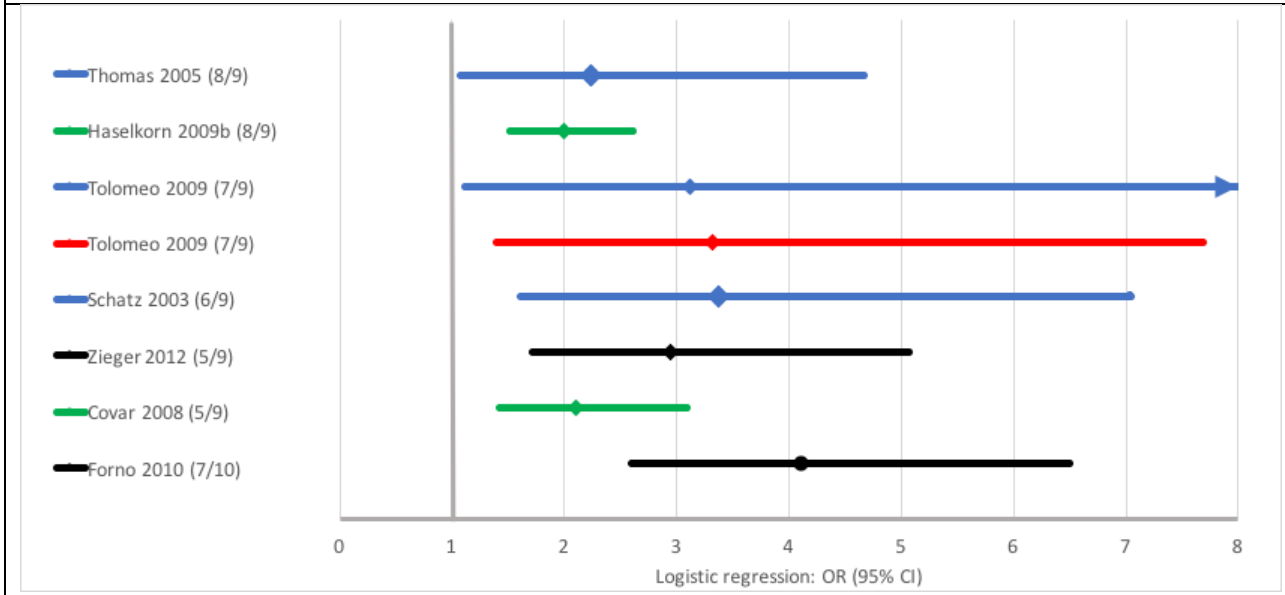
Supplementary table 3. Individual risk factors, Forest plots, decisions of the expert panel

Study design	Size: Number of children	Outcome	Decision rules
◆ Cohort ● Case-control ■ Cross-sectional Quality scores by names of papers	<1,000 1,001 – 10,000 >10,000	Combination outcome Hospitalisation ED visit Oral steroid (OCS) course Urgent/unscheduled care	OR <1.1 no effect, 1.1-1.5 slightly increased risk, 1.5-2.5 moderately increased risk, >2.5 greatly increased risk Interpretation based on number, design and quality of studies, consistency of results, biological plausibility.

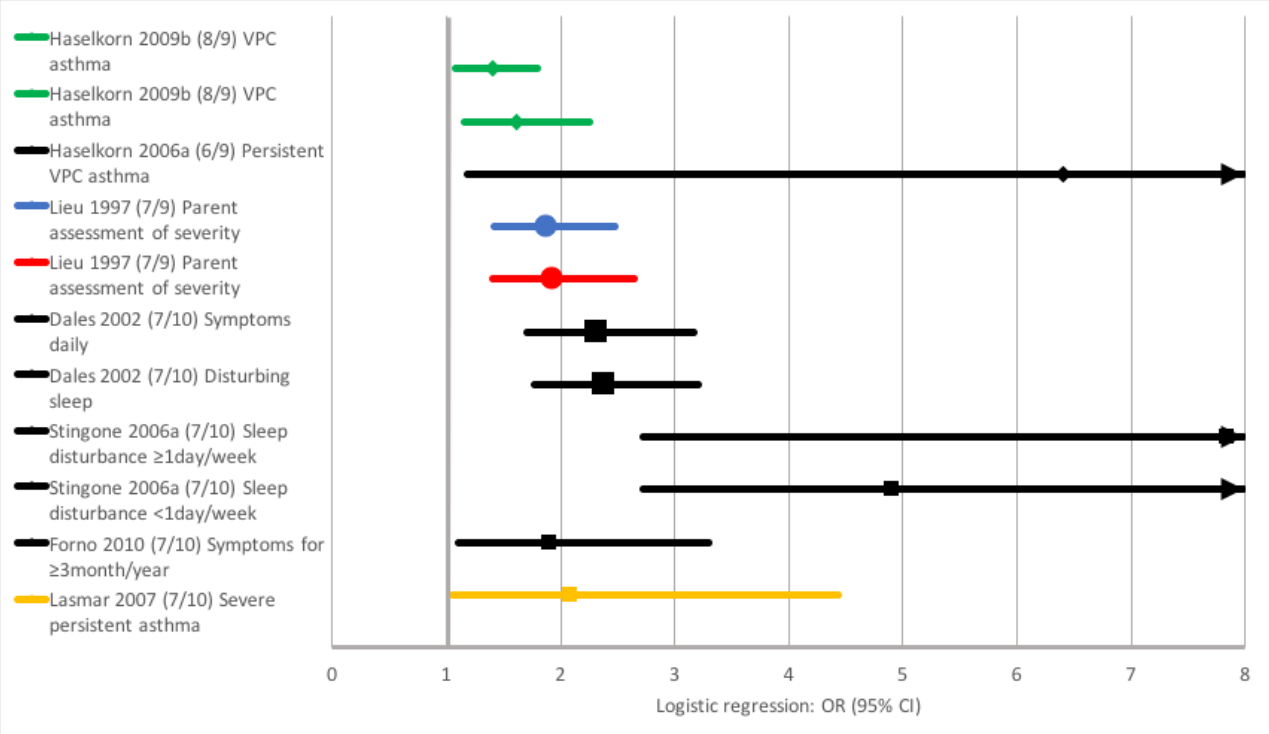
Note: the scale on all the Forest plots has been curtailed at an OR of 8 to enable comparison between the plots for the different factors. If the confidence intervals are very wide, and the upper limit extends beyond the plot this is indicated with a line with an arrow. (95%CI are given in table 2 if required)

Greatly increased risk

Previous attacks

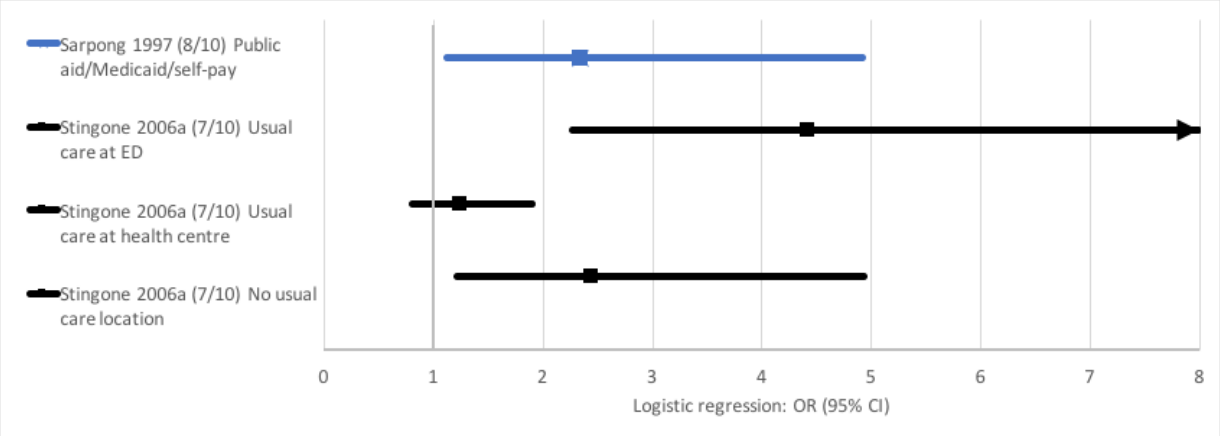
Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Engelkes 2016 (cohort 7/9) prior attack(s) increase risk RR 1.99 (1.40 to 2.83) ■ Wu 2011 (cohort 6/9): Prior exacerbation increases risk (P<0.001) ■ Forno 2010 (cross-sectional; 7/10): Prior OCS course increases risk (P<0.001) ■ Quezada 2016 (cross-sectional; 6/10): Prior OCS course/attack increased risk (P<0.001 or P<0.01) ■ Butz 2000 (cross-sectional; 4/10): Prior nebuliser use increases risk (P<0.001)	Evidence base: 8 cohort studies 3 cross sectional studies Consistent findings: all studies show an increased risk **Greatly increased risk** **Highly confident**

Persistent symptoms

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Robroeks (cohort; 9/9): poor asthma control increases risk (p=0.007) ■ Kwong 2012 (cohort; 6/9): well-controlled or mild intermittent (but not mild persistent) asthma reduces risk compared to severe persistent asthma ■ Halterman 2001 (cohort 5/9): no significant difference between intermittent and persistent asthma in ED visits and OCS use ■ Canino 2012 (cross-sectional; 2/10): unclear outcome	Evidence base: 5 cohort studies 1 case-control 5 cross sectional studies Consistent findings in the higher quality, larger, more robust study designs. Persistent symptoms are associated with an increased risk **Moderately/greatly increased risk** **Highly confident**

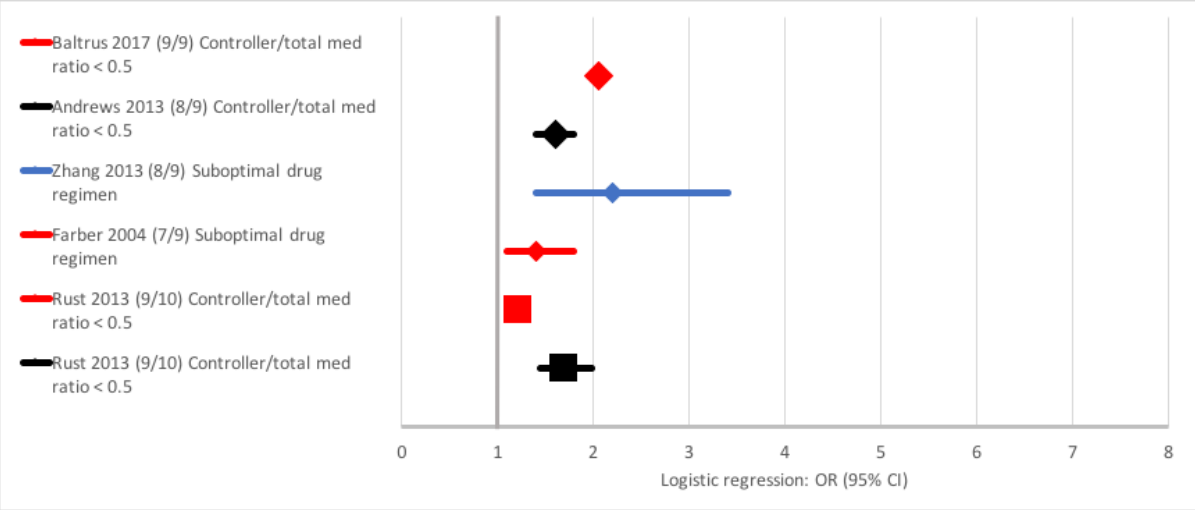
VPC = very poor control; d=day; w=week;

Poor access to healthcare

Odds ratios plotted on a Forest plot	**Results not possible to plot**	**Conclusions**
	■ Halterman 2001 (Cohort, 5/9): no increased risk (Medicaid vs no Medicaid) ■ Wood 2002 (cross-sectional, 5/10): increased risk with poor access to care (3 of 4 results significant) ■ Canino 2012 (cross-sectional, 3/10): increased risk with public insurance and lack of usual care	Evidence base: 1 cohort study 4 cross sectional studies Consistent findings in most studies. US based studies, access defined by healthcare arrangements **Moderately/greatly increased risk** **Moderately confident**

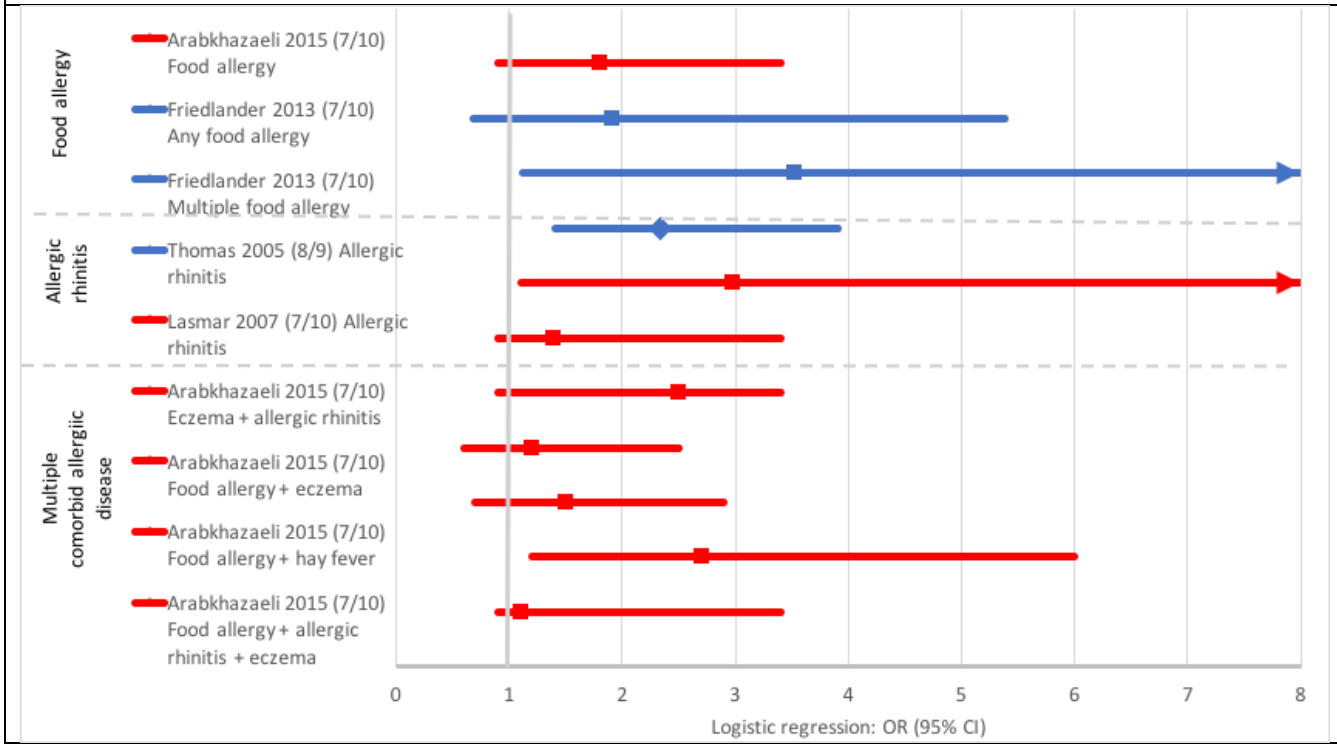
Moderately increased risk

Sub-optimal medication regime (low ratio of inhaled steroid (ICS) to total asthma medication)

Odds ratios plotted on a Forest plot	**Results not possible to plot**	**Conclusions**
	■ Spahn 2009 (cohort 6/9): ICS use in summer had lower autumn hospitalisations than non-users ■ Engelkes 2016 (Cohort, 6/9): increased risk (prior asthma treatment) ■ Farber 2004 (cohort, 8/9): No effect on exacerbations (controller/total ratio) ■ Schatz 2003 (cohort, 6/9): no effect on hospitalization (ICS/total ratio) ■ Vernaccio 2013 (cross-sectional, 8/10): increased risk (no/low controller ratio)	Evidence base: 7 cohort studies 2 cross sectional studies Consistent findings in most studies. **Moderately increased risk** **Highly confident**

Co-morbid atopic/allergic disease (Allergic rhinitis, eczema, and food allergy)

Odds ratios plotted on a Forest plot



Results not possible to plot

- Engelkes 2016 (Cohort, 7/9): No effect (asthma + allergic rhinitis, or eczema)
- Pinto-Pereira 2010 (cross-sectional, 6/10): increased risk (asthma + allergic rhinitis)

Conclusions

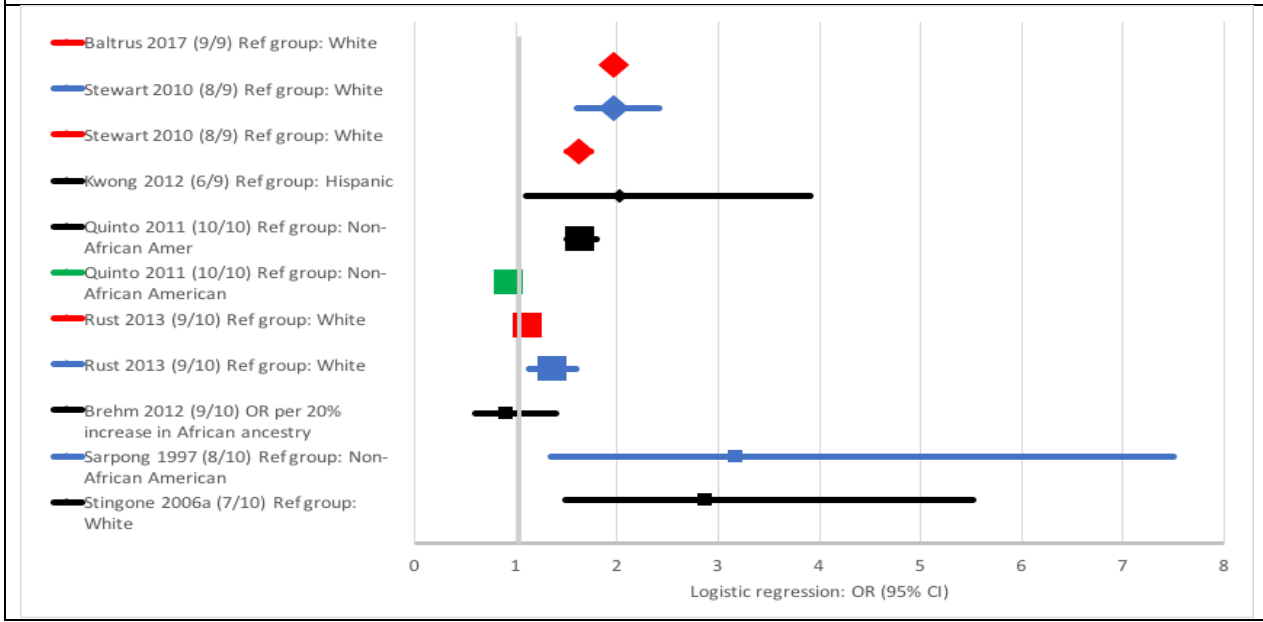
Evidence base:
2 cohort studies
4 cross sectional studies

Most, studies showed an increased risk in children with one or more co-morbid atopic conditions. No consistent difference between the different conditions, or between one, two or three conditions

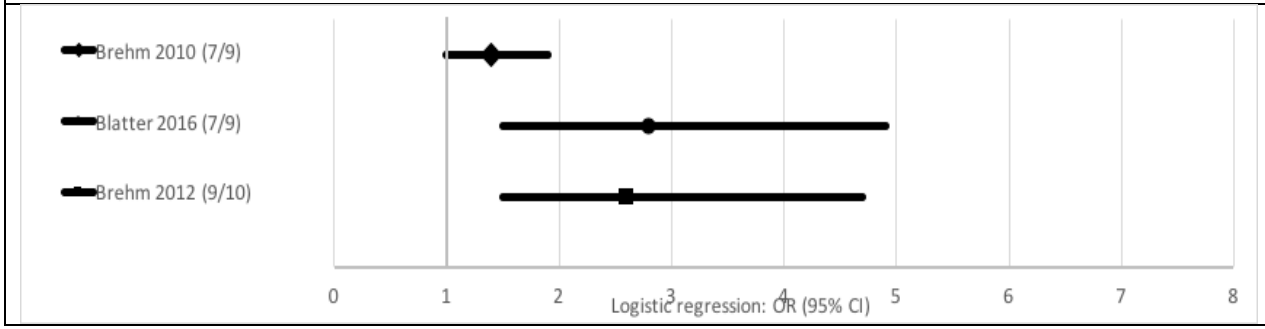
Moderately increased risk

Slightly confident

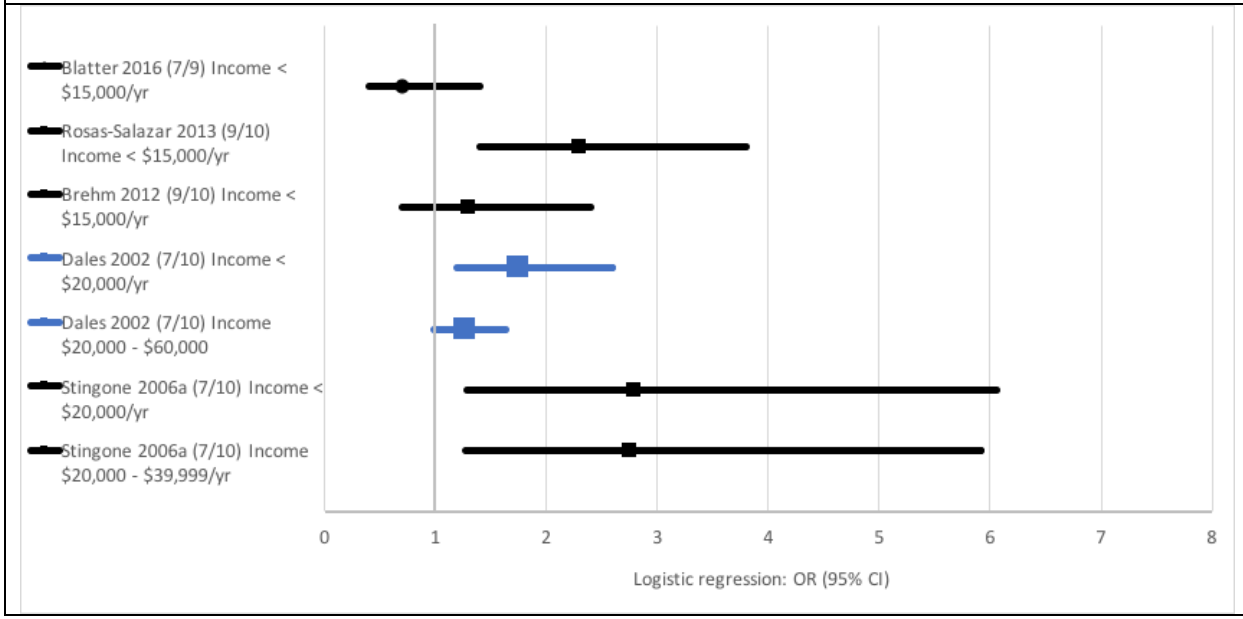
African-American ethnicity

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Halterman 2001 (cohort, 5/9): not significant (Black vs non-Black) ■ Malhotra (cross-sectional, 6/10): increased risk in populations with high ratio of Black/White ■ Quezada (cross-sectional, 6/10): not significant (Black vs Others) ■ Wood 2002 (cross-sectional, 5/10): increased risk (Black vs Hispanic)	Evidence base: 4 cohort studies 8 cross sectional studies Consistent findings in the higher quality, more robust study designs. All these studies were in the US **Moderately increased risk** **Highly confident**

Vitamin D deficiency

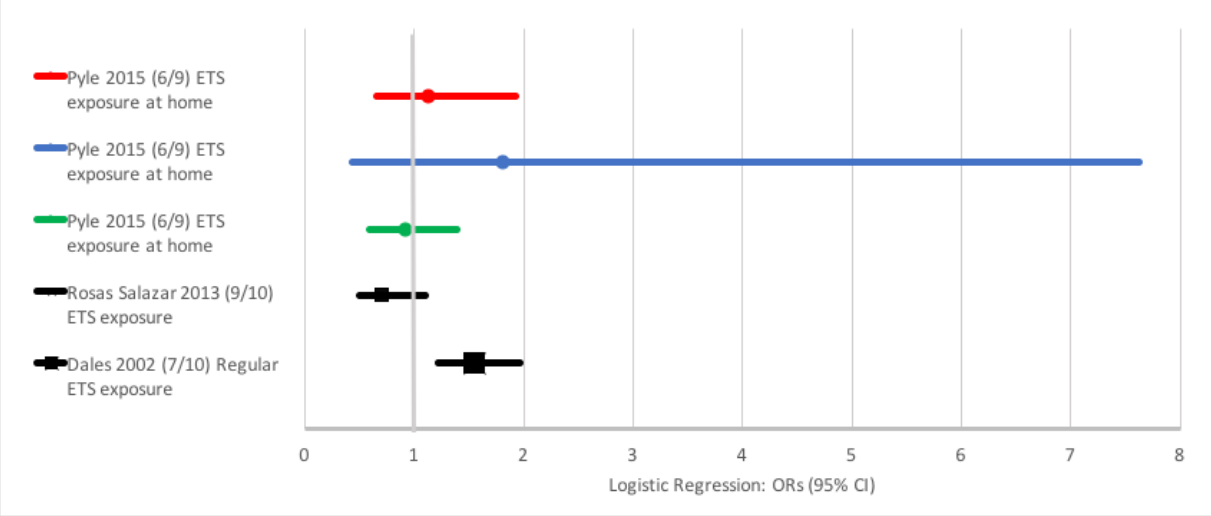
Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Brehm 2012 (Cross-sectional, 9/10: no effect of high vitamin D intake ■ Searing (cross-sectional, 5/10): increased risk associated with vitamin D deficiency	Evidence base: 1 cohort 1 case control study 2 cross sectional studies Small studies **Moderately increased risk** **Slightly confident**

Poverty

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Schatz 2003 (cohort, 6/9): reduced risk (lower family income) P<0.05 ■ Lieu 1997 (case-control, 7/9): as annual income increased, hospitalisation odds decreased. ■ Wood 2002 (cross-sectional, 5/10): increased risk (people denied benefits) no effect (people on benefits) ■ Canino 2012 (cross-sectional, 2/10): increased risk (poverty and neighbourhood risk)	Evidence base: 1 cohort study 2 case control 6 cross sectional studies Most studies showed an increased risk in children living in low income families. **Moderately increased risk** **Moderately confident**

Slightly increased risk

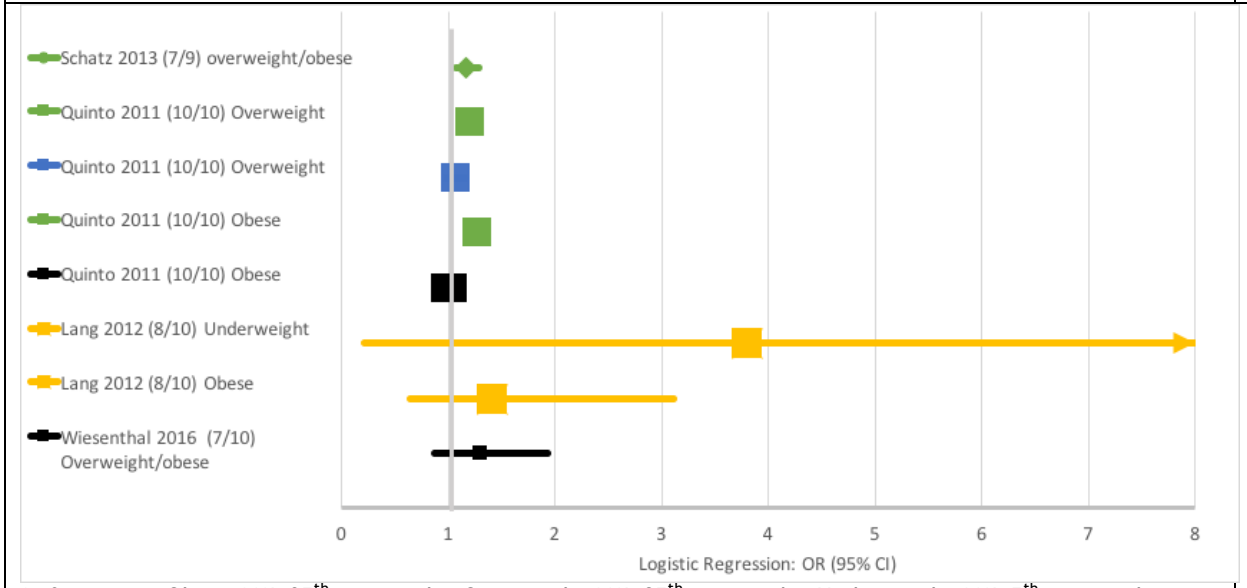
Exposure to environmental tobacco smoke (ETS)

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Rabinovitch 2011 (cohort, 6/9): increased risk (reported and/or cotinine) ■ McCarville 2013 (cross-sectional, 8/10): increased risk (cotinine level); no effect (parental report) ■ Chilmonczyk 1993 (cross-sectional, 7/10): No effect (parental or cotinine report) ■ Quezada 2016 (cross-sectional, 6/10): No effect (parental report) ■ Canino 2012 (cross-sectional, 2/10): increased risk (reported ETS exposure)	Evidence base: 1 cohort 1 case-control 6 cross sectional studies Discrepancy between risk associated with parental report and elevated cotinine. **Slightly increased risk** **Highly confident**

Younger children within the 5-12 age range

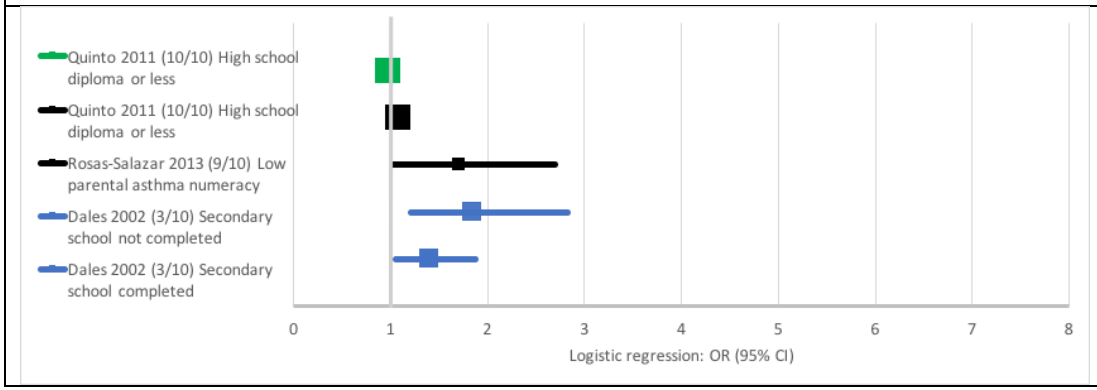
Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
Insufficient ORs to plot	■ Baltrus 2017 (cohort 9/9): reduced risk with increased age ■ Schatz 2003 (cohort, 6/9): increased risk (younger age) P<0.001 ■ Murray 1997 (cohort study 6/9): increased risk 5-9yr olds vs 10-14yr olds ■ Sarpong 1997 (cross-sectional 8/10): each year of age reduced OR 0.77 (0.67 to 0.90) ■ Quezada 2016 (cross-sectional 6/10): increased risk ■ Wood 2002 (cross-sectional 5/10): increased risk	Evidence base: 3 cohort studies 3 cross sectional studies Consistent finding of increased risk in younger children. **Slightly increased risk** **Highly confident**

Obesity/overweight

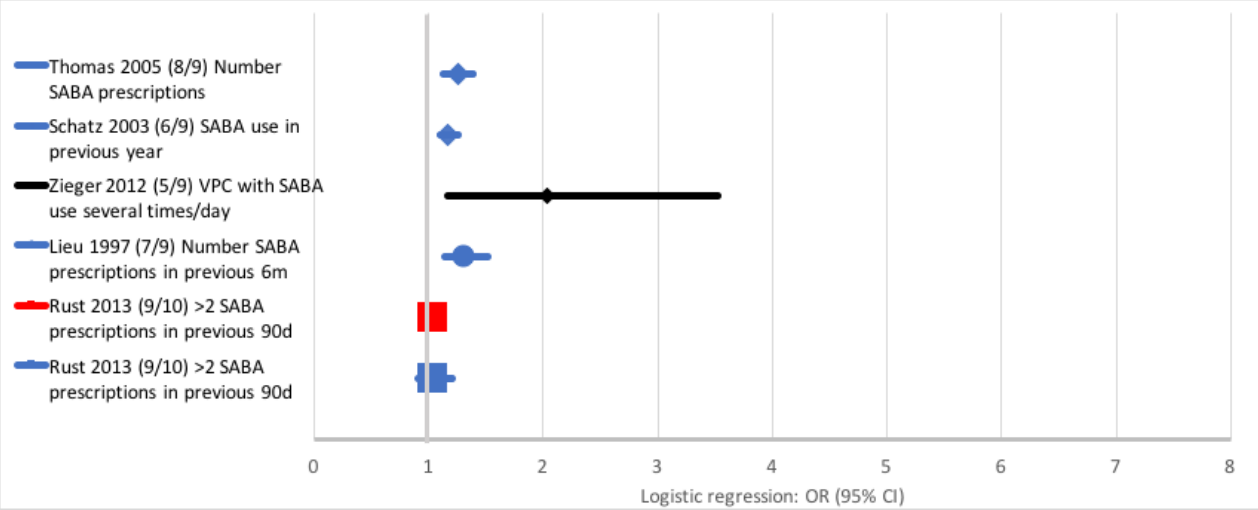
Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Peters 2011 (cohort 8/9) 'No effect in the regression analysis' ■ Black 2013 (cohort 8/9) increased risk ■ Wu 2011 (cohort 6/9) No effect ■ Mahut 2012 (cross sectional 7/10) no effect ■ Quezada 2016 (cross sectional 6/10) No effect ■ Stingone 2011(cross sectional 6/10) increased risk	Evidence base: 4 cohort studies 6 cross sectional studies Consistent finding of slightly increased risk in large population level studies **Slightly increased risk** **Highly confident**

Definitions: Obese BMI>95th percentile; Overweight BMI>85th percentile; Underweight BMI<5th percentile

Low parental education level

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	■ Lieu 1997 (case-control, 7/9): as father's education increased, odds of having ED visit decreased	Evidence base: 1 case control study 3 cross sectional studies All studies have at least one positive outcome **Slightly increased risk. Moderately confident**

Reliever medication use



- Vernachio 2013 (cross-sectional 9/10) Increased risk (≥4 SABA) prescriptions/year). No effect (≤3 SABA/year)
- Quezada (cross-sectional 6/10) Increased risk (>2 doses reliever a week)

Evidence base:
3 Cohort
1 case control
3 cross-sectional studies

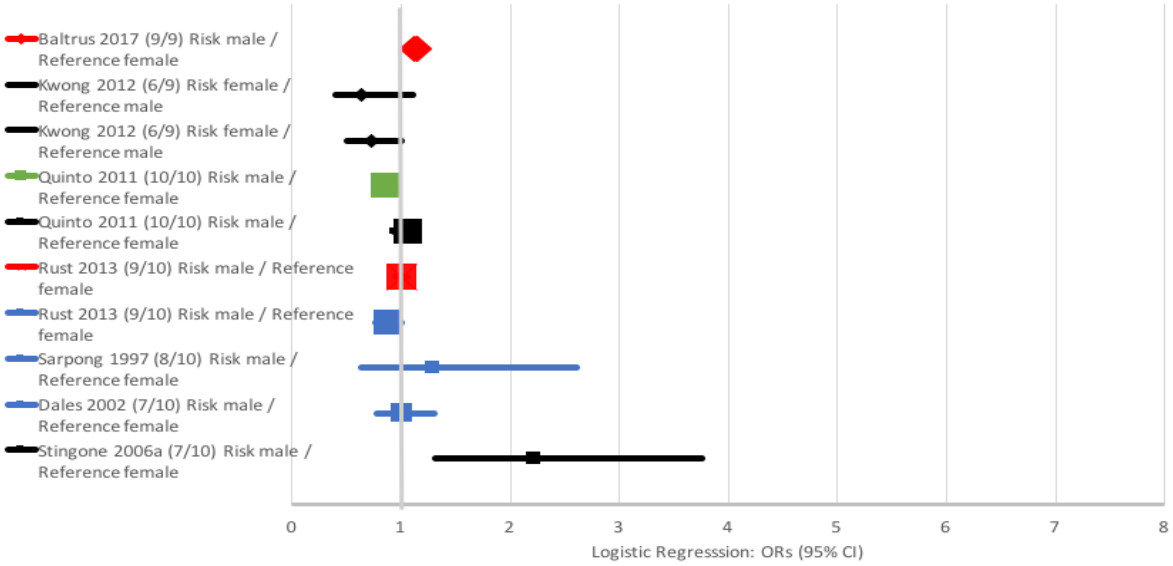
Relatively low doses of SABA; no data on very high doses

Slightly increased risk

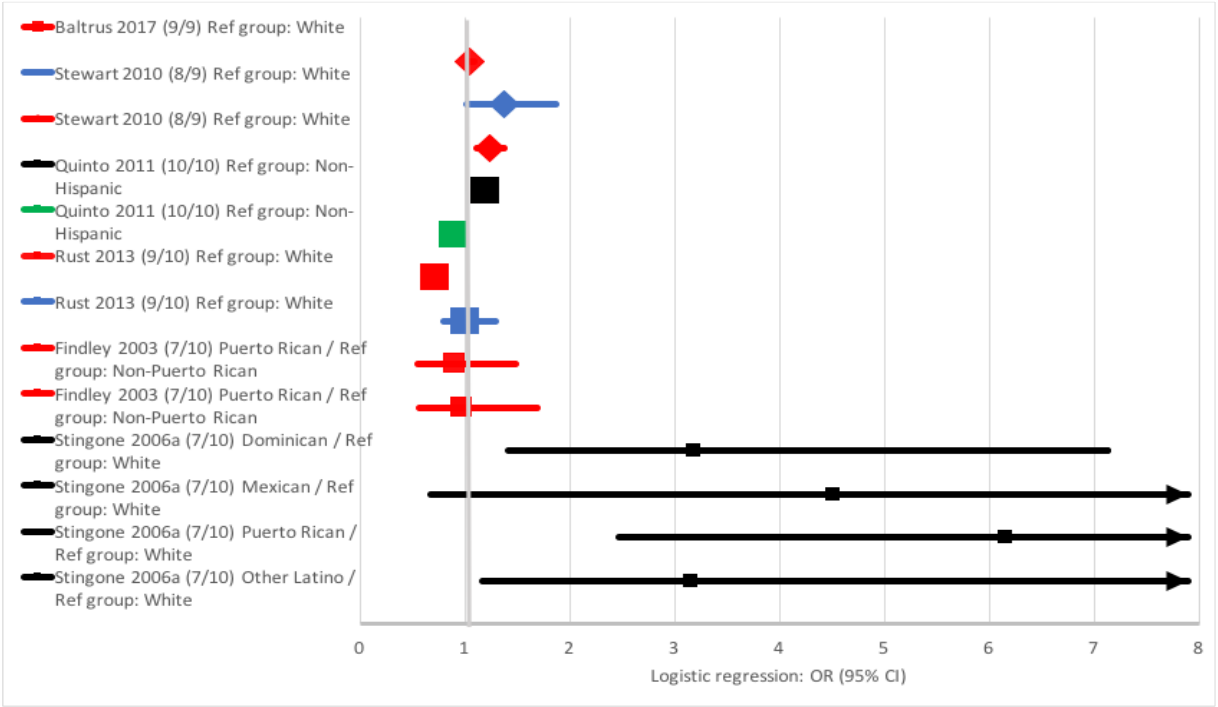
Moderately confident

No increased risk

Gender

Odds ratios plotted on a Forest plot	Results not possible to plot	Conclusions
	No significant gender difference: ■ Engelkes 2016 (cohort 7/9) ■ Schatz 2003 (cohort 6/9) ■ Akinbami 2009 (cross-sectional 6/10) ■ Halterman 2001 (cross-sectional 5/10) ■ Quezada 2016 (cross sectional 6/10) ■ Canino 2012 (cross sectional 2/10) Boys at greater risk: ■ McCarville 2013 (cross sectional 8/10)	Evidence base: 5 cohort 9 cross-sectional studies Consisent finding of no gender difference **Not a risk factor** **Highly confident**

Hispanic ethnicity (US studies)



- Kwong 2012 (cohort 6/9): not significant compared to white population
- McCarville 2013 (cross-sectional, 8/10): not significant results (Hispanic vs non-Hispanic)

Evidence base:
3 cohort studies
6 cross sectional studies

Consistent findings in the higher quality, more robust study designs. All these studies were in the US

No consistent effect

Moderately confident

Urban residence/proximity to major road

Odds ratios plotted on a Forest plot	**Results not possible to plot**	**Conclusions**
Insufficient ORs to plot	■ Halterman 2001 (cohort 5/9) no increased risk of living in urban location ■ Blatter 2016 (case-control 7/9) increased risk per 100m from major road ■ Rust 2013 (cross-sectional 9/10) no increased risk of living in large metropolitan area (n=43,156) ■ Pesek 2010 (cross-sectional 8/10) no increased risk of living in urban location ■ Sarpong 1997 (cross-sectional 8/10) no increased risk of living in urban location ■ Brown 2012 (cross-sectional 7/10) proximity to major road increased risk of hospitalisations but not ED visits.	Evidence base: 1 cohort 1 case control 4 cross-sectional studies 5 studies, including a large high quality cross-sectional study showed no increased risk with urban residence or proximity to major roads. **Not a risk factor** **Moderately confident**

Confounded by severity/indication

<table>
<tr><td>Controller medication use
In 9 of the 16 studies, ICS use was associated with an increased exacerbation risk.
In 3 studies ICS use was associated with no difference in exacerbation risk
In 3 studies ICS use was associated with a reduction in exacerbation risk</td><td>Evidence base:
6 Cohort
2 case control
8 cross-sectional studies</td><td>Confounded by indication</td></tr>
<tr><td colspan="3">Nebuliser use</td></tr>
<tr><td>Odds ratios plotted on a Forest plot</td><td>Results not possible to plot</td><td>Conclusions</td></tr>
<tr><td>Insufficient ORs to plot</td><td>■ Lieu 1997 (Case-control, 7/9)
Increased risk with ownership of a nebuliser
■ Butz 2000 (Cross-sectional, 4/10)
Increased risk with use of nebuliser</td><td>Evidence base:
1 case control study
1 cross sectional studies
Confounded by severity</td></tr>
<tr><td>Ownership of written asthma management plan
One study found that action plan was associated with an increased risk and one with a reduced risk</td><td>Evidence base:
1 case control
1 cross-sectional studies</td><td>Confounded by indication</td></tr>
<tr><td>Routine asthma reviews
All three studies showed that attendance at routine checks was associated with increased risk of exacerbations</td><td>Evidence base:
1 cohort
2 cross-sectional studies</td><td>Confounded by severity</td></tr>
</table>

Inconclusive

Reduced lung function 5 small studies (N<500) with inconsistent findings; the larger cohort stdy (n=1019) had mixed results 1 cross-sectional study (n=1,041) found that reduced pre-bronchodilator FEV_1 was associated with increased of attacks 'at any time during the child's life'. As this outcome included pre-school admissions, potentially confounded with viral associated wheeze, it was unclear whether this reflected the situation in children 5-12yrs.	Evidence base: 3 cohort studies 1 case control study 3 cross sectional	**Inconclusive**
FeNO testing at routine reviews In 2 of the 3 studies, both in small cohorts with relatively severe asthma, FeNO tested at regular visits (2 or 3 monthly did not predict attacks in the subsequent 2 – 3 months. In 1 study, median FeNO at baseline predicted exacerbations in the subsequent year, but was clinically unhelpful because of overlap of FeNO levels in the two groups.	Evidence base: 3 cohort studies	**Inconclusive**
Postive skin prick test (SPT) In the cohort study (n=1,019) and the case control study)n=304), a positive SPT was not associated with an increased risk. In one of the cross-sectional studies a positive SPT (to cat or cockroach) was associated with an increased risk, but a positive SPT to HDM or dog was not. The other showed an associateion of a posituve SPT on ED visits, but not oral stroids courses.	Evidence base: 1 cohort 1 case control 2 cross-sectional studies	**Inconclusive**
History of allergen exposure Inconsistent outcomes to exposure to cockroach, mouse, fungal spores, cats/dogs The larger cross-sectional study (n=2,966) showed an association of attacks with dogs, but not cats; the much smaller cross-sectional study (n=86) showed an association with cockroach infestation. The three cohort studies had mixed outcomes.	Evidence base: 3 cohort 2 cross-sectional studies	**Inconclusive**

Insufficient evidence

Serum total IgE Limited evidence and inconsistent outcomes: The cohort study (n=1,019) was negative; the cross-sectional study (n=465) was positive	Evidence base: 1 cohort 1 cross-sectional study	**Insufficient**
Family history of atopy Limited evidence and inconsistent outcomes The cohort study (n=1,019) was negative; the cross-sectional study (n=465) was positive for paternal hay fever but not for any other family history of atopic conditions.	Evidence base: 1 cohort 1 cross-sectional study	**Insufficient**
Age of onset of asthma Limited inconclusive findings One small (n=200) cross-sectional study showed no association with attacks	Evidence base: 1 cross-sectional study	**Insufficient**
Duration of asthma No consistent effect of duration of asthma The cohort study (n=563) was positive, one cross-sectional study was negative. One study confounded by duration of the outcome (Prior hospitalisation at any time during their life).	Evidence base: 1 cohort 2 cross-sectional studies	**Insufficient**
Co-morbidities Limited inconclusive findings (for Gastro-oesophageal reflux, or diabetes) One very large (n=32,321) showed a positive association of diabetes or GORD with hospitalisations but not oral steroids.	Evidence base: 1 cross-sectional study	**Insufficient**
IQ/special needs Limited inconclusive findings The larger study (n=1,041) was positive but used the unclear outcome 'Prior hospitalisation at any time during their life' and the smaller study was positive for hospitalisations but not ED visits	Evidence base: 2 cross-sectional study	**Insufficient**
Parental health Limited inconclusive findings One positive moderate quality cross –sectional study (n=386)	Evidence base: 1 cross-sectional study	**Insufficient**
Parental marital status Limited inconclusive findings Two moderate quality cross-sectional studies. The larger (n=2,986) was positve for single parent families, but not for separated, divorced or widowed. The smaller study was negative (n=386)	Evidence base: 2 cross-sectional study	**Insufficient**