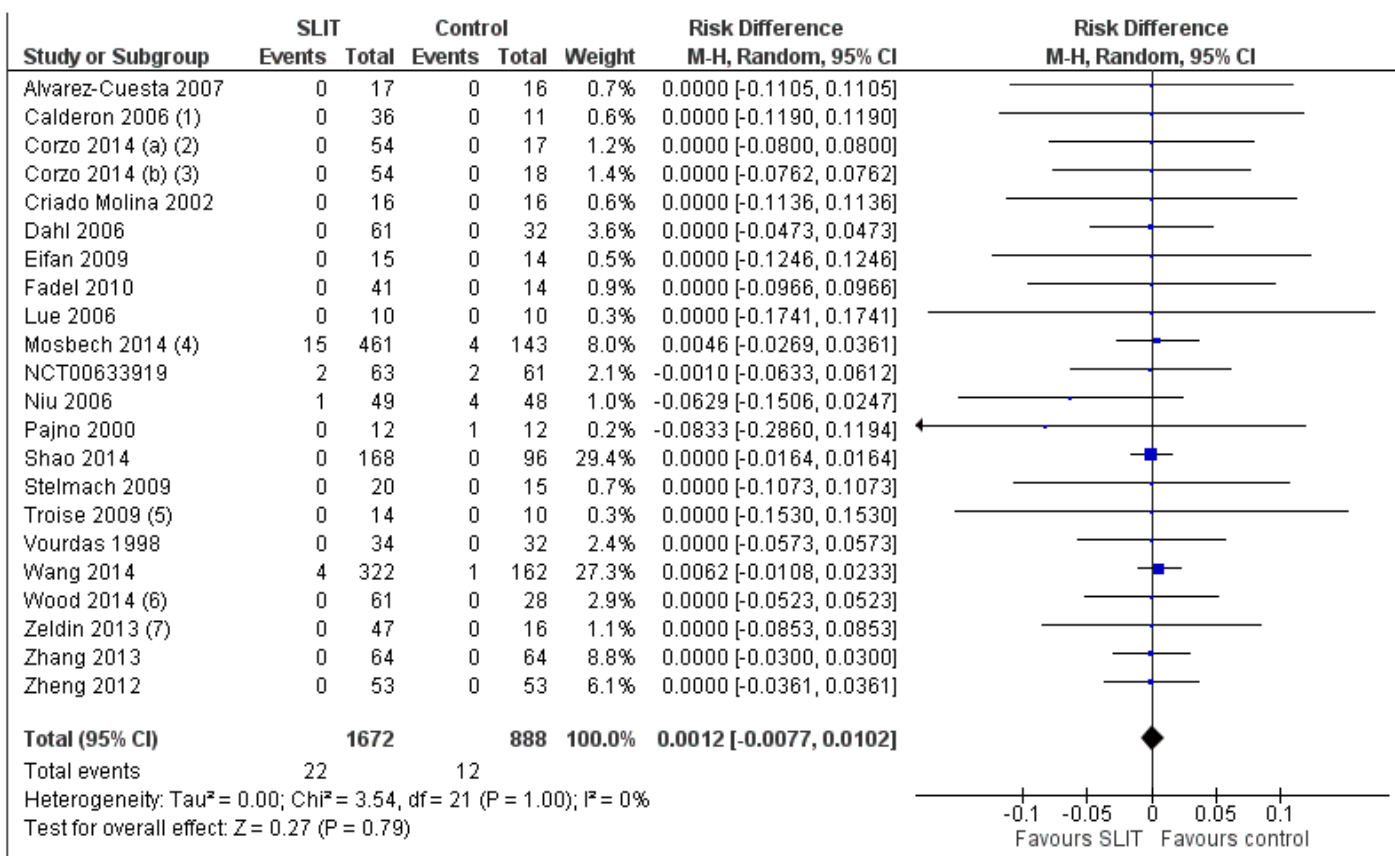
Many different target allergens e.g. HDM, various pollens, cat dander, cockroach

Duration one day to three years

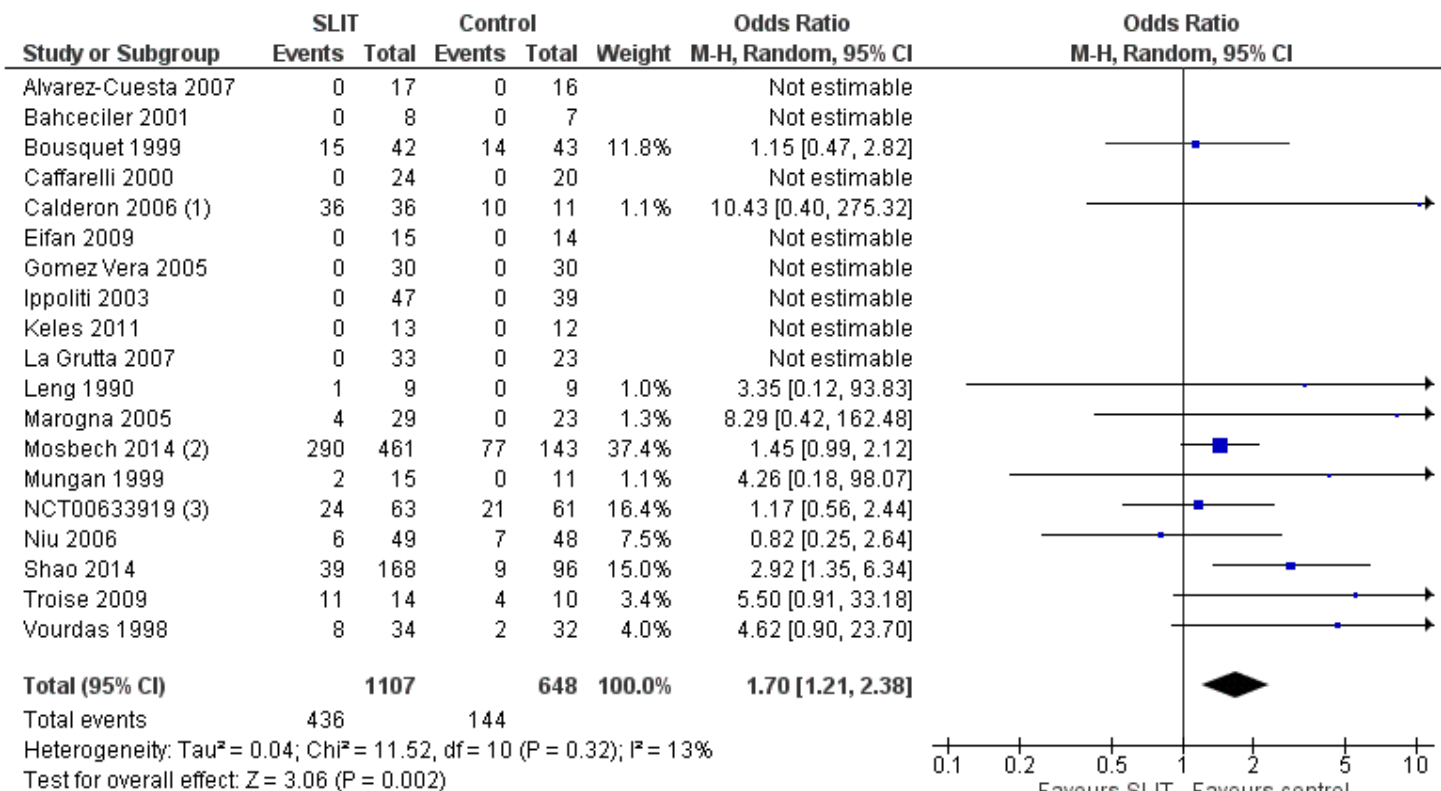
Largest study 834 participants, and the smallest 15



# Sublingual immunotherapy for asthma



# Sublingual immunotherapy for asthma



# Sublingual immunotherapy for asthma

## Bottom line

- Insufficient evidence of efficacy *for asthma*
- Other SRs seem more promising – but included meta-analyses with composite symptom scores and heterogeneity extremely high
- Validated tools such as AQLQ and ACT/ACQ would help
- Appears free from *serious* adverse effects in a mild-moderate asthma population
- Efficacy for allergic rhinitis more conclusive so may not be contraindicated in people with co-morbid asthma



# Improving adherence and inhaler technique



# Improving adherence and inhaler technique

Included RCTs assessing any adherence or inhaler technique intervention vs a control

Both adults and children

Separate comparisons for different types of intervention e.g. education, technology.

Adherence review included 39 studies and 16,303 participants

Inhaler technique review included 29 studies and 2,210 participants





# Improving adherence and inhaler technique

Both adherence and inhaler technique interventions improved adherence and inhaler technique (!)

Measurement variation limited meta-analysis

Quality of life and asthma control often not measured, or measured but not using validated scales

Most studies underpowered or too short to detect differences in clinical outcomes such as exacerbations or admissions



# Improving adherence and inhaler technique

## Bottom line

- Despite over 18,000 people taking part in trials in these two reviews, conclusions are limited
- Cannot say for sure whether interventions lead to clinical benefits
- Many are labour-intensive and time-consuming; realistic?
- More research needed that includes clinical outcomes and combined technique and adherence



# Improving adherence and inhaler technique

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## Paediatric Respiratory Reviews



Available online 8 April 2017

In Press, Corrected Proof — Note to users



Cochrane Corner

### Interventions to improve inhaler technique and adherence to inhaled corticosteroids in children with asthma

Rebecca Normansell<sup>1</sup>,  , Kayleigh Kew<sup>1, 2</sup>, Elizabeth Stovold<sup>1</sup>, Alexander G. Mathioudakis<sup>3</sup>, Emma Dennett<sup>1</sup>

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<https://doi.org/10.1016/j.prrv.2017.03.014>

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# Different and durations of oral steroids for asthma attacks



# Different doses and durations of oral steroids for asthma attacks

Included RCTs assessing any dose or duration of steroids  
versus any other dose or duration

Both adults and children

Separate comparisons adults and children – longer/higher  
dose course vs shorter/lower dose courses and  
prednisolone vs dexamethasone

We included 18 studies and 2,438 participants

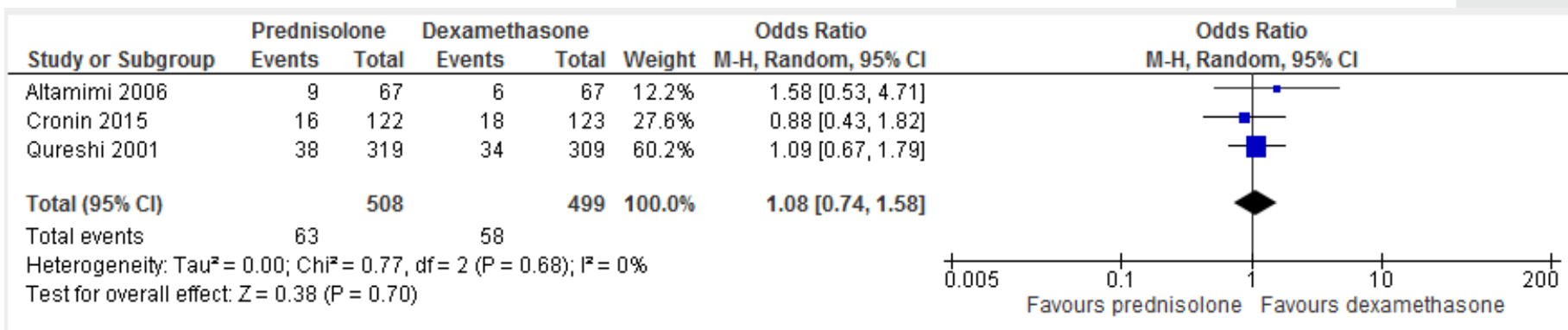


# Different doses and durations of oral steroids for asthma attacks

Two primary outcomes - hospital admission and serious adverse events - events too infrequent

Symptoms reported in different ways

Secondary outcome meta-analysis e.g. relapse, lung function and adverse events limited



# Different doses and durations of oral steroids for asthma attacks

Bottom line:

- No convincing evidence of better outcomes with higher dose/longer courses or fewer side effects with the opposite
- Evidence not strong enough to suggest any change to existing guidelines
- Larger, well-designed trials required to support or challenge current practice



# Different doses and durations of oral steroids for asthma attacks



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## Podcast: Different doses and durations of oral steroids for asthma attacks



*Corticosteroids are a widely used treatment for asthma and a recent addition to the collection of Cochrane Reviews on this condition examines the research that compared different ways of using corticosteroids. Rebecca Normansell (left) and Kayleigh Kew from the Population Health Research Institute at St George's in the University of London in the UK describe the findings of this May 2016 review in this Evidence Pod, starting with Rebecca.*

[Download podcast - Read transcript](#)

This podcast in other languages: [Русский](#)

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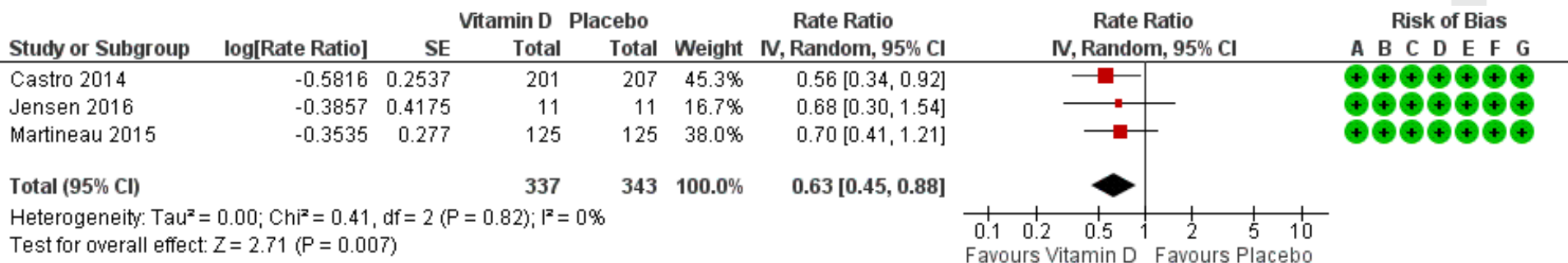
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# Vitamin D for asthma



# Vitamin D for asthma reduces...

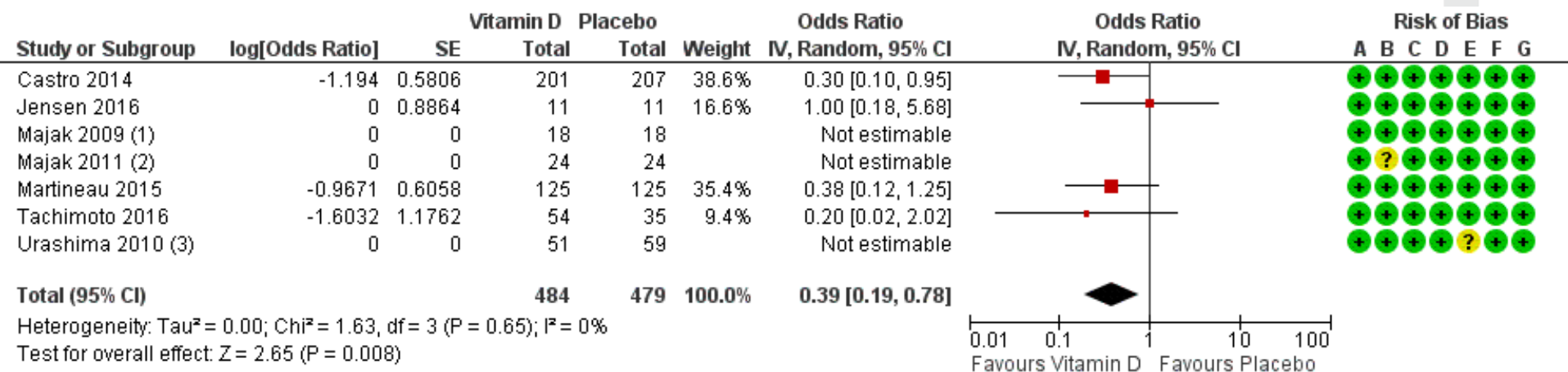


## Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

## Rate Ratio of exacerbations requiring oral steroids

# Vitamin D for asthma also reduces



## Footnotes

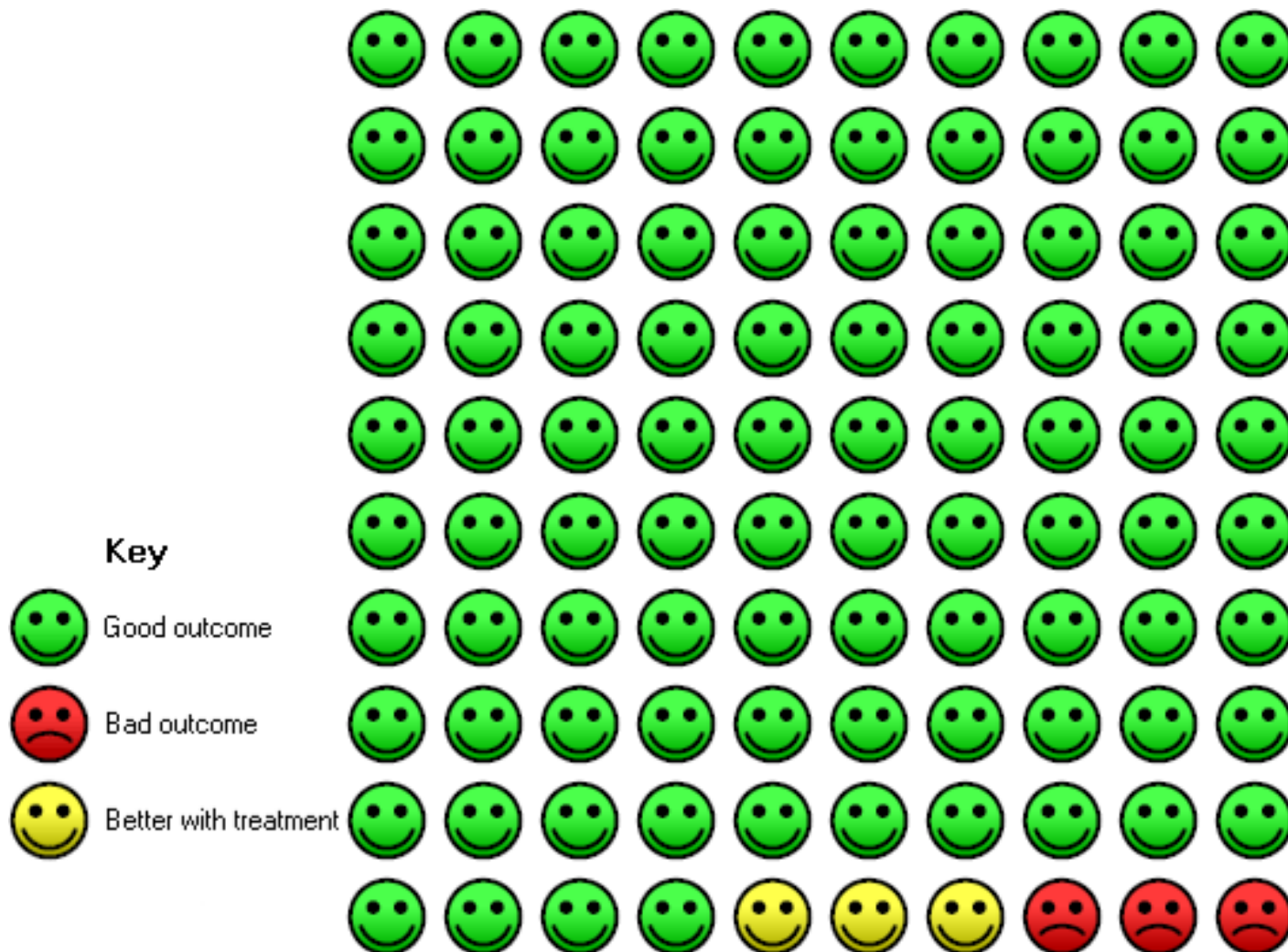
- (1) No events in either arm  
 (2) No events in either arm  
 (3) No events in either arm

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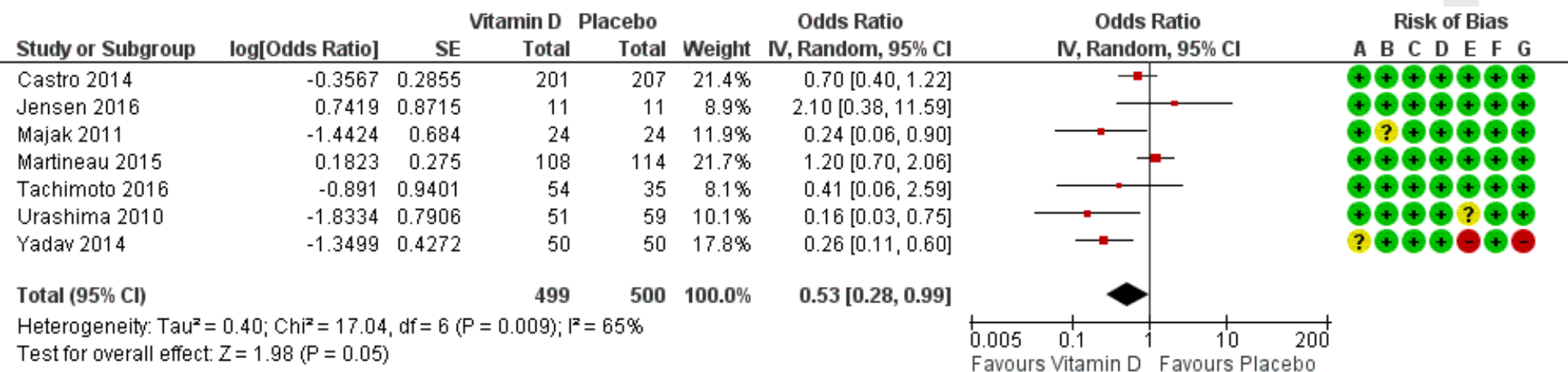
## Adults or children with hospitalisation or ED visit

# The risk is halved:



In the control group 6 out of 100 people had a visit to ED or hospitalisation over 8 months, compared to 3 (95% CI 1 to 5) out of 100 on vitamin D.

# Vitamin D for asthma

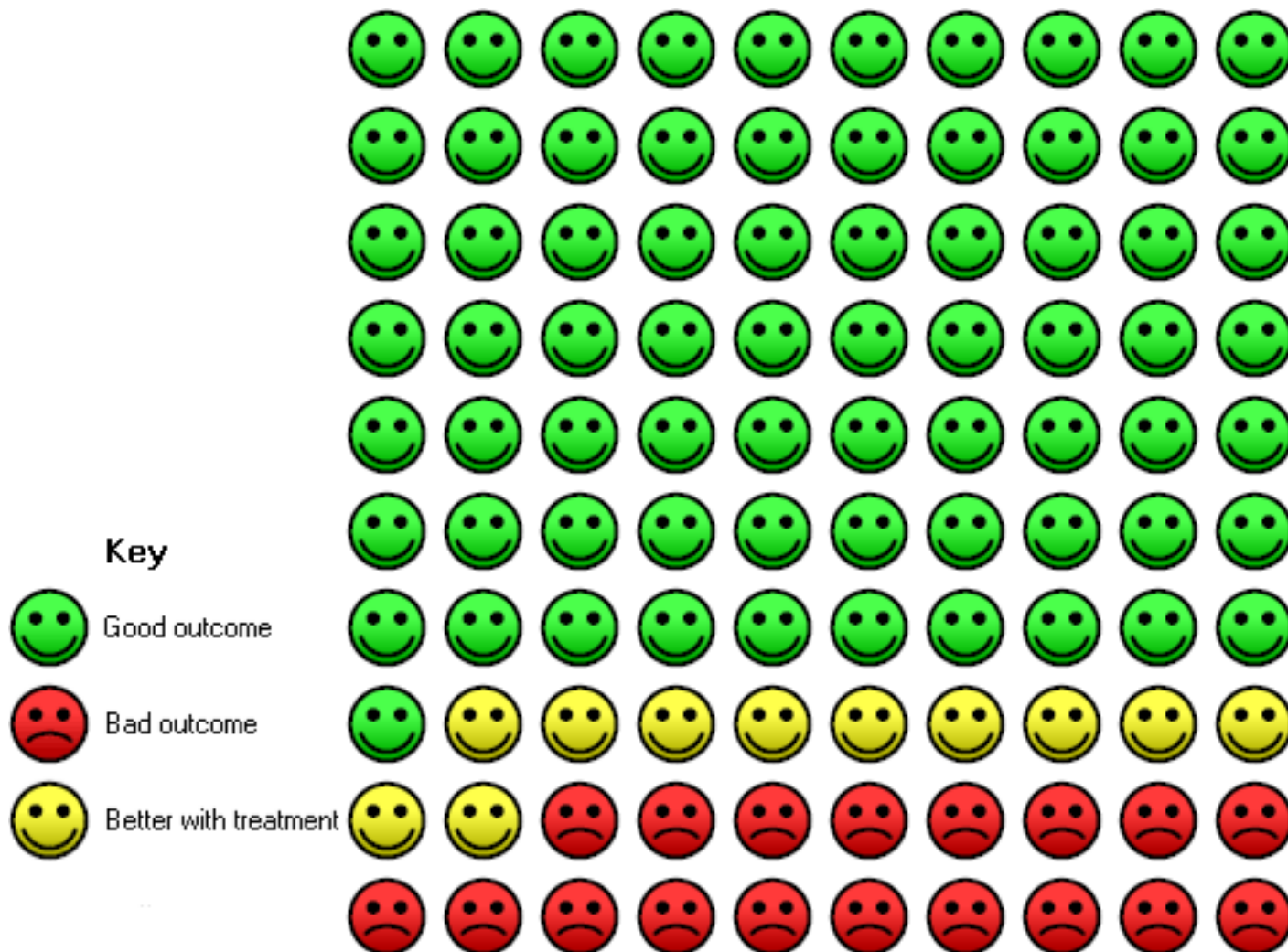


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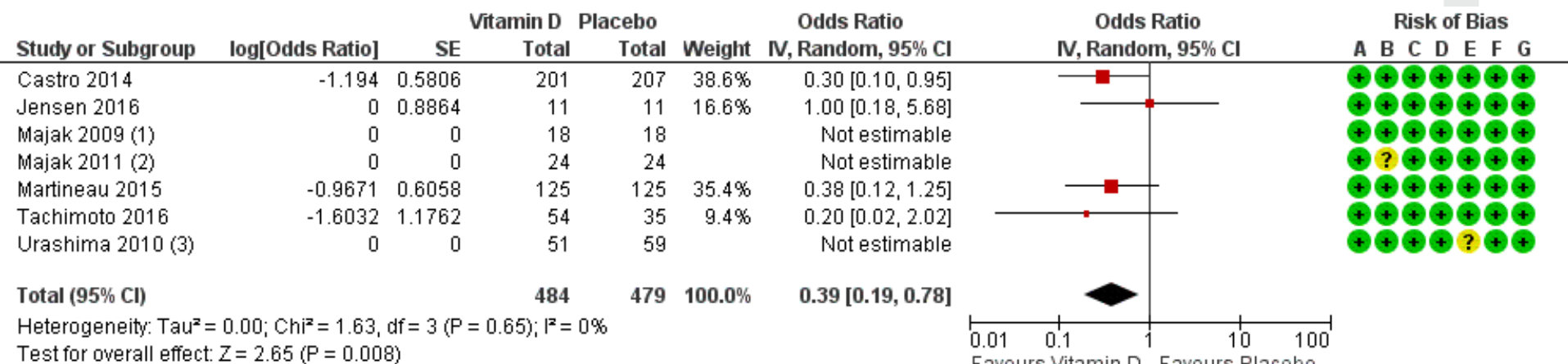
## Adults or children with study-defined exacerbation

# 11 people saved an exacerbation per 100



In the control group 29 out of 100 people had a study-defined exacerbation over 7 months, compared to 18 (95% CI 10 to 29) out of 100 on Vitamin D.

# Grading the evidence was contentious



## Footnotes

- (1) No events in either arm
- (2) No events in either arm
- (3) No events in either arm

## Risk of bias legend

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- (F) Selective reporting (reporting bias)
- (G) Other bias

# Adults or children with hospitalisation or ED visit

## Cochrane review - Authors' conclusions

**Whilst we are confident that Vitamin D reduced the risk of asthma exacerbation in these trials (high quality GRADE assessment), we recognise that there is uncertainty about how these findings might be applied in practice.**

More research is needed to clarify whether there is a difference in effect between adults and children and with respect to asthma severity, baseline vitamin D status and doses.



## Question one – the average effect

- We were confident that there was a reduction in exacerbations
  - In adults or children with mild/moderate asthma
  - From a variety of different countries
  - Given a variety of different Vitamin D treatments



## Question one – the average effect

- Where measured, mean/median baseline serum 25(OH)D concentration ranged from 48 nmol/L, in Castro 2014, to 89 nmol/L, in Majak 2011; a small minority of participants had serum 25(OH)D concentrations in the profoundly deficient range (less than 25 nmol/L).

## Question two – baseline Vitamin D level

- What about IPD data?
- This has now been published in relation to trials on Vitamin D for prevention of respiratory infections
- Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017;356:i6583

## What about IPD data?

**Results** 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001).

## What about IPD data?

### Results (continued)

In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10;  $P$  for interaction=0.05).

## What about IPD data?

### Results (continued)

Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels  $<25$  nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels  $\geq 25$  nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95;  $P$  for interaction=0.006).









## What about IPD data?

### Conclusions

Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

# What have we learnt?

Employed systematic reviewers are amazing!

Dissemination work is hard and time consuming but exciting and rewarding for those involved (but does it really make a difference??)

Working with volunteer authors is like herding cats, but can be done

Slow and steady wins the race

Developed PPI skills

