Original Investigation

Evaluating the Effects of Metformin Use on Height in Children and Adolescents
A Meta-analysis of Randomized Clinical Trials

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IMPORTANCE Metformin hydrochloride use is increasing in children and adolescents. Previous meta-analyses have identified a large variability in the effects of metformin use on body mass index changes but have not considered height changes as a confounder, to our knowledge.

OBJECTIVE To conduct a systematic review and meta-analysis of the effects of metformin use on height in children and adolescents.

DATA SOURCES Computerized databases, including MEDLINE and EMBASE, were searched up to September 9, 2014, for terms related to metformin and childhood or adolescence.

STUDY SELECTION Randomized clinical trials examining the effects of metformin use on height of participants younger than 19 years were considered eligible. Trials with cointerventions other than lifestyle changes were excluded.

DATA EXTRACTION AND SYNTHESIS Height, weight, body mass index, age, sex, metformin dosage, and study duration were independently extracted by 2 reviewers. The weighted mean differences for changes in height, weight, and body mass index were compared between the metformin and control groups using random-effects models.

MAIN OUTCOME AND MEASURE Height changes.

RESULTS Ten studies were included, with a total of 562 participants, 330 (58.7%) of whom were female. The mean age within the studies ranged from 7.9 to 16.1 years, with a high variability in most studies. The duration of metformin interventions lasted from 3 to 48 months. Overall, height changes were not significantly different between the metformin and control groups. However, stratified analyses according to the cumulative metformin dose (in milligrams per day times the number of days of treatment) showed a greater increase in height with metformin use in the 5 studies providing the largest cumulative metformin doses (weighted mean difference, 1.0; 95% CI, 0.0 to 2.0 cm) but not in the 5 studies providing the lowest doses (weighted mean difference, −0.1; 95% CI, −0.7 to 1.0 cm) compared with the control group.

CONCLUSIONS AND RELEVANCE Preliminary evidence suggests a dose-response relationship between metformin use and increases in height in children and adolescents compared with a control group. While an approximate 1-cm increase in height may appear small, it is likely underestimated given that many studies were of short duration and included older adolescents, potentially after epiphyseal growth plate closure.

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Metformin hydrochloride is considered a first therapeutic option for type 2 diabetes mellitus because of its efficacy, safety, and low cost.[1] In addition to improving glycemic control, metformin use can cause modest weight reductions in adults with type 2 diabetes mellitus[2] or prediabetes.[3] There has been increasing off-label use of metformin in children and adolescents,[4] often as part of the management of polycystic ovary syndrome but also for impaired glucose tolerance, nonalcoholic fatty liver disease, and obesity.[5-8] Small reductions in (or even maintenance of) body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) can be meaningful goals for the management of many chronic diseases. For example, clinical guidelines for children and adolescents with type 2 diabetes mellitus support the use of metformin for modest weight loss.[9] While the amount of weight loss may be modest, it compares favorably with weight gain caused by other agents, such as insulin or sulfonylureas.[9]

Most studies in which metformin treatment to children or adolescents has been prescribed have had small sample sizes. Several systematic reviews and a meta-analysis provide pooled estimates of the effects of metformin use on changes in BMI and other relevant variables.[10-12] For example, a large review by McDonagh et al[11] reported a reduction in BMI with metformin use compared with placebo (weighted mean difference [WMD], −1.16). However, they also reported a high and significant degree of heterogeneity among the studies,[11] with the mean difference in BMI ranging from −2.73 to 0.38. The heterogeneous changes in BMI in response to metformin treatment are not well understood. These previous meta-analyses have considered a large variety of potential explanations and subgroup analyses. However, because of the way in which BMI is calculated, it could be important to parse out the effect of metformin on BMI into its height and weight components, which is especially important in youth who (as opposed to adults) still exhibit linear growth. Furthermore, of all the subgroups examined by McDonagh et al,[11] the subgroups defined by a larger proportion of boys or the youngest age showed the greatest reduction in BMI. Hypothetically, these subgroups may represent those more likely to show an increase in height because they were less likely to have experienced epiphyseal growth plate closure. Therefore, the objective of the present systematic review was to examine the effects of metformin use on height changes in randomized clinical trials among children and adolescents.

At a Glance

- Many trials report the effects of metformin use on body mass index (BMI). Given the metformin-induced weight loss in adults, it is often assumed that BMI changes among children and adolescents are due to changes in weight rather than height.
- In this systematic review, 10 studies were included, with a total of 562 participants, 330 (58.7%) of whom were female. In stratified analyses according to the cumulative metformin dose (in milligrams per day times the number of days of treatment), there was a greater increase in height with metformin use in the 5 studies providing the largest cumulative metformin doses but not in the 5 studies providing the lowest doses compared with the control group.
- Additional studies should examine the effects of metformin use on height and consider the effect of confounding factors, such as age and sex.

Methods

Eligibility Criteria

The eligibility of the studies was formulated according to the PICOS criteria (ie, participants, interventions, comparisons, outcomes, and study design). Eligible studies were randomized clinical trials with participants younger than 19 years, regardless of BMI or morbidities. The upper age and study duration limits could be considered too inclusive for examining height changes. However, as the first review in this area to date, to our knowledge, the criteria were selected to be as inclusive as possible and to be in line with previous reviews on BMI.[11] The effects of lowering the age limit or increasing the duration of the studies were considered in sensitivity analyses. Trials with cointerventions other than lifestyle changes were excluded because the cointerventions could have confounded the results. For example, we excluded trials about type 1 diabetes mellitus, in which adjustments in insulin dosages could have occurred in participants randomized to metformin use. Eligible studies were required to report or provide outcomes of BMI and height. No studies were excluded because of the language, date of publication, or publication status.

Data Sources

Search strategies were developed by a librarian (L.S.) with expertise in systematic review searches using the following databases: MEDLINE (1946 to September 9, 2014), EMBASE (1974 to September 9, 2014), PsycINFO (1806 to September 9, 2014), the Cochrane Central Register of Controlled Trials (from inception to September 9, 2014), Web of Science Core Collection (1900 to September 9, 2014), Scopus (1960 to September 9, 2014), and CINAHL Plus With Full Text (1937 to September 9, 2014). Keywords and controlled vocabulary (if available) that were related to metformin (eg, glucophage) were combined with age group terms. A filter was applied to limit the results to randomized clinical trials as much as possible. Reference lists of related studies and previous systematic reviews were also screened for eligible trials. Full details of the database searches are provided in the eTable in the Supplement.

Study Selection and Data Extraction

Two reviewers (N.K. and E.M.-C.) independently screened the search results, determined the eligibility of the studies, extracted the data, and assessed the risk of bias.[13] Discrepancies were resolved by a discussion with a third reviewer (N.G.B.). Sample size, height, weight, BMI, age, sex, metformin dosage, study duration, dropout percentage, and information on lifestyle cointerventions were independently extracted in duplicate. We attempted to contact the authors for missing data (eg, height or SDs) when not reported. The corresponding or first author of each potentially included study was emailed at least twice and asked to provide the data that

may have been missing. Included in the emails were a template table for data entry and an introduction explaining the purpose of the request. When SDs were not available, they were calculated according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[13] For one study,[8] additional data were obtained from a request to the National Institute of Diabetes and Digestive and Kidney Central Repository.

Risk of Bias

The risk of bias was estimated using the Cochrane Collaboration's tool for assessing risk of bias,[13] including questions on randomization, blinding, and allocation concealment. Publication bias was determined by visual inspection of funnel plots, and sensitivity analyses were performed by excluding the studies showing a potential high risk of bias in key domains (eg, studies unable to blind participants because they lacked a placebo group).

Statistical Analysis

The mean difference between the metformin and control groups was calculated in each study by subtracting the mean change (postintervention minus preintervention) in the control group from the mean change in the metformin group. The WMDs were pooled using random-effects models.[13] Each study was weighted in the analyses according to the inverse variance method. As a measure of statistical inconsistency among trials, I^2 was calculated as $100\% \times (Q - df) / Q$, where Q is the Cochrane heterogeneity statistic.[14]

The heterogeneity among the studies was explored with meta-regression, subgroup, and sensitivity analyses. Simple meta-regression analyses were used to examine the relationship between the study or participant characteristics shown in the **Table** as the independent variable and the WMD in height, weight, or BMI as the dependent variable. For these analyses, each study was weighted by the inverse of the variance of the dependent variable. Subgroups were created according to the cumulative metformin dose, which was calculated as the daily metformin dose (in milligrams per day times the number of days of treatment). Because there was no physiological or clinical reason for selecting a cutoff for these subgroup analyses, the studies were grouped as those providing the 5 highest and 5 lowest cumulative metformin doses. This cutoff maximized the number of studies in each subgroup and represented a natural break in the data. The high-dose studies had total exposures of at least 274 g, while the low-dose studies had total exposures of 186 g or less. Sensitivity analyses included the comparison of placebo-controlled trials vs non-placebo-controlled trials. Meta-analyses were performed with review software (RevMan, version 5.1; Cochrane Collaboration), and all other analyses were performed with statistical software (SPSS, version 21.0; IBM).

Results

Twenty-five potentially eligible studies with BMI data were identified through searching of electronic databases, and none were identified via other sources. Details regarding inclusion and exclusion of the studies at each stage are provided in the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram (**Figure 1**). One study[15] of type 2 diabetes mellitus met our inclusion criteria but was excluded because 65% of the participants taking the placebo required rescue medication before the 16-week measurements. Height was available from only 10 studies (6 studies[5,6,16-19] provided the data in the articles, 1 study[8] listed the data from a repository, and the data from 3 studies[17,20,21] were obtained after we contacted the authors).

These 10 studies included a total of 562 children and adolescents at baseline and 477 of these with changes to data. Fifty-nine percent of participants were female (n = 330), the mean age within the studies ranged from 7.9 to 16.1 years, and the mean BMI ranged from 18.4 to 41.0. Details of the study characteristics are listed in the Table.

Overall, metformin use reduced BMI compared with a control group (WMD, −1.0; 95% CI, −1.6 to −0.3 cm; I^2 = 52% and n = 477). However, metformin use did not significantly affect height (WMD, 0.5; 95% CI, −0.2 to 1.1 cm; I^2 = 0% and n = 477) or weight (WMD, −1.4; 95% CI, −3.6 to 0.8 kg; I^2 = 69% and n = 455). However, as shown in **Figure 2**, when the studies were divided into subgroups based on a high or low cumulative metformin dose, the 5 studies that provided the greater amounts of metformin demonstrated a decrease in BMI (WMD, −1.3; 95% CI, −2.1 to −0.4; I^2 = 57% and n = 286) and an increase in height (WMD, 1.0; 95% CI, 0.0 to 2.0 cm; I^2 = 0% and n = 286) but no effect on weight (WMD, −0.6; 95% CI, −3.8 to 2.5 kg; I^2 = 61% and n = 264) compared with a control group. On the other hand, there were no changes in BMI (WMD, −0.6; 95% CI, −1.6 to 0.4; I^2 = 47% and n = 191), height (WMD, 0.1; 95% CI, −0.7 to 1.0; I^2 = 0% and n = 191), or weight (WMD, −1.9; 95% CI, −5.2 to 1.3; I^2 = 75% and n = 191) in the 5 studies that provided the lower doses of metformin compared with a control group.

Meta-regression analyses identified an association between the mean age (in years) of participants within a study and the WMD in BMI (unstandardized coefficient B = 0.28; 95% CI, 0.05-0.51), suggesting that the studies with older participants had smaller reductions in BMI with metformin treatment. There was also an inverse association between the cumulative metformin dose (in grams) and the WMD in BMI (B = −0.001; 95% CI, −0.003 to 0.000). However, the associations between the WMD in height and the mean age (B = −0.08; 95% CI, −0.43 to 0.27) or the cumulative metformin dose (B = 0.001; 95% CI, −0.001 to 0.003) were not statistically significant.

The assessment of the risk of bias revealed that most information was obtained from trials at low risk of bias (eFigure 1 in the Supplement). Although many articles had not reported height, all the trials were considered at a low risk of bias for selective outcome reporting or incomplete outcome data because they had reported the outcomes related to their study objectives. None of the trials were considered to pose a high risk for the items of sequence generation, allocation concealment, or blinding of outcome assessment. However, 3 studies[16,17,20] among the 10 included trials had a potential high risk of bias in the domain of blinding of participants (no placebo group). When the 7 placebo-controlled trials were considered separately in sensitivity analyses, the WMDs were not

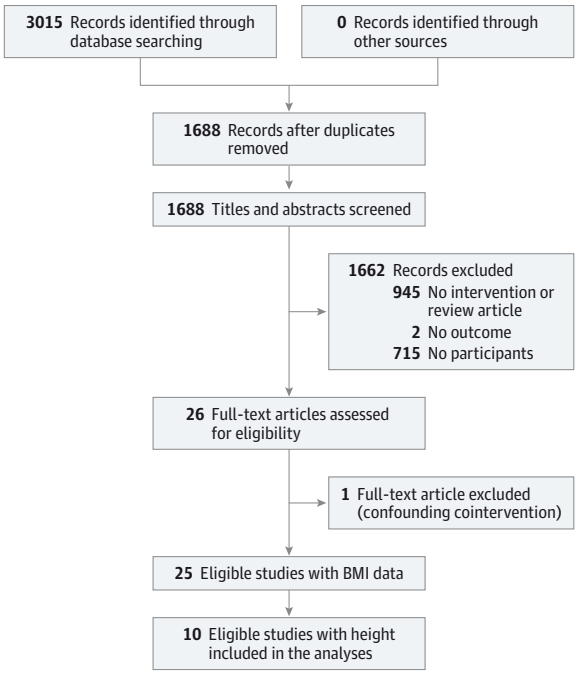
Table. Characteristics of Included Trials

Source	Treatment	Study Characteristic				Participant Characteristic				
		Cumulative Metformin Dose, g	Daily Metformin Dose, mg	Duration of Intervention, mo	Dropouts, %	No. (Female-Male)	Age, Mean (SD), y	BMI, Mean (SD)[a]	Morbidity	Cointervention
Low Cumulative Metformin Dose										
Evia-Viscarra et al,[18] 2012	Metformin	91	1000 (500 at 2 times daily)	3	13	12 (9:3)	12.7 (2.0)	33.4 (5.8)	Obese and insulin resistant	Diet and exercise recommended
	Placebo	NA	NA	As above	20	14 (8:6)	14.1 (1.2)	32.8 (6.4)	As above	As above
Gómez-Díaz et al,[6] 2012	Metformin	155	1700 (850 at 2 times daily)	3	3	28 (16:12)	11.9 (2.4)	31.1 (6.3)	Impaired glucose tolerance	Changes in activity and diet assessed to determine changes
	Placebo	NA	NA	As above	14	24 (13:11)	12.0 (3.0)	27.1 (5.9)	As above	As above
Mauras et al,[20] 2012	Metformin	91-186	500 If <12 y old and 1000 if ≥12 y old (250 or 500 at 2 times daily)	6	34	35 (20:15)	12.3 (3.0)	32.0 (5.9)	Obese	Structured diet and exercise, free access to dietician and exercise facility
	Control	NA	NA	As above	39	31 (16:15)	12.0 (2.2)	33.2 (3.9)	As above	As above
Casteels et al,[21] 2010	Metformin	78-155	425 If <10 y old and 850 if ≥10 y old	6	26	19 (12:7)	16.0 (6.0)	26.0 (6.0)	Motor deficit	Diet and exercise advice
	Placebo	NA	NA	As above	9	23 (11:12)	15.0 (6.0)	27.0 (6.0)	As above	As above
Burgert et al,[5] 2008	Metformin	183	1500 (500 at 3 times daily)	4	12	15 (10:5)	15.0 (2.0)	41.0 (6.0)	Obese	Diet and exercise recommended
	Placebo	NA	NA	As above	24	13 (9:4)	15.0 (1.0)	40.0 (6.0)	As above	As above
High Cumulative Metformin Dose										
Kendall et al,[19] 2013	Metformin	274	1500 (1000 + 500)	6	26	74 (49:25)	13.7 (2.3)	37.1 (5.8)	Obese hyperinsulinemic, impaired fasting glucose, or impaired glucose tolerance	Diet and exercise advice
	Placebo	NA	NA	As above	29	77 (53:24)	13.6 (2.2)	36.0 (6.3)	As above	As above
Ladson et al,[7] 2011	Metformin	365	2000 (500 at 4 times daily)	6	9	11 (11:0)	16.1 (1.5)	37.1 (5.8)	Polycystic ovary syndrome	Structured diet and exercise, with 7% weight loss goal
	Placebo	NA	NA	As above	27	11 (11:0)	15.4 (1.2)	35.9 (6.6)	As above	As above
Lavine et al,[8] 2011	Metformin	670	1000 (500 at 2 times daily)	22	11	57 (10:47)	13.1 (2.4)	34.0 (5.0)	Nonalcoholic fatty liver disease	Physician and dietician provided diet and exercise advice
	Placebo	NA	NA	As above	16	58 (12:46)	12.9 (2.6)	33.0 (6.0)	As above	As above
Ibáñez et al,[16] 2008	Metformin	931	425-850	48	0	19 (19:0)	7.9 (0.6)	18.4 (1.8)	Low birth weight	Changes in activity and diet assessed to determine changes
	Control	NA	NA	As above	0	19 (19:0)	7.9 (0.6)	18.4 (1.8)	As above	As above
Ibáñez et al,[17] 2006	Metformin	931	850	36	0	10 (10:0)	9.0 (0.3)	20.2 (2.5)	Low birth weight	None mentioned
	Control	NA	NA	As above	0	12 (12:0)	9.1 (0.3)	21.0 (2.7)	As above	As above

Abbreviations: BMI, body mass index; NA, not applicable.

[a] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flow Diagram



BMI indicates body mass index.

meaningfully affected, but the 95% CIs for the overall effect were generally wider for BMI (WMD, −0.5; 95% CI, −1.1 to 0.1; I^2 = 16% and n = 374), height (WMD, 0.7; 95% CI, −0.2 to 1.5 cm; I^2 = 0% and n = 374), and weight (WMD, −0.8; 95% CI, −3.4 to 1.8 kg; I^2 = 75% and n = 308).[5-8,18,19,21] Sensitivity analyses revealed similar results when the analyses were performed after lowering the age limit to 14 years or increasing the minimum study duration to 6 months. The funnel plots (eFigure 2 in the Supplement) did not suggest publication bias.

Discussion

Our systematic review and meta-analysis pooled the data from 10 randomized clinical trials, with 562 participants randomized to metformin or control groups. To our knowledge, this is the first meta-analysis to suggest that treatment with metformin may increase height in children and adolescents compared with a control group, particularly when a combination of larger doses and longer treatment duration is used.

Although we are aware of other trials that had suggested an increase in height with metformin use, these studies[22,23] did not meet the inclusion criteria for our review. For example, in their study with a single-group pre-post design, Arslanian et al[23] observed a significant increase in height but no change in weight when adolescent girls with polycystic ovary syndrome were treated with metformin (1700 mg/d) for 3 months. However, without a control group, it is difficult to establish if the increase in height was due to metformin use. Most important, our results suggest that a dose-response relationship may exist between metformin therapy and height changes compared with a control group.

The approximate 1-cm-greater growth in the 5 studies with a larger cumulative metformin dose compared with a control group may seem small, but the findings may still be clinically meaningful. It is important to note that subgroups of participants in these studies may have already experienced epiphyseal growth plate closure and therefore would be unlikely to have additional growth from metformin treatment (eg, the mean [SD] age in the metformin group from the study by Ladson et al[7] was 16.1 [1.5] years). It is possible that longer treatment periods or treatments concentrated at times of greater growth may lead to even greater height changes. Unfortunately, only 2 of our included studies were conducted in children who were younger than 10 years. These 2 studies by Ibáñez et al showed heterogeneous results. One study[17] demonstrated a 2.8-cm greater increase in height in the metformin group for girls approximately 9 years old. In the other study,[16] there was no difference in height changes between girls approximately 8 years old randomized to metformin vs control groups for 4 years (both groups grew by a mean of 26 cm). However, during the last 6 months of the treatment period, the authors noted that the height velocity started to be lower in the untreated (then mostly postmenarcheal) girls than in the treated girls. This finding was supported by a subsequent study[24] from a follow-up period (after the discontinuation of metformin until all the girls of their subgroup had experienced menarche), which suggested that the original metformin treatment period had delayed menarche by approximately 1 year and reduced the target height by 3.6 cm more than in the untreated control group.[24] Therefore, it may be speculated that metformin administration during puberty could enhance or prolong the normally occurring, puberty-induced height change. Longer studies in pubertal participants may reveal a much larger increase in height with metformin use than the overall approximate 1-cm increase suggested by our present meta-analysis.

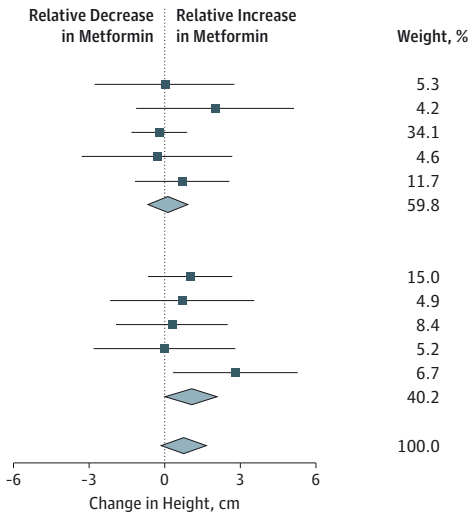
The reasons for the increase in height in the metformin-treated groups are hard to ascertain. Although a larger cumulative metformin dose was the only factor that was significantly associated with the WMD in height, it is difficult to determine if this association was confounded by the duration of treatment, the daily metformin dose (or dosage per kilogram of body weight), or other confounding factors, such as age or sex. Indeed, the study with the highest cumulative metformin dose was also one of the studies with the youngest mean age. A larger number of eligible studies for the meta-regression analyses or the examination of aggregates of individual patient data (not study means) would be helpful to more closely examine this issue.

A complete discussion of the potential mechanisms by which metformin use could increase height in children and adolescents is beyond the scope of this review. However, the following hormones and metabolic pathways have been shown to be affected by metformin and could mediate height changes: insulin or insulinlike growth factor 1,[25] adenosine monophosphate-activated protein kinase or the metabolic target of rapamycin,[26] and sex hormones.[27] For example, an increase in sex hormone–binding globulin as a result of increased insulin

Figure 2. Effects of Metformin Hydrochloride Use on Height, Weight, and Body Mass Index

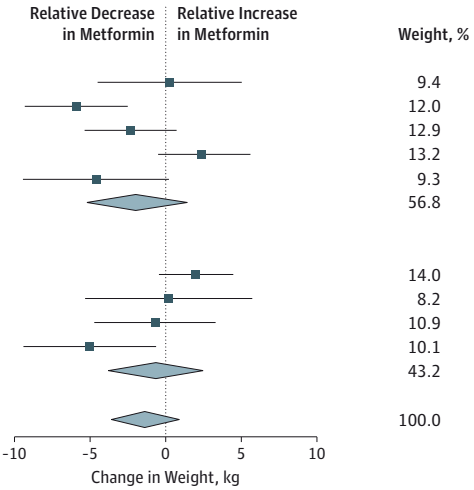
A Effect of metformin use on height

Source	Metformin No.	Metformin Mean (SD)	Control No.	Control Mean (SD)	MD
Low cumulative metformin dose					
Evia-Viscarra et al,[18] 2012	12	1.1 (3.2)	14	1.1 (4.0)	0.0
Gómez-Díaz et al,[6] 2012	28	1.0 (4.7)	24	-1.0 (6.5)	2.0
Mauras et al,[20] 2012	23	3.3 (2.1)	19	3.5 (1.5)	-0.2
Casteels et al,[21] 2010	19	0.6 (3.9)	23	0.9 (5.9)	-0.3
Burgert et al,[5] 2008	15	0.6 (1.4)	14	-0.1 (3.3)	0.7
Subtotal	97		94		0.1
Heterogeneity: $\chi^2=2.17$; $P=.70$; $I^2=0\%$, Overall effect: $z=.33$; $P=.74$					
High cumulative metformin dose					
Kendall et al,[19] 2013	55	2.0 (4.7)	55	1.0 (4.1)	1.0
Ladson et al,[7] 2011	10	0.2 (2.3)	8	-0.5 (3.6)	0.7
Lavine et al,[8] 2011	51	7.9 (4.9)	47	7.6 (6.1)	0.3
Ibanez et al,[16] 2008	19	26.0 (4.4)	19	26.0 (4.4)	0.0
Ibanez et al,[17] 2006	10	18.3 (2.8)	12	15.5 (3.1)	2.8
Subtotal	145		141		1.0
Heterogeneity: $\chi^2=2.96$; $P=.56$; $I^2=0\%$, Overall effect: $z=1.92$; $P=.05$					
Total	242		235		0.5
Heterogeneity: $\chi^2=6.77$; $P=.66$; $I^2=0\%$, Overall effect: $z=1.47$; $P=.14$					
Subgroup differences: $\chi^2=1.64$; $P=.20$; $I^2=38.9\%$					



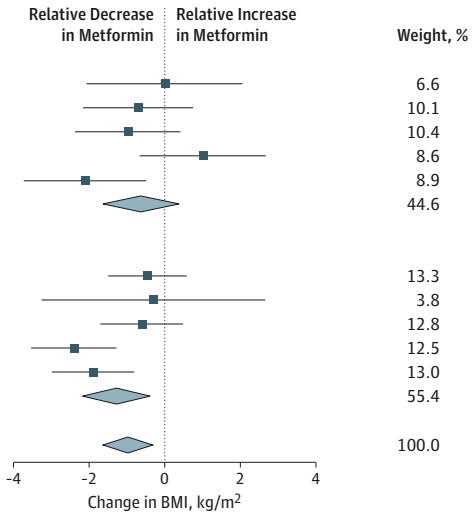
B Effect of metformin use on body weight

Source	Metformin No.	Metformin Mean (SD)	Control No.	Control Mean (SD)	MD
Low cumulative metformin dose					
Evia-Viscarra et al,[18] 2012	12	-0.6 (5.4)	14	-0.9 (7.0)	0.3
Gómez-Díaz et al,[6] 2012	28	-3.8 (6.5)	24	2.1 (6.0)	-5.9
Mauras et al,[20] 2012	23	-4.3 (5.0)	19	-2.0 (4.9)	-2.3
Casteels et al,[21] 2010	19	2.9 (5.1)	23	0.5 (4.2)	2.4
Burgert et al,[5] 2008	15	-1.6 (8.4)	14	3.0 (4.3)	-4.6
Subtotal	97		94		-1.9
Heterogeneity: $\chi^2=15.97$; $P<.01$; $I^2=75\%$, Overall effect: $z=1.17$; $P=.24$					
High cumulative metformin dose					
Kendall et al,[19] 2013	55	2.4 (7.2)	55	0.4 (5.8)	2.0
Ladson et al,[7] 2011	10	-1.8 (5.1)	8	-2.0 (6.5)	0.2
Lavine et al,[8] 2011	51	12.0 (9.7)	47	12.7 (10.4)	-0.7
Ibanez et al,[16] 2008	19	19.0 (4.4)	19	24.0 (8.7)	-5.0
Subtotal	135		129		-0.6
Heterogeneity: $\chi^2=7.67$; $P=.05$; $I^2=61\%$, Overall effect: $z=0.39$; $P=.70$					
Total	232		223		-1.4
Heterogeneity: $\chi^2=25.69$; $P<.01$; $I^2=69\%$, Overall effect: $z=1.23$; $P=.22$					
Subgroup differences: $\chi^2=.33$; $P=.56$; $I^2=0\%$					



C Effect of metformin use on body mass index

Source	Metformin No.	Metformin Mean (SD)	Control No.	Control Mean (SD)	MD
Low cumulative metformin dose					
Evia-Viscarra et al,[18] 2012	12	-0.7 (2.5)	14	-0.7 (2.9)	0.0
Gómez-Díaz et al,[6] 2012	28	-2.2 (2.7)	24	-1.5 (2.6)	-0.7
Mauras et al,[20] 2012	23	-2.1 (2.6)	19	-1.2 (2.0)	-1.0
Casteels et al,[21] 2010	19	1.4 (2.8)	23	0.4 (2.7)	1.0
Burgert et al,[5] 2008	15	-0.9 (2.5)	14	1.2 (1.9)	-2.1
Subtotal	97		94		-0.6
Heterogeneity: $\chi^2=7.52$; $P=.11$; $I^2=47\%$, Overall effect: $z=1.22$; $P=.22$					
High cumulative metformin dose					
Kendall et al,[19] 2013	55	-0.3 (2.7)	55	0.2 (2.9)	-0.5
Ladson et al,[7] 2011	10	-0.8 (2.7)	8	-0.5 (3.5)	-0.3
Lavine et al,[8] 2011	51	1.3 (2.5)	47	1.9 (2.9)	-0.6
Ibanez et al,[16] 2008	19	2.2 (1.0)	19	4.6 (2.3)	-2.4
Ibanez et al,[17] 2006	10	0.6 (1.1)	12	2.5 (1.5)	-1.9
Subtotal	145		141		-1.3
Heterogeneity: $\chi^2=9.35$; $P=.05$; $I^2=57\%$, Overall effect: $z=2.88$; $P<.01$					
Total	242		235		-1.0
Heterogeneity: $\chi^2=18.77$; $P=.03$; $I^2=52\%$, Overall effect: $z=2.97$; $P<.01$					
Subgroup differences: $\chi^2=.94$; $P=.33$; $I^2=0\%$					



Graphs represent the mean difference and 95% CIs from the random effects model. MD indicates mean difference.

sensitivity with metformin use[28] could lead to a lower fraction of circulating free steroids, which in turn may be followed by a later closure of the epiphyses.[29]

Our systematic review is not intended to comment on the desirability of the observed increase in linear growth. It may also be worthwhile to further examine whether metformin use, or the increase in linear growth in this context, is linked to an increased risk for other long-term complications (eg, fractures, reduced bone mineral density, and osteoarthritis), although the study by Ibáñez et al[16] in 2008 did not identify any such bone mineral density changes. Depending on the mechanisms of action, it may be possible that there could be premature closure of the epiphyseal growth plates or terminal stunting in some situations. However, this scenario does not seem likely given that the studies we identified had a large variety of the inclusion criteria, but no findings suggested a decrease in linear growth in the metformin group compared with the control group.

The following limitations should be considered when interpreting our results. Despite our best efforts, we were unable to obtain height data from many studies, even though this information had been collected for the reporting of BMI. Indeed, we identified 25 studies with BMI measurements and were eventually able to collect height data from only 10 studies. In addition, subgroup analyses do not represent randomized comparisons (eg, randomized to a high vs low cumulative metformin dose) and should also be interpreted with some caution. If a dose-response relationship exists, it is also possible that compliance to metformin treatment could have contributed to the heterogeneity of the results. We also must acknowledge that our initial objective was to examine BMI changes and that we did not a priori define our subgroup and sensitivity analyses in regard to height changes. The multiple comparisons that we performed may have increased the chance of false-positive results, and the analyses should therefore be considered exploratory and hypothesis generating. In addition, the observation of significant changes for some variables and subgroups but not for others (eg, significant changes in height but not in weight in the group with a high cumulative metformin dose) may be due to not only the size of changes but also the measurement error for the variable or within the subgroup in question. For example, the reliability of small changes in weight can be largely affected by changes in hydration status or clothing. Efforts to standardize these factors were not often controlled for or reported. On the other hand, the measurement of height may have been more reproducible, which may in part explain why we were able to observe significant changes in height but not in weight.

Conclusions

A greater cumulative exposure to metformin may increase height by a mean of approximately 1 cm in children and adolescents compared with a control group. Compared with control treatment, metformin use also has a modest effect of decreasing BMI, which should be interpreted to reflect not only decreased body mass or adiposity but also increased height. Our results also suggest a need for additional longer-term studies in younger participants because preliminary evidence suggests that these individuals may experience greater increases in height compared with a control group.

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Study concept and design: Kuzik, Boulé.
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