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REVIEW

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

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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.

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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	*N* =	*n* = APR outcome	Age	Steroid	APR outcome	Measurement outcome	Risk factor	Measurement risk factor	Results	Risk of bias: QUIPS domains
Bostrom et al. (2003)[37]	RCT	No	1060	6	1-10 years	Dex (6 mg/m2/day) Pred (40 mg/m2/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	1947	53	0-18 years	Dex (6 mg/m2/day) Pred (60 mg/m2/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	38	38	SR: 51.4 months (29–94) HR: 49.1 months (25-63)	Pred (40 mg/m2/day or 120 mg/m2/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	346	29	1-18 years	Dex (10 mg/m2/day) Pred (60 mg/m2/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	346	29	0,2-17,9 years (median 4.95)	Dex (10 mg/m2/day) Pred (60 mg/m2/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	45	41	7,2 (3.8 SD) years	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	N =	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 - Hormone levels - Neuronal cell destruction - SNPs:ER22/23EK, N363S, 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: - N363S - Bcl1	PCR-RFLP	N363S: 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 Connors, 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)[46]	RCT	No	1603	58	1-18 years	Pred (40 mg/m2/day) Dex (6,5 mg/m2/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
Mrakotsky et al. (2011)[25]	Prospective repeated measures	Yes	60	60	2-17 years	Pred (40 mg/m2/day) Dex (6 mg/m2/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)[52]	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 total ($p = 0.041$), affective ($p = 0.015$) and anxiety problems ($p = 0.050$) 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)[9]	RCT	No	46	46	3–16 years	Dex (6 mg/m2/day)	Behavior	SDQ	Age	Patient 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 study[42]). 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. (*ABCB1*, *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] adrenocorticotropic hormone levels,[4] dexamethasone pharmacokinetics,[53] and neuronal cell destruction[4] 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 three[56–58] 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	*N* =	*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: 51.4 months (29-94)HR: 49.1 months (25-63)	Pred (40 mg/m2/day or 120 mg/m2/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/m2/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/m2/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
Sanford et al. (2008)[57]	Prospective	No	88	88	9.15 (SD 3.24) years	Dex (6, 8 or 12 mg/m2/day)	Sleep parameters	Actigraph 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	*N* =	*n* = Sleep outcome	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	Dex (6, 8 or 12 mg/m2/day)	Sleep parameters	Actigraphy and sleep diary	- Dex PK - Dex dose - Serum albumin - Genotyping	- Liquid chromatography - Per protocol - Standard testing method - DNA-Print Genomics	PK: Increased time above 100nM dex increase in sleep time ($p = 0.05$). Higher AUC (univariate) is l ess sleep efficiency and sleep time. Multivariate NS. Dose: Higher dex dose, less sleep efficiency ($p = 0.0015$) Albumin: NS AHSG SNP: sleep duration and actual sleep time increased IL6 G174C SNP: NS IL6 C634G SNP: NS	1/6 high
Warris et al. (2016)[53]	RCT	Yes	47	47	6,0 (4.0-9.8) years	Dex (6 mg/m2/day)	Sleep	SDSC	- Cortisol - Dex PK	- DST, CLIA - Trough levels	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																		
				Univariate			Multivariate			GRADE Factors[36]								
Potential Risk Factors	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																		
N363S	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																			
				Univariate			Multivariate			GRADE Factors[36]									
Potential Risk Factors	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
ACTH level (higher)	20	1	1	0	1[4]	0	-	-	-	2	x	NA	√	x	x	Unclear	x	+
Dex kinetics	46	1	1	0	1[53]	0	-	-	-	2	√	NA	√	Unclear	x	Unclear	Unclear	+
Neuronal cell destruction	20	1	1	0	1[4]	0	-	-	-	2	x	NA	√	Unclear	x	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, Adrenocorticotropic 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[36]								
Potential Risk Factors	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)	208	3	2	0	2[48,56]	1[13]	0	0	0	1,2	x	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	√	x	Unclear	x	+
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 sleep problems	0	0	0	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	**None existing**
Genetic predisposition																		
AHSG	88	1	1	1[58]	0	0	-	-	-	2	√	NA	√	Unclear	x	Unclear	NA	+
IL-6 (G174C)	88	1	1	0	1[58]	0	-	-	-	2	√	NA	√	Unclear	x	Unclear	NA	+
IL-6 (C634G)	88	1	1	0	1[58]	0	-	-	-	2	√	NA	√	Unclear	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	√	Unclear	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 α2-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 the 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 problemsSleep: Adolescent patients seem at risk for more sleep problems (less sleep duration)
Sex	APR: Boys and girls do not differ in riskSleep: 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 prednisoneSleep: Receiving dexamethasone increased sleep problems compared to prednisone
Steroid dose	APR: Higher dose does not increase risk for APRsSleep: 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 problemsCurrent 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 actigraphyReplication 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.

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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.

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SUPPORTING INFORMATION

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

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