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Modifying bone mineral density, physical function, and quality of life in children with acute lymphoblastic leukemia

Cheryl L. Cox, PhD¹, Liang Zhu, PhD², Sue C. Kaste, DO^{1,3}, Kumar Srivastava, PhD¹, Linda Barnes, BSN, CRA¹, Paul C. Nathan, MD, MSc⁴, Robert J. Wells, MD⁵, and Kirsten K. Ness, PhD¹

¹St. Jude Children's Research Hospital, Memphis, TN

²The University of Texas Health Science Center at Houston, TX

³The University of Tennessee Health Science Center, Memphis, TN

⁴The Hospital for Sick Children, University of Toronto, Toronto, CA

⁵MD Anderson Cancer Center, Houston, TX

Abstract

Background—The early effects of childhood acute lymphoblastic leukemia (ALL) include decreased physical function, bone mineral density (BMD/g/cm²), and health-related quality of life (HRQL). We assessed the capacity of a physical therapy and motivation-based intervention, beginning after diagnosis and continuing through the end of treatment, to positively modify these factors.

Procedure—A 2.5-year randomized controlled trial of 73 patients aged 4 to 18.99 years within 10 days of ALL diagnosis, assessed BMD at baseline (T⁰) and end of therapy (T³), strength, range of motion, endurance, motor skills, and HRQL at T⁰, 8 (T¹), 15 (T²), and 135 (T³) weeks.

Results—There were no significant changes between groups (Intervention, n=33; Usual care, n=40) in BMD ($P=0.059$) at T³, or physical function and HRQL T⁰-T³. While BMD declined in both the intervention (T⁰ = -0.21, T³ = -0.55) and usual care (T⁰ = -0.62, T³ = -0.78) groups, rates of decline did not differ between groups ($P=0.56$). Univariate analysis (n=73) showed associations of higher T³ bone density with: body mass index T¹ ($P=0.01$), T² ($P<0.0001$), T³ ($P=0.01$), T³ ankle flexibility/strength ($P=0.001$), and T² parent ($P=0.02$)/T⁰ child ($P=0.03$) perceptions of less bodily pain.

Conclusions—The intervention delivered during treatment was not successful in modifying BMD, physical function, or HRQL. Physical activity, at the level and intensity required to modify

Correspondence to: Cheryl L. Cox, PhD, 3790 Walnut Grove Road, Memphis, TN 38111; Phone: 901 458 4090; cox1072@bellsouth.net.

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these factors, may not be feasible during early treatment owing to the child's responses to the disease and treatment. Future studies will consider intervention implementation during late maintenance therapy, extending into survivorship.

Keywords

Bone mineral density; pediatric acute lymphoblastic leukemia; health-related quality of life; physical function; late effects

Introduction

Each year, more than 3000 new cases of childhood acute lymphoblastic leukemia (ALL) are diagnosed in the United States ¹. At diagnosis, children experience motor problems, suggesting that the cancer itself results in functional impairment ^{2,3}. Thirty-six percent of children with ALL reported musculoskeletal pain at diagnosis ⁴; as early as 3 days after vincristine administration, are flexia, weakness and atrophy of the extremities, muscle pain/cramps, and decreased range of motion are noted ^{2,5-8}. Decreased ankle dorsiflexion strength, knee extension, and loss of functional mobility are common and may be seen as early as 4-5 months into therapy ^{9,10}. One year or more after completing ALL therapy, children and young adults (5.1-25.2 years of age) had delayed gross motor skills, poor balance, decreased strength, and decreased ankle range of motion; these impairments are responsible for subsequent dysfunction of balance and postural control ¹¹⁻¹³. Pain and fatigue contribute to a cycle of reduced activity, diminished strength and fitness, increased fatigue, and decreased quality of life ¹⁴⁻¹⁶. Children's BMD is reduced early in the course of therapy and remains low after completion of chemotherapy -- associated with type and dose of corticosteroids, methotrexate exposure, cranial irradiation, and physical inactivity ^{17,18}.

With a survival rate exceeding 93% ^{19,20}, children with ALL have a potentially positive future if intervention can diminish early loss of physical function and modify the later effects of therapy. Recent reports ^{21,22} urge early physical activity to minimize the sequelae of treatment in childhood cancer survivors; prescribed physical activity, even at low intensity and duration levels, has demonstrated changes in remarkably short periods of time in young cancer patients and survivors ^{9,18,23-26}. However, the physical activity interventions for ALL that have been tested have started after functional loss has occurred, involved small and/or non-randomized samples, been of short duration, and had minimal or no follow-up to monitor behavior sustainability and durability.

We conducted a randomized trial to evaluate a motivation-based physical activity program beginning within 10 days of diagnosis and extending throughout treatment. We hypothesized that, compared to the usual care group, the intervention group at T³ would maintain or increase BMD over baseline values and demonstrate increased physical function, endurance, and health-related quality of life (HRQL) at 8(T¹), 15(T²), and 135 weeks (T³).

Methods

This 2.5-year randomized trial targeted comparison of changes in BMD, physical function, and HRQL. Subjects were newly diagnosed with ALL and were being treated at any of four

pediatric cancer treatment centers: Aflac Cancer and Blood Disorders Center (Atlanta, GA), Children's Healthcare of Atlanta; MD Anderson (MDA) Cancer Center (Houston, TX); St. Jude Children's Research Hospital (SJCRH; Memphis, TN), and The Hospital for Sick Children (Toronto, Ontario, Canada).

Eligible children were 4 through 18.99 years old; enrolled on or being treated per the SJCRH or Children's Oncology Group (COG) frontline ALL protocol; had started ALL therapy within the past 10 days; could speak and understand English and had at least one parent who could speak, read, and write English; did not have cerebral palsy, second malignancy, chromosome breakage syndrome, or severe congenital immunodeficiency; had the written informed consent of at least one parent/guardian; and provided assent as appropriate. The lower age limit was selected to allow comparison of study outcome measures with existing normative data; the upper age threshold was selected to limit participants to those on the two frontline protocols.

Intervention

The intervention consisted of two components: a strategy^{27, 28} aimed at supporting motivation for long-term behavior change and a set of routine physical therapy exercises targeting strength, range of motion, gross motor skills, and endurance. Advanced practice nurse (APN) visits (in hospital or clinic) occurred twice weekly for the first 4 weeks, once weekly during weeks 5-8, and monthly during weeks 9-135. The physical therapist (PT) visits (in hospital or clinic) occurred once weekly during weeks 1-4, once every other week during weeks 5-8, and once monthly during weeks 9-135.

APN Visits

The goal was to support the patient and their family to become increasingly self-reliant in initiating and sustaining exercise that would help to prevent or modify both early and late effects of therapy. All interactions were directed at meeting three primary needs of the patient and family: relatedness, competency, and autonomy. The APN engaged the patient and parents in dialogue that consistently emphasized the volitional nature of participation in the program and avoided coercive language ("we would like for you to," "you should"). They continually emphasized the child/parent perspective, providing personalized, rather than generic, information.

PT Visits

The stretching, strengthening and counter movement jumping activities were tested in a pilot study among children with ALL²⁹ based on principles pertaining to frequency, duration, and intensity of exercise³⁰ and on the Winningham Program³¹ modified for the pediatric ALL population⁹. Activities within categories were equivalent and achieved the same therapeutic aims; frequency, intensity, and duration of the activities were consistent for all ages. The child's health status guided the PT's intervention approach: for example, if a child were nauseated, the caregiver might perform a passive stretch. The participants were encouraged to perform their exercises at home independently or with parental support 5× weekly 30 minutes per session.

Usual-Care Attention/Control

This group received attention-control visits from the PT at the same intervals and in the same location as the treatment group in order to match the procedures of the intervention group. While the current standard of care for patients with newly diagnosed ALL is activity as tolerated, there is an increased risk of reduced ankle dorsiflexion during vincristine therapy -- the predominant reason for PT referral⁷. We recommended that patients and parents/guardians in the usual care group perform passive ankle stretching to slow the limitation of ankle range of motion. At each visit, the PT instructed/reinforced the patient and caregiver on how to safely perform ankle dorsiflexion passive stretches and trunk stretching exercises at home for 30 seconds 5× weekly. Similarly, the APN visits occurred on the same schedule as for the intervention group, and the APN inquired in a neutral manner about how the patient and family were doing.

Physical Assessments

An assessment practice trial was done 1-2 days prior to the baseline assessment to avoid any learning effects; a second practice trial was completed 2 days before the T¹ assessment, approximately 6-7 weeks after chemotherapy began. T² assessment occurred within approximately 8-9 weeks after completion of induction therapy and the T³ assessment occurred approximately 135 weeks after the start of chemotherapy.

Outcomes

Dual-energy x-ray absorptiometry (DEXA) determined BMD (g/cm²) of the lumbar spine was measured at diagnosis and at week 135 (T³) anteriorly in L1-L4 and laterally in L2-L4 using the GE Lunar Prodigy (Atlanta and Toronto) or the Hologic (SJCRH and MDA). As trabecular bone (lumbar spine) is metabolically more active than cortical bone (total body, hip), the effects of the intervention should be more readily detected by assessing trabecular bone. Consistent with ongoing studies at SJCRH, we contracted with Bioclinica, Inc. (Newtown, PA) to assure site calibration and quality control for comparability of data across the sites and between the two different manufacturers and models of equipment. Height, weight, age, race and gender-adjusted corrected Z-scores constituted the BMD measures and were provided directly to us by Bioclinica. These data are based on The National Health and Nutrition Surveys (NHANES) and are incorporated into the manufacturer's software for the GE Lunar Prodigy and Hologic.

Physical Function—Changes were measured T⁰-T³ in muscular strength (hand grip, knee extension, dorsiflexion) and ankle range of motion (measured by goniometry)³², cardiovascular endurance on the 6-Minute Walk Test³³, and motor proficiency on the Bruininks-Oseretsky Test of Motor Proficiency Short Form (BOTSF-2)³⁴.

HRQL—The Child Health Questionnaire (CHQ), in parallel parent and child forms, measured³⁵ Physical Function, Emotional-Behavioral Role, Physical Role, Bodily Pain, Behavior, Mental Health, Self-esteem, and Family Activities (Likert scale: 1=No problems, 5=Very often or daily problems) T⁰-T³. *Compared to this time last year, how is your/your child's health (Likert Scale 1=Much worse, 5=Much better)* evaluated health comparison.

Children younger than 5 years did not respond to the HRQL items because normative data for that age group are not available.

Physical Activity Patterns—Children's physical activity patterns were evaluated at each assessment period for 7 days using accelerometers (SenseWear Pro III, BodyMedia, Pittsburgh, PA). Successful accelerometer data collection in children with leukemia as young as 4 years³⁶ has been reported. Short gaps (< 20 minutes) or periods specified for light activity (e.g., changing clothes or showering) were filled by using the mean of the 5-minute periods before and after the gap. Unexplained gaps and periods longer than 20 minutes were tracked across days, and participants with more than 1 hour of missing data were assumed to be non-compliant for the designated day (data were recoded as missing). Proprietary algorithms provided the estimated Energy Expenditure (EE) data for each minute, but customized SAS programs, developed by the consultant to the project, were used to create summary data files that included total daily EE estimates (kcal/day, kcal/kg/day) and the percentage of time spent in different intensities of activity (Rest, Light, Moderate, Vigorous). Participants were provided with the same SP3 unit (tracked by serial number) for each assessment period to minimize any risk due to inter-monitor variability.

Independent Variables

Demographics—Child/parental age; gender; race/ethnicity; mother's, father's, and patient's highest level of education; total household income; and parent marital status were obtained from the medical record or data collection forms.

Diagnosis-related information—ALL immunophenotype, diagnosis date, and therapy prescribed were collected from the medical record.

Child data—Height and weight were used to interpret and compare study results with normative data on the physical function and bone density measures and to calculate the accelerometer data.

Somatic/Emotional Distress—To assess the impact of chemotherapy side effects on the physical performance and HRQL measures at baseline and T¹, we administered two of the five subscales from the Behavioral Affective Somatic Experiences Scale (BASES)^{37, 38}.

Adherence to the Intervention—Three measures of adherence were included in the study: number of days accelerometer was worn at each study assessment point (7 days), total number of visits/phone calls with the PT (37 visits) and APN (43 visits), daily physical activity logs (5 days weekly).

Sample Size and Randomization

Sample size was based on a standardized effect size of 0.5 reported for BMD in previous longitudinal studies lasting longer than two years and modified for sick children³⁹. With 38 evaluable patients in each group, this study had 80% power to detect this effect size with a within-participant correlation coefficient of 0.5 and a type I error of 0.05; the study had 86% power to detect the same effect size on each of the HRQL and physical function measures.

On the basis of estimates from SJCRH institutional data, we estimated a 15% refusal rate and a withdrawal/relapse rate of 6%; we set an enrollment/retention goal of 82 participants.

All 211 eligible children were approached to participate in the study. Although 122 children were enrolled, 15 withdrew prior to randomization, with parents citing being too overwhelmed to participate in the study as their primary reason for withdrawal (Fig. 1).

Randomization was done centrally at SJCRH using the randomization scheme proposed by Zelen⁴⁰. The study participants were stratified by three age groups (4-7, 8-12, and 13-18.99 years) to accommodate stages in the development of balance, postural control, and integration of the vestibular systems. Sex and treatment protocol (SJCRH or COG) were also stratification variables, forming 12 strata. Stratified, blocked randomization was used to allocate participants within each of the 12 strata to one of the two groups so that approximately one-half of the participants in a given stratum were assigned to each arm.

Blinding—PTs who performed the functional assessments T⁰-T³ were not informed about group assignment.

Statistical Methods

Descriptive statistics and *P* values based on chi-square or Fisher's exact tests are provided for demographic variables in the intervention and usual care groups. A linear mixed model estimated the effects of group assignment on BMD. We performed analyses with and without adjustment for the stratification variables (age group, sex, and protocol), and the results were similar. Because some strata had very few participants, we reported the result without adjustment^{41,42}. Similar analyses were performed for physical function and parent- and child-reported HRQL. Descriptive statistics are given for these outcomes at each time point in both groups, and *P* values based on two-sample *t* tests or Wilcoxon rank sum tests were calculated for testing differences from T⁰ to T³ between the two groups. Similar analyses were done for HRQL reported by parents and children across the four study assessments. *P* values for comparison of scores between parents and children were calculated based on paired *t*-tests. Finally, we combined both study groups and evaluated the associations between BMI and HRQL with T³ BMD using general linear models. HRQL measures from each of the four time points are reported; however, only the concurrent (T³) physical function measures were included in the univariate analysis of the T³ BMD measure because these variables are correlated with BMD in a cross-sectional fashion. When right, left, and both extremities were significant, we reported an average of the values from both limbs. All models were adjusted for baseline BMD Z-scores by including the baseline score in the model.

Results

In the intervention group, 36 of 53 patients and parents completed all four physical performance and HRQL assessments; in the usual care group, 41 of 54 patients and parents completed all four assessments. For the BMD assessments (T⁰ and T³), 51 in the intervention group and 52 in the usual care group completed T⁰, and 33 in the intervention group and 40 in the usual care group completed T³. There were no differences between the

intervention (n=53) and usual care (n=54) groups on age, sex, race, mother's educational attainment, or BMD at baseline. The patients were predominantly white, male, and diagnosed between 4-9 years or 10-14 years, and most mothers had completed college (Tables 1, 2).

The linear mixed model shows that there was no significant difference in BMD between the intervention and usual care groups (intervention mean= -0.55, usual care mean= -0.78, coefficient of intervention=0.431, SE of coefficient=0.226, $P=0.059$) and the usual care groups and between T0 and T3 ($p=0.538$). There was no interaction between the intervention and time ($P=0.558$). Both groups demonstrated declining BMD over time; rates of decline did not differ between groups ($P=0.558$) (Table 2; Fig. 2). There were no vertebral fractures in either of the study groups.

The usual care group scored better on left active ankle dorsiflexion (a specifically prescribed exercise for this group) at T³ than the intervention group did ($P=0.04$) (Table S1). Although both groups increased their activity level (physical activity, vigorous activity) from T⁰ to T³, the differences were not significant. Both groups' activity levels declined at T², likely a function of intensification of therapy⁴³.

Although, there were minimal group differences at T³, children consistently scored their quality of life better (physical functioning, emotional-behavioral role, physical role, and bodily pain) than did the parent across time points (Table S2). At T² and T³, children and parents were more similar in their assessments regarding mental health.

Most participants in both groups wore their accelerometers 7 days as prescribed (T¹, Intervention = 82%, Usual Care = 84%; T², Intervention = 89%, Usual Care=87%; T³, Intervention=79%, Usual Care=94%); the distribution of the number of wear sessions was similar between the two groups ($P=1.00$ at T¹, 1.00 at T², and 0.13 at T³).

There were no differences between the groups when frequency/duration of countermovement jumps (intervention) were compared to frequency/duration of ankle ($P=0.43$) and trunk ($P=0.39$) rotations (usual care). There were no differences between the groups relative to APN ($P=0.12$) and PT ($P=0.43$) missed appointments; (Intervention, missed APN visits, Mean=4.39, SD=5.41; Usual care, missed APN visits, Mean=2.49, SD=3.60; (Intervention group, missed PT visits, Mean=6.98, SD=5.69; Usual care missed PT visits, Mean=5.69, SD=4.68).

We combined the two parent groups and the two patient groups to examine to what extent any of our variables in isolation might affect T³ BMD (Table 3). These univariate analyses provided information about impairments and quality of life factors to target in subsequent studies. All models were adjusted for baseline BMD Z-scores by including the baseline score in each model.

Discussion

A physical activity program combined with a behavior-change strategy for the duration of ALL treatment did not improve BMD, HRQL or physical function compared to usual care.

Our findings are, however, consistent with a long-term study in which a home-based intervention was found to be no more effective than usual care to improve BMD or physical function in 51 children with ALL, primarily due to poor compliance⁴⁴; we too documented that vigorous exercise decreased in the intervention group from 37 to 16 minutes per day from baseline to T³, consistent with poor adherence to the intervention.

While other studies^{18, 22-26} have shown improvement in these outcomes in late maintenance or survivorship, our study did not generate any data for intervals when children were completely off drug treatment. Beginning shortly after diagnosis and following participants through the end of therapy, however, may have resulted in the study participants/parents simply being too sick/overwhelmed particularly at T⁰-T² to complete the intervention with the frequency and intensity necessary to improve function; they eventually may have experienced intervention fatigue over the 30-month timeframe.

Unsupervised exercise was likely not a sufficient intervention to prevent loss of structure or function during the intensive chemotherapy required to cure disease. Unlike our pilot study²⁹, in which the identical exercises were administered during the maintenance phase of chemotherapy and provided for weekly interventionists' contact, this intervention tapered to monthly interventionists' contact after eight weeks.

Selection bias was certainly a factor in this study. While participants did not differ from non-participants by age or sex, it is possible that children who were sicker or who had more severe musculoskeletal symptoms at diagnosis elected not to participate. A number of parents and children refused participation after initially agreeing to enroll; parents who withdrew prior to and immediately after randomization reported "being unable to think" and not being fully aware of study participation requirements. Avoidance, extreme anxiety, and re-experiencing of events related to their child's diagnosis are reported by nearly all parents in the first two weeks after diagnosis⁴⁵. Finally, parental concerns about radiation exposure reduced the number of evaluable T³ DEXA scans.

Our findings were consistent with previous reports in that children with greater mass and strength had better BMD outcomes⁴⁶. Joyce et al⁴⁷ evaluated the association between extremity muscle mass and bone density among 493 adult survivors of childhood ALL (age range, 20-49 years) and found that muscle mass explained 33% to 56% of the variation in bone density. Herrmann et al⁴⁸ evaluated the combined effects of strength, physical activity, sedentary behavior, and calcaneal bone stiffness among 4,465 children ages 2 to 10 and reported that muscle strength and moderate/vigorous physical activity had the strongest associations with bone stiffness. Unlike previous reports⁴⁹, however, neither study group demonstrated vertebral fractures. To what extent our population's slightly higher than expected BMI values (compared to normative data³) may have been protective against fractures warrants further study.

Finally, prospective studies have indicated that a one-standard deviation decrease in bone mass is linked to a 1.5- to 3-fold increase in the relative risk of fracture⁵⁰. While the BMD Z-scores in this study were only slightly decreased from the mean, they can be used to

counsel patients and parents about healthy lifestyle choices when bone mineral accrual is most active -- during accelerated growth and development.

This study offers a number of insights for future studies. First, by offering study participation at maintenance, in contrast to within 10 days after diagnosis, parents and children will have had a considerable period of time to adjust to the diagnosis and to have hurdled the worst of treatment and disease effects. Fear, anxiety, symptoms, and overall well-being will no longer be the significant threats that they were at diagnosis, thereby potentially facilitating greater participation and commitment to the intervention.

Secondly, we support more frequent contact with the interventionists. While early in the intervention program, the children are learning new skill sets and coping skills, there needs to be the continuing support and emphasis on the lifelong commitment to physical activity to moderate the late effects of therapy.

Finally, different strategies for categories of patients may need to be considered. These might include individualized intense rehabilitation focused on motor impairments and fitness for children who find it difficult to be active on their own and/or the use of low-magnitude stimulation⁵¹ to augment activity in those who are too ill or too fatigued to exercise at sufficient intensity. Pharmacologic agents may be necessary for children with low bone density and associated fracture⁵² who lack the capacity to exercise because of pain and mobility limitations.

Further study is needed to: optimize patient/parent exercise commitment, identify the ideal timing of late or post-therapy exercise programs, and work toward therapy changes that would mitigate decreases in BMD, HRQL, and physical function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALL	Acute lymphoblastic leukemia
BMD	Bone mineral density
HRQL	Health-related quality of life
T⁰	Baseline
T¹	8 weeks after chemotherapy initiation
T²	15 weeks after chemotherapy initiation
T³	135 weeks after chemotherapy initiation
SJCRH	St. Jude Children's Research Hospital
MDA	MD Anderson
COG	Children's Oncology Group

APN	Advanced-practice nurse
PT	Physical therapist
DEXA	Dual-energy x-ray absorptiometry
BOTSF-2	Bruininks-Oseretsky Test of Motor Proficiency Short Form
CHQ	Child Health Questionnaire
BASES	Behavioral Affective Somatic Experiences Scale
NHANES	National Health and Nutrition Examination Survey
SEM	Standard Error of the Mean

Figure 1. Study Consort Diagram

Figure 2. Mean plot with SEM error bars for BMD at T0 and T3

Table 1
Characteristics of the usual care and intervention study groups

Variables	Intervention Group (N=53)		Usual Care Group (N=54)		P value*
	Frequency	%	Frequency	%	
Age					
4-9 years	19	35.8	18	34.0	
10-14 years	19	35.8	20	37.7	
15-18 years	15	28.3	15	28.3	
Sex					0.84
Male	34	64.2	36	66.7	
Female	19	35.8	18	33.3	
Race					0.10
Whitenon-Hispanic	31	58.5	37	68.5	
Hispanic	9	17.0	7	13.0	
Blacknon-Hispanic	3	5.7	7	13.0	
Other	10	18.9	3	5.6	
Mother's educational attainment					0.89
< High school	8	15.4	6	11.5	
High school graduate	19	36.5	19	36.5	
College graduate	25	48.1	26	50.0	
Not reported	0	0	1	1.9	

* From χ^2 statistic

Table 2

Bone mineral density across time-points

	Intervention group, mean (SD)		Usual care group, mean (SD)		P value*
	T ⁰	T ³	T ⁰	T ³	
Bone mineral/density	-0.21 (1.27)	-0.55 (0.86)	-0.62 (1.14)	-0.78 (1.11)	0.61
Sites 1 & 3	-0.18 (1.34)	-0.62 (0.79)	-0.47 (1.21)	-0.80 (1.11)	0.20
Sites 2 & 5	-0.23 (1.24)	-0.49 (0.93)	-0.76 (1.07)	-0.75 (1.31)	0.98

* Differences between groups, T⁰ to T³

Table 3

Significant univariate results, dependent variable = T³BMD

Variable	Category	Estimate	Standard Error	95% CI	P value
Body Mass Index and Physical Function Model					
Body mass index %	T ³	0.89	0.35	(0.21, 1.57)	0.01
Left ankle dorsiflexion strength	T ³	0.10	0.03	(0.04, 0.15)	0.001
Right ankle dorsiflexion strength	T ³	0.09	0.03	(0.03, 0.15)	0.003
Right and left ankle dorsiflexion strength	T ³	0.10	0.03	(0.04, 0.15)	0.001
Health-related Quality of Life Model					
Physical role (child)	T ²	0.01	0.00	(0.00, 0.02)	0.03
Bodily pain (child)	T ⁰	-0.02	0.00	(-0.02, -0.01)	<0.001
Mental health (child)	T ⁰	-0.02	0.01	(-0.03, -0.01)	<0.001
Physical function (parent)	T ²	0.01	0.00	(0.01, 0.02)	0.001
Bodily pain (parent)	T ²	0.02	0.01	(0.01, 0.03)	0.002
Physical role (parent)	T ²	0.01	0.00	(0.00, 0.01)	0.03