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Myopic shift 5 years after IOL implantation in the Infant Aphakia Treatment Study

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Abstract

Purpose—To report the myopic shift at 5 years of age after cataract surgery with IOL implantation for infants enrolled in the Infant Aphakia Treatment Study.

Methods—Refractions were performed at 1 month and every 3 months postoperatively until age 4 and then at ages 4.25, 4.5 and 5 years. The change in refraction over time was estimated by linear mixed model analysis.

Results—IOL implantation was completed in 56 eyes; 43 were analyzed (median age = 2.4 mo, range = 1.0 – 6.8 mo). Exclusions included 11 patients with glaucoma, one patient with Stickler syndrome and one patient with an IOL exchange at 8 months postoperatively. The mean rate of change in a myopic direction from 1 month after cataract surgery up until age 1.5 years was 0.35 D/mo (95% CI = 0.29, 0.40 D/mo); after age 1.5 years the mean rate of change in a myopic direction was 0.97 D/yr (95% CI = 0.66, 1.28 D/yr). The mean refractive change at age 5 years for children 1 month of age at surgery was 8.97 D (95% CI, 7.25, 10.68 D) and for children 6 months of age at surgery was 7.22 D (95% CI, 5.54, 8.91 D). The mean refractive error at age 5 years was −2.53 D (95% CI, −4.05, −1.02)

Conclusion—After IOL implantation during infancy, the rate of myopic shift occurs most rapidly during the first one and one-half years of life. Myopic shift varies significantly amongst patients. If the goal is emmetropia at age 5 years, then the immediate postoperative hypermetropic targets should be +10.5D at 4 to 6 weeks and 8.50 D from 7 weeks to 6 months. However, even

*See Appendix for full listing of Infant Aphakia Treatment Study Group

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using these targets it is likely that many children with require additional refractive correction given the high variability of refractive outcomes.

INTRODUCTION

The human eye usually experiences 3–4 mm of axial elongation during the first year of life.1–3 Concurrently, the cornea and crystalline lens flatten, resulting in a relatively stable refractive error. The myopic shift induced by axial elongation following infantile cataract surgery cannot be fully offset by corneal flattening resulting in overall myopic shift. In aphakic eyes, the myopic shift can easily be corrected as needed by reducing the power of corrective contact lenses or spectacles.4, 5 Similarly small myopic shifts can also be corrected with contact lenses or spectacles in pseudophakic eyes. However large myopic shifts may necessitate an IOL exchange.6 In children with unilateral pseudophakia, a large myopic shift may contribute to the development of significant anisometropia, amblyopia and impaired binocularity, particularly when the IOL is implanted at an early age. While there is no agreement regarding the optimal magnitude of immediate postoperative hypermetropia, most clinicians undercorrect infants after cataract surgery and IOL implantation in anticipation of this myopic shift.7–11 While small case series have reported a mean myopic shift ranging from 5 to 7 D after IOL implantation during infancy, these studies were retrospective with variable lengths of follow-up.12–15 The Infant Aphakia Treatment Study (IATS) is a randomized clinical trial comparing the visual outcome in infants 1–6 months of age who underwent primary implantation of an intraocular lens (IOL) versus being left aphakic and receiving a contact lens correction following cataract surgery in infancy.16, 17 We report the myopic shift experienced by children randomized to IOL correction in the IATS from the time of cataract surgery until age 5 years.

METHODS

The study design, surgical technique, follow-up schedules, patching and optical correction regimens, and examination methods have been reported in detail previously and are only summarized in this report.18 The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the participating institutions and was in compliance with the Health Insurance Portability and Accountability Act. The off-label research use of the Acrysof SN60AT and MA60AC IOLs (Alcon Laboratories, Fort Worth, Texas) was covered by US Food and Drug Administration investigational device exemption # G020021.

Study Design

The main inclusion criteria were a visually significant congenital cataract (≥3 mm central opacity) in one eye, a normal fellow eye and an age of 28 days to <210 days at the time of cataract surgery. Patients were randomized to have either an IOL placed at the time of the initial surgery with spectacle correction of residual hyperopia or to be left aphakic and optically corrected with a contact lens. The randomization was stratified according to the category of the age of the infant at surgery (28 – 48 days versus 49 – 210 days.).
Surgical Technique for IOL Implantation

Infants randomized to the IOL group had their lens aspirated followed by the implantation of an AcrySof SN60AT (Alcon Laboratories, Fort Worth, TX) IOL into the capsular bag. In the event that both haptics could not be implanted into the capsular bag, an AcrySof MA60AC IOL was implanted into the ciliary sulcus. The IOL power was calculated based on the Holladay 1 formula targeting an 8 D under correction (postoperative hypermetropia) for infants <48 days of age and a 6 D under correction for infants aged 48–210 days. Following IOL placement, a posterior capsulectomy and an anterior vitrectomy were performed through the pars plana/plicata.

Optical Correction and Patching Regimen

For patients randomized to the IOL group, spectacles were prescribed prior to the 1-month postoperative visit or at any later visit providing that one of the following conditions existed in the treated eye: hyperopia >1.0 D, myopia >3.0 D or astigmatism >1.5 D. The overall aim was to overcorrect the refractive error by 2.0 D to achieve a near point focus. The prescribed optical correction was to be worn at all times while the patient was awake.

Starting the second postoperative week, parents were instructed to have their child wear an adhesive occlusive patch over the unoperated eye for 1 hour/day per each month of age until age 8 months. Thereafter, patching was prescribed for all waking hours every other day or for one-half of the patient’s waking hours every day.

Definition of Glaucoma

Glaucoma was defined as IOP >21 mmHg with one or more of the following anatomical changes: 1) corneal enlargement; 2) asymmetrical progressive myopic shift coupled with enlargement of the corneal diameter and/or axial length; 3) increased optic nerve cupping defined as an increase of ≥0.2 in the cup-to-disc ratio, or 4) the use of a surgical procedure for IOP control. A patient was designated a glaucoma suspect if there was either: 1) two consecutive IOP measurements above 21 mmHg on different dates after topical corticosteroids had been discontinued without any of the anatomical changes listed above; or 2) glaucoma medications were used to control IOP without any of the anatomical changes listed above.

Patient Follow-up and Measurement of Refractive Error

Refractive error was measured using retinoscopy at follow-up clinical examinations by an IATS certified investigator postoperatively at 1 month, 3 months and then at 3 months (± 2 weeks) intervals until age 4 years (± 2 weeks) and then at ages 4.25, 4.5 and 5 years (± 2 weeks). Refractive error was also measured at an exam under anesthesia using cycloplegic retinoscopy 2–4 weeks prior to a grating acuity assessment performed at age 1 year (± 2 months).

Statistical Analysis

The purpose of the analyses was to determine the rate of change in spherical equivalent refractive error for the treated eyes of patients with an IOL implanted and whether selected
Baseline characteristics affected the rate of change. For the longitudinal analyses, the time factor used in the modeling was the age of the patient. Thus, the statistical models related the refractive error to the patient’s age at the time the refractive error was measured. Patient age was used rather than the time since cataract surgery because the physiological changes that would influence changes in refractive error were thought to be more associated with the age of the patient rather than the time since surgery. However, patients in IATS underwent surgery at ages ranging from 1 to < 7 months and we explored whether the rate of change in refractive error was related to the age at which the cataract surgery was performed.

Individual patient profiles relating refractive error to patient age were plotted to visualize the relationship between refractive error and age and to check for possible errors in data measurement, recording or entry. To explore the potential functional relationship between refractive error and age a locally weighted scatterplot smoother (loess) curve was fit with the fraction of points used set to 0.5 and the number of additional iterations for determining weights in the weighted regression step set to 2.

The refractive error was related to age in years at the follow-up visit using a linear mixed effects model. The model was fit using Proc Mixed in SAS 9.3 with an unstructured covariance matrix and using the restricted maximum likelihood estimation method. Based on examination of the loess curve described above the following piecewise linear mixed effects model with a knot at 1.5 years of age was fit:

\[
(\text{Refractive Error})_{ij} = \beta_1 + \beta_2 \text{Age}_{ij} + \beta_3 (\text{Age}_{ij} - 1.5)^+ + b_{1i} + b_{2i} \text{Age}_{ij} + b_{3i} (\text{Age}_{ij} - 1.5)^+ + \epsilon_{ij}
\]

- \(i\) refers to the \(i^{th}\) patient
- \(j\) refers to the \(j^{th}\) follow-up data point for the patient
- \((\text{Refractive Error})_{ij}\) refers to the refractive error of the \(i^{th}\) patient at the \(j^{th}\) follow-up data point
- \(\text{Age}_{ij}\) refers to the age of the \(i^{th}\) patient at the \(j^{th}\) follow-up data point
- \(\beta_1, \beta_2, \beta_3\) are fixed effects
- \(b_{1i}, b_{2i}, b_{3i}\) are random effects
- \(\epsilon_{ij}\) is random error
- \((\text{Age}_{ij} - 1.5)^+ = 0,\) if \(\text{Age}_{ij} \leq 1.5\) and \(\text{Age}_{ij} - 1.5,\) if \(\text{Age}_{ij} > 1.5\)

For this model, the fixed effects, \(\beta_1, \beta_2, \beta_3\), have the following interpretations: \(\beta_1 = \) Intercept; \(\beta_2 = \) Rate of change (D/yr) in refractive error up until age 1.5 years; \(\beta_2 + \beta_3 = \) Rate of change (D/yr) in refractive error after age 1.5 years up to age 5 years (see results section for rational for choosing age 1.5 years)

To evaluate whether certain baseline characteristics (age at surgery, axial length, average central keratometric power, and the power of the IOL implanted) had an effect on the rate of change in refractive error, main effect and interaction terms were added to the model above separately for each of these characteristics. A statistically significant coefficient for the
interaction of the characteristic with the term $\text{Age}_{ij}$ or with the term $(\text{Age}_{ij} - 1.5)^+$ would indicate that the characteristic had an effect on the change in refractive error before or after age 1.5 years, respectively. Further details regarding this model are presented in the online supplement. A p-value < 0.05 was deemed statistically significant.

RESULTS

Patients

Between December 2004 and January 2009, 114 patients were enrolled with 57 patients randomized to each treatment group. Of the 57 IOL patients, 14 were excluded from the analysis for the following reasons: 11 developed glaucoma; 1 had an IOL exchange at 8 months after cataract surgery following a 8.00 D myopic shift between the visits at 3 and 6 months after surgery; 1 had Stickler’s syndrome; 1 did not receive an IOL because there was stretching of the ciliary processes that was not visible preoperatively even after pupillary dilation and the investigator decided intraoperatively that an IOL could not be safely implanted in this eye. These patients were excluded so that the estimate of the rate of myopic shift would not be affected by conditions that were not experienced by the majority of IOL patients. The analyses were performed using the 43 remaining IOL patients. The median age at cataract surgery was 2.4 months (interquartile range = 1.3 – 3.7 months, range = 1.0 – 6.8 months) with 16 patients (37%) in the younger age stratification group (< 49 days). There were 22 females (51%).

Duration and Completeness of Follow-up

The number of expected follow-up visits per patient at which refractive error was to be measured was 19, 20 or 21 depending on the age of the patient at the time of cataract surgery. Among the 43 IOL patients analyzed, the total expected number of these follow-up visits was 873, of which 824 (94%) were performed; 790 (90%) included a measurement of the refractive error for the treated eye. The number of follow-up visits per patient with a measurement of refractive error is summarized in eTable 1 in the online supplement.

One patient was lost to follow-up after 5 follow-up visits with refractive error measured, the last of which occurred at age 11.2 months (9.9 months after cataract surgery). For the remaining 42 patients the mean ± standard deviation for age at the last follow-up visit was 5.0 ± 0.1 years (range, 4.9 – 5.4 years) and for the length of follow-up after cataract surgery was 4.8 ± 0.2 years (range, 4.5 – 5.3 years).

Rate of Change in Refractive Error

The patient profiles of refractive error vs age are displayed for the 43 patients in eFigures 1A – 1I for groups of 5 patients ordered by age at cataract surgery (see the online supplement). Figure 1 shows the profiles for all patients. eFigure 2 (online supplement) shows the data points without connecting points for individual patients, along with the loess curve. The loess curve suggested that refractive error changed in a linear fashion in a myopic direction as age increased up until 1.5 years of age. After age 1.5 years, refractive error again changed linearly in a myopic direction with age, but the rate of change was markedly less than before age 1.5 years. A regression model with these properties was fit and the estimated regression
coefficients are given in Table 1. Figure 2 shows the data points without connecting points for individual patients, along with the regression line. The mean rate of change in a myopic direction from 1 month after cataract surgery up until age 1.5 years was 4.19 D/yr (95% CI = 3.53, 4.85 D/yr); expressed in D/mo the mean rate of change was 0.35 D/mo (95% CI = 0.29, 0.40 D/mo). After age 1.5 years the mean rate of change in a myopic direction was 0.97 D/yr (95% CI = 0.66, 1.28 D/yr).

We used the model results to estimate the mean change in refractive error in a myopic direction from 1 month after cataract surgery until age 5 years according to the age at which cataract surgery was done (Table 2). The estimated mean refractive change for children 1 month of age at surgery was 8.97 D (95% CI = 7.25, 10.68 D) and for children 6 months of age was 7.22 D (95% CI = 5.54, 8.91 D).

**Actual versus Expected Change in Refractive Error**

To demonstrate the variation in the change in refractive error among patients, we used the model results to calculate the expected change in refractive error for each patient between the visit at 1 month after cataract surgery and the visit at age 5 and compared this value to the actual change experienced by the patient. The expected refractive errors at these two visits were calculated from the model coefficients in Table 1 using the patient’s age at the visits. The difference between the refractive errors at the two visits was then calculated to produce the expected change in refractive error. The expected change can be thought of as the mean change among potential patients whose ages at each of the visits match the ages of the actual patient. (Note that this calculation is not the same as determining the difference between the observed and predicted values for linear regression on independent observations in which the sum of the differences is zero.) Of the 43 patients analyzed, 40 had measurements of refractive error at both the 1 month post-operative and age 5 follow-up visits. The mean difference between the actual and expected change in refractive error (calculated as actual – expected) was −0.74 ± 4.60 D (range = −14.11 to 6.43 D) (eFigure 3). Among the 40 patients, for 9 (23%) the actual change was within 1.00 D of the expected change and for 21 (53%) the actual change was with 3.00 D of the expected change; 8 (20%) had 3.01 – 6.43 D less myopic shift than expected and 11 patients (28%) had 3.01 – 14.11 D greater myopic shift than expected (Table 3). All patients except 2 had a refractive change within 7.00 D of that expected from the model. These 2 patients had large, relatively late occurring, unexplained myopic shifts of about 8.00 D, one between ages 3 and 5 years and the other between ages 4 and 5 years.

**Effect of Baseline Characteristics on the Rate of Change in Refractive Error**

As reported above, the mean rate of change in a myopic direction was 0.35 D/mo (4.19 D/yr) prior to age 1.5 years and 0.97 D/yr after age 1.5. We explored whether the baseline characteristics of age at cataract surgery, axial length, average central keratometric power, and the power of the implanted IOL had an effect on these rates of change. Summary statistics for these characteristics are shown in eTable 2 in the online supplement. The p-values for the interaction terms added to the model to test for an effect on the rate of change before and after age 1.5 years respectively were as follows: age of cataract surgery (0.71, 0.60), axial length (0.78, 0.14), average central keratometric power (0.58, 0.91) and IOL.
power (0.24, 0.051). Therefore, none of these characteristics affected the rate of change in refractive error. Further details on the modeling results are reported in eTables 3A–3D and in eFigures 4A–4D in the online supplement.

**Mean Refractive Error According to Age at Follow-up**

Using the model results in Table 1, we estimated the mean refractive error at ages 1 to 5 years. At age 1 the mean refractive error was 2.94 D (95% CI = 2.19, 3.70 D) and at age 5 was −2.53 D (95% CI = −4.05, −1.02 D) (Table 4).

**Glaucoma Patients**—Although the glaucoma patients were not included in the results presented above, a graph of the refractive errors vs age and also summary statistics of the change in refractive error for the glaucoma patients are included in the online supplement.

**Discussion**

The variability of myopic shift after IOL implantation in infants continues to make selection of an IOL power challenging. In this series of 43 eyes undergoing unilateral IOL implantation when 1 to 6 months of age, we found myopic shift to follow a piecewise linear relationship with markedly more rapid linear rate of myopic shift until age 1.5 years followed by a slower linear rate from age 1.5 to 5 years of age. From one month after cataract surgery until approximately 1½ years of age the rate of myopic shift was 0.35 D/month and after 1.5 years of age this decreased to 0.08 D/month. We cannot assess whether or not this rate of change will persist after age 5. None of the baseline characteristics evaluated including age at cataract surgery, keratometry readings, IOL power, or axial length affected the rate of myopic shift. However, given that the sample size of the study was not based upon assessing these associations, the results should not be considered definitive. McClatchey and co-authors have extensively modeled refractive changes in both aphakic and pseudophakic eyes in several publications 15,21 the most recent model 22 the Rate of Refractive Growth 3 (RRG3), which corrects for both intrauterine eye growth and refraction at the spectacle plane describes a logarithmic rate of refractive growth with the most rapid myopic change in early infancy. In this study we also found a significantly higher rate of refractive change at younger ages using a linear spline model to fit the non-linear data. We noted no correlation between age at surgery and rate of myopic shift in our series, which was also the case with the RRG3 model. 22.

Numerous studies have evaluated myopic shift in pseudophakic patients and recommended immediate postoperative refractive targets to minimize anisometropia. 23–28 However, these recommendations have been almost exclusively for older infants and therefore did not address a population when refractive growth is at its greatest. Most of these investigators recommended post-operative refractive targets of no more than +4.00D for all infants under age 2 years and decreasing amounts in older infants, with little or no differentiation for younger infants.

Very few studies have evaluated myopic shift in very young infants (<6 months of age) after IOL implantation in order to better target immediate post-operative refractions and to minimize later anisometropia. McClatchey et al reported a 6.68D shift after 8 years of follow
up in a large series of pseudophakic eyes undergoing surgery from 3–6 months of age. Lambert and co-authors reported a 5.49 D mean myopic shift over an average of only 13+/−6 months postoperatively in 11 pseudophakic eyes of infants operated at a mean of 10+/−6.6 weeks. Ashworth and co-authors reported a mean myopic shift of 6.26+/−2.91 D in the first 12 months following IOL implantation prior to 10 weeks of age, while those undergoing surgery after 10 weeks but prior to one year had a myopic shift of only 2.33+/−1.99D during this same period. Ashworth et al also noted significantly greater myopic shift in shorter eyes, an association that was not seen in our study.

From the regression model we estimated the mean refractive error at age 5 years to be about −2.50 D. This suggests that if the goal is for emmetropia at age 5 years, then the immediate postoperative hypermetropic targets of 8.00 D at 4 to 6 weeks and 6.00 D from 7 weeks to 6 months used in this study should be increased by approximately 2.50 diopters to 10.50 and 8.50 diopters. However, there are many factors that should be considered when deciding on the most appropriate undercorrection including the likelihood of the child wearing an overcorrection, the refractive error of the fellow eye and the potential for binocular vision. Another factor to consider is the development of glaucoma which can result in increased axial length and myopic shift in young eyes. We have attempted to eliminate this potential confounding factor by excluding the 11 IOL patients diagnosed with glaucoma.

The actual amount of myopic shift varied from the expected amount in a high percentage of patients. Only about 25% of eyes were within 1D of the expected refractive change and 50% within 3D. The remaining 50% ranged from 3D to as much as 14D from the expected refractive change, roughly equally divided between those with substantially less and those with substantially more than the expected change. This variability has important implications when trying to avoid anisometropia later in life. As suggested previously, while targeting an additional 2.50 D of hypermetropia immediately postoperatively would be expected to more accurately compensate for the average myopic shift, the variability in myopic shift among patients will continue to result in unanticipated anisometropia at later ages.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


18. (IATS design paper)


Figure 1.
Refractive error in the treated eye versus age at the follow-up visit for 43 patients treated with an IOL. Graph A shows the lines connecting the values for individual patients and Graph B shows the estimated piecewise linear regression line.
Estimates for the Regression Coefficients (Fixed Effects) in the Linear Mixed Effects Model Relating Refractive Error to Age at Follow-up

<table>
<thead>
<tr>
<th>Model Term</th>
<th>Coefficient</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$\beta_1$</td>
<td>7.13</td>
<td>0.42</td>
<td>&lt; 0.0001</td>
<td>6.28 – 7.98</td>
</tr>
<tr>
<td>Age$_ij$</td>
<td>$\beta_2^\dagger$</td>
<td>−4.19</td>
<td>0.33</td>
<td>&lt; 0.0001</td>
<td>−4.85 – −3.53</td>
</tr>
<tr>
<td>(Age$_ij$−1.5)$^\ddagger$</td>
<td>$\beta_1^\ddagger$</td>
<td>3.22</td>
<td>0.36</td>
<td>&lt; 0.0001</td>
<td>2.50 – 3.94</td>
</tr>
</tbody>
</table>

*a* The complete model is defined in the Methods section.

$^\dagger \beta_2$ = Mean rate of change (D/yr) in refractive error up until age 1.5 years. Expressed in D/mo the estimate is −0.35 (95% CI = −0.40 – −0.29 D/mo).

$^\ddagger \beta_2 + \beta_3$ = Mean rate of change (D/yr) in refractive error after age 1.5 years.

The estimate is −0.97 D/yr with standard error 0.15 and 95% CI = −1.28 – −0.66 D/yr.
Table 2

Estimated Mean Change in Refractive Error in Myopic Direction Between 1 Month Post-op and Age 5 Years According to Age at Cataract Surgery

<table>
<thead>
<tr>
<th>Age at Surgery (mo)</th>
<th>Estimated Change in Refractive Error (D) Between 1 Month Post-op and Age 5 Years</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>8.97 (7.25 – 10.68)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>8.62 (6.91 – 10.32)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>8.27 (6.57 – 9.97)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>7.92 (6.23 – 9.61)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>7.57 (5.89 – 9.26)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>7.22 (5.54 – 8.91)</td>
</tr>
</tbody>
</table>
Table 3

Difference between Actual and Expected Change in Refractive Error From 1 Month Post-op to Age 5 Years

<table>
<thead>
<tr>
<th>Direction of Difference</th>
<th>Difference (D)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual myopic shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>greater than expected</td>
<td>12.53 and 14.11</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td></td>
<td>3.01 – 7.00</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td></td>
<td>1.01 – 3.00</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Within 1.00</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Actual myopic shift</td>
<td>1.01 – 3.00</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>less than expected</td>
<td>3.01 – 7.00</td>
<td>8 (20.0%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>
**Table 4**

Estimated Mean Refractive Error According to Age at Follow-up

<table>
<thead>
<tr>
<th>Age at Follow-up (yr)</th>
<th>Estimated Mean Refractive Error (D) Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.94 (2.19 – 3.70)</td>
</tr>
<tr>
<td>2</td>
<td>0.37 (−0.58 – 1.31)</td>
</tr>
<tr>
<td>3</td>
<td>−0.60 (−1.68 – 0.48)</td>
</tr>
<tr>
<td>4</td>
<td>−1.57 (−2.85 – −0.29)</td>
</tr>
<tr>
<td>5</td>
<td>−2.53 (−4.05 – −1.02)</td>
</tr>
</tbody>
</table>