The Effect of Inhaled Steroids on the Linear Growth of Children With Asthma: A Meta-analysis

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ABSTRACT. *Objective.* **To determine whether inhaled steroid therapy causes delayed linear growth in children with asthma.**

Data Sources. **Medline (1966–1998), Embase (1980–1998), and Cinahl (1982–1998) databases and bibliographies of included studies were searched for randomized, controlled trials of inhaled steroid therapy in children with asthma that evaluated linear growth.**

Study Selection. **Studies were included if they met the following criteria: subjects 0 to 18 years of age with the clinical diagnosis of asthma; subjects randomized to inhaled beclomethasone, budesonide, flunisolide, fluticasone, or triamcinolone versus a nonsteroidal inhaled control for a minimum of 3 months; single- or double-blind; and outcome convertible to linear growth velocity. English- and non–English-language trials were included.**

Data Extraction. **Data were extracted using a priori guidelines. Methodologic quality was assessed independently by both authors. Outcome was extracted as linear growth velocity.**

Results. **Included trials were subgrouped by inhaled steroid. The beclomethasone subgroup, with 4 studies and 450 subjects, showed a decrease in linear growth velocity of 1.51 cm/year (95% confidence interval: 1.15,1.87). The fluticasone subgroup, with 1 study and 183 subjects, showed a decrease in linear growth velocity of .43 cm/year (95% confidence interval: .01,.85). Sensitivity analysis in the beclomethasone subgroup, which evaluated study quality, mode of medication delivery, control medication, and statistical model, showed similar results.**

Conclusions. **This meta-analysis suggests that moderate doses of beclomethasone and fluticasone in children with mild to moderate asthma cause a decrease in linear growth velocity of 1.51 cm/year and .43 cm/year, respectively. The effects of inhaled steroids when given for >54 weeks, or on final adult height, remain unknown.** *Pediatrics* **2000;106(1). URL: http://www.pediatrics.org/cgi/content/full/106/1/e8;** ***asthma, children, growth, inhaled steroid, beclomethasone, fluticasone.***

ABBREVIATIONS. RCT, randomized, controlled trial; WMD, weighted mean difference; CI, confidence interval.

Asthma is a chronic inflammatory disease of the airways affecting an estimated 4.8 million children younger than 18 years of age in the United States.[1] Asthma is responsible for >28 million restricted activity days in children and 2.2 million pediatrician visits annually.[2] Between 1980 and 1993, mortality rates increased 118% and hospitalization rates increased 28% for children with asthma.[3] Children with asthma miss 3 times as much school as children without asthma,[4] and the overall cost of severe asthma in childhood was estimated at $18 000 per child per year.[5] With prevalence rates increasing from 3.1% in 1981 to 6.9% in 1994,[6] asthma is the most common chronic disease in childhood.

These data are striking in light of increased understanding of the pathophysiology of asthma. Recently, for example, the vital role of the inflammatory process in asthma has been recognized and emphasized.[7,8] Studies over the past 15 years have revealed improvement in multiple asthma outcomes in patients treated with inhaled and systemic steroids.[9–16] Inhaled steroids are now recommended for all children with chronic persistent asthma.[8] Evidence that inhaled steroids effectively control asthma in children and minimize pulmonary damage has resulted in a dramatic increase in the use of inhaled steroids in the control of asthma in children.

Despite clear benefits, there are risks to the use of inhaled steroids in children with asthma. These risks include altered hypothalamic-pituitary axis functioning[17–21] with possible resultant delayed linear growth.[22–27] The recent Food and Drug Administration mandate to require labels on inhaled and intranasal corticosteroids warning of a potential reduction in linear growth in children depicts this concern.[28] Attempts to determine the effect of inhaled steroids on linear growth in children with asthma are confounded by poorly controlled asthma, reduced growth rates before puberty, delayed puberty, and frequent use of growth-suppressing systemic steroids.[29–31] The 1 previous systematic review evaluating growth in asthmatic children using inhaled steroids concluded inhaled steroids had no effect.[27] Recent randomized, controlled trials (RCTs), however, conflict with this conclusion.[22–25]

As a result of previous studies with conflicting results, the publication of recent data that could impact the conclusions of the only published meta-analysis, and persistent uncertainty regarding the effect of inhaled steroids on the linear growth of children with asthma, we undertook this systematic review. The aim of this systematic review was to determine whether inhaled steroid use is associated with growth suppression in children with asthma.

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METHODS

Trial Identification

Relevant RCTs in all languages were identified as follows. First, 3 databases were systematically searched for studies on asthma: 1) Medline, from 1966 to 1998; 2) Embase, from 1980 to 1998; and 3) Cinahl, from 1982 to 1998. In Medline, full-text and Medical Subject Heading terms were searched for using "asthma*"; in Embase, a full-text and keyword search was performed using "asthma*"; and in Cinahl, a full-text and Medical Subject Heading terms were searched using "asthma*." The identified records were then imported into a Pro-Cite database. Within this asthma database, we searched across all fields to identify possible RCTs using the terms: "random*" or "trial*" or "placebo*" or "comparative study" or "controlled study" or "double-blind" or "double blind" or "single-blind" or "single blind." The results of this search were downloaded into a new database, which was searched on all fields for "steroid*" or "corticosteroid*" or "glucocorticoid*" or "budesonide" or "flunisolide" or "fluticasone" or "triamcinolone" or "beclomethasone" and "inhal*" and "child*" or "infan*" or "adolescen*" or "pediatr*" or "paediatr*." Each abstract was then reviewed and annotated as: 1) RCT, 2) clearly not RCT, or 3) unclear. All references identified as RCTs or unclear were included for title and abstract review. All non-English language publications that could not be excluded by title or abstract were translated and evaluated in the same manner as English language publications.

Each title and abstract from the search results was reviewed with respect to the inclusion criteria. Any trials not specifically removed for failure to meet the inclusion criteria based on title or abstract were reviewed in detail. Reference lists of all identified RCTs were checked to identify relevant citations. Personal contact with colleagues and researchers working in the field of asthma was made to identify relevant trials and any unpublished data.

Trial Selection and Quality

From the title, abstract, or descriptors, 1 reviewer (P.J.S.) reviewed literature searches, bibliographies, and texts to identify potentially relevant trials for full review. From the full text, 2 reviewers (P.J.S. and D.A.B.) independently selected trials for inclusion into this review based on the following predetermined selection criteria: 1) randomized, single- or double-blind, controlled trials comparing the use of the inhaled steroids beclomethasone, budesonide, flunisolide, fluticasone, or triamcinolone with a nonsteroidal medication; 2) children <18 years old at entry who were not using oral steroids at the beginning of the study; 3) clinical diagnosis of asthma; and 4) treatment for a minimum of 3 months. All doses of inhaled steroids were accepted and classified into the categories of low, medium, or high as defined by the guidelines of the US National Heart, Lung, and Blood Institute.[8] All modes of administration of inhaled steroids, including nebulizer, metered-dose inhaler, diskhaler, or turbuhaler were allowed. Agreement was measured using a κ statistic (a value between 0 and 1 with 0 defining no agreement and 1 defining exact agreement),[32] and disagreement was resolved by consensus.

The internal validity of included trials was assessed independently by both authors using the Jadad scale.[33] In addition, each trial was evaluated for adequacy of randomization.[34,35] Interrater reliability was measured using simple agreement and κ statistics,[32] and discrepancies were resolved by consensus. Where there was uncertainty, authors were contacted to clarify the randomization and blinding methods used.

Data Extraction and Definition of Terms

The primary outcome of interest was linear growth velocity, expressed in centimeters per year. Both authors independently abstracted primary outcome data from each trial, using a standardized data extraction sheet. When necessary, study authors were contacted to obtain information not provided in the primary publication. Data were abstracted for number randomized, number enrolled, number completed, specific medication used, dose and route of medication delivery, duration of intervention, compliance, and mean linear growth velocity for control and intervention groups. Descriptive data were collected on patient baseline characteristics, study definition of asthma, inclusion criteria, and exclusion criteria. The number of withdrawals and reasons for withdrawal in each treatment arm were recorded.

Data Analysis

Meta-analysis was performed on all trials that met the inclusion criteria. This meta-analysis was conducted using the Cochrane Collaboration software program, Review Manager, Version 3.1 (Cochrane Collaboration, Oxford, UK). The mean linear growth velocity of subjects treated with inhaled steroids was compared with the mean linear growth velocity of subjects treated with a nonsteroidal preparation, and the results were expressed as the difference in mean linear growth velocity. A difference of the means (mean difference) of <0 indicates that inhaled steroids have a decelerating effect on linear growth compared with the control medication. The mean difference was calculated for each individual trial, and using the fixed effects model[36] a summary weighted mean difference (WMD) was determined. The weighting method used defines the weight of the trial as the inverse of the variance of the mean difference. One study[23] did not report standard deviations for the linear growth velocities of each group and, therefore, after repeated attempts to contact the author were unsuccessful, we estimated the standard deviations assuming equal deviation in the intervention and control groups. Statistical heterogeneity among trials was assessed by the Q test[37,38] and graphically.[39] Summary WMDs were calculated using the random effects model of DerSimonian and Laird[38] for comparison between statistical models.

Sensitivity analyses were conducted to assess the robustness of the meta-analysis by comparing WMDs among groups redefined by: 1) excluding trials of lower methodological quality (Jadad score <4; randomization score <A),[33,40] 2) excluding trials using the metered-dose inhaler method of medication delivery, and 3) excluding trials using nonplacebo, control medication. A funnel graph of the study weight versus the mean difference of lengths was plotted to determine the existence of publication bias.[39]

RESULTS

Trial Identification and Selection

A total of 159 studies were identified: 93 from the Cochrane Collaboration Asthma Pro-Cite database and 66 from bibliographic searches. No unpublished studies were identified and no additional studies were identified by expert contact. Sixty-seven studies were excluded by title or abstract, leaving 92 trials for full-text review. Of the remaining 92 trials, 87 were excluded for the following reasons: no children in study (20), <12 weeks of inhaled steroids (18), trial not an RCT (14), length not an outcome (14), article was a review paper (5), trial was not an asthma trial (4), trial used inhaled steroid controls (4), trial used a subpopulation of an included or reviewed study (4), article was a letter (3), and author was unable to be contacted (1). This left 5 trials[22–26] for inclusion into the meta-analysis. Substantial interrater agreement for trial inclusion into the meta-analysis was attained (κ = .89).

Description of Trials

Four of the 5 included trials used beclomethasone (dose range: 328–400 μg/day) as the intervention group inhaled steroid,[22–25] while the fifth study,[26] used fluticasone (200 μg/day). All 5 of the trials were double-blind, with 4 of the 5 trials[22,24–26] using off-site personnel for randomization. Ages of the participants ranged from 6 to 16 years old with 4 trials[23–26] including postpubertal children. Three studies[22,23,25] enrolled only patients that had been off of inhaled or systemic steroids for a minimum of 3 months, 1 study[24] required 1 month off inhaled steroids, and 1[26]

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allowed inhaled steroids at the time of enrollment assuming a 3-month stable dose.

Each of the 5 included studies differed slightly on their asthma definition. Four studies[23–26] included pulmonary function test requirements for inclusion, and all 5 required a defined symptom burden. Each study selected a population with mild to moderate asthma[8] thought to have clinically stable asthma at the time of enrollment. Four of the 5 studies[22,23,26] used a diskhaler device for medication delivery, while the fifth[24] used a metered-dose inhaler. The duration of treatment varied from 7 months[22] to 54 weeks.[25] Combination of all 5 trials, representing 855 subjects, revealed a mean age of 9.5 years old, a mean percentage of males of 67.0%, and a mean baseline forced expiratory volume in 1 second of 85.4%. Dropout rates varied from 10.6% to 33.3%. Trials took place in the United States, Canada, or Europe.

All 5 studies calculated growth velocity using the regression coefficient of height on time. Four of the 5 studies[23–26] used a stadiometer to measure height, while the other[22] used a minimeter. Two of the 5[22,26] used growth as the primary outcome, while the other 3[23–25] used growth as a secondary outcome measure. Heterogeneity of all 5 studies was assessed using the Q test resulting in a z value of 7.52 and a P value of $>.999$.

Methodologic Quality

The mean Jadad quality score for the included trials was 4.0 (standard deviation: .71) of a maximum score of 5 (Table 1). Substantial interrater agreement was reached ($\kappa = .76$). Four of the 5 trials reported adequate randomization of treatment allocation using an independent randomization center.[22,23,25,26] Compliance was evaluated in 4 of the 5 studies[22–24,26] and ranged from 75% to 94%. Withdrawal rates were low (range: 10%–33%) and were weighted toward the control arm. Each study adequately addressed the reasons for dropout.

Outcome of Inhaled Steroids on the Linear Growth of Children With Asthma

Subgrouping of studies by inhaled steroid used was determined a priori. Each of the 4 included trials that evaluated beclomethasone[22–25] revealed a decreased linear growth velocity in children using beclomethasone. Meta-analysis of the 4 studies in the beclomethasone subgroup supports the conclusion there is a significant decrease in linear growth in children with mild to moderate asthma using medium-dose inhaled beclomethasone (Fig 1). The typical WMD between 231 children treated with inhaled beclomethasone and 209 children treated with a nonsteroid medication was −1.51 cm/year (95% confidence interval [CI]: −1.15,−1.87). The fluticasone subgroup, consisting of 1 study,[26] revealed a modest statistically significant decrease in linear growth when comparing the moderate strength dose of 200 μg/day with placebo. The mean difference between 96 children treated with inhaled fluticasone 100 μg twice daily and 87 children treated with a placebo was −.43 cm/year (95% CI: −.01,−.85).

Sensitivity Analysis and Publication Bias

Sensitivity analyses were conducted for the outcome linear growth velocity (Table 2). Significant decrease in linear growth velocity remained when trials were grouped as: 1) high-quality trials, 2) trials with adequate treatment allocation, 3) trials using methods of medication delivery other than metered-dose inhaler, or 4) trials using placebo controls (Tables 1 and 2). Use of a random effects model did not significantly affect the outcome. Sensitivity analyses of treatment duration (less than or greater than 6 months), inhaled steroid dose (low, medium, or high as defined by the National Heart, Lung, and Blood Institute guidelines), and subject age (older or younger than 13 years of age) were not performed attributable to lack of study variation or inability of authors to stratify their data based on age.

A funnel plot[41] of the 4 beclomethasone studies, graphing the study weight (the inverse of the variance of the mean difference) on the y-axis and the mean difference of lengths on the x-axis revealed no obvious exclusion of studies concluding a small measure of effect (Fig 2). Although caution must be exercised in interpreting a funnel plot with only 4 points, our plot suggests no obvious publication bias.

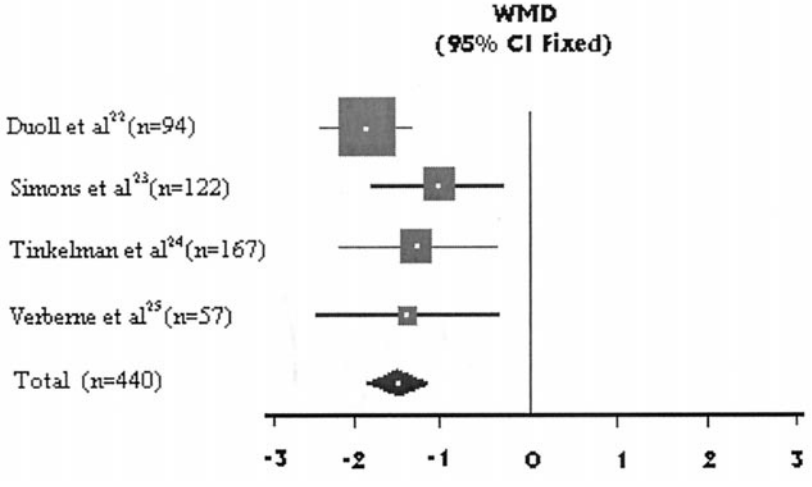

Fig 1. Inhaled beclomethasone in children with asthma: using the fixed effects model WMDs in linear growth velocity and 95% CIs. Negative values for WMD show adverse effects in linear growth velocity from inhaled beclomethasone. Box areas are proportional to study weights.

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TABLE 1. Methodologic Quality of Included Trials

Reference	Quality Score	Concealment of Treatment Allocation	Number in Arm	Medication	Duration	Dropouts	Subgroup Data
Doull et al[22]	4	Adequate	46	Beclomethasone	7 mo	6/52	No
			48	Placebo		4/52	
Simons et al[23]	3	Unclear	67	Beclomethasone	12 mo	14/81	Salmeterol as control
			58	Salmeterol		22/80	
			55	Placebo		25/80	
Tinkelman et al[24]	5	Adequate	86	Beclomethasone	48 wk	16/102	Theophylline as control
			81	Theophylline		11/92	
Verberne et al[25]	4	Adequate	32	Beclomethasone	54 wk	3/35	Salmeterol as control
			25	Salmeterol		7/32	
Allen et al[26]	4	Adequate	85	Fluticasone 50 μg BID	52 wk	19/85	Fluticasone
			96	Fluticasone 100 μg BID		17/85	
			87	Placebo		30/87	

TABLE 2. Sensitivity Analysis of Primary Outcome of Linear Growth Velocity: Beclomethasone Subgroup

Description	Reference of Included Trials	Summary WMD (95% CI)
All trials	Doull et al,[22] Simons et al,[23] Tinkelman et al,[24] Verberne et al[25]	−1.51 cm/y (−1.15,−1.87)
Quality ≥4	Doull et al,[22] Tinkelman et al,[24] Verberne et al[25]	−1.65 cm/y (−1.23,−2.06)
Quality <4	Simons et al[23]	−1.08 cm/y (−.35,−1.81)
Concealment adequate	Doull et al,[22] Tinkelman et al,[24] Verberne et al[25]	−1.65 cm/y (−1.23,−2.06)
Concealment not adequate	Simons et al[23]	−1.08 cm/y (−.35,−1.81)
Delivery method: diskhaler	Doull et al,[22] Simons et al,[23] Verberne et al[25]	−1.54 cm/y (−1.15,−1.94)
Delivery method: metered-dose inhaler	Tinkelman et al[24]	−1.30 cm/y (−.38,−2.23)
Control: placebo	Doull et al,[22] Simons et al[23]	−1.57 cm/y (−1.15,−1.99)
Control: theophylline or salmeterol	Tinkelman et al,[24] Verberne et al[25]	−1.35 cm/y (−.66,−2.03)

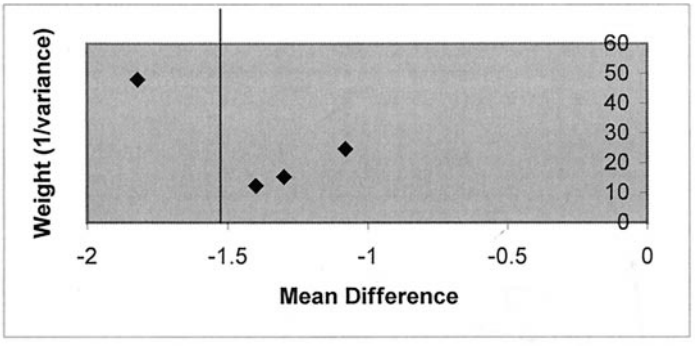

Fig 2. Funnel plot of the study weight (defined by 1/variance) versus mean difference for studies included in the meta-analysis of linear growth velocity in the beclomethasone subgroup.

DISCUSSION

Our meta-analysis results suggest that a moderate dose[8] of the inhaled steroid beclomethasone significantly decreases the linear growth velocity of children with mild to moderate asthma. Similarly, a moderate dose[8] of the inhaled steroid fluticasone significantly decreases the linear growth velocity of children with mild to moderate asthma. Caution must be used when generalizing about fluticasone, however, because only 1 study was incorporated and the magnitude of effect was smaller than that of beclomethasone.

Review of the Hill[42] criteria for causal inference strengthens these conclusions. First, the quality of the included trials is outstanding, as each was a RCT that passed a rigorous set of a priori inclusion criteria. In addition, each included study earned a high quality score. Second, the size of the measure of effect is large and of clear clinical significance. Third, the effect of inhaled steroids on linear growth is consistent across all 4 beclomethasone trials, despite a wide variety of ages, ethnicities, medication delivery systems, and treatment durations. This consistency is graphically depicted by overlap of the 4 CIs of the measures of effect. Fourth, there is substantial indirect evidence that supports the likelihood of this finding. Systemic steroids are well-known to cause significant growth delay through the inhibition of the hypothalamic-pituitary axis,[27–29] and inhaled steroids have been shown to frequently depress the hypothalamic-pituitary axis, thus revealing significant systemic absorption.[17–21] In addition, recent evidence suggests that nasal steroids may also affect growth velocity,[28] further demonstrating that topical steroids in commonly used doses may be absorbed enough to affect growth. Fifth, many of the plausible alternative explanations of the observed effects, including selection bias, publication bias, and trial heterogeneity have been minimized or eliminated by the rigorous methodology of this review. The sixth and final criterion for causal inference, that of a dose–response relationship between inhaled steroids

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and linear growth delay, was not evaluated because all studies satisfying the inclusion criteria used moderate doses of the inhaled steroid beclomethasone or fluticasone.

Potential weaknesses of meta-analysis include the incorporation of within study biases and the introduction of between study biases. These biases have been shown to result in conflicting results between meta-analysis and single large RCTs.[43–45] To minimize bias within selected trials during study selection, we used predetermined inclusion and exclusion criteria. Requiring randomization and a control population minimizes the likelihood of selection bias within individual trials. We evaluated for biases within individual trials by using both the validated Jadad scale of study quality and the Cochrane scale of randomization quality. Both approaches allowed sensitivity analysis of studies of higher quality, which did not substantially affect our conclusions. High quality scores suggest only valid trials were included in this review. Between study bias, which is introduced when trials are combined, is caused by publication bias, selection bias, or substantial trial heterogeneity. Publication bias was assessed using a funnel plot,[41] and no publication bias was evident (Fig 2). Using strict inclusion and exclusion criteria minimized selection bias. No small studies or prematurely terminated studies, which tend toward extreme findings,[43] were selected for inclusion. Trial heterogeneity was evaluated by the Q test, which revealed no evidence of significant study heterogeneity. In addition, the similar conclusions of the fixed effects and random effects models strengthen the conclusion of minimal trial heterogeneity. Finally, graphical analysis shows CI overlap, which adds further strength to the assumption, the trials are similar and combinable.[39] The high Q test value, the similar measures of effect of the fixed effects and random effects model, and the overlap of individual CIs provide strong evidence the trials are similar and thus combinable.

This meta-analysis supports a statistically significant decrease in the linear growth velocity of children with mild to moderate asthma treated with moderate doses of the inhaled steroid beclomethasone. This is the opposite conclusion of the only other published meta-analysis.[27] There are several possible reasons for this discrepancy. First, more data of higher quality have become available since the publication of the first meta-analysis. Second, to minimize selection bias of within study populations, we used only RCTs, whereas the previous meta-analysis incorporated only cohort studies. Third, to promote equivalent control and study populations, our control populations consisted of only children with asthma, whereas the previous meta-analysis allowed control populations of children without asthma. Fourth, we used and described a specific, extensive a priori search strategy to minimize study selection bias, whereas the previous meta-analysis did not state the search strategy. Fifth, we included studies that either directly measured growth velocity or had outcomes that could be converted to growth velocity, whereas the previous meta-analysis excluded all studies using growth velocity or summary statistics in the outcome. Sixth, although not an a priori exclusion criterion, all studies included in our analysis had loss to follow-up at 33% or less, whereas the previous meta-analysis included studies with much larger losses to follow-up. Overall, the increased methodologic rigor of our study together with the availability of recent RCT data are anticipated to result in less effect of within and between study selection bias, publication bias, and information bias on our measure of effect and conclusions.

Several limitations of this meta-analysis exist. First, the use of the linear growth velocity outcome measure assumes the effect of inhaled steroids on growth to be linear. This may not be the case. Simons et al[23] suggest the majority of growth delay occurs within the first 3 months of inhaled steroid therapy, with growth velocities of subjects using inhaled steroids similar to those using placebo after 3 months of treatment. If growth delay is confined to the first 3 months of therapy, then the implications for growth in long-term therapy are less significant. In contrast, Tinkelman et al[24] found growth velocity differences between 6 months and 12 months similar to those between 0 months and 6 months of beclomethasone therapy. We were unable to stratify by duration of therapy in this meta-analysis and, therefore, unable to address this important issue.

A second limitation of this study was the inability to determine whether variable effects of inhaled steroid occurred in children of different ages. It was suggested by Tinkelman et al[24] that postpubertal adolescent growth rate was less affected by inhaled steroids than the growth rate of prepubertal children. The number of subjects in the Tinkelman study who were postpubertal was too small for meaningful analysis, however. Similar negligible effects were found in 1 trial evaluating adolescents treated with the inhaled steroid budesonide.[46] Two of the other beclomethasone studies included[23,25] had postpubertal subjects as well but did not stratify based on pubertal status. Consequently, we were unable to stratify our results based on age or pubertal status of the subjects.

A third limitation of this meta-analysis is the lack of included trials evaluating the effect of >54 weeks of inhaled steroids on growth. Several studies have attempted to evaluate the effect of long-term inhaled steroids on linear growth in children with asthma[47–49]; however, none was an RCT. The conclusions of several cohort studies have been that inhaled steroids do not have long-term growth effects when used up to 5 years; however, flaws exist within each of the study designs. Examples of such flaws that may greatly impact results are the lack of control subjects with asthma,[48–51] variation of the dose or regimen used within study populations,[47–51] possible selection bias,[47–51] and uncertain dropout rates.[47,51] All of these flaws could bias the measure of effect toward the null. For example, 1 study tracks height differences each 6 months for 5 years and does not show any differences in height between intervention and control patients at 6 or 12 months. If our study results are valid, then this suggests a methodologic

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problem with this cohort study that biases the results toward the null. Without using randomization, blinding, and appropriate control groups, these data must be viewed with caution.

A fourth limitation of this meta-analysis is the within study selection bias that could occur from patient dropouts. The majority of dropouts in all 5 studies were from the control group, many of whom dropped out because of worsening disease. It is conceivable that children with more severe disease, whose growth would be slower based on disease severity alone, were more likely to drop out, leaving a subset of faster growing subjects in the control group for comparison. The end result would be a biased widening of the mean difference in linear growth velocity expressed as a summary statistic. An argument against this bias is found in the intention-to-treat analysis of Tinkelman et al,[24] who found similar changes in growth velocity occurred when analyzing the control group with or without dropouts. Intention-to-treat analysis was not performed in the other 4 studies included in this review.

Finally, potential questions regarding the value of a meta-analysis that summarizes 5 studies with consistent conclusions may arise. In our opinion, these questions are misguided. As stated previously, discrepant findings are found within and between cohort studies, RCTs, and the 1 published meta-analysis regarding the effect of inhaled steroids on the linear growth of children with asthma. The technique of meta-analysis addresses discordant studies by dictating a priori delineation of methodologically sound criteria to select, in an unbiased manner, studies most likely to be valid. In this meta-analysis, all 5 studies that emerged happened to have similar results. The final act of statistically combining the consistent individual study results into a single result is secondary to the systematic and unbiased selection of the studies themselves. Rather than minimizing the value of the technique, we think this unbiased and systematic selection of 5 studies with similar conclusions greatly strengthens the summary conclusion and validates the meta-analysis methodology.

CONCLUSION

In summary, the use of moderate doses of the inhaled steroid beclomethasone in children with mild to moderate asthma has been shown to significantly affect linear growth. It would be inappropriate to judge the effect of moderate doses of inhaled fluticasone based on the 1 included study; however, a statistically significant difference was revealed. The negative effect on linear growth velocity needs to be weighed against the known positive effects of inhaled steroids on such outcomes as quality of life, symptom days, severity of exacerbations, decreased lung architectural changes, and health care utilization before clinical significance is clear. Additionally, whether inhaled steroids in doses presently used in children with asthma affect final adult height remains unanswered. Finally, we are unable to determine the effect of low-dose or high-dose inhaled steroids, or the effect of nonbeclomethasone or nonfluticasone inhaled steroids on linear growth with this meta-analysis. Until these questions are answered, the risks of this highly effective class of medications will remain unknown. This meta-analysis suggests that if inhaled steroids are required to control asthma in a child, then careful monitoring of height and an emphasis on using the lowest possible effective dose would be appropriate steps in minimizing their effects on growth.

REFERENCES

1. Centers for Disease Control and Prevention. Asthma—United States, 1989–1992. *MMWR CDC Surveill Summ*. 1995;43:952–955
2. Gergen PJ, Mullally DI, Evans R. National survey of prevalence of asthma among children in the United States, 1976 to 1980. *Pediatrics*. 1988;8:1–7
3. Centers of Disease Control and Prevention. Surveillance for asthma—United States, 1960–1995. *MMWR CDC Surveill Summ*. 1998;47(suppl 1):1–27
4. Fowler MG, Davenport MG, Garg R. School functioning of US children with asthma. *Pediatrics*. 1992;90:939–944
5. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med*. 1992;326:862–866
6. Adams PF, Marano MA. Current estimates from the National Health Interview Survey, 1994. *Vital Health Stat*. 1995;10:94
7. National Asthma Education and Prevention Program. *Expert Panel Report I: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Institutes of Health; 1991
8. National Asthma Education and Prevention Program. *Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Institutes of Health; 1997
9. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis*. 1993;148:S1–S26
10. Dahl R, Lundback E, Malo JL, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest*. 1993;104:1352–1358
11. Fabbri L, Burge PS, Croonenborgh L, et al. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax*. 1993;48:817–823
12. Gustafsson P, Tsanakas J, Gold M, et al. Comparison of the efficacy and safety of inhaled fluticasone 200 μg/day with inhaled beclomethasone dipropionate 400 μg/day in mild and moderate asthma. *Arch Dis Child*. 1993;69:206–211
13. Haahtela T, Jarvinen M, Kava T, et al. Comparison of a β2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med*. 1991;325:388–392
14. Jeffery PK, Godfrey RW, Adelroth E, et al. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis*. 1992;145:890–899
15. Raffery P, Tucker LG, Frame MH, et al. Comparison of budesonide and beclomethasone dipropionate in patients with severe chronic asthma: assessment of relative prednisone-sparing effects. *Br J Dis Chest*. 1985;79:244–250
16. Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or β2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis*. 1992;146:547–554
17. Boorsma M, Andersson N, Larsson P, et al. Assessment of the relative systemic potency of inhaled fluticasone and budesonide. *Eur Respir J*. 1996;9:1427–1432
18. Brown PH, Matusiewicz SP, Shearing C, et al. Systemic effects of high dose inhales steroids: comparison of beclomethasone dipropionate and budesonide in healthy subjects. *Thorax*. 1993;48:967–973
19. Clark DJ, Grove A, Cargill RI, et al. Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients. *Thorax*. 1996;51:262–266
20. Prahl P. Adrenocortical suppression following treatment with beclomethasone dipropionate and budesonide. *Clin Exp Allergy*. 1991;21:145–146
21. Tabachnik E, Zadik Z. Diurnal cortical secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. *J Pediatr*. 1991;118:2974–2977
22. Doull IJM, Freezer NJ, Holgate ST. Growth of pre-pubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med*. 1995;151:1715–1719

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23. Simons FER, Dolovich J, Moore DW, et al. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med*. 1997;337:1659–1665
24. Tinkelman DG, Red CE, Nelson HS, et al. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic mild to moderately severe asthma in children. *Pediatrics*. 1993; 92:64–77
25. Verberne AAPH, Frost C, Roorda RJ, et al. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med*. 1997;156:688–695
26. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. *J Pediatr*. 1998;132:472–477
27. Allen E, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol*. 1994;93: 967–976
28. Food and Drug Administration. FDA requires new pediatric labeling for inhaled, intranasal corticosteroids. Available at: http://www.fda.gov. Accessed November 9, 1998. Talk paper
29. Allen DB. Growth suppression by glucocorticoid therapy. In: Vassallo J, ed. *Endocrinology and Metabolism Clinics in North America*. Philadelphia, PA: WB Saunders Co; 1996:699–717
30. Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child*. 1986; 61:1049–1055
31. Kamada AK, Szefler SJ. Glucocorticoids and growth in asthmatic children. *Pediatr Allergy Immunol*. 1995;6:145–154
32. Landis B, Koch GC. The measurement of observer agreement for categorical data. *Biometrics*. 1977;3:159–174
33. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12
34. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412
35. Chalmers TC, Celano P, Sacks HS, et al. Bias in treatment assignment in controlled clinical trials. *N Engl J Med*. 1983;309:1358–1361
36. Rothman KJ. *Modern Epidemiology*. Boston, MA: Little Brown and Co; 1986:177–236
37. Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care*. 1990;6:5–30
38. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188
39. Walker AM, Mertin-Moreno JM, Artalejo FR. Odd man out: a graphical approach to meta-analysis. *Am J Public Health*. 1988;78:961–966
40. Mulrow CD, Oxman AD, eds. *Cochrane Collaboration Handbook*. In: The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration. Oxford, UK: Update Software; 1996. Updated quarterly
41. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *J Natl Cancer Inst*. 1989;81:107–115
42. Hill AB. The environment and disease: association of causation. *Proc R Soc Med*. 1965;58:295–300
43. Borzak S, Ridker PM. Discordance between meta-analysis and large-scale randomized controlled trials. *Ann Intern Med*. 1995;123:873–877
44. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *Br Med J*. 1997;315:629–634
45. Cappelleri JC, Ioannidis JPA, Schmid CH, et al. Large trials vs. meta-analysis of smaller trials: how do their results compare? *JAMA*. 1996; 276:1332–1338
46. Merkus PJFM, van Essen-Zandvliet EEM, Duiverman EJ, et al. Long-term effects of inhaled corticosteroids on growth rates in adolescents with asthma. *Pediatrics*. 1993;91:1121–1126
47. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med*. 1994;88:373–381
48. Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child*. 1986; 61:1049–1055
49. Godfrey S, Balfour-Lynn L, Tooley M. A three to five year follow-up of the use of the aerosol steroid, beclomethasone dipropionate, in childhood asthma. *J Allergy Clin Immunol*. 1978;62:335–339
50. Ninan TK, Russell G. Asthma, inhaled corticosteroid treatment and growth. *Arch Dis Child*. 1992;67:703–705
51. Wolthers OD. Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticosteroids. *Eur Respir J*. 1996;9:821–827

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