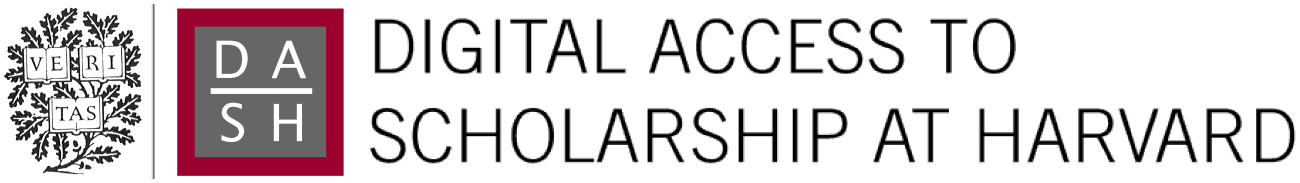

Effect of Succimer on Growth of Preschool Children with Moderate Blood Lead Levels.

Effect of Succimer on Growth of Preschool Children with Moderate Blood Lead Levels

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Growth deficits associated with lead exposure might be ameliorated by chelation. We examined the effect of succimer on growth in 780 children 12–33 months old who had blood lead levels of 20–44 μg/dL and were randomized to receive up to three 26-day courses of succimer or placebo in a multicenter, double-blind trial. The difference in changes in weight and height between succimer and placebo groups at 1–34 months was calculated by fitting cubic splines. The difference in height change in children on succimer compared with placebo was –0.27 cm [95% confidence interval (95% CI), –0.42 to –0.11] from baseline to 9 months, when 99% of children had completed treatment, and –0.43 cm (95% CI, –0.77 to –0.09) during 34 months of follow-up. Similar differences in weight gain were not statistically significant. Although succimer lowers blood lead in moderately lead-poisoned children, it does not have a beneficial effect on growth and may have an adverse effect. *Key words:* **blood lead levels, chelation, children, clinical trial, growth, succimer.** *Environ Health Perspect* **112:233–237 (2004). doi:10.1289/ehp.6331 available via** *http://dx.doi.org/* **[Online 22 October 2003]**

National surveys have documented 1- to 2-cm deficits in children's heights for each 10-μg/dL difference in blood lead levels (Ballew et al. 1999; Frisancho and Ryan 1991; Schwartz et al. 1986), a finding replicated by several clinical studies (Angle and Kuntzleman 1989; Bithoney 1989; Lauwers et al. 1986; Routh et al. 1979). Weight has been less consistently associated with lead exposure (Ballew et al. 1999; Bithoney 1989; Johnson and Tenuta 1978; Kim et al. 1995; Schwartz et al. 1986). The cross-sectional designs of most studies limit inferences about the relationship of blood lead to child growth. Longitudinal data are required to discern growth effects during and after adverse exposures (Prader et al. 1963; Tanner 1990). Observational studies have shown that delays associated with lead exposure are followed by catch-up growth when blood levels decline (Shukla et al. 1989, 1991). Animal studies have suggested that growth delay may be caused by decreased caloric intake associated with anorexia, not by direct effects of lead (Hammond and Succop 1995; Hammond et al. 1993).

If lead exposure indeed contributes to height and weight deficits, chelation to reduce blood levels might ameliorate them. Studies of chelation with ethylenediamine-tetraacetate (EDTA) are not conclusive and are limited by small sample sizes (Huseman et al. 1992; Markowitz et al. 1990). We examined the effect of succimer on height and weight growth of children with moderate blood lead levels during and after administration of succimer or placebo within a 34-month period in the context of a randomized clinical trial. We hypothesized that succimer would have a beneficial effect on growth during but not after treatment—that we would observe group differences in growth rate during the period of treatment, which was < 9 months for most subjects.

Materials and Methods

The children were participants in the Treatment of Lead-Exposed Children (TLC) trial (TLC Trial Group 1998), a randomized, multicenter, placebo-controlled, double-blind clinical trial of succimer, an orally active drug that forms water-soluble complexes with lead, increasing its urinary excretion (Mann and Travers 1991). The TLC trial tested the primary hypothesis that preschool children with moderate blood lead levels treated with succimer would perform better than those receiving placebo on tests of cognitive development, behavior, and neuropsychological function administered 3 years after treatment (TLC Trial Group 1998, 2000). Height and blood pressure were secondary outcomes of the trial. The research protocol was approved by institutional review boards at the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention (CDC), the Harvard School of Public Health, and the four clinical centers (Newark, NJ; Baltimore, MD; Philadelphia, PA; and Cincinnati/Columbus, OH).

Referral criteria included age of 12–33 months projected at randomization, blood lead level between 20 and 44 μg/dL, no more than two residences, and suitability for psychometric tests in English or Spanish (TLC Trial Group 1998). Exclusion criteria were history of significant developmental delay; renal, hepatic, or congenital heart disease; anemia not attributable to iron deficiency; low birth weight; and prior chelation therapy.

At the first TLC visit, we measured height and weight and obtained venous blood samples to measure blood lead level, ferritin, hemoglobin, platelet and neutrophil counts, red cell distribution width (RDW), and liver enzymes. Children with hemoglobin levels < 9.0 g/dL were excluded. Those with increased RDW and hemoglobin between 9.0 and 10.0 g/dL were prescribed a 90-day course of iron at 3 mg/kg/day, and enrollment was delayed until iron deficiency was resolved. We gave all families a month's supply of a chewable supplement providing 100% or more of the recommended dietary allowances (Food and Nutrition Board 1989) for children for selected vitamins and minerals, including iron, zinc, and copper, and 100 mg calcium.

At the second TLC clinic visit 1 month later, the child was enrolled in the study if blood lead remained between 20 and 44 μg/dL. Before therapy was initiated, homes were cleaned to reduce lead dust exposure or families were moved to lead-safe housing. We randomized 780 children: 396 to succimer and 384 to placebo. Treatment assignments were randomized within strata of clinical center, six categories of body surface area, blood lead (≤ 25 μg/dL or > 25 μg/dL), and, in Newark only, English or Spanish language testing (TLC Trial Group 1998). Treatment with succimer or placebo was started within 2 weeks of the second qualifying blood lead. Treated children

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were assigned to a dosing regimen providing 1,050 mg/m^2/day of succimer for the first 7 days, and then 700 mg/m^2/day from 8 to 26 days, a week longer than the regimen described on the product label (Chemet; McNeil Consumer Products, Fort Washington, PA). We suspended vitamin–mineral supplements during the treatment period.

Children could receive up to three courses of succimer if blood lead was ≥ 15 µg/dL 42 days after initiating the first or second round of treatment. The timing of this visit was somewhat variable, conducted at a median of 48 days (5–95% range, 41–101 days) for the first course and at a similar range for the second course. Among children given succimer who completed the first round, 83% required a second course; 83% of those completing a second round required a third course. Children given placebo were assigned to retreatment to match the frequency of retreatment of those receiving succimer within blocks used for initial randomization. At the conclusion of treatment, vitamin–mineral supplementation was resumed for the duration of the study. Children returned for clinical examination and repeat measures of blood lead level, height, and weight every 3 months during the first 2 years and at 4-month intervals in the third year. Clinicians provided follow-up care for post-treatment blood lead levels according to CDC guidelines (CDC 1991).

Data collection. **Questionnaires.** Age and sex were obtained by caregiver interview at referral for eligibility. Birth weight, history of disqualifying medical conditions, race/ethnicity, medical insurance, and participation in federal health and welfare programs were reported at the first and second prerandomization clinic visits.

Biochemical measures. The Nutritional Biochemistry Branch of the CDC measured blood lead levels using methods described by Miller et al. (1987) and tested the evacuated blood collection tubes for lead contamination. This CDC lab also measured ferritin; hemoglobin was determined at local laboratories (TLC Trial Group 1998).

Anthropometry. TLC staff obtained heights and weights according to accepted guidelines [Lohman et al. 1988; World Health Organization (WHO) 1995] modified for outpatient settings (Gortmaker et al. 1999). We measured weight on a balance beam or digital scale recorded to the nearest 0.1 kg or ounce. Length and stature measures were measured to the nearest 0.1 cm using infant length boards or stadiometers, respectively. Clinic equipment was calibrated weekly or every 100 children using standard weights and measuring rods.

The study protocols specified length measures on children < 24 months old and stature at ≥ 24 months (Lohman et al. 1988; WHO 1995). We corrected heights for position, converting supine to standing measures by subtracting an age-independent constant (Hamill et al. 1979; Mei et al. 1998). For children with missing values for position, we assumed that recumbent lengths were measured for children < 24 months old and stature measured on older children. To estimate the value of the difference due to position in the TLC, we fitted a child-specific growth curve against age to the standing measurements for 297 children who had both supine and standing measurements and calculated deviations from this curve for supine measurements for each individual. This analysis yielded 824 deviations with the average value equal to 0.49 cm. All supine measures were subsequently adjusted to standing height by subtracting 0.49 cm.

Statistical methods. We calculated treatment- and time-specific mean blood lead levels by locally weighted regression (Cleveland and Devlin 1988) using S-Plus software (Mathsoft, Seattle, WA) as described in Chambers and Hastie (1993). Average post-randomization blood lead level was calculated for each child by connecting the visit-specific measurements of blood lead level by straight lines and calculating the area under the resulting curve divided by the length of the interval.

We used cubic B-splines (Venables and Riley 1997) to fit individual growth curves to each child's repeated measurements. We selected this analytic approach for two reasons. First, the rates of height and weight growth of children in this age group are nonlinear, declining with age. Although the time scale in this study was months since randomization, not child age, we would have needed to control for age with a quadratic rather than linear function. Second, we hypothesized that succimer would protect growth during the period of treatment but not after treatment. Thus, we anticipated a nonlinear response across the study period; for example, we hypothesized catch-up growth in children receiving succimer from baseline to 9 months, followed by a similar growth rate in the two groups from 10 to 34 months. We estimated the change in height and change of weight at any given time after treatment began by subtracting the fitted values at initiation of treatment from the fitted values of height and weight at that time point. This procedure produced child-specific curves showing height and weight changes from baseline to 34 months of follow-up. For subjects whose last measurement was earlier than 34 months, the curve was fitted up to the time of this measurement. Figure 1 shows an example of a smooth curve fitted to observed height measurements for an individual child using these methods. The goodness of fit was excellent; the mean R^2 values for observed and fitted values over subjects were 0.98 for height and 0.97 for weight.

From the analysis of height growth, we eliminated 2.7% of subjects with fewer than six measurements, and an additional 2.7% with missing baseline covariates from the adjusted analysis. Ninety-four percent of children were included in the covariate-adjusted analysis at 6 months, 92% at 24 months, and 88% at 34 months of follow-up. Corresponding numbers were similar for weight growth analyses. We conducted analysis of covariance of change in fitted values for height and weight from initiation of treatment at multiple time points from 1 to 34 months. We estimated the difference in height and weight change between the children given succimer and those given placebo, adjusting for baseline age, blood lead level, ferritin and hemoglobin, sex, race/ethnicity (African-American vs. other), clinical center and baseline *Z*-score for height or weight (corresponding to the outcome of interest). For baseline weights and heights, we calculated age- and sex-specific *Z*-scores (Dean et al. 1995), using the closest measure collected within 1 month of randomization. Because children with larger *Z*-scores would be expected to grow faster independent of any treatment effect, we estimated the magnitude of the association of baseline height *Z*-score with height change at 34 months. We included reported birth weight in initial models but excluded it from final analyses to maximize sample size for the covariance analyses. Similar results were obtained in models that included birth weight. S-Plus software (Venables and Riley 1997) was used for the robust analysis of covariance, following an approach similar to that discussed by Ramsay and Silverman (1997).

In response to reviewer comments and to assess the robustness of the cubic spline analysis, we also conducted a growth analysis (Laird and Ware 1982), using age as the metameter and time on study as a covariate. We assumed that height (or weight) at a specific follow-up time is a function of subject's

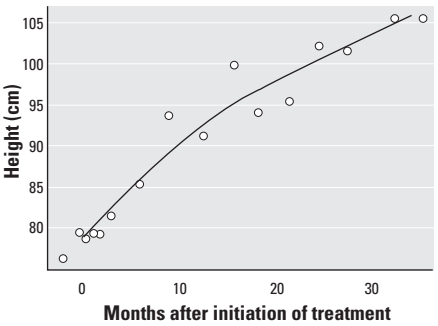

Figure 1. Smooth curve fitted to observed height data. A change of height Ch(t) at time t from the initiation of treatment is defined as the difference between the fitted value of height and fitted height value of height at the baseline: Ch(t) = $h(t) - h(0)$.

current age, squared current age, race/ethnicity (African American vs. other), sex, clinical center, treatment group, and interaction of treatment group with time from the initiation of treatment. We also assumed random intercepts and coefficients for age and the square of age. The coefficient of the interaction term in this model represents the difference between treatment groups in the average growth velocity across the follow-up period. This analysis was done using SAS PROC MIXED (SAS Institute 1992).

Results

Baseline health and sociodemographic characteristics of the children were balanced across succimer and placebo groups (Tables 1 and 2). Of these low-income, urban families, fewer than 5% received no public assistance; about three-quarters were enrolled in Medicaid, in the Food Stamp Program, and in the Special Supplemental Nutrition Program for Women, Infants, and Children (TLC Trial Group 1998). At baseline, mean blood lead levels were 25.9 (SD = 4.8) μg/dL in children randomized to receive placebo and 26.5 (SD = 5.4) μg/dL in children randomized to receive succimer.

After 9 months of follow-up, 99% had completed treatment. The 34-month trajectories of mean blood lead levels in the children receiving placebo and succimer appear in Figure 2. The largest estimated difference in mean blood lead level, 11 μg/dL (0.5 μmol/L), was seen 1 week after initiating the first round of treatment. Blood lead levels partially rebounded after successive rounds, whereas the mean blood lead levels of children given placebo declined smoothly but slowly. Averaged over time, the mean blood lead level of succimer-treated children was 4.5 μg/dL [95% confidence interval (CI), 3.7–5.3 μg/dL] lower than that of placebo children during the 6-month period after initiation of treatment, and 2.7 μg/dL (95% CI, 1.9–3.5 μg/dL) lower during the 12-month period after initiation of treatment (TLC Trial Group 2000). From 12 to 34 months, mean blood lead levels did not differ significantly in children randomized to succimer and placebo (Figure 2).

Succimer was associated with slower growth in height and in weight in the first 34 months from randomization. Figure 3 shows the differences between groups in height and weight changes from baseline to 34 months with pointwise 95% CIs, estimated by fitting cubic splines. Differences between height changes of succimer- and placebo-treated children emerged in the first 6–9 months, whereas weight discrepancies increased gradually to 18 months. Table 3 displays numerical values of the difference for selected times after the initiation of treatment. Mean differences in height change [Ch(succimer) – Ch(placebo)] were –0.27 cm (95% CI, –0.42 to –0.11 cm) at 9 months and –0.43 cm (95% CI, –0.77 to –0.09 cm) at 34 months, adjusted for covariates. We examined whether the small and nonsignificant group difference in baseline height influenced these effects. Using baseline height *Z*-score as one of the covariates in the adjusted model shown in Table 3, we found, as expected, that children with higher *Z*-scores at baseline grew faster than those with lower *Z*-scores during the study period. The magnitude of underlying group differences in growth rate was quite small, however. For example, an increase in baseline height *Z*-score by one unit was associated with an additional height change of 0.88 cm (95% CI, 0.71–1.05 cm) at 34 months. With the exceptionally small group difference in baseline height *Z*-scores, the magnitude of the corresponding adjustment (0.88 cm/unit × 0.013 units = 0.01 cm) was much smaller than the primary effect at 34 months (0.43 cm). Children given succimer also appeared to gain less weight than did placebo children during the study period, although these adjusted differences were not statistically significant: –0.02 kg (95% CI, –0.10 to 0.05 kg) at 9 months and –0.12 kg (95% CI, –0.35 to 0.10 kg) at 34 months of follow-up.

In the analysis based on random-effects models, the estimated height growth rate in children receiving succimer was slower by 0.13 cm (95% CI, 0.00–0.26 cm) per year, adjusted for covariates. Weight growth velocity was 0.10 kg (95% CI, –0.02 to 0.21 kg) per year slower in children on succimer, compared with those receiving placebo.

Discussion

In the TLC trial, succimer lowered blood lead levels in children with moderate lead exposure but did not have a beneficial effect on growth during or after active treatment. Blood lead levels on average were 2.7/μg/dL lower among children given succimer than among those receiving placebo in the first 12 months after initiation of treatment (TLC Trial Group 2000). In this study, we found no significant group differences in blood lead levels from 12 to 34 months of follow-up. Children given succimer had a –0.27-cm group difference in height change from baseline to 9 months and a –0.43-cm difference at 34 months. Height change differences between treatment groups at 9 and 34 months were not significantly different, however, so we could not conclude that group differences had widened after treatment. Weight gain patterns were similar, but group differences did not achieve statistical significance.

Table 1. Baseline health status characteristics of randomized subjects by treatment group: TLC trial.

	Placebo		Succimer	
	No.	Mean ± SD	No.	Mean ± SD
Age (months)	384	24.5 ± 5.5	396	24.4 ± 5.7
Blood lead (μg/dL)	384	25.9 ± 4.8	396	26.5 ± 5.4
Hemoglobin (g/dL)	384	11.7 ± 0.9	393	11.7 ± 0.9
Ferritin (μg/dL)	380	28.5 ± 19.6	393	28.1 ± 17.6
Birth weight (g)	361	3,169 ± 620	380	3,136 ± 551
Height (cm)	380	85.5 ± 5.7	388	85.3 ± 6.0
Height-for-age *Z*-score	380	–0.11 ± 1.01	388	–0.12 ± 1.01
Weight (kg)	374	12.3 ± 1.9	389	12.3 ± 2.0
Weight-for-age *Z*-score	374	–0.02 ± 1.18	389	0.01 ± 1.25
Body surface area (m^2)	384	0.5 ± 0.1	396	0.5 ± 0.1

Table 2. Sociodemographic characteristics of randomized subjects by treatment group: TLC trial.

	Placebo No. (%)	Succimer No. (%)
Females	165 (43.0)	178 (45.0)
African American	292 (76.0)	309 (78.0)
Study center		
Baltimore	104 (27.1)	109 (27.5)
Newark	102 (26.6)	106 (26.8)
Philadelphia	83 (21.6)	82 (20.7)
Cincinnati/Columbus	95 (24.7)	99 (25.0)

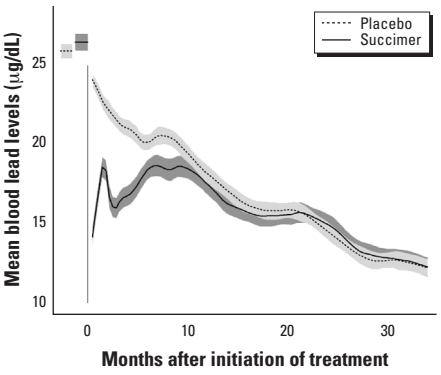

Figure 2. Mean blood lead levels and pointwise 95% CIs (shaded areas) at baseline and after the initiation of treatment in children in succimer and placebo groups. Rectangles in the upper left show the mean and 95% CIs for the baseline values. Means for the curves were calculated by locally weighted regression.

Few studies have examined the relationship of lead-chelating agents to postnatal growth. Among infant rhesus monkeys with blood lead levels comparable with those of children in the TLC trial, two 19-day courses of succimer did not significantly affect weight, length, or head circumference growth up to 2 years of age (Lasky et al. 2001). EDTA had no effect on height growth of lead-exposed children during treatment (Markowitz et al. 1990), whereas one case study reported partial catch-up after therapy (Huseman et al. 1992).

The mechanism by which succimer would have an adverse effect on growth is unknown. Succimer has an unpleasant odor and taste and could have affected children's appetite (Mann and Travers 1991) or the effort that caregivers spent feeding the children. A vented plastic cylinder of 200 mg of active drug inside each bottle of placebo provided an obvious sulfur smell when opened, but placebo tablets were odorless. More families reported difficulty with administration of succimer than with placebo (Rogan et al. 2001). Blood lead levels were unlikely to explain group differences in height change. During active treatment, blood lead levels were always lower in children on succimer, and rebounds did not exceed baseline (20–44 μg/dL; TLC Trial Group 2000). In the period from 10 to 34 months after treatment, blood lead levels did not differ. Diuresis of minerals associated with linear growth in children, such as zinc (Brown et al. 2002), theoretically could have contributed to differences in height change. A modest 1.6-fold increase in zinc excretion was documented in a 5-day clinical trial of succimer in children with high blood levels (Graziano et al. 1992) but not among children with moderate blood lead levels (Graziano et al. 1988). The number and duration of treatment courses were greater in the TLC trial, but multivitamin and mineral supplements including zinc were provided participants to prevent cation diuresis (TLC Trial Group 1998).

The TLC study was a 3-year, randomized, controlled trial of succimer, permitting examination of hypothesized effects during and after treatment. Randomization within strata ensured a relatively even distribution of subject characteristics across treatment arms. Other study strengths included a high retention rate and standardization of measurement techniques and quality control of data collection across the study sites. One limitation of the study was our inability to adjust for unmeasured covariates (e.g., dietary intake), but randomization provides the highest level of protection against bias due to imbalances. Information on time-dependent changes in dietary intake or other unmeasured covariates during active treatment might have provided insight into mechanisms for observed effects, but would not have changed group differences. We were unable to adjust for differences in growth rate before randomization, but analyses suggested that the 0.2-cm group difference in baseline heights would have a negligible influence on the effect observed at 34 months. Inclusion of other covariates known to be associated with growth velocity or potential confounders of the lead–growth relationship in the adjusted models slightly increased the magnitude and precision of the unadjusted effect estimates, particularly for height. The growth curve analysis produced a strikingly similar estimate of the difference in growth rates between treatment groups, demonstrating that the findings were robust.

The difference in growth rates between treatment groups was marginally significant in all of the analyses we considered. Nevertheless, results failed to support the hypothesis that succimer treatment would have a beneficial effect on growth in children with moderate lead exposure, either during or after treatment, and suggested that it may have adverse effects. Primary results of the TLC trial also provided no evidence that succimer improved scores on tests of cognition, behavior, or neuropsychologic function in children with moderate blood lead levels (Rogan et al. 2001). The possibility of an adverse effect on growth seen in the TLC trial strengthens the conclusion that succimer, although effective in reducing blood levels during active treatment, does not have beneficial effects on development in preschool children with moderate lead exposure.

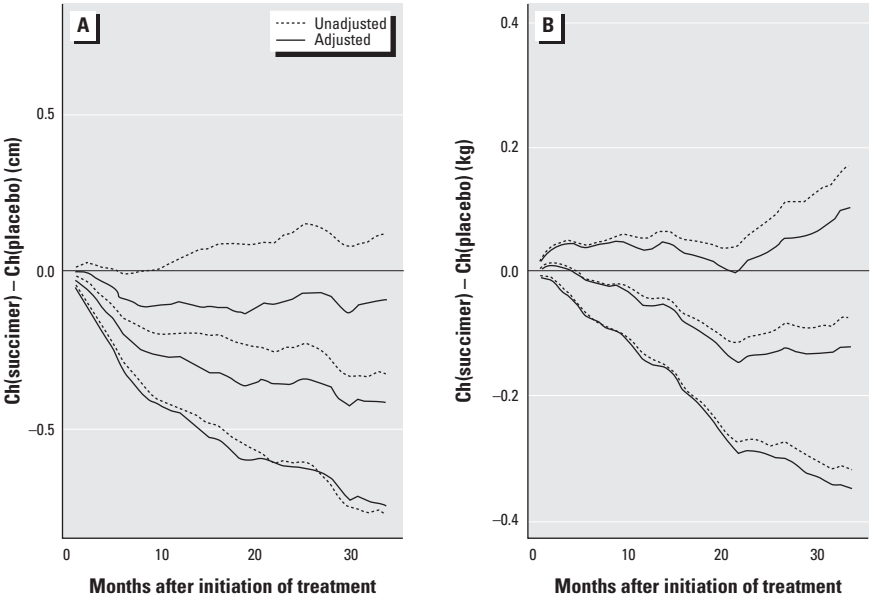

Figure 3. Estimates of the difference in the means of changes in height (*A*) and weight (*B*) from baseline of children in succimer and placebo groups. The upper and lower curves show pointwise 95% CIs for the estimates, and the central curves show the estimated differences. A change of height Ch(*t*) and of weight Cw(*t*) at time *t* from the initiation of treatment is defined as the difference between the fitted value and fitted value at the baseline: Ch(*t*) = *h*(*t*) – *h*(0) and Cw(*t*) = *w*(*t*) – *w*(0).

Table 3. Mean (95% CI) differences in height and weight changes between succimer and placebo groups: TLC trial.

Study month	Height (cm)		Weight (kg)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
6	–0.15 (–0.30 to –0.01)	–0.20 (–0.32 to –0.09)	–0.01 (–0.07 to 0.04)	–0.02 (–0.07 to 0.04)
9	–0.20 (–0.40 to 0.00)	–0.27 (–0.42 to –0.11)	–0.02 (–0.10 to 0.06)	–0.02 (–0.10 to 0.05)
12	–0.20 (–0.45 to 0.04)	–0.28 (–0.46 to –0.10)	–0.04 (–0.13 to 0.05)	–0.05 (–0.14 to 0.03)
18	–0.23 (–0.55 to 0.09)	–0.37 (–0.60 to –0.13)	–0.08 (–0.21 to 0.05)	–0.10 (–0.22 to 0.02)
24	–0.25 (–0.62 to 0.13)	–0.36 (–0.64 to –0.09)	–0.10 (–0.27 to 0.07)	–0.14 (–0.29 to 0.02)
34	–0.33 (–0.79 to 0.12)	–0.43 (–0.77 to –0.09)	–0.07 (–0.32 to 0.17)	–0.12 (–0.35 to 0.10)

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