Supplementary appendix:

Safety of SABA monotherapy in asthma management: a systematic review and meta-analysis

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Sensitivity analysis:

Discontinuations due to adverse events (DAEs)

Base case fixed-dose SABA and base case as-needed SABA

Pooled incidence was reduced to 2.7% following sensitivity analysis limited to studies of fixed-dose SABA with durations of 12–16 weeks. Heterogeneity was reduced from high to moderate. Taylor 1998 (1) and Hamilos 2008(2) were removed because of 24-week and 52-week durations, respectively. For the as-needed SABA sensitivity analysis, pooled incidence of DAEs was reduced slightly to 3.5% with consistent heterogeneity; Condemi 1997 (3) and Hamilos 2007 (2) were removed because of a 24-week duration.

No sensitivity analysis by asthma severity was necessary for the fixed-dose SABA group as all patients in these trials had mild-to-moderate asthma. For the as-needed SABA group, analysis was limited to studies that enrolled patients with mild-to-moderate asthma. This analysis returned results for DAEs similar to the base case (3.9%), with a minor increase in heterogeneity.

Jacobson 1999 (4) and ZuWallack 2000 (5) were excluded owing to inclusion of patients with moderate-to-severe asthma.

Base case ICS versus SABA

Sensitivity analysis was limited to trials comparing ICS with SABA at durations of 12–16 weeks.

This result of this analysis was almost identical to the base case analysis (odds ratio (OR) 0.51, 95% CI [0.34, 0.78]). There was an increase to 28.8% in heterogeneity.

For asthma severity, sensitivity analysis was limited to trials comparing ICS with SABA in patients with mild-to-moderate asthma. The result of this analysis was almost identical to the base case analysis (OR 0.50, 95% CI [0.32, 0.76]). Heterogeneity increased to 26.2%.

Serious adverse events (SAEs)

Base case fixed-dose SABA and base case as-needed SABA

Sensitivity analysis was limited to studies with durations of 12–16 weeks.

For the fixed-dose SABA group, there was a minor reduction in the proportion of patients with SAEs. Pooled incidence was 1.3% compared with the base case of 1.9%. No heterogeneity was present when the data were limited to 12 weeks, with Hamilos 2007(2) removed because of a 52-week duration. For the as-needed SABA group, the results of the meta-analysis did not change notably. Pooled incidence increased slightly from 1.88% (base case) to 1.98%. Heterogeneity increased to 57.1%, with Condemi 1997 (3), Nathan 1999 (6), and Beasley 2019(7) removed because of 24-, 26- and 52-week durations. For asthma severity, analysis was limited to studies of patients with mild-to-moderate asthma taking as-needed SABA. This analysis resulted in a lower incidence of SAEs than was reported for the base case (1.4% vs. 1.9%), and heterogeneity decreased to 21.4%. Jacobson 1999 was removed because it included patients with moderate-to-severe asthma.

Base case ICS vs. SABA

When the analysis was limited to 12-week data, results were similar to the base case analysis. OR was 0.92 (95% CI [0.34, 2.44]) with no heterogeneity. For sensitivity analysis limiting asthma severity to mild-to-moderate asthma, odds of experiencing SAEs increased from the base case analysis (OR 1.07, 95% CI [0.41,2.79]), with no heterogeneity. When studies that considered asthma exacerbations as an SAE were excluded, OR decreased to 0.84 from a base case of 0.95 and heterogeneity remained absent.

Table S1. Search terms used in EMBASE database search via OvidSP

Category	Search Number	Search Terms	Results
Population	1	exp asthma/ or asthma$.ti,ab.	304992
Intervention	2	(Short-Acting Beta-Agonist$ or SABA).ti,ab,kw.	2157
	3	salbutamol/	37126
	4	(salbutamol or "2 tert butylamino 1 (4 hydroxy 3 hydroxymethylphenyl)ethanol" or "4 [2 (tert butylamino) 1 hydroxyethyl] 2 (hydroxymethyl)phenol" or aero-clenil or aeroclenil or ah-3365 or ah3365 or albuterol or almotex or "alpha (tert butylaminomethyl) 4 hydroxy 3 (hydroxymethyl)benzyl alcohol" or "alpha (tert butylaminomethyl) 4 hydroxy meta xylene alpha,alpha' diol" or "alpha 1 [[(1,1 dimethylethyl)amino]methyl] 4 hydroxy 1,3 benzenedimethanol" or asmacaire or asmadil or asmalin or asmasal or asmatol or asmaven or asmavent or asmidon or asmol or bronchospray or broncho-spray or bronter or brytolin or butahale or buto-asma or butomix or butotal or butovent or buventol or cibutamol or cletal or cybutol or dilatamol or ecovent or emplusal or exafil or farcolin or frespire or glisend or grafalin or krosalburol or libretin or loftan or mozal or novosalmol or parasma or proventil or prox-s or pulmol-s or repetabs or respolin or salamol or salbuair or salbulin or salbumol fort or salbupart or salbuvent or salden or salgem or salmol or saltos or solbutamol or spacehaler or sultanol or venetlin or ventilan or ventodisk or ventodisks or ventol or volmac).ti,ab,kw.	15436
	5	levalbuterol/	914
	6	(levalbuterol or levolin or levosalbutamol or xopenex$).ti,ab,kw.	281
	7	pirbuterol/	844
	8	(pirbuterol or pyrbuterol or "CP-24,314-1" or Maxair or CP24315-1 or CP-24315-1 or CP243151).ti,ab,kw.	173
	9	or/2-8	41448
	10	1 and 9	20025
Outcomes	11	(ae or it or to).fs.	1886306
	12	exp adverse drug reaction/	558564

	13	exp side effect/	591949
	14	exp drug safety/	456846
	15	exp "drug toxicity and intoxication"/	182694
	16	toxic hepatitis/	12887
	17	exp drug hypersensitivity/	58996
	18	exp postmarketing surveillance/	37029
	19	phase 4 clinical trial/	4387
	20	drug recall/	703
	21	(safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti.	1495980
	22	(side effect* or safety or unsafe).ti,ab.	1220307
	23	((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab.	889101
	24	((drug or chemically) adj induced).ti,ab.	65105
	25	(toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab.	990155
	26	(warning* or recall* or withdrawn* or withdrawal*).ti.	45943
	27	(death or deaths or fatal or fatality or fatalities).ti.	185808
	28	or/11-27	5331109
	29	10 and 28	7126
Study Design	30	Clinical study/	156004
	31	Case control study/	175683
	32	Family study/	25316
	33	Longitudinal study/	158889

	34	Retrospective study/	1111495
	35	Prospective study/	702244
	36	Randomized controlled trials/	208366
	37	35 not 36	694220
	38	Cohort analysis/	735238
	39	(Cohort adj (study or studies)).mp.	359971
	40	(Case control adj (study or studies)).tw.	145817
	41	(follow up adj (study or studies)).tw.	66670
	42	(observational adj (study or studies)).tw.	195730
	43	(epidemiologic$ adj (study or studies)).tw.	111991
	44	(cross sectional adj (study or studies)).tw.	258810
	45	or/30-34,37-44	3124385
	46	Clinical Trial/	1009389
	47	Randomized Controlled Trial/	669339
	48	controlled clinical trial/	463593
	49	multicenter study/	295408
	50	Phase 3 clinical trial/	54946
	51	Phase 4 clinical trial/	4387
	52	exp RANDOMIZATION/	91750
	53	Single Blind Procedure/	43317
	54	Double Blind Procedure/	186210
	55	Crossover Procedure/	67704

	56	PLACEBO/	369212
	57	randomi?ed controlled trial$.tw.	263399
	58	rct.tw.	42975
	59	(random$ adj2 allocat$).tw.	47241
	60	single blind$.tw.	27352
	61	double blind$.tw.	221876
	62	((treble or triple) adj blind$).tw.	1398
	63	placebo$.tw.	329163
	64	Prospective Study/	702244
	65	or/46-64	2540998
	66	Case Study/	79952
	67	case report.tw.	456575
	68	abstract report/ or letter/	1205314
	69	Conference proceeding.pt.	0
	70	Editorial.pt.	698260
	71	Letter.pt.	1184218
	72	Note.pt.	859147
Filters & Combination	73	or/66-69,70-72	3356645
	74	65 not 73	2411231
	75	45 or 74	4663904
	76	29 and 75	3301
	77	(exp animal/ or nonhuman/) not exp human/	6623757

	78	76 not 77	3291
	79	limit 78 to english language	3139
	80	conference abstract.pt.	4147285
	81	79 not 80	2867
	82	limit 80 to yr="2019-current"	756564
	83	79 and 82	64
	84	81 or 83	2931
	85	limit 84 to yr="1996 -Dec 2021"	2386

Table S2. Search terms used in MEDLINE database search via OvidSP

Category	Search Number	Search Terms	Results
Population	1	exp asthma/ or asthma$.ti,ab.	185757
Intervention	2	(Short-Acting Beta-Agonist$ or SABA).ti,ab,kw.	1083
	3	exp albuterol/	10151
	4	(salbutamol or "2 tert butylamino 1 (4 hydroxy 3 hydroxymethylphenyl)ethanol" or "4 [2 (tert butylamino) 1 hydroxyethyl] 2 (hydroxymethyl)phenol" or aero-clenil or aeroclenil or ah-3365 or ah3365 or albuterol or almotex or "alpha (tert butylaminomethyl) 4 hydroxy 3 (hydroxymethyl)benzyl alcohol" or "alpha (tert butylaminomethyl) 4 hydroxy meta xylene alpha,alpha' diol" or "alpha 1 [[(1,1 dimethylethyl)amino]methyl] 4 hydroxy 1,3 benzenedimethanol" or asmacaire or asmadil or asmalin or asmasal or asmatol or asmaven or asmavent or asmidon or asmol or bronchospray or broncho-spray or bronter or brytolin or butahale or buto-asma or butomix or butotal or butovent or buventol or cibutamol or cletal or cybutol or dilatamol or ecovent or emplusal or exafil or farcolin or frespire or glisend or grafalin or krosalburol or libretin or loftan or mozal or novosalmol or parasma or proventil or prox-s or pulmol-s or repetabs or respolin or salamol or salbuair or salbulin or salbumol fort or salbupart or salbuvent or salden or salgem or salmol or saltos or solbutamol or spacehaler or sultanol or venetlin or ventilan or ventodisk or ventodisks or ventol or volmac).ti,ab,kw.	10102
	5	levalbuterol/	11
	6	(levalbuterol or levolin or levosalbutamol or xopenex$).ti,ab,kw.	169
	7	pirbuterol.nm.	113
	8	(pirbuterol or pyrbuterol or "CP-24,314-1" or Maxair or CP24315-1 or CP-24315-1 or CP243151).ti,ab,kw.	125
	9	or/2-8	14752
	10	1 and 9	6966
Outcomes	11	(ae or co or de).fs.	6407120
	12	exp "drug-related side effects and adverse reactions"/	121768
	13	psychoses, substance-induced/	5340
	14	exp drug hypersensitivity/	47447

	15	exp product surveillance, postmarketing/	16597
	16	clinical trial, phase IV.pt.	2150
	17	drug recalls/	141
	18	safety-based drug withdrawals/	405
	19	abnormalities, drug-induced/	14635
	20	(safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti.	1187271
	21	(side effect* or safety or unsafe).ti,ab.	805937
	22	((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab.	581923
	23	((drug or chemically) adj induced).ti,ab.	49023
	24	(toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab.	725151
	25	(warning* or recall* or withdrawn* or withdrawal*).ti.	40164
	26	(death or deaths or fatal or fatality or fatalities).ti.	169213
	27	or/11-26	8265078
	28	10 and 27	3926
Study Design	29	Randomized Controlled Trials as Topic/	146944
	30	randomized controlled trial/	539728
	31	Random Allocation/	105709
	32	Double Blind Method/	166235
	33	Single Blind Method/	30670
	34	clinical trial/	530166
	35	clinical trial, phase i.pt.	22055
	36	clinical trial, phase ii.pt.	35504
	37	clinical trial, phase iii.pt.	18801

	38	clinical trial, phase iv.pt.	2150
	39	controlled clinical trial.pt.	94322
	40	randomized controlled trial.pt.	539728
	41	multicenter study.pt.	300465
	42	clinical trial.pt.	530166
	43	exp Clinical Trials as topic/	361648
	44	or/29-43	1448954
	45	(clinical adj trial$).tw.	407141
	46	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	182015
	47	PLACEBOS/	35607
	48	placebo$.tw.	227438
	49	randomly allocated.tw.	31583
	50	(allocated adj2 random$).tw.	35045
	51	or/45-50	689612
	52	44 or 51	1744488
	53	case report.tw.	340870
	54	letter/	1146955
	55	historical article/	364814
	56	or/53-55	1835594
	57	52 not 56	1704804
	58	Epidemiologic studies/	8763
	59	exp case control studies/	1208725
	60	exp cohort studies/	2187492
	61	Case control.tw.	135799
	62	(cohort adj (study or studies)).tw.	243388

	63	Cohort analy$.tw.	9320
	64	(Follow up adj (study or studies)).tw.	51670
	65	(observational adj (study or studies)).tw.	125876
	66	Longitudinal.tw.	271719
	67	Retrospective.tw.	606361
	68	Cross sectional.tw.	407825
	69	Cross-sectional studies/	381002
	70	or/58-69	3302896
	71	57 or 70	4558684
	72	28 and 71	2286
	73	exp animals/ not exp humans/	4871099
	74	72 not 73	2274
Filters & Combination	75	limit 74 to english language	2141
	76	limit 75 to yr="1996 -Dec 2021"	1528

Table S3. Study, Patient and Treatment Characteristics of the 42 identified studies included in the assessment of feasibility for conducting meta-analysis

Author, year	Country	Study Design	Overall Sample Size	Blinding	Single or Multicenter	Planned Study Duration	Intervention (dose and frequency)	Comparator (dose and frequency)	Included in analysis? If not, exclusion reason
Azzi, 2019 (8)	Australia	Cross-sectional study	412	NA	Multiple	NR	SABA (NR)	No comparator	No- Non RCT
Nwaru, 2020 (9)	Sweden	Retrospective cohort study	365,324	NA	Multiple	Drugs collected from pharmacies in any 1-year period during 2006–2014	SABA (NR)	No comparator	No- Non RCT
Baumgarten, 2000 (10)	Germany	RCT	423	Double-blind	Multiple	4 weeks	SALB HFA (100 mcg, as needed)	SALB CFC (100 mcg, prn)	No- Treatment duration <12 weeks
Beasley, 2019 (7)	New Zealand, UK, Italy, and Australia	RCT	226	Open-label	Multiple	52 weeks	BUD + FORM: 200 mcg + 6 mcg, one inhalation prn for symptom relief BUD alone: 200 mcg, one inhalation-BID	ALB: 100 mcg, two inhalations prn for symptom relief	Yes
Bensch, 2001 (11)	US	RCT	541	Double-blind	Multiple	12 weeks	FORM: 12 and 24 mcg, BID	1) ALB- 180 mcg, QID 2) PBO (ALB prn)	Yes

Berger, 2002(12)	US	RCT	809	Double-blind	Multiple	12 weeks	FP 250 mcg, QD	PBO (ALB as needed)	Yes
Berkowitz, 1998 (13)	US	RCT	339	Double-blind	Multiple	8 weeks	BDP: 336 mcg/day, QID TAC: 800 mcg/day, QID	PBO (ALB prn)-90 mcg/puff	No- Treatment duration <12 weeks
Bernstein, 1998 (14)	US	RCT	121	Double-blind	Multiple	6 weeks	TAC- 100 mcg, four inhalation per actuation	PBO (ALB prn)	No- Treatment duration <12 weeks
Bronsky, 1998 (15)	US	RCT	328	Double-blind	Multiple	8 weeks	BDP: 336 mcg/day, four inhalations BID TAC: 800 mcg/day, four inhalations BID	PBO (ALB prn 90 mcg/puff	No- Treatment duration <12 weeks
Bronsky, 1999 (16)	NR	RCT	51	Blinded	NR	8 weeks	ALB: NR, two puffs BID and prn	HFA-134a ALB: NR, two puffs BID and prn	No- Treatment duration <12 weeks
Busse, 1998 (17)	US	RCT	538	Double-blind	Multiple	12 weeks	SAL: 42 mcg, BID	PBO (ALB prn)	No- LABA monotherapy
Chervinsky, 1999 (18)	US	RCT	352	Double-blind	Multiple	52 weeks	SAL: 50 mcg, BID	PBO (ALB prn)	No- LABA monotherapy
Condemi, 1997 (3)	US	RCT	291	Double-blind	Multiple	24 weeks	FP: 250 mcg, BID TAC: 200 mcg, QID	PBO (ALB prn)	Yes

Donohue, 2016 (19)	US	RCT	226	Double-blind	Multiple	4 week	Ipratropium bromide + ALB: 18 mcg + 103 mcg (equivalent to 90mcg ALB base)	ALB: 120 mcg from the canister valve and 108 mcg from the actuator mouthpiece (equivalent to 90 mcg ALB base)	No- Treatment duration <12 weeks
Drazen, 1996 (20)	US	RCT	255	Double-blind	Multiple	16 weeks	Regularly scheduled ALB: NR, QID	ALB prn	Yes
D'Urzo, 2001 (21)	NR	RCT	911	Double-blind	Multiple	24 weeks	SAL: 50 mcg, BID	PBO (SALB prn)	No- LABA monotherapy
FitzGerald, 1999 (22)	Canada	RCT	271	Double-blind	Multiple	24 weeks	FORM: 12 mcg, BID ALB: 200 mcg, QID	ALB prn: 200 mcg, prn	Yes
Galant, 1996 (23)	US	RCT	353	Double-blind	Multiple	12 weeks	FP: 50 and 100 mcg, BID Theophylline: 100 mg, BID	PBO (ALB prn)	Yes
Galant, 1999(24)	US	RCT	213	Double-blind	Multiple	12 weeks	FP: 500 mcg, BID for 12 weeks	PBO (ALB prn)	Yes
Hamilos, 2007 (2)	US	RCT	746	Open-label	Multiple	12 months	Levalbuterol: 90 mcg: 2 actuations of 45 mcg, QID	ALB: 180 mcg: 2 actuations of 90 mcg, QID	Yes

Jacobson, 1999 (4)	US	RCT	538	Double-blind	Multiple	12 weeks	TAC: 450, 900, and 1800 mcg*	PBO (ALB prn)	Yes
Kavuru, 2000 (25)	US	RCT	356	Double-blind	Multiple	12 weeks	SAL+ FP: 50 mcg+100 mcg, BID	SAL: 50 µg, BID FP: 100 µg, BID PBO (ALB prn)	Yes
Kemp, 1998 (26)	US	RCT	451	Double-blind	Multiple	12 weeks	SAL: 50 mcg, BID	ALB: 180 mcg, QID PBO (ALB prn)	Yes
Kemp, 1998 (27)	US	RCT	506	Double-blind	Multiple	12 weeks	SAL: 42 mcg, BID	PBO (ALB prn	No- LABA monotherapy
Malmstrom, 1999 (28)	Global	RCT	895	Double-blind	Multiple	12 weeks	Montelukast: 10 mg, QD	Inhaled BDP: 100 mcg/puff, BID PBO (SALB prn): 100 mcg/puff	Yes
Meltzer, 2009 (29)	US	RCT	446	Double-blind	Multiple	12 weeks	Ciclesonide: 80 and 160 mcg, BID	PBO (ALB prn)	Yes
Middle, 2002 (30)	South Africa	RCT	65	Evaluate or blind	Multiple	NR	SALB: 800 and 1600 mcg, four to seven days apart	PBO (SALB): NR	No- Treatment duration <12 weeks
Nathan, 1999 (6)	US	RCT	386	Double-blind	Multiple	26 weeks	SAL: 42 mcg, BID BDP: 84 mcg, QID	PBO (ALB prn)	Yes

Nathan, 2006 (31)	US	RCT	365	Double-blind	Multiple	12 weeks	Twice daily: FP + SAL: 220 + 42 mcg (two inhalations of 110/21 mcg) FP: 220 mcg (two inhalations of 110 mcg) SAL: 42 mcg (two inhalations of 21mcg)	PBO (ALB prn)	Yes
Nelson, 1999(32)	US	RCT	283	Double-blind	Multiple	12 weeks	ALB via DPI 90 mcg/actuation QID vs. MDI 108mcg/ actuation	ALB 100 mcg, two inhalations, as needed	Yes
Pearlman, 1999 (33)	US	RCT	136	Double-blind	Multiple	4 weeks	FP: 88 mcg SAL: 42 mcg SAL+ FP: 43 mcg+ 220 mcg FP: 220 mcg SAL+ FP: 42 mcg + 88 mcg, BID (all)	PBO (ALB prn)	No- Treatment duration <12 weeks
Pleskow, 2003 (34)	US	RCT	554	Double-blind	Multiple	12 weeks	FORM: 24 mcg, BID FORM: 12 mcg, BID ALB: 180 mcg, QID for 12 weeks	PBO (ALB): NR, NR	Yes

Ramsdell, 1998 (35)	US	RCT	101	Double-blind	Multiple	6 weeks	TAC: 100 mcg/ actuation, BID	PBO (ALB prn)	No- Treatment duration <12 weeks
Salat, 2000 (36)	Eastern European countries	RCT	547	Double-blind	Multiple	12 weeks	SALB: 200 mcg, QIDHFA	SALB: 200 mcg, QID CFC	Yes
Sheffer, 1996 (37)	US	RCT	307	Double-blind	Multiple	12 weeks	FP: 25, 50 and 100 mcg, BID	PBO (ALB prn)	Yes
Tammivaara, 1997 (38)	Finland	RCT	115	Open-label	Multiple	12 weeks	SALB: 100 mcg, BID	NR	Yes
Taylor, 1998(1)	New Zealand	RCT (Crossover)	165	Double-blind	Multiple	24 weeks	SAL: 50 mcg, BID SALB: 400 mcg, QID	PBO (SALB prn): Identical to the study drug	Yes
Tinkelman, 1998 (39)	US	RCT	565	Double-blind	Multiple	12 weeks	ALB: two puffs, QID	PBO (ALB prn): two puffs, QID	Yes
Welch, 1999 (40)	US	RCT	514	Double-blind	Multiple	8 weeks	TAC: 150, 300 and 600 mcg/day, one, two or four inhalations BID	PBO (ALB prn): one, two or four inhalations BID	No- Treatment duration <12 weeks
Wenzel, 1998 (41)	US	RCT	539	Double-blind	Multiple	12 weeks	SAL: 42 mcg, BID	PBO (ALB prn): 180 mcg, BID	No- LABA monotherapy

Wolfe, 2000 (42)	US	RCT	498	Double-blind	Multiple	12 weeks	SAL: 42 and 50 mcg, two inhalations BID and one inhalation BID, respectively	PBO (ALB prn): NR	No- LABA monotherapy
ZuWallack, 2000 (5)	US	RCT	253	Double-blind	Multiple	Placebo control: 12 weeks Open-label: 54 weeks	FP: 250 mcg, BID	PBO (ALB prn): NR, BID	Yes

Abbreviations: ALB, albuterol; BID, two times a day; BDP, beclomethasone dipropionate; BUD, budesonide; CFC, chlorofluorocarbon; DPI, dry powder inhaler; FORM, formoterol; FP, fluticasone propionate; HFA, hydrofluoroalkane; LABA, long-acting beta agonist; MDI, metered dose inhaler; NA, not applicable; PBO, placebo; prn, as-needed; SALB, salbutamol; SAL, salmeterol; TAC, triamcinolone acetonide; QD, once-daily; QID, 4 times daily.

Table S4. Cochrane risk of bias assessment analysis for studies included in the analysis (43)

Study	Randomization process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported result		Overall bias	
	Algorithm result	Assessor's judgment	Algorithm result	Assessor's judgment	Algorithm result	Assessor's judgment	Algorithm result	Assessor's judgment	Algorithm result	Assessor's judgment	Algorithm result	Assessor's judgment
Beasley, 2019	Low score	Low score	Some concerns	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Low score	Low score	Some concerns	Some concerns
Bensch, 2001	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Berger, 2002	Low score	Low score	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Low risk	Low risk
Condemi, 1997	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Drazen, 1996	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
FitzGerald, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Kemp, 1998	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Nelson, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Pleskow, 2003	Low score	Low score	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Low risk	Low risk
Taylor, 1998	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns

Tinkelman, 1998	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Hamilos, 2007	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Low score	Low score	Some concerns	Some concerns
Salat, 2000	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Tammivaara, 1997	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	High risk	High risk	High risk	High risk
Galant, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Galant, 1996	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jacobson, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	High risk	High risk
Malmstrom, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Meltzer, 2009	Low score	Low score	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Low risk	Low risk
Nathan, 1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Nathan, 2006	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
Sheffer, 1996	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns
ZuWallack, R, 2000	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns

Kavuru, 2000	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low score	Low score	Some concerns	Some concerns

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