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# Parental functioning during maintenance treatment for childhood acute lymphoblastic leukemia: Effects of treatment intensity and dexamethasone pulses

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## Abstract

**Background:** During maintenance treatment, Dutch pediatric patients with medium-risk (MR) acute lymphoblastic leukemia (ALL) receive intravenous chemotherapy and cyclic dexamethasone. Dexamethasone affects child's sleep and behavior. Standard-risk (SR) patients only receive oral chemotherapy, without dexamethasone. Effects of stratified therapy on *parents* are not well known. This study compares parental sleep, distress and quality of life (QoL) with the general population, between MR and SR groups, and on- and off-dexamethasone (MR group).

**Procedure:** One year after diagnosis, parents of MR patients completed the Medical Outcomes Study (MOS) sleep, distress thermometer for parents and Short Form-12 (SF-12) *twice*; once on-dexamethasone and once off-dexamethasone. SR parents completed one measurement. Sleep problems, distress and QoL scores (off-dexamethasone) were compared to reference values and between MR and SR. Score differences on- and off-dexamethasone were assessed by multilevel regression analysis.

**Results:** Parents (80% mothers) of 121 patients (57% males; 75% MR, 25% SR) completed 191 measurements. Compared to reference values, parents reported more sleep disturbances, higher distress, and lower mental QoL. Additionally, MR parents reported clinical distress (score  $\geq 4$ ), whereas SR parents (on average) did not (mean  $4.8 \pm 2.4$  vs  $3.5 \pm 2.4$ ,  $P = .02$ ). Within the MR group, outcomes did not significantly differ on- and off-dexamethasone.

**Conclusions:** Parents of ALL patients report sleep problems, high distress, and QoL impairment. Within the MR group, parental functioning did not differ on- and off-dexamethasone. However, MR parents reported clinical distress more often than SR parents, possibly reflecting differences in prognostic estimates and treatment

**Abbreviations:** ALL, acute lymphoblastic leukemia; CBT-I, cognitive behavioral therapy for insomnia; CNS, central nervous system; DCOG, Dutch Childhood Oncology Group; HR, high risk; MCS, mental component summary score; MOS, Medical Outcomes Study; MR, medium risk; PCS, physical component summary score; QoL, quality of life; SF-12, Short Form-12; SLP-9, nine-item sleep problems index; SR, standard risk

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burden. This perhaps includes the overall strain of cyclic dexamethasone. This study highlights the need for psychosocial support throughout treatment, regardless of risk stratification.

#### KEYWORDS

ALL, dexamethasone, parents, psychosocial, quality of life, sleep

## 1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer. Survival rates have reached over 90% due to the establishment of intense chemotherapy regimens and enhanced supportive care.<sup>1</sup> However, chemotherapeutic agents can cause significant short- and long-term side effects; hence, treatment intensity is ideally adjusted according to an individual patient's risk profile.<sup>1,2</sup>

In the Netherlands, the majority of pediatric patients with ALL (from 1 year of age) are treated according to the frontline Dutch Childhood Oncology Group (DCOG) ALL11 protocol (since 2012).<sup>3</sup> This protocol distinguishes three risk groups: the most favorable standard-risk (SR) group, comprising approximately 25% of patients; the medium-risk (MR) group, comprising approximately 70% of patients; and the high-risk (HR) group, only comprising about 5% of patients.

The induction phase of treatment is generally the same across all risk groups. After induction, either directly or during central nervous system (CNS)-targeted therapy, HR patients continue with a different, more intense treatment regimen, with or without an allogeneic stem cell transplant. Differentiation between SR and MR treatment occurs after CNS-targeted therapy. Total treatment duration across these risk groups is generally 2 years.<sup>3</sup>

During SR maintenance, patients only receive oral chemotherapy (daily mercaptopurine and weekly methotrexate) at home, and visit the hospital every 2-3 weeks. Patients in MR maintenance receive daily oral mercaptopurine at home, weekly intravenous methotrexate at the hospital, and intravenous vincristine (with asparaginase during the first 4 months) every 3 weeks. Vincristine is known for inducing peripheral neuropathy, possibly leading to pain and obstipation.<sup>4</sup> Furthermore, MR patients receive intrathecal chemotherapy under procedural anesthesia every 18 weeks. And finally, patients in MR maintenance receive cyclic dexamethasone treatment, as opposed to those in SR maintenance, which means 5 days of high-dose dexamethasone (6 mg/m<sup>2</sup>/day) every 3 weeks during approximately 1.5 years.<sup>3</sup>

Dexamethasone is a glucocorticoid with many well-known adverse effects on the child's behavior, sleep, and general quality of life (QoL).<sup>5-9</sup> The recurrent pattern of this treatment puts a high burden on both the patient and their families, certainly on parents. In qualitative research, parents have reported very high emotional impact of the dexamethasone treatment and identified it as *the* major stressor during the overall relatively stable maintenance period.<sup>10,11</sup>

In general, it is known that parents of pediatric cancer patients are at risk for impaired QoL, both during and after treatment, and that major determinants of adverse QoL outcomes are sleep problems

and distress.<sup>12-17</sup> Specifically during ALL maintenance treatment, reports on parental psychosocial functioning are sparse, but they show high prevalence of sleep disturbances and significant emotional distress.<sup>18-23</sup>

However, quantitative studies regarding the specific effects of cyclic dexamethasone during ALL maintenance on parental outcomes are lacking. Additionally, although different risk groups entail different prognostic estimates and treatment intensity, which may influence parental well-being, no previous studies have been performed on the general effects of ALL risk-group stratification on parents' sleep, distress, and QoL.

Since the child's well-being is very closely related to parents' well-being (and vice versa), it is for the benefit of the whole family to optimize parental functioning.<sup>24</sup> Yet more knowledge is needed first. This study therefore aims to assess sleep, distress, and QoL in parents of patients with ALL during maintenance therapy, and compare this with the general population and between the MR and SR groups. Furthermore, this study aims to assess differences *within* the MR group, comparing a week with and a week without dexamethasone.

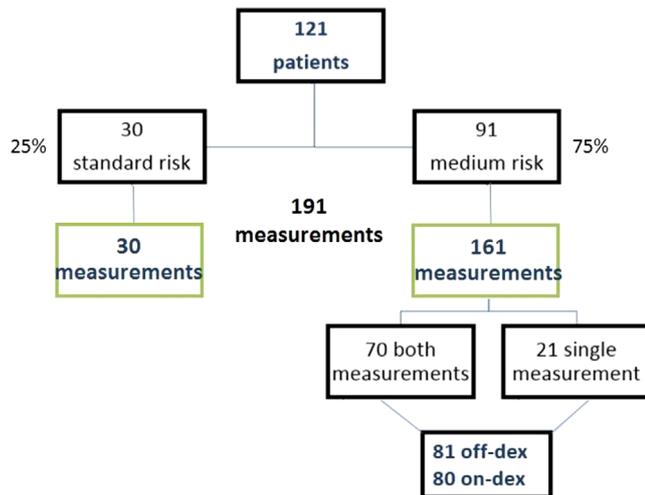
## 2 | METHODS

Results of this study were derived from the nationwide, longitudinal ALL11 add-on Sleep in children with Acute lymphoblastic leukemia And their Parents (SLAAP) study (SLEEP). A detailed description of the study is described elsewhere.<sup>25</sup> Pediatric patients from 2 years of age and their parents were eligible, if sufficiently fluent in Dutch to complete questionnaires independently, and if the child was being treated according to the DCOG ALL11 protocol in one of the participating pediatric oncology centers in the Netherlands. Parents as well as patients aged 12 years and above provided written informed consent. Parental outcomes were assessed with questionnaires.

Assessment took place approximately 1 year after diagnosis, during the relatively stable phase in maintenance therapy. During this phase of treatment, MR patients no longer received asparaginase. Parents of SR and HR patients completed one measurement, whereas parents of MR patients completed two; one in a week *with* dexamethasone (on-dexa), and one in a week *without* (off-dexa). Families could choose to start with either the on-dexa or the off-dexa measurement (Figure 1). The on-dexa measurement started on the first day of the 5 days of dexamethasone treatment (child's actigraphy assessment); yet, the parental outcomes described in this manuscript were assessed with questionnaires, which could be completed at any day during the

Treatment cycle	Cycle 1		Cycle 2		Cycle 3	
Day during cycle	With DEX Day 1-5	Without DEX Day 6-21	With DEX Day 1-5	Without DEX Day 6-21	With DEX Day 1-5	Without DEX Day 6-21
Scenario A						
Scenario B						

**FIGURE 1** Schedule of measurements with and without dexamethasone (medium-risk patients). DEX, dexamethasone; light blue bars reflect the measurement week with dexamethasone, and dark blue bars the measurement without dexamethasone



**FIGURE 2** Overview of measurements completed by parents of standard- and medium-risk patients, respectively

measurement week. Questionnaires were completed by one parent, on paper or online through a secured portal (respondent's preference). Since only one HR patient participated, data from this patient and his parents were excluded from analysis in this manuscript.

The Institutional Review Board of the Erasmus Medical Center approved this study (MEC-2012-187).

## 2.1 | Outcome measures

### 2.1.1 | Parental sleep

The Medical Outcomes Study (MOS) sleep scale is a 1-week, validated and reliable retrospective instrument with 12 items and six subscales.<sup>26</sup> The latter include: (a) sleep disturbance (problems with falling asleep initially and falling back asleep after nightly awakenings, four items); (b) sleep adequacy (getting enough sleep and feeling rested in the morning, two items); (c) daytime somnolence (daytime naps and feeling somnolent, three items); (d) snoring (one item); (e) awakening short of breath or with headache (one item), and (f) quantity of sleep (one item). Quantity of sleep is scored as the average hours slept per night, with optimal sleep duration defined as between 7 and 8 h per night. The other scales are scored on a 0-100 possible range, with higher scores indicating more sleep problems on each scale (except for sleep adequacy, where higher scores reflect better sleep). Nine of these items (all but the items on quantity of sleep, snoring,

and daytime naps) are scored into a sum score, the nine-item sleep problems index (SLP-9). The SLP-9 ranges from 0 to 100 and includes all items except those on quantity of sleep, snoring, and daytime naps; thus, representing symptoms consistent with insomnia-like troubled initiation or maintenance of sleep, and daytime consequences of poor sleep. The SLP-9 score is presented in this study. The MOS manual was used to construct the score and handle missing values.<sup>27</sup> Dutch reference values for healthy adults are available.<sup>28</sup>

### 2.1.2 | Parental distress

The distress thermometer for parents (DT-P) consists of a thermometer on which parents rate their overall distress regarding physical, emotional, social, and practical issues on a scale of 0-10, with 4 or higher indicating clinical levels of distress.<sup>29</sup> The validity and internal consistency of this instrument are good.<sup>29</sup> Dutch reference values for parents of healthy children are available.<sup>30</sup>

### 2.1.3 | Parental QoL

The Short Form-12 (SF-12) is a generic QoL instrument. It measures functional health and well-being by means of two summary scores: the physical component summary score (PCS) and mental component summary score (MCS). The MCS and PCS are norm-based standardized summary scores with a mean of 50 and standard deviation (SD) of 10 in the general US population.<sup>31</sup> Higher scores indicate better QoL. Missing values were not imputed. The SF-12 has adequate validity and reliability, and age- and sex-specific Dutch reference values for healthy adults are available.<sup>31,32</sup>

## 2.2 | Statistical analysis

### 2.2.1 | Description of parental sleep, distress, and QoL

Mean SLP-9 and distress scores for all parents (using the off-dexa assessment in MR parents) were compared to reference values with one-sided *t*-tests. For QoL, age- and sex-specific reference values were used and Z-scores were calculated. Additionally, prevalence rates of clinically relevant sleep problems, clinical distress, and impaired QoL were assessed. For distress, the previously established cut-off of 4 or higher was used to indicate clinical levels of distress. For sleep and

QoL, SD cut-offs were used, which have been described in previous literature.<sup>33</sup> Parents with SLP-9, MCS, or PCS scores > 1 SD above the Dutch reference's mean were considered to have clinically relevant sleep problems or impaired (physical/mental) QoL, respectively.

## 2.2.2 | Comparison of parental sleep, distress, and QoL between the SR and MR groups

Mean scores of SR parents were compared to mean off-dexa scores for MR parents by linear regression analysis. Considering the differences in psychosocial outcomes between mothers and fathers,<sup>12</sup> analyses were corrected for parent's sex.

## 2.2.3 | Comparison of parental sleep, distress, and QoL on- versus off-dexa (MR group)

Mean on-dexa scores for MR parents were compared to off-dexa scores by multilevel linear regression analysis with random intercept. Since in 15% of patients, the parent respondent differed between the on- and off-dexamethasone measurement, all analyses were corrected for parent's sex.

All analyses were done with IBM SPSS Statistics version 26.0.

## 3 | RESULTS

### 3.1 | Study population

One hundred fifty-one families provided written informed consent (response rate 67%).<sup>25</sup> Parents of 121 pediatric patients with ALL participated at this time point. Patients (58% boys, median age 5.8 years) were stratified to the SR group (25%) or MR group (75%). Mean time since diagnosis was  $12.9 \pm 1.0$  months at the first measurement for all patients, and  $14.1 \pm 1.2$  months at the second measurement (only MR patients).

Parents completed a total of 191 measurements. Thirty measurements were completed by parents of SR patients and 161 by parents of MR patients (80 in a week *with* dexamethasone and 81 in a week *without* dexamethasone). Within the MR group, 21 families completed a single measurement and 70 families completed both measurements (85% by the same parent) (Figure 2). Overall, respondents were mostly mothers (80%), with a mean age of  $39 \pm 6$  years. Parent and patient characteristics are summarized in Table 1.

### 3.2 | Description of parental sleep, distress, and QoL

Table 2 shows SLP-9, distress, PCS and MCS scores for parents of pediatric patients with ALL (SR and MR off-dexa combined) and Dutch reference values. Compared to reference values, parents of pediatric

**TABLE 1** Parent's and patient's characteristics

	Standard-risk patients (n = 30)	Medium-risk patients (n = 91)
<i>Child's sex</i>		
Boys: n (%)	16 (53)	54 (59)
Girls: n (%)	14 (47)	37 (41)
<i>Child's age at measurement</i>		
Median years (range)	5.1 (3.0-16.5)	6.2 (2.4-19.0) <sup>a</sup>
<i>Child's time since diagnosis</i>		
Mean time in months (SD)	13.0 (1.0)	12.9 (1.1) <sup>a</sup>
<i>Parent's sex</i>		
Fathers: n (%)	3 (10)	17 (19) <sup>a</sup>
Mothers: n (%)	27 (90)	74 (81) <sup>a</sup>
<i>Parent's age at measurement</i>		
Mean years (SD)	38.0 (5.3)	39.5 (6.6) <sup>a</sup>

<sup>a</sup> Indicating n/median/mean at first measurement (MR patients).

**TABLE 2** Mean scores of parents of pediatric patients with ALL (standard-risk and medium-risk off-dexamethasone) compared to reference values

	Parents of patients with ALL (off-dexa) n = 101-111	Dutch reference	P-value (one-sided t-test)
Mean SLP-9 score (SD)	34.0 (18.1)	21.7 (13.8)	<.001
% Clinically relevant	40	16	-
Mean distress score (SD)	4.5 (2.4)	3.2 (2.7)	<.001
% Clinical distress	66	38	-
Mean PCS score (SD)	53.7 (7.2)	52.5 (7.3)-54.8 (5.9) <sup>a</sup>	-
Mean Z-score (SD)	0.05 (1.0)	0	.6
% Clinically impaired	13	16	-
Mean MCS score (SD)	43.9 (10.2)	48.7 (10.3)-51.2 (8.3) <sup>a</sup>	-
Mean Z-score (SD)	-0.53 (1.1)	0	<.001
% Clinically impaired	36	16	-

Abbreviations: ALL, acute lymphoblastic leukemia; MCS, mental component summary; PCS, physical component summary; SLP-9, nine-item sleep problems index.

<sup>a</sup> Age- and sex-specific reference values for healthy adults aged between 30 and 60 years lie in this range.

**TABLE 3** Regression analysis: mean scores of parents of standard- and medium-risk patients (off-dexa), and corrected regression coefficients (B, SE)

	Parents of children with SR ALL n = 26-30	Parents of children with MR ALL (off-dexa) n = 75-81	B (SE) <sup>a</sup>	95% CI	P-value
Mean SLP-9 score (SD)	34.8 (18.0)	33.7 (18.2)	-0.76 (3.9)	-8.52, 7.00	.8
% Clinically relevant	33	42	-	-	-
Mean distress score (SD)	3.52 (2.35)	4.82 (2.40)	1.29 (0.55)	0.19, 2.38	.02
% Clinical distress	54	71	-	-	-
Mean PCS score (SD)	54.6 (7.6)	53.3 (7.1)	-1.58 (1.59)	-4.74, 1.58	.3
Mean Z-score (SD)	0.21 (1.0)	-0.01 (1.0)	-0.23 (0.22)	-0.66, 0.21	.3
% Clinically impaired	7	16	-	-	-
Mean MCS score (SD)	45.8 (10.6)	43.2 (10.1)	-2.70 (2.25)	-7.17, 1.77	.2
Mean Z-score (SD)	-0.32 (1.1)	-0.61 (1.0)	-0.29 (0.23)	-0.75, 0.17	.2
% Clinically impaired	24	40	-	-	-

Abbreviations: MCS, mental component summary; MR ALL, medium-risk acute lymphoblastic leukemia; off-dexa, week without dexamethasone; PCS, physical component summary; SE, standard error; SLP-9, nine-item sleep problems index; SR ALL, standard-risk acute lymphoblastic leukemia.

<sup>a</sup> Indicating the difference between parents of SR and MR patients, corrected for parent's sex.

**TABLE 4** Multilevel analysis: mean scores (SE) of parents of medium-risk patients on- and off-dexa, corrected for dependency of measurements, and corrected regression coefficients (B, SE)

	Parents of children with MR ALL off-dexa n = 75-81	Parents of children with MR ALL on-dexa n = 72-80	B (SE) <sup>a</sup>	95% CI	P-value
Mean SLP-9 score (SE)	33.9 (1.90)	34.8 (1.91)	1.47 (1.78)	-2.07, 5.02	.4
Mean distress score (SE)	4.83 (0.28)	5.09 (0.28)	0.26 (0.39)	-0.52, 1.04	.5
Mean PCS score (SE)	53.3 (0.77)	52.5 (0.77)	-0.74 (0.86)	50.7, 61.2	.4
Mean Z-score (SE)	-0.02 (0.11)	-0.12 (0.11)	-0.11 (0.12)	-0.35, 0.14	.4
Mean MCS score (SE)	43.0 (1.15)	42.9 (1.15)	-0.22 (1.16)	-2.54, 2.09	.8
Mean Z-score (SE)	-0.63 (0.12)	-0.66 (0.12)	-0.03 (0.12)	-0.27, 0.20	.8

Abbreviations: MCS, mental component summary; MR ALL, medium-risk acute lymphoblastic leukemia; off-dexa, week without dexamethasone; on-dexa, week with dexamethasone; PCS, physical component summary; SE, standard error; SLP-9, nine-item sleep problems index.

<sup>a</sup> Indicating the difference between the on- and off-dexa measurements, corrected for parent's sex.

patients with ALL reported significantly more sleep problems, higher levels of distress, and lower mental QoL, but similar physical QoL. Prevalence of clinically relevant sleep problems and mental QoL impairment was 40% and 36%, respectively (compared to 16% [1 SD] in the general population). Prevalence of clinical distress was 66%, compared to 38% in parents of healthy children.

### 3.3 | Comparison of parental sleep, distress, and QoL between the SR and MR group

Table 3 shows SLP-9, distress, PCS and MCS scores for parents by risk group. On average, parents of MR patients (off-dexa) reported higher distress (mean score  $4.8 \pm 2.4$ ) than parents of SR patients (mean score  $3.5 \pm 2.4$ ;  $P = .02$ ). Other outcomes did not significantly differ between parents of SR and MR patients.

### 3.4 | Comparison of parental sleep, distress, and QoL on- versus off-dexa (MR group)

Table 4 shows SLP-9, distress, PCS and MCS scores for parents of MR patients, with and without dexamethasone. Outcomes did not significantly differ between on- and off-dexa.

## 4 | DISCUSSION

This study aimed to assess sleep, distress, and QoL in parents of pediatric patients with ALL during maintenance therapy. We found that parents across both the SR and MR groups reported more sleep problems, distress, and mental QoL impairment—as compared to reference values. Unexpectedly, within the MR group, we did not find differences in these parental outcomes between a week

with and without dexamethasone. However, when comparing the different risk groups, parents of MR patients report clinical distress levels more often than SR patients; hence, this might reflect the differences between these risk groups in treatment intensity and hospital visits, occurrence of complications, and prognostic estimates.

Regarding treatment differences, patients with SR ALL receive oral chemotherapy and visit the hospital only every 2-3 weeks, whereas MR patients have weekly intravenous chemotherapy. For parents, frequent hospital visits put a high strain on their working and social life, which is stressful.<sup>34,35</sup> Additionally, SR patients have a less toxic regimen than MR patients, with fewer short- and long-term adverse effects.<sup>2</sup> Also 5-year overall survival (OS) is better. In the previous DCOG ALL treatment protocol (ALL10), OS was 99% for SR patients with an event-free survival (EFS) of 93%, compared to 93% OS and 89% EFS in MR patients.<sup>2</sup> This difference in prognostic estimates between SR and MR patients might also play a role in increased distress in parents of MR patients. Yet this is not entirely supported by previous literature, which documents that parents lack accurate prognostic awareness<sup>36</sup> and their perception of prognosis does not influence their well-being.<sup>13</sup>

Another factor that we expected to influence outcomes in parents of MR patients is the cyclic dexamethasone treatment. This treatment may cause clinically relevant adverse psychological side effects in up to 35% of pediatric patients with ALL,<sup>37</sup> thus indirectly affecting parental functioning as well. However, we did *not* find any additional adverse effects of dexamethasone on the parental outcomes that we measured. This may have been the case for several reasons. First, since there is vast heterogeneity in the severity of side effects in patients, it could be that families with the highest dexamethasone burden did not participate in the on-dexa measurement. Furthermore, the timing of the off-dexa measurement (just before the start of a new dexamethasone block) may have been suboptimal because it might be that we captured some anticipatory effects in parents from the off-dexa week. Finally, it is possible that there is no specific additional effect of dexamethasone on the (generic) parental outcomes that we measured. If this is the case, there might still be an "overall" dexamethasone strain, as reflected by the clinical distress levels in these parents.

Several clinical implications can be derived from this study. First, attention to the psychosocial well-being of parents should not stop during maintenance treatment. Also, the parents of children in the most favorable SR group should be sufficiently supported in the hospital by the psychosocial team, even in this stable phase with relatively low frequency of hospital visits. The urge for systematic screening for psychosocial risk throughout treatment phases has already been stressed in the Standards of Psychosocial Care for Parents of Children with Cancer, yet this is still not routine practice in many hospitals.<sup>24,38</sup>

Second, considering the high prevalence (40%) of sleep problems, the health burden that they entail and their chronic nature, early and ongoing attention to sleep is justified.<sup>39,40</sup> The sample described in this study was also measured approximately 4 months after their child's diagnosis and prevalence of sleep problems at that time point was 50%

(*data not yet published*). This means that only a small proportion of parents have recovered since the start of maintenance. Evidence-based interventions to improve sleep exist (eg, cognitive behavioral therapy for insomnia [CBT-I]), and these could perhaps be incorporated in this relatively stable phase of treatment.<sup>41-43</sup> CBT-I can be offered online and might simultaneously improve distress and HRQoL, as shown in other populations.<sup>44,45</sup> Thus, CBT-I could be a brief and feasible intervention that may have broad implications for caregiver functioning.

Third, although we did not capture an additional adverse effect of dexamethasone treatment on parental functioning in the MR group, we believe that it is still important to support families during the intensive dexamethasone weeks. Ongoing education on common side effects and guidance in handling children's behavior may be useful. Besides, in the future hydrocortisone addition during dexamethasone weeks might alleviate side effects,<sup>37</sup> but this is currently being investigated further.

Finally, since child and parental functioning are closely related, optimizing other supportive care for the child (eg, adequate pain management and attention to child's sleep) remains important.

This study has several limitations. First, no sex-specific reference values were available on the MOS sleep scale. Since women report more sleep problems than men<sup>33,40</sup> and 80% of our sample were mothers, this might have led to an overestimation of these problems. Second, the SR group in our sample was small ( $n = 30$ ); hence, it could be that this study had insufficient power to find significant differences with the MR group for some of the parental outcomes. Third, although this was not a formal exclusion criterion, only one parent of a HR patient participated in this study (excluded from analysis), which may indicate participation bias and might have led to an underestimation of parental difficulties. And finally, besides sex and risk group, we did not take into account other factors, such as demographics, that could potentially influence some of the parental outcomes. Future studies should longitudinally assess parental outcomes in this population to discover which parents are most at risk for adverse outcomes.

In conclusion, sleep problems, distress, and mental QoL impairment are prevalent among parents of children with ALL across both the SR and MR groups, even in the relatively stable maintenance phase. Parents of MR patients reported higher and clinical levels of distress as compared to the SR group, but outcomes did not differ between a week with dexamethasone and a week without. Considering the overall outcomes, we believe that this study mainly highlights the need for ongoing psychosocial support across all risk groups and during the entire treatment phase.

#### CONFLICT OF INTEREST

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (Raphaële van Litsenburg) upon reasonable request.

## FUNDING INFORMATION

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