Corticosteroids and bone health in people with asthma: a systematic review and meta-analysis

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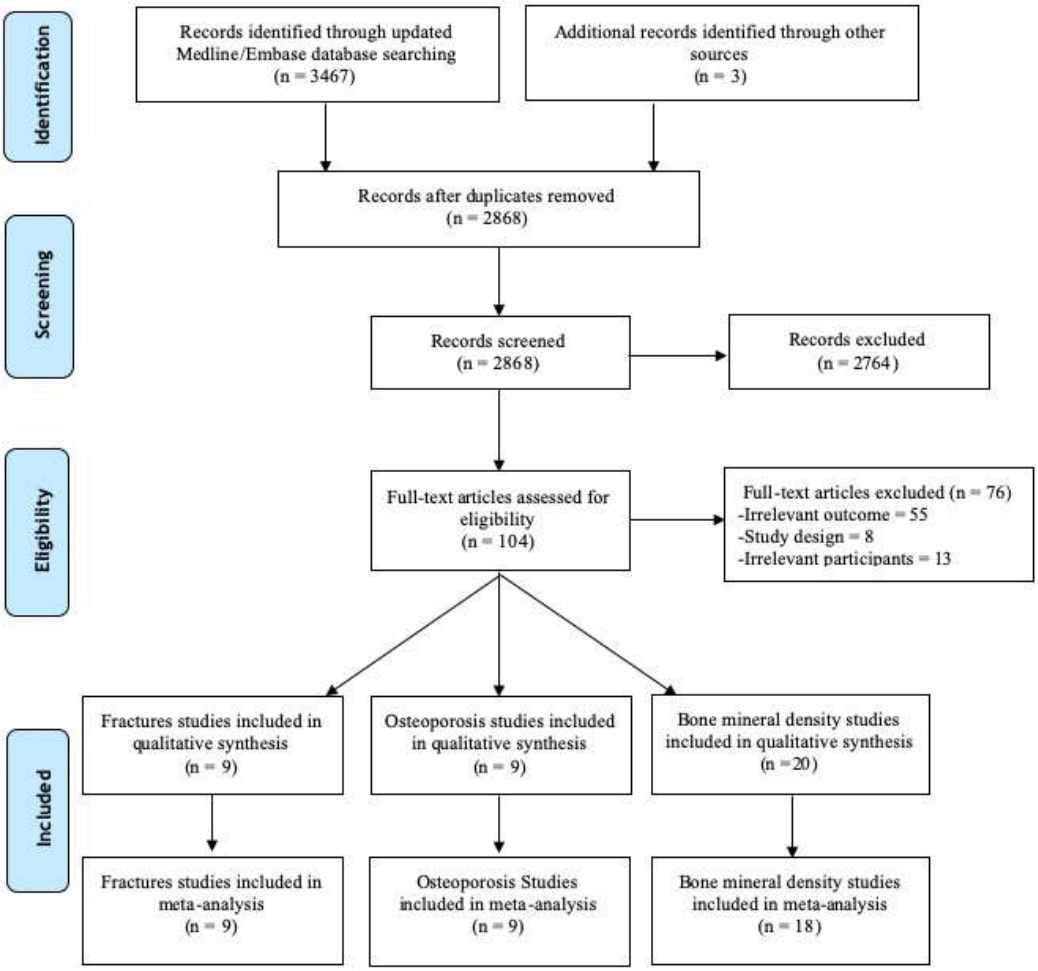
Supplemental material

e-Methods



e-Figure 1. Flow chart of studies

e-Table 1. Medline (via Ovid) and EMBASE (via Ovid) search terms for primary studies.

Search terms
1. Exp Asthma/
2. Asthma$.mp
3. (((inhaled or oral) and (corticosteroid$1 or steroid$1 or glucocorticoid$1)) or steroid$1 or glucocorticoid$1 or corticosteroid$1 or beclometasone or beclomethasone or fluticasone or budesonide or mometasone or triamcinolone or ciclesonide or prednisolone).mp
4. (osteoporosis or fracture$1 or (fracture$1 adj2 risk) or (osteoporosis adj2 risk) or (bone adj2 density) or (bone$1 or bone-resorption) or (bone$1 adj2 fracture$1) or (bone adj2 loss) or (osteoporotic adj1 fracture$1) or (fracture$1 adj1 bone$1)).mp
5. 1 or 2
6. 3 and 4 and 5

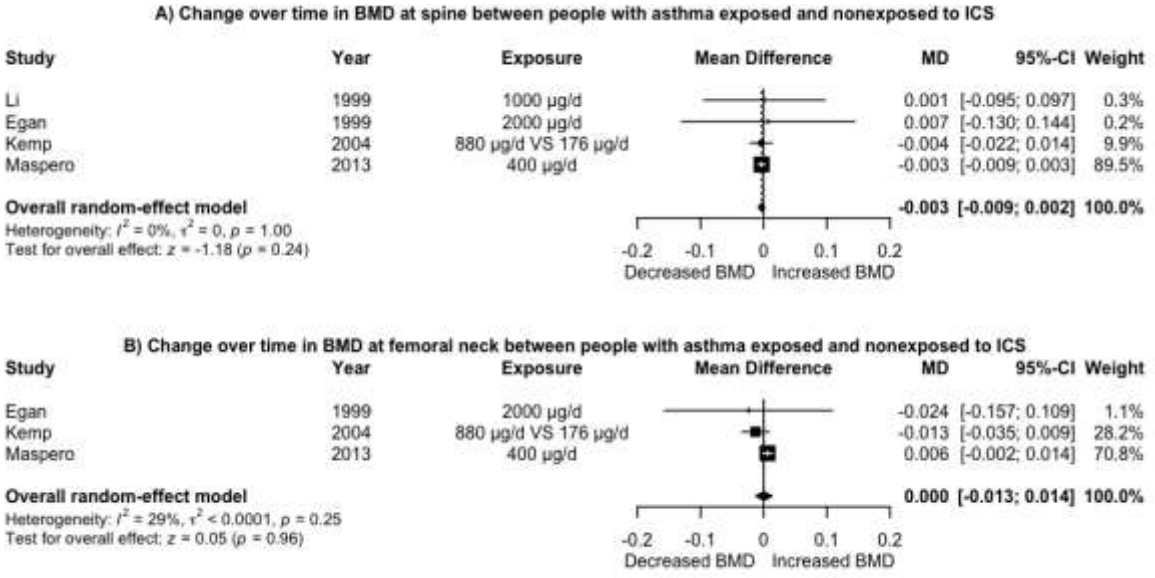
e-Results

Change in BMD over time

e-Table 2. Details of the included studies having the BMD mean change over time between the comparison groups as outcome.

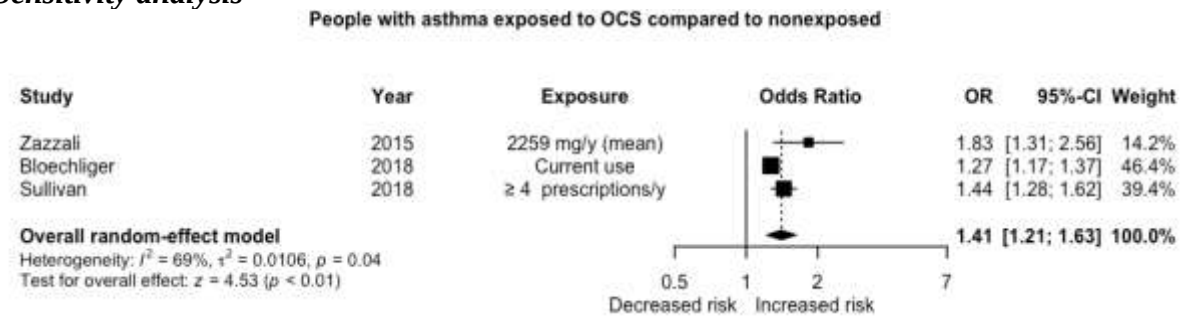
Study, Year	Study Design, Country	Comparison Groups	Sampling (Cases/Controls)	Mean Age (yrs.) (Cases/Controls)	Female (%)	Type of corticosteroid	Corticosteroid exposure	Mean BMD change over time (95% CI) between comparison groups
People with asthma exposed to OCS/ICS vs people with asthma nonexposed or exposed to low dose								
Egan, 1999	RCT, UK	High ICS **VS** low ICS	16/16	33/30	46.9	BDP	High ICS: 1000-2000µg/d Low ICS: ≤400µg	Total body: 0.009 (-0.069 to 0.087) L2-L4 spine: 0.047 (-0.092 to 0.186) Femoral neck: -0.024 (-0.144 to 0.096)
Li, 1999	RCT, USA	ICS **VS** placebo	32/32	28/31.1	14	FP	500µg twice/d for 104 weeks	L2-L4 spine: 0.001 (-0.024 to 0.026)
***Kaye, 2000**	RCT, USA	ICS **VS** no steroids	11/18	39/39	55.2	FLUNI	500µg/d	L2-L4 spine: 0.059 Femoral neck: -0.072 Ward's triangle: -0.055 Trochanter: 0.01
Matsumoto, 2001	Cross-sectional, Japan	Low ICS **VS** high ICS	9/26	60.6	57.1	BDP	High ICS: Mean ICS daily dose: 1,268µg during the study. Low ICS: Mean ICS daily dose: 615µg during the study.	L2-L4 spine: -0.015 (-0.047 to 0.017)
***Tattersfield, 2001**	RCT, France, New Zealand, Spain, UK	ICS **VS** no steroids	74/78	36/36	53	BDP	BDP: 499µg/d	Total body: -0.006 L2-L4 spine: -0.008 Femoral neck: -0.005
Kemp, 2004	RCT, USA	ICS **VS** placebo		30.3/28.4	14	FP	88µg or 440 µg twice daily for 104 weeks	L2-L4 spine: -0.004 (-0.022 to 0.014) Femoral neck: -0.013 (-0.035 to 0.009) Total body: -0.003 (-0.015 to 0.009)
Maspero, 2013	RCT, Europe, America, Africa, Caribbean	ICS **VS** placebo	424/142	29.2/28.2	63.4	MF, ML	MF 400µg/d, for 52 weeks	L2-L4 spine: -0.003 (-0.009 to 0.003) Femoral neck: 0.006 (-0.002 to 0.014)
People with asthma exposed to OCS/ICS vs healthy controls								
Luengo, 1997	Case-control, Spain	ICS **VS** healthy subjects	48/48	56/55	68.8	BDP, BUD	Cases: ≥1 yr. Mean daily dose: 662µg Mean duration: 10.6 yrs	L2-L4 spine: 0 (-0.073 to 0.073)
Egan, 1999	RCT, UK	ICS **VS** healthy subjects	32/7	34.5/32	43.5	BDP	1000-2000µg/d	Total body: 0.09 (-0.038 to 0.218) L2-L4 spine: 0.058 (-0.091 to 0.207) Femoral neck: 0.027 (-0.106 to 0.160)

**Not able to calculate the 95%CI due to lack of data.*

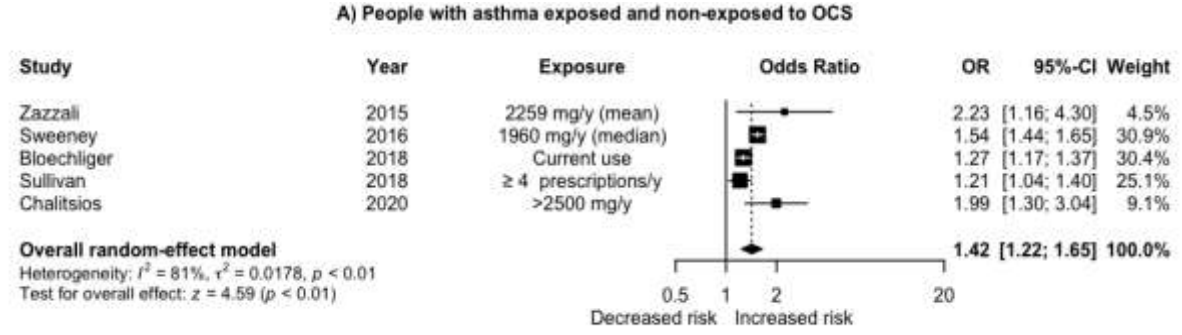


e-Figure 2. Meta-analysis of RCT of change over time in BMD at (A) spine and (B) femoral neck between people with asthma exposed to ICS and nonexposed. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '0' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.

Sensitivity analysis



e-Figure 3. Meta-analysis of observational studies on odds ratio of osteoporosis in asthma. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '1' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.



e-Figure 4. Meta-analysis of observational studies on odds ratio of fractures in asthma. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '1' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.

Quality assessment

e-Table 3. Quality assessment of the included RCTs according to Cochrane risk of bias RoB 2 tool.

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Egan, 1999	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Li, 1999	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Kaye, 2000	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Tattersfield, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	**Some concerns**
Kemp, 2004	Low risk	Low risk	Some concerns	Low risk	Low risk	**Low risk**
Maspero, 2013	Low risk	Some concerns	Some concerns	Low risk	Low risk	**Some concerns**

e-Figure 2. Traffic light plot depicting the risk of bias of RCT according to Cochrane risk of bias RoB 2 tool.

e-Table 4. Quality assessment of the included observational studies according to Newcastle-Ottawa scale.

Study[a]	Selection	Comparability	Outcome	Overall risk
Adinoff, 1983	3	0	3	**6**
Ip, 1994	3	2	3	**8**
Boulet, 1994	2	1	2	**5**
Herrala,1994	3	1	3	**7**
Gagnon, 1997*	1	0	2	**3**
Luengo, 1997	3	2	2	**7**
Wisniewski, 1997*	1	0	2	**3**
Laatikainen, 1999*	1	1	2	**4**
Fujita, 2001	2	2	2	**6**
Matsumoto, 2001*	1	1	2	**4**
Sivri, 2001	2	2	2	**6**
El, 2005	2	1	2	**5**
Johannes, 2005	1	2	3	**6**
Monadi, 2005	1	2	2	**5**
Sosa, 2006	1	1	2	**4**
Yanik, 2009	1	0	2	**3**
Zazzali, 2015	3	2	1	**6**
Sweeney, 2016*	2	2	3	**7**
Daugherty, 2017	3	2	2	**8**
Bloechlinger, 2018	2	2	3	**7**
Price, 2018	2	2	3	**7**
Sullivan, 2018	3	2	2	**8**
Chalitsios, 2020	2	2	3	**7**

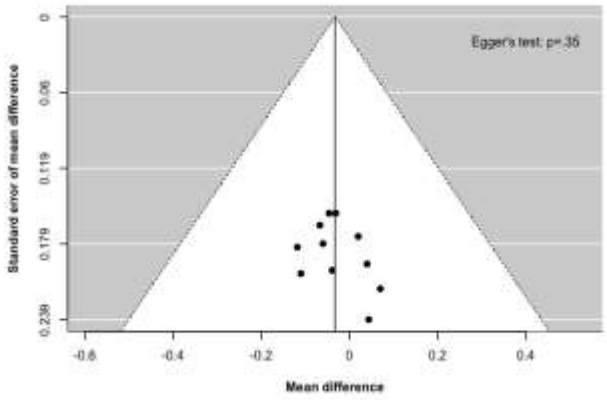
[a]*If a study name includes an (*) then is it is a cross-sectional study with a maximum overall score equal to 7. Otherwise, it is a cohort/case-control study with a maximum overall score equal to 9. Selection: maximum four stars; Comparability: maximum two starts; Outcome: maximum three starts. Selection*: maximum three stars; Comparability: maximum two starts; Outcome: maximum two starts.*

e-Table 5. Financial disclosures of included studies.

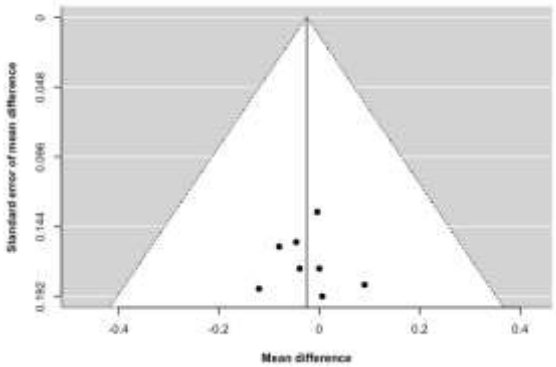
Study*, year	Funding
Wisniewski, 1997	The authors thank Astra Draco and Astra Clinical Research. Unit for help and financial support.
Fujita, 2001	The present study was supported by a grant from Shiga Foundation for Higher Research Promotion at the University of Shiga Prefecture.
Tattersfield, 2001	This study was funded by AstraZeneca R&D, Lund.
Sosa, 2006	This work was supported by a grant from Italfarmaco Laboratories, Spain.
Monadi, 2015	This study was funded by the Vice-Chancellor of Research and Technology, Babol University of Medical Sciences, Babol, Iran.
Sweeney, 2016	This work was supported by unrestricted research grants from Glaxo Smith Kline and F Hoffmann-La Roche Ltd and was performed in collaboration with the Respiratory Effectiveness Group.
Daugherty, 2017	The study was funded by GSK.
Blochliger, 2018	This study was supported by an unconditional grant from F. Hoffmann-La Roche Ltd.
Price, 2018	This study was funded by AstraZeneca.
Chalitsios, 2020	The study was funded by a research award from the British Medical Association.

**If a study is not included in the table it means that it does not report a funding statement.*

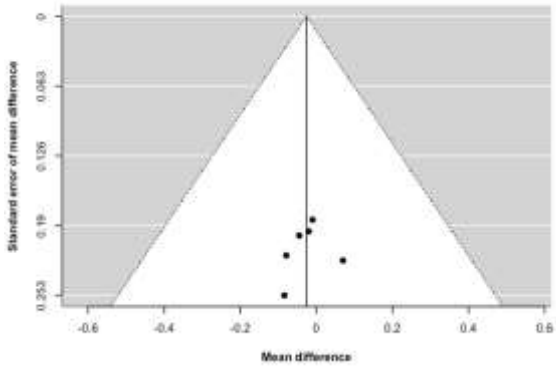
Funnel plots & Egger's test



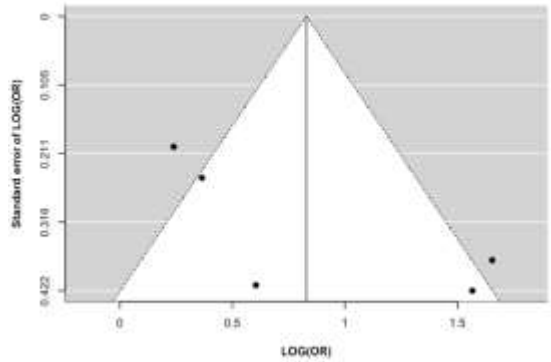
e-Figure 3. Funnel plot with Egger's test for meta-analysis of mean difference in BMD at spine comparing people with asthma exposed to ICS and healthy controls.



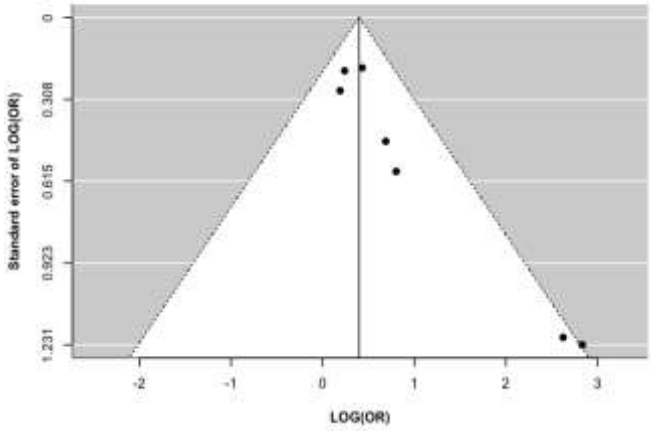
e-Figure 4. Funnel plot for meta-analysis of mean difference in BMD at femoral neck comparing people with asthma exposed to ICS and healthy controls.



e-Figure 5. Funnel plot for meta-analysis of mean difference in BMD at spine comparing people with asthma exposed to ICS and not exposed to ICS people with asthma.



e-Figure 6. Funnel plot for meta-analysis of risk of osteoporosis comparing people with asthma exposed to OCS and not exposed to OCS people with asthma.



e-Figure 7. Funnel plot for meta-analysis of risk of osteoporosis comparing people with asthma exposed to OCS and not exposed to OCS people with asthma.