

REVIEW

Risk factors for steroid-induced adverse psychological reactions and sleep problems in pediatric acute lymphoblastic leukemia: A systematic review

Annelienke M. van Hulst¹  | Shosha H. M. Peersmann¹ | Erica L. T. van den Akker² | Linda J. Schoonmade³ | Marry M. van den Heuvel-Eibrink¹ | Martha A. Grootenhuis¹ | Raphaële R. L. van Litsenburg¹

¹Princess Maxima Center, CS Utrecht, The Netherlands

²Erasmus MC- Sophia Children's Hospital, CE Rotterdam, The Netherlands

³Vrije Universiteit Amsterdam, MB Amsterdam, The Netherlands

Correspondence

Raphaële R. L. van Litsenburg, Princess Maxima Center, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands.
Email: R.R.L.vanLitsenburg@prinsesmaximacentrum.nl

Abstract

Objective: Steroids play an essential role in treating pediatric acute lymphoblastic leukemia (ALL). The downside is that these drugs can cause severe side effects, such as adverse psychological reactions (APRs) and sleep problems, which can compromise health-related quality of life. This study aimed to systematically review literature to identify risk factors for steroid-induced APRs and sleep problems in children with ALL.

Methods: A systematic search was performed in six databases. Titles/abstracts were independently screened by two researchers. Data from each included study was extracted based on predefined items. Risk of bias and level of evidence were assessed, using the Quality in Prognosis Studies tool and the Grading of Recommendations Assessment, Development and Evaluation tool, respectively.

Results: Twenty-four articles were included. APR measurement ranged from validated questionnaires to retrospective record retrieval, sleep measurement included questionnaires or actigraphy. Overall, quality of evidence was very low. Current evidence suggests that type/dose of steroid is not related to APRs, but might be to sleep problems. Younger patients seem at risk for behavior problems and older patients for sleep problems. No studies describing parental stress or medical history were identified. Genetic susceptibility associations remain to be replicated.

Conclusions: Based on the current evidence, conclusions about risk factors for steroid-induced adverse psychological reactions or sleep problems in children with ALL should be drawn cautiously, since quality of evidence is low and methods of measurement are largely heterogeneous. A standardized registration of steroid-induced APRs/sleep problems and risk factors is warranted for further studies in children with ALL.

Annelienke M. van Hulst and Shosha H. M. Peersmann shared first authorship and both authors contributed equally.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Psycho-Oncology* published by John Wiley & Sons Ltd.

KEYWORDS

acute lymphoblastic leukemia, behavior and behavior mechanisms, child, drug-related side effects and adverse reactions, quality of life, risk factors, sleep, steroids

1 | INTRODUCTION

Glucocorticoids, such as prednisone and dexamethasone, were among the first drug classes successfully used in the treatment of childhood acute lymphoblastic leukemia (ALL) and are still regarded as cornerstones of ALL therapy.¹ These drugs have contributed substantially to the current 5-year overall survival of more than 90% in developed countries.² However, glucocorticoids can also cause severe side effects, such as osteonecrosis, hyperlipidemia, hyperglycemia, altered body composition, and thromboembolisms.³ Besides these physical toxicities, steroid treatment can cause severe adverse psychological reactions (APRs). These include mood swings, behavioral changes, but also anxiety, psychosis and depression.^{4,5} Steroid related APRs in ALL are experienced as the most detrimental contributor to impaired health-related quality of life (HRQoL) by both patients and parents.⁶ Reports on estimated frequencies of steroid-induced APRs in children range from 5% to 75%.^{5,7–10}

Closely related to APRs and also common in children with ALL are sleep problems, with an estimated prevalence of 19%–87%.^{9,11} Steroid-induced APRs and sleep problems are often studied and reported as separate phenomena in pediatric ALL literature.^{9,12,13} However, sleep problems interrelate with APRs by being both a symptom of certain APRs, such as depression or psychosis, as well as a risk factor to develop APRs.¹⁴ Additionally, during ALL steroid-treatment sleep problems significantly impact the quality of life of children.¹⁵

An important step to handle both APRs and sleep problems, is to identify potential risk factors, making early recognition of susceptible patients possible. This may allow implementation of early intervention strategies to potentially prevent or overcome APRs and sleep problems and their related HRQoL impairments. This was recently acknowledged by the International Psycho-Oncology Society Pediatrics Special Interest Group which published a call for awareness of sleep problems in pediatric oncology. One of their recommendations was to identify risk factors.¹⁶ In adults (both with and without cancer diagnosis), a higher steroid dose as well as past psychiatric history increases the risk of APRs.^{17,18} In children, only the use of dexamethasone (in comparison to prednisone) appears to influence the occurrence of steroid-induced APRs.¹⁹ Known risk factors for sleep problems in the general population are female sex, familial (genetic) predisposition, history of sleep problems, personality type or having a parent with depression.^{20–23} Although some possible risk factors for APRs and sleep problems have been described, findings in pediatric oncology are often conflicting or not specific for steroid-induced problems.^{5,24,25}

Therefore, this systematic review aimed to summarize all available literature to identify potential risk factors for steroid treatment-induced APRs and sleep problems in children with ALL. APRs and sleep problems are closely linked and may influence each other, however since both phenomena are often described separately, we reviewed them individually as well.

To address our aim, we formulated several research questions (with reference to patient population, interventions, comparisons, and outcomes [PICO]). Our patient population encompassed children (0 till 18 years old) with ALL receiving steroid treatment. The outcome parameters were either APRs or sleep problems (or both). Based on previous literature, we hypothesized that the following risk factors might contribute to APRs and/or sleep problems (interventions and comparisons): sociodemographic factors (age and sex),^{5,24} treatment factors (type and dose of steroid),^{5,10,19,24,26} parental factors (coping strategies, stress),^{27–29} (medical) history,^{20,30} and genetic predisposition.^{24,31} However, we did not limit our search on these risk factors. See Supplement 1 for a complete overview of the PICOs.

2 | METHODS

The protocol of this study was based on the PRISMA statement.³² The study was registered in PROSPERO international prospective register of systematic reviews during the data extraction phase (registration number CRD42020167173).

2.1 | Search strategy and information sources

A comprehensive search was performed using the bibliographic databases Pubmed, Embase.com, Scopus, the Cochrane Library, Cinahl (via Ebsco), and PsycINFO (via Ebsco) from inception to 15 August 2019 in collaboration with a medical librarian (Linda J. Schoonmade, Annelienke M. van Hulst and Shosha H.M. Peersmann). Search terms included controlled terms (MeSH in PubMed, Emtree in Embase, Thesaurus terms in Cinahl and PsycInfo) as well as free text terms. The following search terms were used (including synonyms and closely related words) as index terms or free-text words: “ALL” and “children” and ‘steroids” and “adverse effects” or “APR” or “sleep problems.” The search was performed without date or language restrictions. Duplicate articles were excluded. The full search strategy for all databases can be found in the Supplementary information (Supplement 2). In addition, reference lists of all included studies and relevant reviews were manually searched (cross-reference check) for potential additional studies by two authors (Annelienke M. van Hulst and Shosha H.M. Peersmann).

2.2 | Eligibility criteria and study selection

All studies were independently screened by two researchers (Annelienke M. van Hulst and Shosha H.M. Peersmann). First, studies were screened on title and abstract using reference program Rayyan.³³ Studies that met the following predefined inclusion criteria were included: (a) *study population of children aged 0–18 years old*, (b) *diagnosed with ALL*, (c) *receiving steroids* (e.g., *dexamethasone*, *prednisone*) *as part of their leukemia treatment*, (d) *including an APR or sleep outcome*. All types of outcome measurements (questionnaires, observational, chart review, and actigraphy) were deemed eligible.

Studies were excluded if they only entailed adults or animals, were nonpeer reviewed (congress abstract/poster), only reported neurocognitive measures or nonacute behavioral or sleep outcomes (late effects). Second, full-texts were screened and included if any of the risk factors of behavior and sleep mentioned above were evaluated. As stated before, risk factors that were not predefined could also be included. Studies were excluded if no original data was reported (reviews), it entailed a duplicate, a case report (series) or if full-text was unavailable. Case reports and relevant reviews were set aside to check references. In addition, articles that reported on outcomes of ALL trials were kept apart, as these articles were not designed to meet aforementioned inclusion criteria, but were regarded as potentially discussing APRs or sleep problems as part of toxicity registration during trials. Therefore, the full texts of these articles were reviewed as well.

2.3 | Data extraction

Data from each study were extracted independently by two authors (Annelienke M. van Hulst and Shosha H.M. Peersmann) based on predefined items: study design, number of participants, mean age, type and dose of steroids, type of APR/sleep outcome, method of measuring APR/sleep outcome, risk factors, method of measuring risk factors and results (often descriptive/percentages). Disagreements were resolved by consensus (Annelienke M. van Hulst and Shosha H.M. Peersmann). If necessary, a third reviewer was consulted (Raphaële R. L. van Litsenburg).

2.4 | Assessment of risk of bias of individual studies

To assess risk of bias, the Quality in Prognosis Studies (QUIPS) tool was used. The QUIPS systematically appraises risk of bias in individual studies of prognostic (risk) factors.³⁴ The Cochrane Prognosis Methods Group recommends the use of this instrument.³⁵ The QUIPS ascertains high, moderate or low risk of bias on six domains: (1) *study participation*, (2) *study attrition*, (3) *prognostic factor measurement*, (4) *outcome measurement*, (5) *study confounding*, and (6) *statistical analysis and reporting*. Each study was independently rated using the QUIPS tool by Annelienke M. van Hulst and Shosha H.M. Peersmann after

which the scores were discussed to resolve any disagreements. A third reviewer was available when necessary (Raphaële R. L. van Litsenburg). In line with the recommendations of Hayden and colleagues (2013), we assessed each domain and did not rate a summated risk of bias score for individual studies based on the six domains.³⁴ See Table S3a for definitions and application of the QUIPS domains.

To summarize the quality of individual study results, we took into account: the number of QUIPS domains scoring high on risk of bias, the sample size of APRs/sleep outcomes and whether a study was a priori designed to study risk factors of steroid-induced APRs or sleep problems. We considered a study of lower quality when it entailed more high risk of bias domains, was not a priori designed and had a small sample size. A color coding was used to indicate our considerations: red (lower quality), orange (medium quality), and green (higher quality).

2.5 | Assessment of grading evidence across studies and synthesis of results

To systematically evaluate the quality of summated evidence for each study question and to identify the level of evidence for each risk factor of either APR or sleep problems, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.³⁶ This tool is recommended by the Cochrane Prognosis Methods Group.³⁵ The GRADE includes a synthesis of results (combined number of participants, studies, cohort phase study and either a positive, negative or no effect) and scores each factor of the GRADE framework: (a) *study limitations*, (b) *inconsistency*, (c) *indirectness*, (d) *imprecision*, (e) *publication bias*, (f) *effect sizes*, and (g) *dose effect*. See Table S3b for definitions and application of the GRADE domains.

All evidence for each PICO (Supplement 1) was independently assessed by Annelienke M. van Hulst and Shosha H.M. Peersmann. Besides the predefined PICOs, we also identified new risk factors from literature. Taking into account the combined GRADE synthesis and ratings, the overall level and quality of evidence was determined: + very low, ++ low, +++ moderate, or ++++ high quality. Individual synthesis and ratings (Annelienke M. van Hulst and Shosha H.M. Peersmann) were discussed until consensus was reached. If necessary, a third reviewer was consulted (Raphaële R. L. van Litsenburg). The results of the grading provide an overview of the results per risk factor and the (gaps of) evidence for each risk factor of developing either APRs or sleep problems.

3 | RESULTS

Our search yielded 8626 unique records after duplicate removal (Supplement 4: PRISMA Flow diagram). Hundred and ninety full texts were screened of which 23 articles were included. Furthermore, 245 ALL trial papers were screened of which one article was eligible, resulting in a total of 24 articles included in this review.

TABLE 1 Results per APR study

Study	Study design	A priori design for risk factors		Age	n = APR outcome	N =	Steroid	APR outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
		No	Yes										
Bostrom et al. (2003) ³⁷	RCT	No	No	1-10 years	6	1060	Dex (6 mg/m ² /day) Pred (40 mg/m ² /day)	Neuropsychiatric toxicities	Toxicity questions	Type of steroid	Assigned by protocol	Dex: 6 events (dysesthesia and agitation) Pred: 0 events (not tested)	4/6 high
Domenech et al. (2014) ³⁸	RCT	No	No	0-18 years	53	1947	Dex (6 mg/m ² /day) Pred (60 mg/m ² /day)	Personality change	Reported grade III/IV toxicity (WHO criteria)	Type of steroid	Assigned by protocol	Dex: 2.5% Pred: 3.0% (NS)	2/6 high
Drigan et al. (1992) ⁴⁸	Prospective	Yes	Yes	SR: 51.4 months (29-94) HR: 49.1 months (25-63)	38	38	Pred (40 mg/m ² /day) or 120 mg/m ² /day	Behavior changes	Conners Parent -teacher hyperkinesis Index	- Steroid dose - Age (<4/>4) - Sex	- Assigned by protocol - Patient record - Patient record	High dose pred: higher listlessness (p < 0.04). No other disturbances. Age: No difference Sex: Girls listlessness (p < 0.01). No other disturbances.	4/6 high
Eipel et al. (2013) ⁴⁰	Retrospective	No	No	1-18 years	29	346	Dex (10 mg/m ² /day) Pred (60 mg/m ² /day)	Seriously altered behavior or steroid psychosis	Collected retrospectively	- SNP: N363S - Age (<2/2-11/12-18) - Sex	- Allele specific PCR - Patient record - Patient record	N363S: 8.6% versus 6.3% (carriers vs. non-carriers) (p = 1.0) Age and sex NS	4/6 high
Eipel et al. (2016) ³⁹	Retrospective	No	No	0.2-17.9 years (median 4.95)	29	346	Dex (10 mg/m ² /day) Pred (60 mg/m ² /day)	Seriously altered behavior or steroid psychosis	Collected retrospectively	SNPs: - N363S - Bcl1 - ER22/23EK	- Allele specific PCR - Allele specific PCR - Melting curve analysis	N363S NS (p = 1.0) Bcl1 NS (p = 0.405) ER22/23EK NS (p = 0.695)	4/6 high
Eiser et al. (2006) ⁵¹	RCT	Yes	Yes	7.2 (3.8 SD) years	41	45	Dex or Pred	Child difficulties	Child Difficulties Questionnaire	Type of steroid	Assigned by protocol	No significant difference	3/6 high

TABLE 1 (Continued)

Study	Study design	A priori design for risk factors	Yes	No	n = outcome	n = APR outcome	Age	Steroid	APR outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Felder-Puig et al. (2007) ⁷	Prospective	Yes	37	20	9.27 (3.96 SD) years	Dex (10 mg/m2/day) Pred (60 mg/m2/day)	Adverse psychological reactions	CBCL	- Type of steroid levels - Hormone levels - Neuronal cell destruction - SNPs:ER22/23EK, N3635, Bcl1	- Per protocol - Venous blood samples - 14-3-3 protein level in CSF - TaqMan PCR	Dex OR 2.2 (CI 0.5-9.1) High cortisol and/or ACTH OR 5.0 (CI 0.9-28.1) Neuronal cell destruction no evidence SNPs no correlation	3/6 high		
Harris et al. (1986) ⁴¹	Prospective	No	16	16	4-16 years	Pred (60 mg/m2/day)	Behavior	Corticosteroid symptom inventory	Age (4-5/7-10/12-16)	Patient record	Trend of more behavioral symptoms in younger children (<7 years)	5/6 high		
Hough et al. (2016) ⁴²	RCT	No	3126	18	1-25 years (median 5 years)	Dex (6 or 10 mg/m2/day)	Steroid induced psychosis	Prospectively collected SAE	Age (<16/≥16)	Patient record	<16 years: 0.4%, ≥16 years: 2.2% (p < 0.05)	4/6 high		
Igarashi et al. (2005) ⁴³	RCT	No	359	3	1-10 years	Pred (40-60 mg/m2/day) Dex (6-8 mg/m2/day)	Neuropsychiatric adverse event	Observation (collected retrospectively)	Type of steroid	Assigned by protocol	Dex: 3 neuropsychiatric adverse events Pred: 0 events (p = 0.24)	4/6 high		
Kaymak Cihan et al. (2017) ⁴⁴	Retrospective	No	49	13	1.4-17 years	Pred (40-60 mg/m2/day) Dex (10 mg/m2/day)	Depression symptoms (according to CTCAE 4.0)	Collected retrospectively	SNPs: N3635, Bcl1	PCR-RFLP	N3635: No SNP present Bcl1: Depression symptoms more frequent among carriers (40.7% vs. 11.8%, p = 0.040)	4/6 high		
Marino et al. (2009) ⁴⁵	Retrospective	No	36	25	5.3 (1.3-16) years	Dex (10 mg/m2/day) Pred (60 mg/m2/day)	Neuropsychiatric signs	Collected retrospectively	Polymorphisms in ABCB1, NR3C1, GST, IL-10 genes	- PCR-RFLP - PCR-RFLP - PCR-ASO - PCR-RFLP	No correlation between neuropsychiatric toxicity and genotype	4/6 high		
Messina et al. (1989) ⁴⁹	Prospective	No	26	23	8 (3-16) years	Pred (60 mg/day)	Mood, activity level and behavior	- CBCL, CDI, Conners Parent Questionnaire	- Platelet MAO activity - Prior pred exposure - Age - Sex	- Radiochemical assay - Patient record - Patient record - Patient record	MAO activity: Correlated with steroid induced changes in CBCL and Conners, not CDI Prior pred exposure: NS Age: NS Sex: NS	4/6 high		

(Continues)

TABLE 1 (Continued)

Study	Study design	A priori design for risk factors	N	n = APR outcome	Age	Steroid	APR outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Mitchell et al. (2005) ¹⁶	RCT	No	1603	58	1-18 years	Pred (40 mg/m ² /day) Dex (6.5 mg/m ² /day)	Acute behavioural toxicity (grade III/IV)	Reported by clinician	- Type of steroid - Age (<2/2-9/≥10) - Sex	- Assigned by protocol - Patient record - Patient record	Dex: 6% versus pred 1% (p < 0.0001) Age: NS Sex: Depression in girls, aggression in boys (both trend)	2/6 high
Mirakotsky et al. (2011) ²⁵	Prospective repeated measures	Yes	60	60	2-17 years	Pred (40 mg/m ² /day) Dex (6 mg/m ² /day)	Neurobehavioral problems	CBCL	- Type of steroid - Age (2-<6/≥6-17) - Sex - Cumulative steroid dose	- Assigned by protocol - Patient record - Patient record - Per protocol	Dex versus pred: NS Age: 2-<6 years more problems than ≥6-17 years Sex: NS Cumulative steroid dose: NS	1/6 high
Pound et al. (2012) ³²	Prospective	Yes	43	43	7 (SD 4.1) years	Pred or Dex	Behavioral problems	CBCL	- Type of steroid - Age (<5, >5) - Sex	- Assigned by protocol - Patient record - Patient record	Dex: ≤5 years no difference >5 years: More affective (p = 0.041), anxiety problems (p = 0.015) and (p = 0.050) Age: ≤5 years: Higher internalizing (p = 0.003), externalizing (p = 0.005) and total problems (p = 0.003). >5 years: Higher externalizing (p = 0.021), aggressive behavior (p = 0.017) and oppositional defiant problems (p = 0.036) Sex: NS	0/6 high
Warris et al. (2016) ⁷	RCT	No	46	46	3-16 years	Dex (6 mg/m ² /day)	Behavior	SDQ	Age	Patent record	No relation between age and dex induced behavior problems	1/6 high

TABLE 1 (Continued)

Study	Study design	A priori design for risk factors	N =	n = APR outcome	Age	Steroid	APR outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Warris et al. (2016) ⁵³	RCT	Yes	46	46	6.0 (4.0-9.8) years	Dex (6 mg/m2/day)	Behavior	SDQ	- Cortisol - Dex PK	- DST, CLIA - Trough levels	Cortisol: Baseline and AUC not correlated with behavior; Cortisol suppression correlated with SDQ conduct and impact score. Trough levels: No correlation with behavior	2/6 high
Yetgin et al. (2003) ⁴⁷	RCT	No	205	3	5.5 years (11 months-16 years)	Pred (60 mg/m2/day) HDMP (600-900 mg/m2/day)	Behavioral disturbance	Unknown	Type and dose of steroid	Per protocol	HDMP: 3 behavioral disturbances, pred: 0. NS	4/6 high

Note: Age reported as mean or range. Color coding: red (lower quality), orange (medium quality), green (higher quality).

Abbreviations: ABCB1, ATP-Binding, Cassette B1; ACTH, Adrenocorticotropic Hormone; APR, Adverse Psychological Reaction; ASO, allele-specific oligonucleotide; AUC, Area Under the Curve; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CI, Confidence Interval; CLIA, Chemiluminescence-based Immunoassay; CSF, Cerebrospinal Fluid; CTCAE, Common Terminology Criteria for Adverse Events; Dex, Dexamethasone; DST, Dexamethasone Suppression Test; GST, glutathione and glutathione-S-transferase; HDMP, High Dose Methylprednisolone; HR, High Risk; IL-10, interleukin-10; MAO, monoamine oxidase; NS, Not Significant; OR, Odds Ratio; PCR, Polymerase Chain Reaction; PK, Pharmacokinetics; Pred, Prednisone; RCT, Randomized Controlled Trial; RFLP, restriction fragment length polymorphism; RR, Relative Risk; SAE, Serious Adverse Event; SD, Standard Deviation; SDQ, Strength and Difficulties Questionnaire; SNP, Single Nucleotide Polymorphism; SR, Standard Risk; WHO, World Health Organization.

Nineteen studies reported on risk factor(s) for steroid-induced APRs, whereas seven studies reported on risk factor(s) for steroid-induced sleep problems. Two studies described risk factors for both APRs and sleep problems. See Tables 1 and 2 for all study characteristics, results and quality of each individual study based on risk of bias. Table S7 depicts the risk of bias domain scoring within the separate studies. The summated evidence for each identified risk factor of either APRs or sleep problems and the evaluation of evidence using GRADE is shown in Tables 3 and 4, respectively.

3.1 | Adverse psychological reactions

Different APRs were described in the included articles: neuropsychiatric signs, toxicities, or adverse events, personality or behavioral change, steroid psychosis, child difficulties, psychiatric disorders and (neuro)behavioral problems. The measurement of these APRs ranged from using validated questionnaires to retrospective collection from patient files. Eleven studies collected any information of APRs without the use of a validated questionnaire.^{37–47} The other eight studies used five different parent reported questionnaires: Conners rating scale,^{48,49} Child Difficulties questionnaire,^{50,51} Child Behavior Checklist,^{4,25,49,52} Children's Depression Inventory,⁴⁹ and the Strength and Difficulties Questionnaire.^{9,53} Assessment of the different risk factors depended on the nature of the risk factor. For example, sociodemographic factors were retrieved from patient records, whereas treatment factors usually were per protocol. APRs were measured during (remission-)induction^{4,37–40,43–47} or maintenance phase^{9,25,37,41,46,48,49,51–53} (unclear in one study⁴²). Overall, the quality of evidence regarding risk factors for APRs was very low (Table 3).

3.1.1 | Sociodemographic factors (age and sex)

Nine studies evaluated age as a risk factor for steroid-induced APRs. Three studies found younger age (0–6 years old) to be a risk factor for behavioral problems of which two were of higher quality.^{25,41,52} One study of lower quality comparing patients aged 10–15 years with 16–24 years old described an increased frequency of steroid-induced psychosis in the older age group.⁴² Five studies of lower quality found no significant impact of age on the development of steroid-induced behavior problems or psychosis.^{9,40,46,48,49} Two studies used age as interval variable,^{9,49} but most studies used age group categories with variable ranges to compare differences.^{25,40–42,46,48,52} Regarding sex, four out of five studies (of which two high quality) did not find a significant difference between boys and girls.^{40,46,49,52} Only one lower quality study found an effect on one of their measured domains: listlessness. Girls seem to be at risk for listlessness; however no effect on all other domains (attention/hyperactivity, emotional liability, and depressed mood) was found.⁴⁸ All analyses regarding age and sex were univariate, no multivariate analyses were conducted. Overall, sex seems no risk factor for APRs,

but certain age groups might be at risk for specific APRs. The evidence that younger children (0–6 years old) are at risk for behavioral problems is stronger, than the evidence that teenagers are at risk for psychosis. The latter needs to be confirmed in higher quality studies.

3.1.2 | Treatment factors (type of steroid, steroid dose, and cumulative dose)

Six out of eight studies did not find more APRs when comparing dexamethasone to prednisone treatment, including four higher quality articles.^{4,25,37,38,43,51} Although the majority reports that steroid type is not a risk factor, evidence is not undisputed: two high quality studies did report more APRs during dexamethasone treatment.^{46,52}

Steroid dose was investigated in four studies (one of higher quality).^{25,47–49} Three report no increased risk of APRs with increasing dose, one low quality study reports an effect on one of their measures domains (listlessness), but not on all other APR domains.⁴⁸ Steroid dose seems no risk factor based on current evidence, which is overall of low quality. Only one study evaluated the risk of cumulative steroid dose and did not find an increased risk on APRs with a higher dose of prednisone nor dexamethasone.²⁵ All studies on the risk of APRs by steroid type and dose were univariate, no multivariate analyses were used.

3.1.3 | Parental factors

We did not identify any studies describing steroid-induced APRs and parental factors with our search.

3.1.4 | Medical history

With our search, we did not find any studies describing medical history as a risk factor for steroid-induced APRs.

3.1.5 | Genetic predisposition

Five articles studied the influence of genetic variation on steroid induced APRs,^{4,39,40,44,45} of which Eipel et al. described the same patient cohort twice.^{39,40} This was the largest patient cohort, consisting of 346 patients. The other studies included 37, 47, and 36 participants, respectively.^{4,44,45}

All studies used a candidate gene approach, usually focusing on the glucocorticoid receptor gene (*NR3C1*; Table S5a). One study also included three other genes: the ATP-Binding Cassette B1 (*ABCB1*) gene, glutathione and glutathione-S-transferase (*GST*) gene and interleukin-10 (*IL-10*) gene.⁴⁵ None of the studies adjusted for multiple testing or controlled for confounding variables. Furthermore, none of the studies included a replication cohort. One study used a

validated questionnaire to measure APRs,⁴ the other studies used retrospectively collected toxicity data.^{39,40,44,45}

The *Bcl-1* polymorphism on the GR gene was studied in four patient cohorts,^{4,39,44,45} and only Kaymak Cihan et al. found a positive association between the homozygous CC genotype and the occurrence of depression symptoms during steroid treatment (Table S5a). This result has not been replicated in another cohort. The *ER22/23EK* and *N363S* GR gene polymorphisms were studied in respectively three^{4,39,45} and four patient cohorts^{4,39,40,44,45} of which none found a significant association with an APR outcome. The SNPs in the three additional genes described by Marino et al. (*ABC1*, *GST* and *IL-10*) were studied in 36 patients, no significant association with the occurrence of neuropsychiatric signs was found.⁴⁵

3.1.6 | Other factors

Several additional possible risk factors were identified during our literature search. Only a serum elevated monoamine oxidase was correlated with steroid-induced behavioral changes.⁴⁹ However, monoamine oxidase changes appears to be an effect of stress, rather than a risk factor.^{54,55} Cortisol levels,^{4,53} adrenocorticotrophic hormone levels,⁴ dexamethasone pharmacokinetics,⁵³ and neuronal cell destruction⁴ were studied but not confirmed as significant risk factors for APRs, possibly due to small sample sizes ($n = 37$ and $n = 46$).

3.2 | Sleep problems

Risk factors for steroid-induced sleep problems were evaluated in seven studies of which three⁵⁶⁻⁵⁸ reported secondary analyses of the cohort originally collected by Hinds et al.¹³ Four papers used an objective measuring method: actigraphy.^{13,56-58} Three papers used (parent-reported) subjective methods: 28-day sleep diary,¹² the Sleep Disturbance Scale for Children (SDSC) questionnaire^{12,53} and a self-constructed item rating sleep disturbance.⁴⁸ All studies measured sleep problems during maintenance phase of treatment. Overall, the quality of evidence regarding risk factors for sleep problems was very low to low (Table 4), mostly due to the limited amount of studies conducted in this area.

3.2.1 | Sociodemographic factors (age and sex)

The influence of age on sleep problems was investigated in three studies (two cohorts). A higher quality study found that age was associated with sleep duration. Older children were in bed less during dexamethasone treatment and older age was also associated with less total daily sleep minutes, however other sleep parameters did not differ significantly between age groups.¹³ In the same cohort, Rogers et al. reports no difference in age on actigraphic circadian parameters,⁵⁶ in coherence with Drigan et al. who also did not find a difference in age on sleep disturbances.⁴⁸ However, this is a low

quality evidence paper, using subjective measurement for sleep. Evidence for age as a risk factor is limited to only one high quality paper on well-defined sleep parameters. Older children might have a higher risk of impaired sleep duration during steroid use, but age as risk factor for impaired circadian parameters is not found. Replication studies are needed to confirm which age group is particularly at risk for specific sleep problems.

Sex as risk factor was investigated in four studies (two cohorts) of which three of high quality^{13,56,58} and one of lower quality.⁴⁸ Two studies in the same cohort^{13,58} reported no sex difference on most actigraphic sleep parameters, but boys did experience more nocturnal awakenings, whereas girls napped more in univariate analyses.¹³ In a multivariable analysis, only the parameter wake time after sleep onset (WASO) was decreased in girls and increased in boys during dexamethasone treatment.⁵⁷ In the same cohort, Rogers et al. also did not find significant sex differences in the circadian rhythm parameters.⁵⁶ Drigan et al. described that parents reported girls to have an increased risk for steroid-induced sleep disturbance.⁴⁸ However, their 1-item parent reported question to assess sleep is not a validated questionnaire, making this evidence of lower quality. The quality of evidence investigating sex as a risk factor is overall low. It suggests that sex does not impact most sleep parameters (e.g., sleep quality), however some parameters (nocturnal awakenings, napping, WASO) may be impacted differently for boys and girls.

3.2.2 | Treatment factors (type of steroid and steroid dose)

Only one study compared type of steroid as a risk factor for sleep problems. Using multivariate analyses, it was found that children receiving prednisone experienced better sleep quality and fewer night awakenings during steroid treatment in comparison with dexamethasone.¹² Although this single study is of higher quality, evidence regarding type of steroid as a risk factor is scarce and therefore rated as very low quality in the GRADE.

Four studies (two cohorts) compared the effect of steroid dose on sleep problems. Three of the studies in the same cohort drew the conclusion that a higher steroid dose gave rise to more sleep problems.^{13,56,58} Only one other study with a different cohort evaluated steroid dose and found that steroid dose was not related to sleep disturbance.⁴⁸ However, this study is of lower quality partly due to methodological problems with the validity of the measurement method. Overall, the review suggests, without clear evidence, that steroid type and dose might have an impact on sleep problems, but this is only based on one cohort of patients and therefore of low to very low quality.

3.2.3 | Parental factors

We did not find any studies describing steroid-induced sleeping problems and parental factors with our search.

TABLE 2 Results per Sleep study

Study	Study design	A priori design for risk factors	Yes	No	n = Sleep outcome	Age	Steroid	Sleep outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Daniel et al. (2016) ¹²	Prospective	Yes	81	61	6.21 (SD 2.22) years	Dex or Pred	Sleep parameters	28-day sleep diary	Type of steroid	Assigned by protocol	Pred better sleep quality (p = 0.014) and fewer night awakenings (p = 0.013)	0/6 high	
Drigan et al. (1992) ⁴⁸	Prospective	Yes	38	38	SR: 5.1.4 months (29-94)HR: 49.1 months (25-63)	Pred (40 mg/m ² /day or 120 mg/m ² /day)	Sleep disturbance	Additional 1 item rating sleep disturbance	- Steroid dose - Age (<4/>4) - Sex	- Assigned by protocol - Patient record - Patient record	High dose pred: no difference Age: No difference Sex: Girls more sleep disturbance (p < 0.05)	4/6 high	
Hinds et al. (2007) ¹³	Prospective	Yes	100	88	9.24 (SD 3.23) years	Dex (6-12 mg/m ² /day)	Sleep parameters	Actigraphy and sleep diary	- Age (<7/7-12/>13) - Sex - Steroid dose	All patient record	Age: older children less sleep duration (p = 0.018), less sleep minutes/24 h (p = 0.002) Sex: Boys more awakenings (p = 0.020), girls more naps (p = 0.027) Steroid dose: higher dose associated with sleep efficiency (p = 0.012), sleep minutes (p = 0.13) and nocturnal awakenings (p = 0.034)	1/6 high	
Rogers et al. (2014) ⁵⁶	Prospective	No	82	82	8.8 (SD 3.3) years	Dex (6.8 or 12 mg/m ² /day)	Circadian activity rhythms	Actigraphy and sleep diary	- Dex dose - Age (5-12/13-17) - Sex	- Per protocol - Patient record - Patient record	High dose: NS for circadian parameters Age: NS Sex: NS	2/6 high	
Sarford et al. (2008) ⁵⁷	Prospective	No	88	88	9.15 (SD 3.24) years	Dex (6.8 or 12 mg/m ² /day)	Sleep parameters	Actigraphy and sleep diary	- Sex	- Patient record	Boys increased WASO Girls decreased WASO	1/6 high	

TABLE 2 (Continued)

Study	Study design	A priori design for risk factors	No	Yes	n = Sleep outcome	N =	Age	Steroid	Sleep outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Vallance et al. (2010) ⁵⁸	Prospective	No	88	88	9.24 (SD 3.23) years	88	9.24 (SD 3.23) years	Dex (6, 8 or 12 mg/m ² /day)	Sleep parameters	Actigraphy and sleep diary	- Dex PK dose - Dex albumin - Genotyping	- Liquid chromatography - Per protocol - Standard testing method - DNA-Print Genomics	PK: Increased time above 100nmM dex increase in sleep time (p = 0.05). Higher AUC (univariate) is less sleep efficiency and sleep time. Multivariate NS.	1/6 high
Warris et al. (2016) ⁵³	RCT	Yes	47	47	6.0 (4.0-9.8) years	47	6.0 (4.0-9.8) years	Dex (6 mg/m ² /day)	Sleep	SDSC	- Cortisol - Dex PK	- DST, CLIA - Trough levels	Albumin: NS AHSG SNP: sleep duration and actual sleep time increased IL6 G174C SNP: NS IL6 C634G SNP: NS Cortisol: Baseline and AUC not correlated with sleep. Cortisol suppression not correlated with sleep. Trough levels: No correlation with sleep	2/6 high

Note: Age reported as mean or range. Color coding: red (lower quality), orange (medium quality), green (higher quality).

Abbreviations: AUC, area under the curve; CLIA, chemiluminescence-based immunoassay; Dex, Dexamethasone; DST, Dexamethasone Suppression Test; HR, high risk; NS, not significant; PK, pharmacokinetics; Pred, prednisone; RCT, randomized controlled trial; SD, standard deviation; SDSC, Sleep Disturbance Scale for Children; SNP, single nucleotide polymorphism; SR, standard risk; WASO, wake time after sleep onset.

TABLE 3 GRADE adverse psychological reactions

Outcome: Adverse psychological reactions																		
Potential Risk Factors	Univariate				Multivariate				GRADE Factors ³⁶									
	Number of participants	Number of studies	Number of cohorts	+	0	-	+	0	-	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect sizes	Dose effect	Overall quality
Age (younger age)	331	9	9	3 ^{25,41,52}	5 ^{9,40,46,48,49}	1 ⁴²	-	-	-	1.2	x	x	✓	Unclear	x	Unclear	x	+
Sex (boys)	191	5	5	0	4 ^{40,46,49,52}	1 ⁴⁸	-	-	-	1.2	x	✓	✓	Unclear	x	Unclear	NA	+
Type of steroid (Dex)	284	8	8	2 ^{46,52}	6 ^{4,25,37,38,43,51}	0	-	-	-	1.2	✓	x	✓	Unclear	✓	Unclear	Unclear	+
Steroid dose (higher)	124	4	4	1 ⁴⁸	3 ^{25,47,49}	0	-	-	-	1.2	x	✓	✓	Unclear	x	Unclear	Unclear	+
Cumulative steroid dose (higher)	60	1	1	0	1 ²⁵	0	-	-	-	2	✓	NA	✓	✓	x	Unclear	Unclear	++
Parental coping strategy	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	None existing
Parental stress	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	None existing
History of psychiatric problems	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	None existing
Genetic predisposition																		
N263S	87	5	4	0	5 ^{4,39,40,44,45}	0	-	-	-	1.2	x	✓	✓	Unclear	✓	Unclear	NA	+
Bcl1	67	4	4	1 ⁴⁴	3 ^{4,39,45}	0	-	-	-	1.2	x	x	✓	Unclear	✓	Unclear	NA	+
ER22/23EK	67	3	3	0	3 ^{4,39,45}	0	-	-	-	1.2	x	✓	✓	Unclear	✓	Unclear	NA	+
ABCB1 gene	25	1	1	0	1 ⁴⁵	0	-	-	-	1	x	NA	✓	Unclear	x	Unclear	NA	+
GST gene	25	1	1	0	1 ⁴⁵	0	-	-	-	1	x	NA	✓	Unclear	x	Unclear	NA	+
IL-10 gene	25	1	1	0	1 ⁴⁵	0	-	-	-	1	x	NA	✓	Unclear	x	Unclear	NA	+
Platelet MAO activity (higher)	23	1	1	1 ⁴⁹	0	0	-	-	-	1	x	NA	✓	Unclear	x	Unclear	x	+
Cortisol levels (higher)	66	2	2	0	2 ^{4,53}	0	-	-	-	2	x	✓	✓	x	x	Unclear	x	+

TABLE 3 (Continued)

Outcome: Adverse psychological reactions																			
Potential Risk Factors	Number of participants	Number of studies	Number of cohorts	Univariate			Multivariate			GRADE Factors ³⁶									
				+	0	-	+	0	-	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect sizes	Dose effect	Overall quality	
ACTH level (higher)	20	1	1	0	1 ⁴	0	-	+	0	-	2	x	NA	√	x	x	Unclear	x	+
Dex kinetics	46	1	1	0	1 ⁵³	0	-	-	-	2	√	NA	√	Unclear	x	Unclear	Unclear	x	+
Neuronal cell destruction	20	1	1	0	1 ⁴	0	-	-	-	2	x	NA	√	Unclear	x	Unclear	Unclear	x	+

Notes: Phase = phase of investigation. For uni- and multivariate analyses: + = number of significant effects with a positive value; 0 = number of non-significant effects; - = number of significant effects with a negative value. Below the reference for each study is depicted. For GRADE factors: √ = no serious limitations; x = serious limitations (or not present for moderate/large effect size, dose effect); unclear = unable to rate item based on available information. For overall quality of evidence: + = very low; ++ = low; +++ = moderate, ++++ = high.

Abbreviations: ABCB1, ATP-Binding Cassette B1; ACTH, Adrenocorticotrophic Hormone; Dex, Dexamethasone; GRADE, Grading of Recommendations Assessment Development and Evaluation; GST, glutathione and glutathione-S-transferase; IL-10, interleukin-10; MAO, monoamine oxidase, NA, not applicable.

TABLE 4 GRADE sleep problems

Outcome: Sleep problems		Univariate			Multivariate			Grade Factors ^{3,6}									
		Number of participants	Number of studies	Number of cohorts	+	-	0	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect sizes	Dose effect	Overall quality	
Potential Risk Factors																	
Age (younger age)	208	3	2	0	2 ^{48,56}	1 ¹³	0	0	0	0	1.2	x	Unclear	x	Unclear	Unclear	+
Sex (girls)	208	4	2	2 ^{13,48}	1 ⁵⁶	1 ¹³	0	0	1 ⁵⁷	1.2,3	√	x	Unclear	x	Unclear	NA	++
Type of steroid (Dex)	61	1	1	-	-	-	1 ¹³	0	0	2	√	NA	√	x	Unclear	Unclear	++
Steroid dose (higher)	208	4	2	3 ^{13,56,58}	1 ⁴⁸	0	-	-	-	1.2	√	√	x	√	Unclear	x	+
Parental coping strategy	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	None existing
Parental stress	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	None existing
History of sleep problems	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	None existing
Genetic predisposition																	
AHSG	88	1	1	1 ⁵⁸	0	0	-	-	-	2	√	NA	√	x	Unclear	NA	+
IL-6 (G174C)	88	1	1	0	1 ⁵⁸	0	-	-	-	2	√	NA	√	x	Unclear	NA	+
IL-6 (C634G)	88	1	1	0	1 ⁵⁸	0	-	-	-	2	√	NA	√	x	Unclear	NA	+
Dex kinetics	134	2	2	1 ⁵⁸	1 ⁵⁸	0	0	1 ⁵⁸	0	2	√	√	Unclear	x	Unclear	x	++
Albumin level (higher)	88	1	1	0	1 ⁵⁸	0	-	-	-	2	√	NA	√	x	Unclear	x	+

Note: Phase = phase of investigation. For uni- and multivariate analyses: + = number of significant effects with a positive value; 0 = number of non-significant effects; - = number of significant effects with a negative value. Below the reference for each study is depicted. For GRADE factors: √ = no serious limitations; x = serious limitations (or not present for moderate/large effect size, dose effect); unclear = unable to rate item based on available information. For overall quality of evidence: + = very low; ++ = low; +++ = moderate; ++++ = high.

Abbreviations: AHSG, α2-Heremans-Schmid glycoprotein; Development, and Evaluation; Dex, Dexamethasone; GRADE, Grading of Recommendations Assessment; IL-6, interleukin-6; NA, not applicable.

3.2.4 | Medical history

With our search, we did not identify any studies describing medical history as a risk factor for steroid-induced sleeping problems.

3.2.5 | Genetic predisposition

Only one study ($n = 72$) investigated genetic variation as possible risk factor for steroid-induced sleep problems in ALL.⁵⁸ Vallance et al. studied 99 polymorphic loci in candidate genes associated with glucocorticoid metabolism. They included actigraphy data of 72 Caucasian patients, no replication cohort was used. They did not adjust for multiple testing and did not describe controlling for confounding variables (Table S5b).

Three different SNPs in two genes were described in relation to dexamethasone induced sleeping problems. A homozygous variant in the $\alpha 2$ -Heremans-Schmid glycoprotein (AHSG) gene was associated with longer sleep time and longer sleep duration during dexamethasone treatment.⁵⁸ Carriership of two SNPs in the Interleukin-6 (IL-6) gene was not significantly associated with sleep problems during dexamethasone treatment (Table S5b).⁵⁸

3.2.6 | Other factors

We identified two additional studied risk factors for sleep problems. Dexamethasone pharmacokinetics was investigated in two ALL studies. One study ($n = 24$) did not find an association of higher dexamethasone levels (trough levels following four days of dexamethasone) with sleep problems.⁵³ Another study ($n = 100$) described that a decrease of the cumulative time above a threshold of 100 nM dexamethasone was associated with increased actual sleep time. Furthermore, in a univariate analysis wake after sleep onset (WASO) increased and sleep efficiency and sleep time decreased as the dexamethasone area under the curve increased. However, multivariate analysis did not reveal statistical evidence independent of the dexamethasone area under the curve level.⁵⁸ The same group studied albumin levels and the occurrence of sleep problems and did not find a significant relation between both.⁵⁸

4 | DISCUSSION

Overall, evidence regarding risk factors for steroid-induced APRs and sleep problems in children with ALL is low, studies are scarce and the quality of summated evidence is low to very low. Therefore, the current summary should be interpreted with caution. Nevertheless, acquired data suggest that sex, type of steroid and (cumulative) steroid dose are no clear risk factors for steroid-induced APRs. A younger age (0-6 years old) seems to be a risk factor for behavioral problems. Older age seems more a risk factor for sleep problems. Sex does not seem a risk factor for overall sleep disturbance, but might

be for specific sleep parameters. Steroid dose and type appear to be a risk factor for steroid-induced sleep problems, although these findings are only based on one patient cohort. We did not find any studies which analyzed parental stress/coping or medical or sleep history as risk factor for APRs/sleep problems. Genetic susceptibility associations are weak and not replicated, therefore no conclusions can be drawn. Overall, more high quality evidence and replication studies are needed to confirm our identified findings.

In this review, APRs and sleep were evaluated as two independent phenomena. Indeed, both are usually described separately in literature. However, sleep problems can also be either an effect of or a trigger for APRs.¹⁴ The exact mechanism of how behavior and sleep are impacted by steroids is unknown but is thought to be caused by their effect on the glucocorticoid receptor and by their disruptive nature on the diurnal rhythm of the hypothalamic-pituitary-adrenal (HPA-) axis, and to suppression of endogenous cortisol production.⁵⁹ Cortisol has a high affinity for the mineralocorticoid receptor (MR) in the brain, whereas exogenous steroids such as dexamethasone have a higher affinity for the glucocorticoid receptor (GR).⁶⁰ In patients treated with steroids, the hypothesis is that the GR in the brain is stimulated, whereas the MR is not activated. This disturbance of GR:MR balance is thought to deregulate the stress-system and enhance vulnerability to stress-related disorders.⁶⁰ Furthermore, disruption of the diurnal rhythm at any level of the HPA-axis can disturb the regulation of the sleep-wake rhythm. Cortisol is secreted in a circadian rhythm which has its nadir in the night, important for falling asleep, and a peak when waking up.⁶¹ Glucocorticoid replacement therapy has been shown to be permissive for rapid eye movement sleep and sleep consolidation in patients with adrenal insufficiency who experience disturbed sleep phases.⁶²

The heterogeneity of studied APRs and sleep problems makes it difficult to generalize conclusions regarding risk factors. For example, young children seem to be at risk for behavioral problems,^{25,41,52} whereas older children seem to experience more steroid-induced psychosis.⁴² These are two different outcomes within the spectrum of APRs, and it is possible that for each APR different risk factors exist. Another explanation is that some APRs are better recognized in different age groups, or that younger children might not have developed the skills necessary to control their behavior. Age differences also differ per investigated domain of sleep problems, for example when measured in circadian parameters no differences were found, but when measured in sleep parameters, older children appear to have more sleep problems.

Another source of heterogeneity complicating the generalization of conclusions, is the methodology of measuring APRs and sleep problems, which differed considerably between studies. Several large randomized controlled trials^{37,38,42,46} reported APRs as part of toxicity registration. This could potentially give an underestimation of the problem, since usually only extreme cases (toxicity grade III or IV) are reported. Nevertheless, grade II/IV toxicities include side effects that are clinically relevant. These studies found an APR incidence of 0,1-6,0% in their population, remarkably lower than the

reported 19–86% in prospective studies which used validated questionnaires to measure APRs as primary outcome parameter.^{4,9,41,48,52} Sleep problems were not registered as toxicity in any of the trials, which recently led to a call for action to start screening for sleep problems.¹⁶

Since dexamethasone is more potent and penetrates the central nervous system better than prednisone,⁶³ and as dexamethasone has a higher affinity for the GR, it is conceivable that more APRs or sleep problems may be expected with dexamethasone treatment. Contrary to this expectation results were conflicting. Most (6/8) studies of which four of higher quality did not find a difference between dexamethasone and prednisone with regard to developing APRs.^{4,25,37,38,43,47,51} This is in line with a previous review investigating neuropsychological side effects of dexamethasone versus prednisone.¹⁰ Oppositely, two other high quality studies did find more APRs during dexamethasone treatment^{46,52} and one described significantly more dexamethasone related sleep problems.¹² Despite being a possible risk factor, dexamethasone has a higher anti-leukemic activity and will probably remain the preferred steroid in the treatment of ALL. Although it was expected that a higher steroid dose might predispose for APRs or sleep problems as well, this was not reported. Steroid dose was not related to APRs in four studies of which one of high quality.^{25,47–49} This is surprising, since in adults dosage appears to be the most significant risk factor.⁶⁴ Evidence is contradictory in children with chronic diseases, though dexamethasone levels and pharmacokinetics may play a role in the occurrence of steroid-induced toxicities. Dexamethasone clearance is known to be higher in younger children, which might explain the inter-patient variability.⁶⁵ Furthermore, even the lowest steroid dose children with ALL receive during their treatment is very high compared to adults or other pediatric patients with diseases such as asthma. This could possibly explain why we did not find a difference comparing steroid dose in the occurrence of APRs in children with ALL.

When looking into treatment related risk factors, it is important to realize that not only steroids can cause APRs or sleep problems. Other ALL treatment components, such as methotrexate, might cause synergistic toxicity.⁸ Also, a higher steroid dose and dexamethasone, both risk factors for sleep problems, are commonly used in treatment protocols for children with higher risk ALL. These children are treated with more chemotherapy compared to lower risk groups, which could explain a higher occurrence of sleep problems as well. Furthermore, the distress associated with being confronted with ALL and subsequent treatment regimen can cause both APRs and sleep problems on its own.^{66,67}

We hypothesized that a (family) history of psychiatric or sleep problems might predispose for steroid-induced adverse events, since in the general or adult oncology population this factor increases the risk of developing APRs or sleep problems.^{64,68} However, no studies assessed this risk factor for steroid-induced APR or sleep problems. Only case reports describing steroid-induced APRs in patients with a (family) history of psychiatric symptoms were found. However, case reports of patients with psychiatric deterioration without such histories were described as well. See Tables S6a and S6b for an overview

of these case reports, including references. No case reports regarding steroid-induced sleep problems were found. Larger studies focusing on (medical) history and the occurrence of both APR and sleep problems are warranted. Besides a history of psychiatric or sleep problems, it is conceivable that certain family risk factors (e.g., family background, premorbid functioning), parenting stress, but also received psychosocial support can influence the coping strategies of parents and may thereby influence their perceptions of problems during steroid treatment.^{27,66,69,70} None of these possible risk factors have been studied in steroid-induced APRs or sleep problems.

Genetic predisposition may contribute to the inter-individual differences in developing steroid-induced APRs or sleep problems. Several studies have identified relevant SNPs in the GR gene, which could contribute to differences in increased glucocorticoid sensitivity as well as APRs such as depression.^{71,72} Only one of our included studies found a significant association between a SNP and APR: Kaymak Cihan et al. described that carriers of the *Bcl1* polymorphism were more susceptible for depression symptoms.⁴⁴ However, this result was not replicated, nor did the other included studies find this association.^{4,39,45} No other SNPs were found to be associated with APRs. Genetic predisposition for sleep problems is complex and correlations depend on the definition of sleep outcome.^{73,74} Vallance et al. studied several polymorphisms that may contribute to inter-patient variability of steroid-induced sleep problems, using a candidate gene approach.⁵⁸ Only one polymorphism (rs4918, *AHSG* gene) was associated with impaired sleep both on and off dexamethasone treatment in children with ALL.⁵⁸ *AHSG* is a hepatic protein, associated with type 2 diabetes.⁷⁵ During dexamethasone treatment, the rs4918 polymorphism may be associated with longer sleep duration.⁵⁸ However, this finding remains to be replicated. In general, the quality of the included studies on the influence of genetic variation on steroid-induced APRs and sleep problems is very low (Table S5a and S5b). Most patient cohorts were very small which could explain the inability to demonstrate significant differences between genetic profiles. Other limitations include the lack of adjustments for multiple testing and confounding variables, as well as the absence of a replication cohort. This makes it impossible to provide evidence based recommendations regarding genetic susceptibility. Larger studies with proper replication are warranted.

4.1 | Study limitations

Some strengths and limitations should be discussed. For our systematic review, we used six different search engines and did not limit our search on our predefined risk factors (PICO's). This generated an extensive and complete search result and cross reference check did not reveal any new evidence. Furthermore, two high quality tools (QUIPS and GRADE) were used. Both tools complementarily facilitate a structured assessment and interpretation of results. All evidence screening, data extraction and assessment was performed by two independent researchers, limiting inter-individual differences. A limitation includes that the interpretability of the results of this

TABLE 5 Summary of findings, gaps of knowledge and recommendations

Summary of findings	
Age	APR: younger patients (0-6 years old) seem more at risk for behavioral problems Sleep: Adolescent patients seem at risk for more sleep problems (less sleep duration)
Sex	APR: Boys and girls do not differ in risk Sleep: most sleep parameters are not differently impacted, however WASO, napping and number of nocturnal awakening may differ for boys and girls
Steroid type	APR: No clear difference between dexamethasone versus prednisone Sleep: Receiving dexamethasone increased sleep problems compared to prednisone
Steroid dose	APR: Higher dose does not increase risk for APRs Sleep: Higher dose does increase risk for sleep problems
Gaps of knowledge	Recommendations
Scarce evidence on prospectively measured steroid-induced APR and sleep problems and related risk factors (only 6 out of 245 clinical pediatric ALL trials reported APR/sleep problems)	Systematically monitor psychological and sleep toxicities in new studies and specifically in clinical pediatric ALL trials.
Lack of high quality studies investigating steroid-induced APR and sleep problems Current evidence is of very low quality.	Develop larger studies which are a priori designed to investigate risk factors for steroid-induced APR and sleep problems. Use validated measures to study APR and sleep, e.g. validated questionnaires, sleep diary or actigraphy Replication studies, particularly for sleep problems, to increase quality of evidence.
Studies investigating parental coping, stress, family and medical history are currently lacking.	Include parental coping, stress, family and medical history in new studies, since they are potentially risk factors.
Genetic susceptibility studies are scarce, patient cohorts are small, no adjustments for multiple testing or confounding variables are made and findings remain to be replicated	Larger studies on the influence of genetic variation are needed, including appropriate replication cohorts

Abbreviations: ALL = acute lymphoblastic leukemia, APR = adverse psychological reaction

review is overall of very low quality of evidence, partly due to the average high risk of bias within single studies. This indicates that more extensive research designed to primarily investigate steroid-induced APRs and sleep is warranted.

We included a screen of 245 papers that reported on outcomes of clinical pediatric ALL trials. Of these 245, only six mentioned either APRs or sleep problems as a steroid-induced toxicity, of which one was included in our review.⁴² Numerous large trial papers which included (randomization for) steroids did not report APRs or sleep problems as adverse events, even though other toxicities such as osteonecrosis or infections were prospectively collected.⁷⁶⁻⁷⁸ These trials are mainly designed to improve (event free) survival, and/or to a lesser extent to decrease treatment induced toxicity. APRs and sleep problems are common (steroid-induced) toxicities, which can influence HRQoL substantially. An integrated system to measure and report both toxicities should be implemented in upcoming treatment protocols. Integration of patient-reported outcome measures (PROMs) could be valuable to establish a systematic approach.^{79,80}

4.2 | Clinical implications and conclusions

Based on this systematic review of literature, we conclude that there is no high level of evidence for risk factors for developing steroid-

induced APR or sleep problems in children with ALL. There are few high quality prospective studies and patient numbers are small. Methods of measurement are heterogeneous and evidence is weak. However, current evidence suggests that type and dose of steroids are not related to APRs, but may be related to sleep problems. Younger patients seem at risk for behavioral problems and older patients for sleep problems. Overall, these conclusions should be interpreted with caution. We made recommendations to improve evidence for findings regarding risk factors for steroid-induced APRs and sleep problems (Table 5). One important recommendation is to implement a standardized prospective registration of both steroid-induced APRs and sleep problems and risk factors in future studies in children with ALL, since identifying children at risk and determining effective care can improve health-related quality of life during treatment.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Annelienke M. van Hulst  <https://orcid.org/0000-0002-1006-3481>

REFERENCES

- Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. *Lancet Oncol*. 2010;11(11):1096-1106.
- Pui CH, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. *J Clin Oncol*. 2015;33(27):2938-U24.
- Schmiegelow K, Muller K, Mogensen SS, et al. Non-infectious chemotherapy-associated acute toxicities during childhood acute lymphoblastic leukemia therapy. *F1000Res*. 2017;6:444.
- Felder-Puig R, Scherzer C, Baumgartner M, et al. Glucocorticoids in the treatment of children with acute lymphoblastic leukemia and hodgkin's disease: a pilot study on the adverse psychological reactions and possible associations with neurobiological, endocrine, and genetic markers. *Clin Cancer Res*. 2007;13(23):7093-7100.
- Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child*. 2005;90(5):500-506.
- McGrath P, Pitcher L. Enough is enough': qualitative findings on the impact of dexamethasone during reinduction/consolidation for paediatric acute lymphoblastic leukaemia. *Support Care Cancer*. 2002;10(2):146-155.
- Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of long-course oral corticosteroids in children. *PLoS One*. 2017;12(1):e0170259.
- Hochhauser CJ, Lewis M, Kamen BA, Cole PD. Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. *Support Care Cancer*. 2005;13(12):967-974.
- Warris LT, van den Heuvel-Eibrink MM, Aarsen FK, et al. Hydrocortisone as an intervention for dexamethasone-induced adverse effects in pediatric patients with acute lymphoblastic leukemia: results of a double-blind, randomized controlled trial. *J Clin Oncol*. 2016;34(19):2287-2293.
- Warris LT, van den Heuvel-Eibrink MM, den Hoed MA, Aarsen FK, Pieters R, van den Akker EL. Does dexamethasone induce more neuropsychological side effects than prednisone in pediatric acute lymphoblastic leukemia? A systematic review. *Pediatr Blood Cancer*. 2014;61(7):1313-1318.
- Zupanec S, Jones H, Stremmler R. Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents. *J Pediatr Oncol Nurs*. 2010;27(4):217-228.
- Daniel LC, Li Y, Kloss JD, Reilly AF, Barakat LP. The impact of dexamethasone and prednisone on sleep in children with acute lymphoblastic leukemia. *Support Care Cancer*. 2016;24(9):3897-3906.
- Hinds PS, Hockenberry MJ, Gattuso JS, et al. Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer*. 2007;110(10):2321-2330.
- Hertenstein E, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Med Rev*. 2019;43:96-105.
- van Litsenburg RR, Huisman J, Hoogerbrugge PM, Egeler RM, Kaspers GJ, Gemke RJ. Impaired sleep affects quality of life in children during maintenance treatment for acute lymphoblastic leukemia: an exploratory study. *Health Qual Life Outcomes*. 2011;9:25.
- Daniel LC, van Litsenburg RRL, Rogers VE, et al. A call to action for expanded sleep research in pediatric oncology: a position paper on behalf of the International Psycho-Oncology Society Pediatrics Special Interest Group. *Psychooncology*. 2019.29(3):465-474.
- Acute adverse reactions to prednisone in relation to dosage. *Clin Pharmacol Ther*. 1972;13(5):694-698.
- Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am J Psychiatry*. 2012;169(5):491-497.
- Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. *Mayo Clin Proc*. 2014;89(6):817-834.
- Belmon LS, van Stralen MM, Busch V, Harmsen IA, Chinapaw MJM. What are the determinants of children's sleep behavior? A systematic review of longitudinal studies. *Sleep Med Rev*. 2019;43:60-70.
- Hamilton JL, Ladouceur CD, Silk JS, Franzen PL, Bylisma LM. Higher rates of sleep disturbance among offspring of parents with recurrent depression compared to offspring of nondepressed parents. *J Pediatr Psychol*. 2020;45(1):1-11.
- Harvey CJ, Gehrman P, Espie CA. Who is predisposed to insomnia: a review of familial aggregation, stress-reactivity, personality and coping style. *Sleep Med Rev*. 2014;18(3):237-247.
- Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep*. 2006;29(1):85-93.
- Steur LMH, Kolk RHE, Mooij F, et al. The prevalence and risk factors of sleep problems in pediatric oncology: its effect on quality of life during and after cancer treatment. *Expert Review of Quality of Life in Cancer Care*. 2016;1(2):19.
- Mrakotsky CM, Silverman LB, Dahlberg SE, et al. Neurobehavioral side effects of corticosteroids during active treatment for acute lymphoblastic leukemia in children are age-dependent: report from Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *Pediatr Blood Cancer*. 2011;57(3):492-498.
- Pepin AJ, Cloutier-Bergeron A, Malboeuf-Hurtubise C, et al. Adverse neuropsychological effects associated with cumulative doses of corticosteroids to treat childhood acute lymphoblastic leukemia: a literature review. *Crit Rev Oncol Hemat*. 2016;107, 138-148.
- McCarthy MC, Bastiani J, Williams LK. Are parenting behaviors associated with child sleep problems during treatment for acute lymphoblastic leukemia? *Cancer Med*. 2016;5(7):1473-1480.
- van der Geest IM, van den Heuvel-Eibrink MM, Passchier J, van den Hoed-Heerschop C, Pieters R, Darlington AS. Parenting stress as a mediator of parents' negative mood state and behavior problems in children with newly diagnosed cancer. *Psychooncology*. 2014;23(7):758-765.
- Williams LK, Lamb KE, McCarthy MC. Behavioral side effects of pediatric acute lymphoblastic leukemia treatment: the role of parenting strategies. *Pediatr Blood Cancer*. 2014;61(11):2065-2070.
- Judd LL, Schettler PJ, Brown ES, et al. Adverse consequences of glucocorticoid medication: psychological, cognitive, and behavioral effects. *Am J Psychiatry*. 2014;171(10):1045-1051.
- Derijk RH, de Kloet ER. Corticosteroid receptor polymorphisms: determinants of vulnerability and resilience. *Eur J Pharmacol*. 2008;583(2-3):303-311.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
- Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158(4):280-286.
- <https://methods.cochrane.org/prognosis/tools>.
- Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev*. 2013;2:71.
- Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101(10):3809-3817.

38. Domenech C, Suci S, De Moerloose B, et al. Dexamethasone (6 mg/m²/day) and prednisolone (60 mg/m²/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. *Haematologica*. 2014;99(7):1220-1227.
39. Eipel O, Hegyi M, Csordas K, et al. Some GCR polymorphisms (N363S, ER22/23EK, and Bcl-1) may influence steroid-induced toxicities and survival rates in children with ALL. *J Pediatr Hematol Oncol*. 2016;38(5):334-340.
40. Eipel OT, Nemeth K, Torok D, et al. The glucocorticoid receptor gene polymorphism N363S predisposes to more severe toxic side effects during pediatric acute lymphoblastic leukemia (ALL) therapy. *Int J Hematol*. 2013;97(2):216-222.
41. Harris JC, Carel CA, Rosenberg LA, Joshi P, Leventhal BG. Intermittent high dose corticosteroid treatment in childhood cancer: behavioral and emotional consequences. *J Am Acad Child Psychiatry*. 1986;25(1):120-124.
42. Hough R, Rowntree C, Goulden N, et al. Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003. *Br J Haematol*. 2016;172(3):439-451.
43. Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisolone for the outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo Children's Cancer Study Group L95-14 protocol. *J Clin Oncol*. 2005;23(27):6489-6498.
44. Kaymak Cihan M, Karabulut HG, Yurur Kutlay N, Ilgin Ruhi H, Tukun A, Olcay L. Association between N363S and Bcl1 polymorphisms of the glucocorticoid receptor gene (NR3C1) and glucocorticoid side effects during childhood acute lymphoblastic leukemia treatment. *Turk J Haematol*. 2017;34(2):151-158.
45. Marino S, Verzegnassi F, Tamaro P, et al. Response to glucocorticoids and toxicity in childhood acute lymphoblastic leukemia: role of polymorphisms of genes involved in glucocorticoid response. *Pediatr Blood Cancer*. 2009;53(6):984-991.
46. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005;129(6):734-745.
47. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison with conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic leukemia for long-term follow-up. *Leukemia*. 2003;17(2):328-333.
48. Drigan R, Spirito A, Gelber RD. Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. *Med Pediatr Oncol*. 1992;20(1):13-21.
49. Messina CA, Freides D, Faraj BA, Abdel-Mageed A, Ragab AH. The behavioral correlates of increased platelet monoamine oxidase in children. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*. 1989;2(4):11.
50. Eiser C, Eiser JR, Mayhew AG, Gibson AT. Parenting the premature infant: balancing vulnerability and quality of life. *J Child Psychol Psychiatry*. 2005;46(11):1169-1177.
51. Eiser C, Davies H, Jenney M, Stride C, Glaser A. HRQOL implications of treatment with dexamethasone for children with acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer*. 2006;46(1):35-39.
52. Pound CM, Clark C, Ni A, Athale U, Lewis V, Halton JM. Corticosteroids, behavior, and quality of life in children treated for acute lymphoblastic leukemia; a multicentered trial. *J Pediatr Hematol Oncol*. 2012;34(7):517-523.
53. Warris LT, van den Akker EL, Aarsen FK, et al. Predicting the neurobehavioral side effects of dexamethasone in pediatric acute lymphoblastic leukemia. *Psychoneuroendocrinology*. 2016;72:190-195.
54. Kiive E, Merenakk L, Harro M, Harro J. Changes in platelet monoamine oxidase activity, cholesterol levels and hyperactive behaviour in adolescents over a period of three years. *Neurosci Lett*. 2005;384(3):310-315.
55. Soliman A, Udemgba C, Fan I, et al. Convergent effects of acute stress and glucocorticoid exposure upon MAO-A in humans. *J Neurosci*. 2012;32(48):17120-17127.
56. Rogers VE, Zhu S, Ancoli-Israel S, Hinds PS. Impairment in circadian activity rhythms occurs during dexamethasone therapy in children with leukemia. *Pediatr Blood Cancer*. 2014;61(11):1986-1991.
57. Sanford SD, Okuma JO, Pan J, et al. Gender differences in sleep, fatigue, and daytime activity in a pediatric oncology sample receiving dexamethasone. *J Pediatr Psychol*. 2008;33(3):298-306.
58. Vallance K, Liu W, Mandrell BN, et al. Mechanisms of dexamethasone-induced disturbed sleep and fatigue in paediatric patients receiving treatment for ALL. *Eur J Cancer*. 2010;46(10):1848-1855.
59. Gordijn MS, Rensen N, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. *Cochrane Database Syst Rev*. 2015;8:CD008727.
60. de Kloet ER. From receptor balance to rational glucocorticoid therapy. *Endocrinology*. 2014;155(8):2754-2769.
61. Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *J Clin Endocrinol Metab*. 2005;90(5):3106-3114.
62. Garcia-Borreguero D, Wehr TA, Larrosa O, et al. Glucocorticoid replacement is permissive for rapid eye movement sleep and sleep consolidation in patients with adrenal insufficiency. *J Clin Endocr Metab*. 2000;85(11):4201-4206.
63. Veerman AJ, Kamps WA, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). *Lancet Oncol*. 2009;10(10):957-966.
64. Ismail MF, Lavelle C, Cassidy EM. Steroid-induced mental disorders in cancer patients: a systematic review. *Future Oncol*. 2017;13(29):2719-2731.
65. Yang L, Panetta JC, Cai XJ, et al. Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia. *J Clin Oncol*. 2008;26(12):1932-1939.
66. Myers RM, Balsamo L, Lu X, et al. A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Cancer*. 2014;120(9):1417-1425.
67. Steur LMH, Grootenhuis MA, Van Someren EJW, et al. High prevalence of parent-reported sleep problems in pediatric patients with acute lymphoblastic leukemia after induction therapy. *Pediatr Blood Cancer*. 2020;67(4):e28165.
68. Sivertsen B, Harvey AG, Pallesen S, Hysing M. Trajectories of sleep problems from childhood to adolescence: a population-based longitudinal study from Norway. *J Sleep Res*. 2017;26(1):55-63.
69. Kazak AE, Abrams AN, Banks J, et al. Psychosocial assessment as a standard of care in pediatric cancer. *Pediatr Blood Cancer*. 2015;62(Suppl 5):S426-S459.
70. Kunin-Batson AS, Lu X, Balsamo L, et al. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: a prospective longitudinal study. *Cancer*. 2016;122(10):1608-1617.
71. Manenshijn L, van den Akker EL, Lamberts SW, van Rossum EF. Clinical features associated with glucocorticoid receptor polymorphisms. An overview. *Ann N Y Acad Sci*. 2009;1179:179-198.
72. Spijker AT, van Rossum EF. Glucocorticoid receptor polymorphisms in major depression. Focus on glucocorticoid sensitivity and neurocognitive functioning. *Ann N Y Acad Sci*. 2009;1179:199-215.

73. Barclay NL, Gregory AM. Quantitative genetic research on sleep: a review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties. *Sleep Med Rev.* 2013;17(1):29-40.
74. Byrne EM. The relationship between insomnia and complex diseases-insights from genetic data. *Genome Med.* 2019;11(1).
75. Siddiq A, Lepretre F, Hercberg S, Froguel P, Gibson F. A synonymous coding polymorphism in the alpha2-Heremans-schmid glycoprotein gene is associated with type 2 diabetes in French Caucasians. *Diabetes.* 2005;54(8):2477-2481.
76. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study-dana-farber cancer institute ALL consortium protocol 00-01. *J Clin Oncol.* 2013;31(9):1202-1210.
77. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood.* 2019;133(14):1548-1559.
78. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from children's oncology group study AALL0232. *J Clin Oncol.* 2016;34(20):2380-2388.
79. Engelen V, Haverman L, Koopman H, et al. Development and implementation of a patient reported outcome intervention (QLIC-ON PROfile) in clinical paediatric oncology practice. *Patient Educ Couns.* 2010;81(2):235-244.
80. van Kooten J, van Litsenburg RRL, Yoder WR, Kaspers GJL, Terwee CB. Validation of the PROMIS sleep disturbance and sleep-related impairment item banks in Dutch adolescents. *Qual Life Res.* 2018; 27(7):1911-1920.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: van Hulst AM, Peersmann SHM, van den Akker ELT, et al. Risk factors for steroid-induced adverse psychological reactions and sleep problems in pediatric acute lymphoblastic leukemia: A systematic review. *Psychoncology.* 2021;30:1009–1028. <https://doi.org/10.1002/pon.5654>