Supplemental Digital Content - Factors associated with delirium in children: a systematic review and meta-analysis

Content of the Supplemental Digital Content (SDC):

- SDC 1 – PRISMA checklist
- SDC 2 – full search strategy
- SDC 3 – Table with characteristics of included studies
- SDC 4 – NOS
- SDC 5 – Univariate and multivariate outcomes of factors associated with pediatric delirium
- SDC 6 – Forest plots
- SDC 7 – Funnel plots, publication bias

SDC 1 - PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7

SDC 1 - PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8-9 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 8
Study characteristics	17	Cite each included study and present its characteristics.	Page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9, suppl 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12-14
	23b	Discuss any limitations of the evidence included in the review.	Page 14-15
	23c	Discuss any limitations of the review processes used.	Page 14-15
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 17
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 17
Competing interests	26	Declare any competing interests of review authors.	Page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

SDC 2 – Search strategy

Embase.com

('delirium'/exp OR 'intensive care psychosis'/de OR (delir* OR delire* OR ((intensive-care OR icu OR nicu OR picu) NEAR/3 psychosis)):ab,ti) AND ('risk factor'/de OR 'probability'/de OR 'odds ratio'/de OR 'disease predisposition'/exp OR (('cohort analysis'/de OR 'prospective study'/de OR 'retrospective study'/de) AND ('risk'/exp OR 'prediction'/de OR 'predictive value'/de)) OR (((risk* OR predict*) NEAR/3 factor*) OR predispos* OR Susceptib* OR at-risk OR ((odds OR risk) NEXT/1 ratio*) OR (relative NEXT/1 (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR Predict*))):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR pediatrics/exp OR childhood/exp OR 'child nutrition'/de OR 'infant nutrition'/exp OR 'child welfare'/de OR 'child abuse'/de OR 'child advocacy'/de OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child death'/de OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR 'pediatric anesthesia'/de OR 'pediatric intensive care unit'/de OR 'neonatal intensive care unit'/de OR 'prematurity'/de OR (adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti,kw) NOT [conference abstract]/lim

Medline ALL Ovid

(exp Delirium / OR (delir* OR delire* OR ((intensive-care OR icu OR nicu OR picu) ADJ3 psychosis)).ab,ti.) AND (Risk Factors / OR Odds Ratio / OR Disease Susceptibility / OR ((exp Cohort Studies/) AND (Risk / OR Probability /)) OR (((risk* OR predict*) ADJ3 factor*) OR predispos* OR Susceptib* OR at-risk OR ((odds OR risk) ADJ ratio*) OR (relative ADJ (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR Predict*))).ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Child Behavior"/ OR exp "Parent Child Relations"/ OR exp "Pediatrics"/ OR "Child Nutrition Sciences"/ OR "Infant nutritional physiological phenomena"/ OR exp "Child Welfare"/ OR "Child Development"/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Child Rearing"/ OR exp "Child development Disorders, Pervasive"/ OR "Child Psychiatry"/ OR "Child Psychology"/ OR "Hospitals, Pediatric"/ OR exp "Intensive Care Units, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs).ab,ti,kf.)

Web of Science Core Collection

TS=(((delir* OR delire* OR ((intensive-care OR icu OR nicu OR picu) NEAR/2 psychosis))) AND ((((risk* OR predict*) NEAR/2 factor*) OR predispos* OR Susceptib* OR at-risk OR ((odds OR risk) NEAR/1 ratio*) OR (relative NEAR/1 (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR

Predict*)))) AND ((adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs))) AND DT=(article)

Cochrane CENTRAL register of Trials

((delir* OR delire* OR ((intensive NEXT care OR icu OR nicu OR picu) NEAR/3 psychosis)):ab,ti) AND ((((risk* OR predict*) NEAR/3 factor*) OR predispos* OR Susceptib* OR at NEXT risk OR ((odds OR risk) NEXT/1 ratio*) OR (relative NEXT/1 (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR Predict*))):ab,ti) AND ((adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre NEXT matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti)

CINAHL EBSCOhost

(MH Delirium + OR TI(delir* OR delire* OR ((intensive-care OR icu OR nicu OR picu) N2 psychosis)) OR AB(delir* OR delire* OR ((intensive-care OR icu OR nicu OR picu) N2 psychosis))) AND (MH Risk Factors OR MH Odds Ratio OR MH Disease Susceptibility OR ((MH Prospective Studies +) AND (MH Probability)) OR TI(((risk* OR predict*) N2 factor*) OR predispos* OR Susceptib* OR at-risk OR ((odds OR risk) N1 ratio*) OR (relative N1 (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR Predict*))) OR AB(((risk* OR predict*) N2 factor*) OR predispos* OR Susceptib* OR at-risk OR ((odds OR risk) N1 ratio*) OR (relative N1 (risk* OR odds)) OR RR OR ((cohort* OR prospect* OR retrospect*) AND (risk OR Predict*)))) AND (MH Child+ OR MH Infant+ OR MH Adolescence+ OR TI(adolescen* OR infan* OR newborn* OR (new N1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under N1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs) OR AB(adolescen* OR infan* OR newborn* OR (new N1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under N1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs))

SCD 3 - Table with characteristics of included studies

Author (Country)	**Design**	**Setting, Age, Sample size**	**Criterium for delirium,** Frequency of assessment (follow up)	**Prevalence PD**	**Factors studied***
Koth, 2021 (USA) (43)	Retro. Cohort study Single center	PCICU Age: 61% < 2 yrs N=942	CAPD ≥ 9 Twice a day, during PCICU stay	67.3% (634/942)	Age <2 yrs*, Genetic or congenital condition, Single ventricle physiology, STAT category*, Aortic cross-clamp time (min), AKI*, MV*, PELOD score*, Restraint, ECMO, CRRT, Benzodiazepines*, Opioids*, Dexmedetomidine*
Ge, 2021 (China) (44)	Retro. Cohort study Single center	PICU Age (mon): 19.5 (23.6) [a] N=639	CAPD ≥ 9 Twice a day, during PICU stay	31.3% (200/639) Hypoactive: 36% Hyperactive: 41% Mixed: 23%	Age*, MV*, Hypoxic*, Septic, Metabolic*, Benzodiazepines, Restraints, LOS, PRISM IV, CRP, Infection*, Hypoxia
Yontem, 2021 (Turkey) (39)	Pros. cohort study Single center	PICU Age (mon): 43.0 (IQR 17-123) [b] N=142	CAPD ≥ 9 Twice a day, during PICU stay	9.9% (14/142) Hypoactive: 14.3% Hyperactive: 57.1% Mixed: 28.6%	Psychosocial intervention*, Respiratory support, Opiates, Benzodiazepines, Vasoactive drugs, Corticosteroid, Physical restraint, PIM, LOS PICU*
Flores, 2021 (Brazil) (25)	Pros. cohort study Single center	PICU Age (mon): 47 (58.1) [a] N=65	CAPD ≥ 9 SOS-PD	7.7% (5/65)	Age, Gender, MV, Antiemetic, Anticholinergic
Stegmann, 2021 (Argentina) (45)	Pros. cohort study Single center	PICU Age (yrs): 2 (IQR 3 - 7) [b] N=116	CAPD ≥ 9 Twice a day, during PICU stay	52.6% (61/116)	MV, Sedoanalgesia, Opiates, Physical restraint
Traube, 2021 (USA) (40)	Pros. Point prevalence study Multicentre (n=11)	Pediatric ward – hematopoietic cell transplantation Age: 4 yrs (median), 45% < 5 yrs N=106 (883 hospital days)	CAPD ≥ 9 Twice a day, during 10 days	45% (48/106)	Age*, Oxygen supply, Steroids
Gupta, 2020 (USA) (41)	Pros. cohort study Single center	PICU Age: 39% < 2 yrs N=95	CAPD ≥ 9 Twice a day, during PICU stay	20% (19/95)	Age*, MV*, Vasoactive drugs*, Benzodizepines*, Opioids*, LOS PICU
Staveski, 2020 (USA) ((34)	Pros. Point prevalence study Multicentre (n=27)	PCICU, postoperative cardiac surgery patients Age (mon): 2.5 (1.5-6.5) [b] N=181	CAPD ≥9	40% (73/181)	MV*, ECMO support, Vasoactive infusion, Tot. number invasive catheters, CRRT, VAD support, Pain score, SBS score*, WAT-1, Opioids*, Midazolam, Restraints not in use, No physical therapy/ambulation schedule*, Immobility (out of bed), Parents not at bedside*, Window in patient's room

Author (Country)	**Design**	**Setting, Age, Sample size**	**Criterium for delirium,** Frequency of assessment (follow up)	**Prevalence PD**	**Factors studied***
Dechnik, 2020 (USA) (23)	Retro. cohort study Single center	PICU patients Age: 0-21yrs N=734	CAPD ≥9 delirium/coma/DFCF Once a day	37.3% (274/734) Hypoactive: 71% Hyperactive: 6% Mixed: 23%	CRP level, Procalcitonin
Meyburg, 2020 (Germany) (27)	Pros. cohort study Single center	PICU patients after major surgery Age: 3.5±4.7[a] (0-18 yrs) N=93	CAPD (post.op delirium) Twice daily (during 5 days) CAPD≥9 Mild PD: 1 day Severe PD: ≥2 days	66% (61/93) Mild: 32% Severe: 33%	Anticholinergic drugs, Age, Infection, MV
Dervan, 2020 (USA) (24)	Retro. cohort study Single center	PICU patients with LOS > 48 hours Age: 0-21 yrs N = 908	CAPD ≥ 9 Twice daily (throughout admission)	69% (629/908)	Age*, PCPC*, MV*, Restraint*, PELOD, Benzodiazepines*, Dexmedetomidine*, Opiates, Clonidine, ICU days at sedation state*, PRIMS*
Ramirez, 2019 (Colombia) (31)	Pros. cohort study Single center	PICU patients Age: 11 yrs (5-14)[b] N=156	pCAM-ICU	18.6% (29/156)	Intellectual disability*, Deep sedation, Tachycardia*, Hypertension, Hyperthermia (≥38.0◦C), Infection, Respiratory failure, MV*, Liver failure*, Neurological disease*, Seizures, Skin damage, Restricted mobility, Anticholinergic drugs*, Benzodiazepines, Psychotropic agents*
Winsnes, 2019 (USA) (38)	Pros. cohort study Single center	Pediatric hematology, oncology, and bone marrow transplant (PHO) patients Age: 0-21 yrs N=807 admissions (223 unique patients)	CAPD ≥ 9 Twice daily (during admission)	4.9% (40/807)	Diagnose*, LOS PICU*, Fever, Isolation, Pain, Benzodizepines*, Opioids*, Anticholinergic*, Antihistamines, Steriods
Alvarez, 2018 (USA) (22)	Pros. cohort study Single center	PCICU patients Age: 24 mo (IQR 2-72) [b] N=99 (n=88, underwent cardiac surgery)	CAPD ≥ 9 Twice daily (during 14days)	57% (56/99) Hypoactive: 52% Hyperactive: 5% Mixed: 43%	Age*, MV*, Benzodiazepines*, STS-EACTS score*
Meyburg, 2018 (Germany) (26)	Pros. cohort study Single center	PICU patients after major surgery Age: 3.5±4.7[a] (0-18 yrs) N=93	CAPD ≥ 9 Twice daily (during 5 days)	66% (61/93) Mild PD: 32% Severe PD: 33%	Age*, Infection*, MV*, number of invasive catheters, Cumulative doses Drugs

Author (Country)	**Design**	**Setting, Age, Sample size**	**Criterium for delirium,** Frequency of assessment (follow up)	**Prevalence PD**	**Factors studied***
			Mild PD: 1 day Severe PD: ≥2 days		
Mody, 2018 (USA) (28)	Retro. cohort study Single center	PICU patients Age: 0 – 21 yrs <1: 25% 1-2: 20% 3-5: 20% 6-12: 17% >12: 18% N= 580 patients, unit of measurement PICU day	CAPD ≥ 9 Daily (throughout admission)	21% (487 of the 2,291 days) Hypoactive: 52% Hyperactive: 8% Mixed: 38%	Day prior Delirious*, Benzodiazepines*, Opioids*, Restraints, MV*, Coma status*
Nellis, 2018 (USA) (29)	Pros. cohort study Single center	PICU patients Age: 2.8 (0.6-10.9) [b] N= 1547 (n=166 with RBC transfusion)	CAPD ≥ 9 Once a day (throughout admission)	30% (43/141 subjects developed new delirium within 72 hours of RBC transfusion)	RBC transfusion*
Patel, 2017 (USA) (30)	Pros. cohort study Single center	PCICU patients Age: 0 – 21 yrs 0-2: 41.8% 3-5: 24.7% 6-13: 14.9% >13: 18.6% N = 194 patients, unit of measurement PICU day	CAPD ≥ 9 Twice daily (throughout admission)	49% (95/194)	Age*, Developmental delay*, Cyanotic heart disease*, Restraint, MV, Benzodiazepines, Opioids, Dexmedetomidine, Vasoprosessors, Rachs score*
Smith, 2017 (USA) (33)	Pros. cohort study Single center	PICU patients Age: 20 (11-37) [b] (6 m – 5 yrs) N=300	pCAM-ICU Daily (during 14days)	44% (132/300)	Age, PRISM, Benzodiazepines*
Traube, 2017a (United States, the Netherlands, New Zealand, Australia and Saudi Arabia) (37)	Pros. Point prevalence study Multicentre (n=25)	PICU patients Age: 0-21 yrs N=994	CAPD ≥ 9	25% (209/835)	Age*, MV*, Benzodiazepines*, Restraints*, Opiates*, Vasopressor*, Antiepileptics*, General anaesthesia*
Traube, 2017b (USA) (35)	Retro. cohort study Single center	Pediatric cancer Age: 2 mo-21 yrs	CAPD ≥ 9	18.8% (35/186)	Age*, Diagnosis*, Narcotics*, Benzodiazepines*, Steroids, Postoperative status*

Author (Country)	**Design**	**Setting, Age, Sample size**	**Criterium for delirium,** Frequency of assessment (follow up)	**Prevalence PD**	**Factors studied***
		N=186 (319 admissions)	Daily (throughout admission)		
Traube, 2017c (USA) (36)	Pros. cohort study Single center	PICU patients Age: 0-21 yrs N=1547	CAPD ≥ 9 Twice daily (throughout admission)	17.3% (267/1547) hypoactive (46%) mixed (45%) Hyper (8%)	Age*, POM*, Pre-existing medical condition, Developmental delay*, MV*, Coma*, Benzodiazepines*, Narcotics, Vasoactive drug, Corticosteroids, Anticholinergic*, In-hospital mortality
Silver 2015 (USA) (32)	Pros. cohort study Single center	PICU patients Age: 0-21 yrs N=99 (unit of measurement PICU day)	CAPD ≥ 9 Twice daily (3-5 days during validation)	21% (21/99)	Age*, Develop delay*, MV*, Deep sedation, PIM2
Schieveld, 2008 (Netherlands) (42)	Pros. cohort study Single center	PICU patients with a psychiatry consultation Age: 4.4±4.9[a] N=877	Child neuropsychiatrist using DSM-IV	4.5% (40 / 877)	Age, MV, PICU admission, PRISM2, PIM

a mean±SD; b median (IQR); yrs – years; mon – months; * factors tested in multivariable analysis; ADS - Anticholinergic Drug Scale; CRP - C-reactive protein; PICU – Pediatric Intensive Care Unit; PCICU - Pediatric Cardiac Intensive Care Unit; Pros. – prospective; Retro. – retrospective; RBC – Red blood cell; ns – not significant; CPB time – Cardio Pulmonary Bypass time; LOS – Length of Stay; POM – probability of mortality; MV – Mechanical ventilation; PRISM – Pediatric Risk of Mortality; PIM – Pediatric Index of Mortality; RACHS - Risk Adjustment for Congenital Heart Surgery score; STAT - Society of Thoracic Surgeons – European Association for Cardio-Thoracic Surgery (STAT) score; TDD - total daily dose; AKI - acute kidney injury; PELOD - Pediatric Logistic Organ Dysfunction; ECMO - extracorporeal membrane oxygenation; CRRT - continuous renal replacement therapy

SDC 4 – Quality Assessment by Newcastle-Ottawa Scale

Author (year)	Selection	Comparability	Outcome	Total
Koth (2021)	4	2	3	9
Ge (2021)	4	2	3	9
Yontem (2021)	4	2	3	9
Flores (2021)	4	2	3	9
Stegmann (2021)	4	1	1	6
Traube (2021)	4	2	2	8
Gupta (2021)	4	2	3	9
Staveski (2020)	4	2	2	8
Dechnik (2020)	4	2	3	9
Meyburg (2020)	4	1	3	8
Dervan (2020)	4	2	3	9
Ramirez (2019)	3	2	1	6
Winsnes (2019)	4	2	3	9
Alvarez (2018)	4	2	3	9
Meyburg (2018)	4	2	3	9
Mody (2018)	4	1	1	6
Nellis (2018)	4	2	3	9
Patel (2017)	4	2	3	9
Smith (2017)	4	2	3	9
Traube (2017a)	4	2	2	8
Traube (2017b)	4	2	3	9
Traube (2017c)	4	2	2	8
Silver (2015)	4	2	2	8
Schieveld (2008)	4	0	3	7

SDC 5 – Table of Univariate and multivariate outcomes of factors associated with pediatric delirium

Author (Country)	Factors studied	Univariate OR (95%CI) or bivariate analyses/unadjusted (delirium free vs. delirium positive)	Multivariate OR (95%CI) or adjusted analysis
Koth, 2021 (USA) (43)	Age <2 yrs (n, %)	78 (14) vs 495 (86) (p<0.01)	7.9 (5.0-12.5) [d]
	Genetic or congenital condition (n, %)	30 (19) vs 126 (81) (p<0.01)	-
	Single ventricle physiology (n, %)	34 (24) vs 105 (76) (p=0.02)	-
	STAT category (n, %)		
	- 1-2	163 (46) vs 190 (54) (p<0.01)	-
	- 3-5	41 (13) vs 277 (87)	1.0 (0.5-1.7) [d]
	Aortic cross-clamp time (min)	59 (39-86) vs 67 (42-105) (p=0.02)	-
	AKI (grade) (n, %)		1.6 (1.0-1.6) [d]
	- none	226 (42) vs 314 (58) (p<0.01)	
	- grade 1	33 (20) vs 133 (80)	
	- grade 2	12 (10) vs 103 (90)	
	- grade 3	3 (4) vs 71 (96)	
	MV (n, %)	120 (20) vs 483 (80) (p<0.01)	1.8 (1.4-2.5) [d]
	Highest PELOD score	5 (3-9) vs 11 (7-13) (p<0.01)	1.0 (0.9-1.1) [d]
	Total days of restraint (days) [b]	1 (1-1) vs 3 (2-7) (p<0.01)	-
	ECMO (n, %)	0 (0) vs 32 (100) (p<0.01)	-
	CRRT (n, %)	0 (0) vs 18 (100) (p<0.01)	-
	Benzodiazepines:		
	- Mean TDD benzodiazepine	0 (0-0) vs 0.01 (0-0.04) (p<0.01)	-
	- > median exposure	-	2.4 (1.2-4.9) [d]
	Opioids:		
	- Mean TDD opioid	0.1 (0.01-0.2) vs 0.5 (0.2-2.1) (p<0.01)	-
	- > median exposure	-	3.3 (1.5-7.2) [d]
	Dexmedetomidine		
	- Mean TDD	0.5 (0-1.6) vs 2.6 (0.2-5.4) (p<0.01)	-
	- > median exposure		1.9 (0.9-4.0) [d]
Ge, 2021 (China) (44)	Age, < 12 mon (n, %)	282 (66.2) vs 155 (77.5) (p=0.001)	0.69 (0.56-0.85) [d]
	MV (n, %)	45 (10.3) vs 93 (46.5) (p<0.001)	3.78 (2.25-6.35) [d]
	Hypoxic (n, %)	91 (20.7) vs 122 (61.0) (p<0.001)	2.69 (1.53-4.71) [d]
	Septic (n, %)	56 (12.8) vs 51 (25.5) (p<0.001)	-
	Metabolic (n, %)	70 (15.9) vs 106 (53.0) (p<0.001)	3.73 (2.08-6.71) [d]
	Benzodiazepines (n, %)	72 (16.4) vs 66 (33.0) (p<0.001)	-
	Restraints	385 (87.7) vs 192 (96.0) (p<0.001)	-
	LOS, > 7 days (n, %)	67 (15.3) vs 91 (45.5) (p<0.001)	1.10 (1.04-1.16) [d]
	PRISM IV, score > 7	136 (31.0) vs 120 (60.0) (p<0.001)	2.20 (1.42-3.41) [d]
	CRP > 10mg/L	296 (67.5) vs 160 (80.0) (p<0.001)	1.01 (1.00-1.02) [d]
	Duration infection, days [a]	0.81 (1.86) vs 4.4 (7.60) (p<0.001)	1.22 (1.10-1.36) [d]
	Duration Hypoxia, days [a]	0.53 (1.46) vs 3.14 (6.19) (p<0.001)	-
Yontem, 2021 (Turkey) (39)	Psychosocial intervention	103 (80.5) vs 5 (35.7) (p=0.001)	0.237 (1.04-17.24) [d]
	Respiratory support	56 (43.8) vs 10 (71.4) (p=0.04)	-
	Opiates	23 (18) vs 6 (42.9) (p=0.03)	-
	Benzodiazepines	32 (25) vs 7 (50) (p=0.04)	-
	Vasoactive drugs	30 (23.4) vs 7 (50) (p=0.03)	-
	Corticosteroid	45 (35.2) vs 9 (64.3) (p=0.03)	-
	Physical restraint	36 (28.1) vs 9 (64.3) (p=0.006)	-
	PIM [b]	3.4 (1.2-9.4) vs 23.7 (2.4-43.4) (p=0.03)	-
	Length of PICU stay [b]	5 (4-9) vs 7.5 (6-13) (p=0.01)	1.095 (1.006-1.192) [d]
Flores, 2021 (Brazil) (25)	Age <2 yrs (n, %)	31 (47.7) vs 5 (7.7) (p=0.06)	ND
	Female (n, %)	30 (46.1) vs 5 (7.7) (p=0.05)	
	MV (n, %)	44 (66.2) vs 1 (1.5) (p=0.034)	
	Antiemetic (n, %)	58 (89.2) vs 2 (3.1) (p=0.002)	
	Anticholinergic (n, %)	57 (87.7) vs 3 (4.6) (p=0.044)	
Stegmann, 2021 (Argentina) (45)	MV	1.40 (0.69-2.62) [c]	ND
	Sedoanalgesia	1.51 (0.86-2.62) [c]	
	Opiates	1.78 (0.94-3.21) [c]	
	Physical restraint	2.97 (1.14-6.55) [c]	
Traube, 2021 (USA) (40)	Age < 5 yrs vs older (%)	60% (<5yrs) vs 33% (p=0.008)	0.41 (0.17-0.99) (>5 yrs) [d]
	Oxygen supply (n, %)	42 (40) vs 74 (70) (p=0.027)	

Author (Country)	Factors studied	Univariate OR (95%CI) or bivariate analyses/unadjusted (delirium free vs. delirium positive)	Multivariate OR (95%CI) or adjusted analysis
	Steroids (n, %)	36 (34) vs 64 (60) (p=0.016)	
Gupta, 2020 (USA) (41)	Age category: - *< 2 yrs* - *2-5* - *5-12* - *12+* MV, time spend (hrs) [b] Vasoactive drugs Daily benzo dose (mg/kg/day) [b] Daily opioid dose (mg/kg/day) [b] Length of PICU stay (days) [b]	 35 (46) vs 2 (11) (p=0.012) 9 (12) vs 3 (16) 17 (22) vs 5 (26) 15 (20) vs 9 (47) 153 (94-282) vs 349 (171-987) (p<0.001) 23 (30) vs 11 (58) (p=0.033) 1 (0-3) vs 2 (2-4) (p=0.009) 1 (0-3) vs 3 (1-4) (p=0.023) 8 (5-14) vs 16 (9-41) (p<0.001)	 - Ref - 3.76 (0.38-37.24) [d] - 6.52 (0.81-52.27) [d] - 25.33 (2.82-227.64) [d] 1.004 (1.001-1.007) [d] 0.36 (0.07-1.97) [d] 1.06 (0.69-1.63) [d] 1.98 (1.13-3.46) [d] -
Staveski, 2020 (USA) ((34)	MV (duration, days)[b] ECMO support (n, %) Vasoactive infusion (n, %) Tot. number invasive catheters [b] CRRT (n, %) VAD support (n, %) Pain score, most recent [b] SBS score, [b] WAT-1, current [b] Opioid or sedative administered (<4 hr) (n, %) Opioid administered (24 hr of CAPD) (n, %) Morphine exposure (mg/kg/d)[b] Sedative administered (24 hr of CAPD) (n, %) Midazolam exposure (mg/kg/d)[b] Restraints not in use (n, %) No physical therapy/ambulation schedule (n, %) Immobility (out of bed) (n, %) Parents not at bedside (n, %) Window in patient's room (n,%)	5.1 (1.3-10.9) vs 12.8 (2.9-19.5) (p=0.02) 11 (10) vs 18 (25) (p=0.02) 28 (26) vs 40 (55) (p<0.001) 3 (2-4) vs 4 (3-6) (p=0.001) 1 (1) vs 5 (7) (p=0.09) 6 (6) vs 4 (6) (p=0.96) 0 (0-1) vs 0 (0-3) (p=0.001) 0 (-1-0) vs -1 (-1-0) (p=0.001) 1 (0-3) vs 2 (1-4) (p=0.04) 52 (48) vs 62 (85) (p<0.001) 30 (28) vs 33 (45) (p=0.03) 0.36 vs 1.80 (p<0.001) 16 (15) vs 26 (36) (p=0.005) 0.24 vs 1.14 (p=0.07) 105 (97) vs 68 (93) (p=0.27) 69 (64) vs 62 (85) (p=0.02) 73 (68) vs 23 (32) (p<0.001) 40 (37) vs 44 (60) (p=0.008) 106 (98) vs 70 (96) (p=0.48)	 1.30 (1.06-1.60) [d] 4.01 (1.21-13.27) [d] 3.49 (1.32-9.28) [d] 1.35 (1.06-1.73) [d] 4.40 (1.41-13.68) [d] 2.31 (1.01-5.31) [d]
Dechnik, 2020 (USA) (23)	CRP level (mg/dL) [b] Procalcitonin (ng/mL) [b]	6.40 (1.60–15.6) vs 5.60 (1.28–13.0) (p=0.117) 1.13 (0.30–5.65) vs 0.50 (0.14–2.94) (p<0.001)	ND
Meyburg, 2020 (Germany) (27)	Anticholinergic drugs (ADS) [a] - *PD (no vs yes)* Age, years [a] Infection (n, %) [a] MV (hr) [a]	 2.5 (range 0-5.4) vs 3.2 (range 0-6.2)(p < 0.05) 6.4 (5.7) vs 1.9 (2.8) (p<0.001) 3 (9.4) vs 16 (26.2) (p=0.008) 14.3 (18.8) vs 55.2 (58.1) (p<0.001)	 ND
Dervan, 2020 (USA) (24)	Age category: - *< 2 yrs* - *2-5* - *5-12* - *12+* PCPC >=3 MV Restraint exposure PELOD - benzo - dexmed - opiates - clonidine	Age - ref - 0.91 (0.82, 1.00) [e] - 0.71 (0.63, 0.81) [e] - 0.60 (0.53, 0.68) [e] 1.50 (1.39, 1.63) [e] 1.84 (1.68–2.02) [e] 1.65 (1.54–1.78) [e] 1.05 (1.04–1.06) [e] 1.58 (1.43–1.75) [e] 1.72 (1.58–1.87) [e] 1.25 (1.12–1.38) [e] 1.40 (1.30–1.51) [e]	 8.2 (5.0-13.3) (Age < 2) [d] - - - 7.2 (4.3-11.9) (PCPC >1) [d] 3.9 (1.6-10) (MV 3-6days)[d] 1.3 (1.0-1.7) [d] - 3.4 (2.0-6.0) [d] 2.5 (1.3-5.2) [d] - -

Author (Country)	Factors studied	Univariate OR (95%CI) or bivariate analyses/unadjusted (delirium free vs. delirium positive)	Multivariate OR (95%CI) or adjusted analysis
	ICU days at sedation state PRIMS	1.16 (1.12–1.20) [e] - ND	1.5 (1.3-1.7) [d] 1.1 (1.0-1.1) [d]
Ramirez, 2019 (Colombia) (31)	Intellectual disability Deep sedation (RASS ≤ 3) Tachycardia Hypertension Hyperthermia (≥38.0◦C) Infection Respiratory failure Mechanical ventilation Liver failure Neurological disease Seizures Skin damage Restricted mobility Anticholinergic drugs Benzodiazepines Psychotropic agents	6.36 (1.79-22.61) [d] 5.90 (2.09-16.67) [d] 2.93 (1.17-7.68) [d] 4.34 (1.82-10.34) [d] 3.88 (1.23-12.24) [d] 2.77 (1.21-6.32) [d] 2.91 (1.14-7.44) [d] 9.07 (2.91-28.27) [d] 14.54 (1.45-145.33) [d] 5.04 (1.91-13.30) [d] 4.92 (1.15-21.00) [d] 3.35 (1.72-9.60) [d] 3.62 (1.57-8.37) [d] 3.98 (1.70-9.34) [d] 4.84 (2.06-11.41) [d] 3.65 (1.44-9.23) [d]	17.54 (3.23-95.19) [d] - 4.74 (1.21-18.51) [d] - - - - 18.80 (4.29-82.28) [d] 54.88 (4.27-705.33) [d] 4.41 (1.23-15.83) [d] - - - 3.23 (1.02-10.26) [d] - 4.88 (1.42-16.73) [d]
Winsnes, 2019 (USA) (38)	Diagnose BMT vs Onco LOS – 5-14d LOS – 15+d Fever Isolation Pain Benzo Opioids Anticholinergic Antihistamines Steriods	6.8 (3.1-14.5) [d] 12.6 (3.3-82) [d] 76.2 (22.1-479.6) [d] 6.4 (3.1–14.1) [d] 2.5 (1.3–4.9) [d] 3.2 (1.4–7.2) [d] 1.2 (1.1–1.3) [d] 1.2 (1.2–1.3) [d] 1.1 (1.0–1.2) [d] 1.1 (1.1–1.2) [d] 1.2 (1.1–1.2) [d]	5.5 (1.9-15.7) [d] 3.26 (0.89-13.62) [d] 7.43 (2.31-29.45) [d] - - - 4.2 (1.5-13.7) [d] 4.6 (1.4-21.3) [d] 3.4 (1.3-8.9) [d] - -
Alvarez, 2018 (USA) (22)	Age < 1 yrs (n, %) MV (n, %) Benzo (n, %) STS-EACTS score >3	8 (19) vs 36 (64) (p<0.001) 24 (56) vs 42 (72) 29 (67) vs 40 (71) 5 (13.9) vs 18 (34.6) (p=0.044)	0.35 (0.19-0.64) [d] 4.1 (1.7-9.89) [d] 3.78 (1.46-9.79) [d] 1.08 (0.25-4.64) [d]
Meyburg, 2018 (Germany) (26)	Age, years [a] Infection (OR) MV (hr) [a] number of invasive catheters * Cumulative doses Drugs *	6.4 (5.7) vs 1.9 (2.8) (p<0.001) 2.68 (1.70–4.24) 14.3 (18.8) vs 55.2 (58.1) (p<0.001) Correlation: 0.352 (p<0.001) *	9.0 (1.6–51.0) (Infants) [d] 2.95 (1.0-8.7) [d] 1.43 (1.13-1.80) [d]
Mody, 2018 (USA) (28)	Delirious, day prior Benzodiazepines Opioids Restraints MV Coma status	27% vs 65% (p<0.001) 14% vs 38% (p<0.001) 14% vs 30% (p<0.001) 18% vs 18% (p<0.001) 12% vs 42% (p<0.001) ND	8.16 (5.67–11.74) [d] 2.02 (1.39–2.93) [d] 1.09 (0.75-1.59) [d] - 3.92 (2.59 – 5.92) [d] 0.85 (0.51–1.41) [d]
Nellis, 2018 (USA) (29)	RBC transfusion	6.28 (4.46-8.85) [d]	2.16 (1.4-3.4) [d]
Patel, 2017 (USA) (30)	Age (n, %) *- 0-2* *- 3-5* *- 6-13* *> 13* Developmental delay Cyanotic heart disease Restraint, yes (n, %) Respiratory support, MV (n, %) Benzo (n, %) Opioids (n, %)	 28 (28) vs 53 (56) (p<0.001) 25 (25) vs 23 (24) 18 (18) vs 11 (12) 28 (28) vs 8 (8) 9 (9) vs 21 (22) (p=0.021) 26 (26) vs 59 (62) (p<0.001) 134 (21) vs 265 (69) (p<0.001) 124 (19) vs 256 (67) (p<0.001) 158 (24) vs 201 (53) (p<0.001) 520 (82) vs 360 (95) (p<0.001)	 - ref - 0.30 (0.12-0.70) [d] - 0.30 (0.10-0.87) [d] - 0.06 (0.02-0.22) [d] 3.38 (1.18-9.66) [d] 2.43 (1.16-5.09) [d] - - - -

Author (Country)	Factors studied	Univariate OR (95%CI) or bivariate analyses/unadjusted (delirium free vs. delirium positive)	Multivariate OR (95%CI) or adjusted analysis
	Dexmed (n, %) Vasoprosessors (n, %) Rachs score	134 (21) vs 191 (50) (0<0.001) 67 (10) vs 94 (25) (p<0.001) -	- - 2.93 (1.32-6.50) [d]
Smith, 2017 (USA) (33)	Age PRISM Benzo (mg/kg/day; 0 vs 0.73)	0.51 (0.35–0.76) [d] 2.25 (1.28–3.94) [d] 2.25 (1.28–3.94) [d]	Risk PD following Day 2.83 (1.27–6.59) [d]
Traube, 2017a (United States, the Netherlands, New Zealand, Australia and Saudi Arabia) (37)	Age < 2yrs (n, %) MV (n, %) Benzo (n, %) Restraints (n, %) Opiates (n, %) Vasopressor (n, %) Antiepileptics (n, %) General anaesthesia (n, %)	236 (67.6) vs 113 (32.4) (p=0.049) 92 (47.4) vs 102 (52.6) (p<0.001) 136 (52.7) vs 122 (47.3) (p<0.001) 16 (27.6) vs 42 (72.4) (p<0.001) 231 (59.7) vs 156 (40.3) (p<0.001) 61 (50.3) vs 60 (49.6) (p<0.001) 59 (52.2) vs 54 (47.8) (p<0.001) 86 (78.9) vs 23 (21.1) (p<0.052)	0.7 (0.5-1.0) (> 2yrs) [d] 1.7 (1.1-2.7) [d] 2.2 (1.5-3.3) [d] 4.0 (2.0-7.7) [d] 2.3 (1.5-3.5) [d] 2.4 (1.5-3.8) [d] 2.9 (1.8-4.8) [d] 0.4 (0.3-0.8) [d]
Traube, 2017b (USA) (35)	Age ≤ 5 yrs (n, %) Diagnosis, brain tumor (n, %) Narcotics, yes (n, %) Benzodiazepines, yes (n, %) Steroids, yes (n, %) Postoperative status (n, %)	107 (82.2) vs 23 (17.7) (p=0.033) 24 (86.6) vs 11 (31.4) (p<0.001) 145 (83.3) vs 29 (16.7) (p=0.023) 100 (79.4) vs 26 (20.6) (p<0.001) 73 (81.1) vs 17 (18.9) (p=0.05) -	2.61 (1.12 – 6.08) [d] 4.72 (1.20 – 18.57) [d] 1.80 (0.74 – 4.35) [d] 3.71 (1.79 – 7.71) [d] - 3.27 (1.27 – 8.42) [d]
Traube, 2017c (USA) (36)	Age, yrs (n, %) *- 0-2 yrs* *- >2-5* *- >5-13* *- > 13* POM (n, %) *≤ 0.8%* *>0.8% and ≤1.4%* *> 1.4%* Pre-existing medical condition, yes (n, %) Developmental delay, yes (n, %) MV, yes (n, %) Coma, yes (n, %) Benzodiazepines, yes (n, %) Narcotics, yes (n, %) Vasoactive drug, yes (n, %) Corticosteroids, yes (n, %) Anticholinergic, yes (n, %) In-hospital mortality, yes (n, %)	 478 (37.3) vs 114 (42.7) (p=0.031) 253 (19.8) vs 64 (23.9) 298 (23.3) vs 52 (19.5) 251 (19.6) vs 37 (13.9) 465(36.3) vs 53 (19.9) (p<0.001) 440 (34.4) vs 69 (25.8) 375 (46.0) vs 145 (54.3) 857 (66.9) vs 211 (79.0) (p<0.001) 207 (16.2) vs 112 (41.9) (p<0.001) 455 (35.6) vs 187 (70.0) (p<0.001) 44 (3.4) vs 93 (34.8) (p<0.001) 255 (19.9) vs 188 (70.4) (p<0.001) 474 (37.0) vs 190 (71.2) (p<0.001) 48 (3.8) vs 61 (22.9) (p<0.001) 502 (39.2) vs 137 (51.3) (p<0.001) 907 (70.9) vs 235 (88.0) (p<0.001) 12 (0.9) vs 14 (5.2) (p<0.001)	 Reference 0.61 (0.39-0.94) [d] 0.41 (0.26-0.65) [d] 0.40 (0.24-0.64) [d] Reference 1.274 (0.83-1.98) [d] 1.531 (1.016-2.318) [d] - 3.314 (2.328-4.724) [d] 1.634 (1.155-2.314) [d] 4.244 (2.684-6.783) [d] 5.245 (3.710-7.455) [d] - - - 2.169 (1.412-3.416) [d] -
Silver 2015 (USA) (32)	Age, yrs (n, %) *0-2* *2-5* *5-13* *>13* Develop delay MV Deep sedation (RASS-3) PIM2 (severity of illness) [b]	 61 (30.7) vs 16 (30.2) 30 (15.1) vs 20 (37.8) 54 (27.1) vs 15 (28.3) 54 (27.1) vs 2 (3.8) (p<0.001) 41 (20.6) vs 27 (51.1) (p<0.001) 33 (16.6) vs 29 (54.7) (p<0.001) 4 (2.0) vs 11 (21.2) (p<0.001) 1.1 vs 2.8 (p=0.01)	 3.43 (0.70 – 16.78) [d] 8.80 (1.82 – 42.53) [d] 2.99 (0.58 – 15.41) [d] Reference 3.45 (1.54 – 7.76) [d] 3.86 (1.81 – 8.24) [d] - -
Schieveld, 2008 (Netherlands) (42)	Age [a] MV (n, %) PICU admission, neurological disorder (n, %) PRISM2 scores PIM	4.3 (4.8) vs 7.7 (5.8) (p<0.001) 333 (39.8) 34 (85) (p<0.001) 159 (19) vs 16 (40) (p=0.018) 4.9 (2.3-10.1) [c] 6.7 (3.0-15.0) [c]	ND

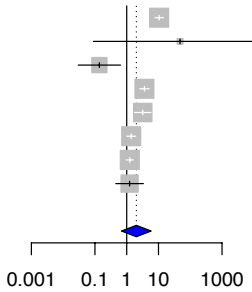
Legend: [a] mean±SD; [b] median (IQR); [c] RR – Risk Ratio; [d] OR – Odds Ratio; [e] IRR – Incidence Risk Ratio; [e] RRR Relative Risk Ratio; CI – confidence interval; ADS - Anticholinergic Drug Scale; CRP - C-reactive protein; PICU – Pediatric Intensive Care Unit; PCICU - Pediatric Cardiac Intensive Care Unit; Pros. – prospective; Retro. – retrospective; RBC – Red blood cell; ns – not significant; CPB time – Cardio Pulmonary Bypass time; POM – probability of mortality; MV – Mechanical ventilation; PRISM – Pediatric Risk of Mortality; PIM – Pediatric Index of Mortality; ND – no data; RASS – Richmond Agitation Sedation Score; RACHS - Risk Adjustment for Congenital Heart Surgery score; min – minutes; STAT - Society of Thoracic Surgeons – European Association for Cardio-Thoracic Surgery (STAT) score; TDD - total daily dose; AKI - acute kidney injury; PELOD - Pediatric Logistic Organ Dysfunction; ECMO - extracorporeal membrane oxygenation; CRRT - continuous renal replacement therapy**.**

SDC 6 – Forest plots

Age < 2 years

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Koth, 2021 (USA)	495	634	78	308	10.50	[7.64; 14.44]	15.4%
Flores, 2021 (Brazil)	5	5	31	60	47.72	[0.09; 25442.01]	1.4%
Gupta, 2020 (USA)	2	19	35	76	0.14	[0.03; 0.64]	9.9%
Dervan, 2020 (USA)	281	629	51	279	3.61	[2.56; 5.08]	15.3%
Patel, 2017 (USA)	53	95	28	99	3.20	[1.76; 5.81]	14.5%
Traube, 2017a (USA)	113	209	236	514	1.39	[1.00; 1.91]	15.4%
Traube, 2017c (USA)	114	267	478	1280	1.25	[0.96; 1.63]	15.5%
Silver, 2015 (USA)	8	21	26	78	1.23	[0.45; 3.34]	12.6%
Random effects model		**1879**		**2694**	**2.01**	**[0.69; 5.88]**	**100.0%**

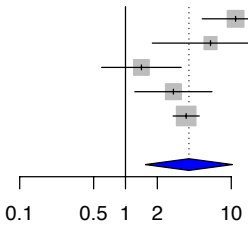
Heterogeneity: I^2 = 95% [92%; 97%], $p < 0.01$



Developmental delay

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Dervan, 2020 (USA)	154	629	8	279	10.98	[5.31; 22.70]	21.0%
Ramirez, 2019 (Colombia)	6	29	5	127	6.37	[1.79; 22.61]	12.7%
Meyburg, 2018 (Germany)	30	61	13	32	1.41	[0.60; 3.36]	18.5%
Patel, 2017 (USA)	21	95	9	99	2.84	[1.23; 6.57]	19.0%
Traube, 2017c (USA)	112	267	207	1280	3.75	[2.82; 4.98]	28.8%
Random effects model		**1081**		**1817**	**3.98**	**[1.54; 10.26]**	**100.0%**

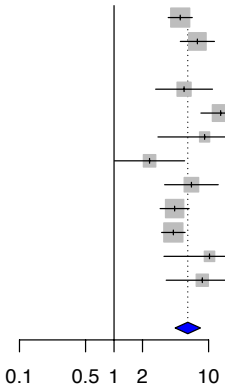
Heterogeneity: I^2 = 72% [29%; 89%], $p < 0.01$



Mechanical ventilation

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Koth, 2021 (USA)	483	634	120	308	5.01	[3.74; 6.72]	14.1%
Ge, 2021 (China)	93	200	45	439	7.61	[5.02; 11.53]	11.9%
Gupta, 2020 (USA)	19	19	76	76			0.0%
Staveski, 2020 (USA)	37	73	17	108	5.50	[2.75; 10.99]	7.7%
Dervan, 2020 (USA)	320	629	20	279	13.41	[8.29; 21.69]	10.8%
Ramirez, 2019 (Colombia)	9	29	6	127	9.07	[2.91; 28.27]	4.0%
Alvarez, 2018 (USA)	42	56	24	43	2.38	[1.01; 5.57]	6.0%
Patel, 2017 (USA)	77	95	39	99	6.58	[3.43; 12.64]	8.2%
Traube, 2017a (USA)	102	209	92	514	4.37	[3.07; 6.22]	13.0%
Traube, 2017c (USA)	187	267	455	1280	4.24	[3.18; 5.64]	14.2%
Silver, 2015 (USA)	12	21	9	78	10.22	[3.37; 30.98]	4.2%
Schieveld, 2008 (Netherlands)	34	40	333	837	8.58	[3.56; 20.65]	5.8%
Random effects model		**2272**		**4188**	**6.02**	**[4.43; 8.19]**	**100.0%**

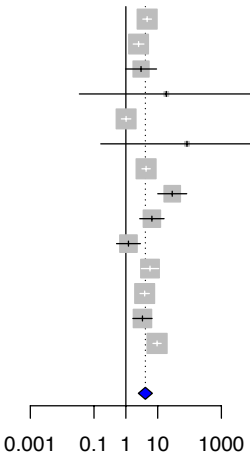
Heterogeneity: I^2 = 64% [31%; 81%], $p < 0.01$



Benzodiazepines

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Koth, 2021 (USA)	355	634	66	308	4.67	[3.41; 6.39]	9.4%
Ge, 2021 (China)	66	200	72	439	2.51	[1.70; 3.70]	9.2%
Yontem, 2021 (Turkey)	7	14	32	128	3.00	[0.98; 9.21]	6.1%
Flores, 2021 (Brazil)	5	5	44	60	18.62	[0.03; 9982.34]	0.5%
Traube, 2021 (USA)	85	161	378	722	1.02	[0.72; 1.43]	9.3%
Gupta, 2020 (USA)	19	19	53	76	83.09	[0.16; 42330.16]	0.5%
Dervan, 2020 (USA)	421	629	89	279	4.32	[3.20; 5.84]	9.4%
Ramirez, 2019 (Colombia)	23	29	15	127	28.62	[10.04; 81.60]	6.4%
Winsnes, 2019 (USA)	34	40	355	767	6.58	[2.73; 15.85]	7.1%
Alvarez, 2018 (USA)	40	56	29	43	1.21	[0.51; 2.86]	7.2%
Patel, 2017 (USA)	59	95	22	99	5.74	[3.06; 10.77]	8.2%
Traube, 2017a (USA)	122	209	136	514	3.90	[2.78; 5.46]	9.3%
Traube, 2017b (USA)	26	40	100	279	3.32	[1.66; 6.66]	8.0%
Traube, 2017c (USA)	188	267	255	1280	9.57	[7.11; 12.87]	9.5%
Random effects model		**2398**		**5121**	**4.10**	**[2.48; 6.80]**	**100.0%**

Heterogeneity: I^2 = 90% [85%; 93%], $p < 0.01$

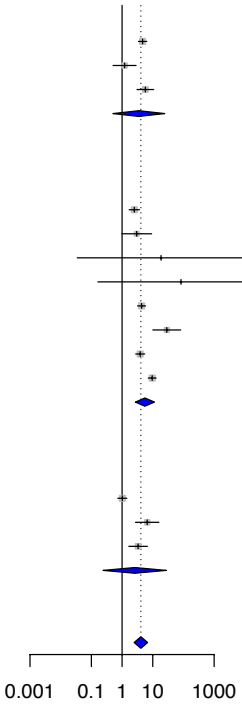


Subgroup analysis benzodiazepines

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Population = PCICU							
Koth, 2021 (USA)	355	634	66	308	4.67	[3.41; 6.39]	9.4%
Alvarez, 2018 (USA)	40	56	29	43	1.21	[0.51; 2.86]	7.2%
Patel, 2017 (USA)	59	95	22	99	5.74	[3.06; 10.77]	8.2%
Random effects model		**785**		**450**	**3.51**	**[0.50; 24.52]**	**24.8%**
Heterogeneity: I^2 = 79% [32%; 93%], $p < 0.01$							
Population = PICU							
Ge, 2021 (China)	66	200	72	439	2.51	[1.70; 3.70]	9.2%
Yontem, 2021 (Turkey)	7	14	32	128	3.00	[0.98; 9.21]	6.1%
Flores, 2021 (Brazil)	5	5	44	60	18.62	[0.03; 9982.34]	0.5%
Gupta, 2020 (USA)	19	19	53	76	83.09	[0.16; 42330.16]	0.5%
Dervan, 2020 (USA)	421	629	89	279	4.32	[3.20; 5.84]	9.4%
Ramirez, 2019 (Colombia)	23	29	15	127	28.62	[10.04; 81.60]	6.4%
Traube, 2017a (USA)	122	209	136	514	3.90	[2.78; 5.46]	9.3%
Traube, 2017c (USA)	188	267	255	1280	9.57	[7.11; 12.87]	9.5%
Random effects model		**1372**		**2903**	**5.55**	**[2.72; 11.32]**	**50.8%**
Heterogeneity: I^2 = 85% [72%; 92%], $p < 0.01$							
Population = Ped Onco							
Traube, 2021 (USA)	85	161	378	722	1.02	[0.72; 1.43]	9.3%
Winsnes, 2019 (USA)	34	40	355	767	6.58	[2.73; 15.85]	7.1%
Traube, 2017b (USA)	26	40	100	279	3.32	[1.66; 6.66]	8.0%
Random effects model		**241**		**1768**	**2.58**	**[0.24; 27.59]**	**24.4%**
Heterogeneity: I^2 = 90% [75%; 96%], $p < 0.01$							
Random effects model		**2398**		**5121**	**4.10**	**[2.48; 6.80]**	**100.0%**

Heterogeneity: I^2 = 90% [85%; 93%], $p < 0.01$

Test for subgroup differences: χ^2_2 = 1.78, df = 2 (p = 0.41)

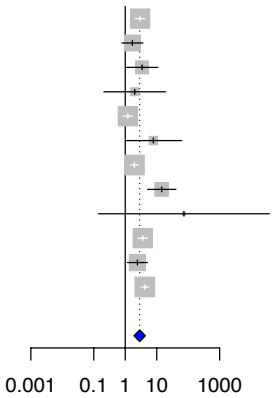


Legend: PCICU - pediatric cardiac intensive care unit; PICU - pediatric intensive care unit; Ped Onco - pediatric oncology

Opioids

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Koth, 2021 (USA)	571	634	232	308	2.97	[2.06; 4.29]	12.7%
Ge, 2021 (China)	12	200	16	439	1.69	[0.78; 3.64]	8.7%
Yontem, 2021 (Turkey)	6	14	23	128	3.42	[1.08; 10.82]	5.7%
Flores, 2021 (Brazil)	4	5	40	60	2.00	[0.21; 19.09]	2.1%
Traube, 2021 (USA)	102	161	424	722	1.22	[0.85; 1.73]	12.9%
Gupta, 2020 (USA)	18	19	53	76	7.81	[0.98; 62.05]	2.4%
Dervan, 2020 (USA)	448	629	156	279	1.95	[1.46; 2.62]	13.4%
Winsnes, 2019 (USA)	36	40	295	767	14.40	[5.07; 40.87]	6.4%
Patel, 2017 (USA)	95	95	92	99	73.31	[0.14; 37901.77]	0.3%
Traube, 2017a (USA)	156	209	231	514	3.61	[2.52; 5.15]	12.8%
Traube, 2017b (USA)	29	40	145	279	2.44	[1.17; 5.07]	9.0%
Traube, 2017c (USA)	190	267	474	1280	4.20	[3.15; 5.60]	13.4%
Random effects model		**2313**		**4951**	**2.88**	**[1.89; 4.37]**	**100.0%**

Heterogeneity: I^2 = 78% [62%; 87%], $p < 0.01$

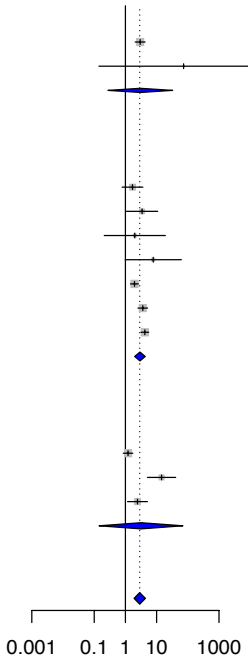


Subgroup analysis opioids

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Population = PCICU							
Koth, 2021 (USA)	571	634	232	308	2.97	[2.06; 4.29]	12.7%
Patel, 2017 (USA)	95	95	92	99	73.31	[0.14; 37901.77]	0.3%
Random effects model		**729**		**407**	**3.00**	**[0.28; 32.63]**	**13.0%**
Heterogeneity: I^2 = 1%, p = 0.32							
Population = PICU							
Ge, 2021 (China)	12	200	16	439	1.69	[0.78; 3.64]	8.7%
Yontem, 2021 (Turkey)	6	14	23	128	3.42	[1.08; 10.82]	5.7%
Flores, 2021 (Brazil)	4	5	40	60	2.00	[0.21; 19.09]	2.1%
Gupta, 2020 (USA)	18	19	53	76	7.81	[0.98; 62.05]	2.4%
Dervan, 2020 (USA)	448	629	156	279	1.95	[1.46; 2.62]	13.4%
Traube, 2017a (USA)	156	209	231	514	3.61	[2.52; 5.15]	12.8%
Traube, 2017c (USA)	190	267	474	1280	4.20	[3.15; 5.60]	13.4%
Random effects model		**1343**		**2776**	**2.92**	**[1.98; 4.32]**	**58.6%**
Heterogeneity: I^2 = 66% [24%; 85%], $p < 0.01$							
Population = Ped Onco							
Traube, 2021 (USA)	102	161	424	722	1.22	[0.85; 1.73]	12.9%
Winsnes, 2019 (USA)	36	40	295	767	14.40	[5.07; 40.87]	6.4%
Traube, 2017b (USA)	29	40	145	279	2.44	[1.17; 5.07]	9.0%
Random effects model		**241**		**1768**	**3.15**	**[0.14; 69.71]**	**28.3%**
Heterogeneity: I^2 = 90% [74%; 96%], $p < 0.01$							
Random effects model		**2313**		**4951**	**2.88**	**[1.89; 4.37]**	**100.0%**

Heterogeneity: I^2 = 78% [62%; 87%], $p < 0.01$

Test for subgroup differences: χ^2_2 = 0.02, df = 2 (p = 0.99)

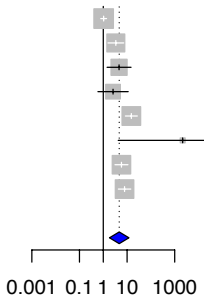


Legend: PCICU - pediatric cardiac intensive care unit; PICU - pediatric intensive care unit; Ped Onco - pediatric oncology

Physical restraints

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Koth, 2021 (USA)	238	634	113	308	1.04	[0.78; 1.38]	17.1%
Ge, 2021 (China)	192	200	385	439	3.37	[1.57; 7.22]	14.4%
Yontem, 2021 (Turkey)	9	14	36	128	4.60	[1.44; 14.66]	11.6%
Staveski, 2020 (USA)	5	73	3	108	2.57	[0.60; 11.12]	9.6%
Dervan, 2020 (USA)	267	629	13	279	15.09	[8.46; 26.92]	15.6%
Ramirez, 2019 (Colombia)	29	29	15	127	2160.34	[4.25; 1098893.87]	1.1%
Patel, 2017 (USA)	73	95	36	99	5.81	[3.10; 10.89]	15.3%
Traube, 2017a (USA)	42	209	16	514	7.83	[4.29; 14.29]	15.4%
Random effects model		**1883**		**2002**	**4.67**	**[1.82; 11.96]**	**100.0%**

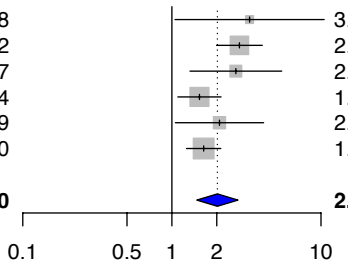
Heterogeneity: I^2 = 93% [89%; 96%], $p < 0.01$



Steroids

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Yontem, 2021 (Turkey)	9	14	45	128	3.32	[1.05; 10.50]	4.1%
Traube, 2021 (USA)	76	161	173	722	2.84	[1.99; 4.04]	23.0%
Winsnes, 2019 (USA)	29	40	380	767	2.68	[1.32; 5.45]	9.4%
Traube, 2017a (USA)	85	209	159	514	1.53	[1.10; 2.14]	24.3%
Traube, 2017b (USA)	17	40	73	279	2.09	[1.06; 4.12]	10.0%
Traube, 2017c (USA)	137	267	502	1280	1.63	[1.25; 2.13]	29.1%
Random effects model		**731**		**3690**	**2.02**	**[1.47; 2.77]**	**100.0%**

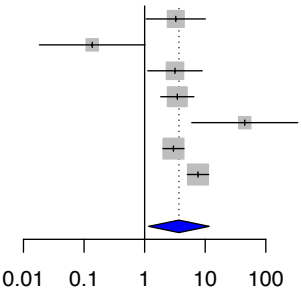
Heterogeneity: I^2 = 48% [0%; 80%], $p = 0.08$



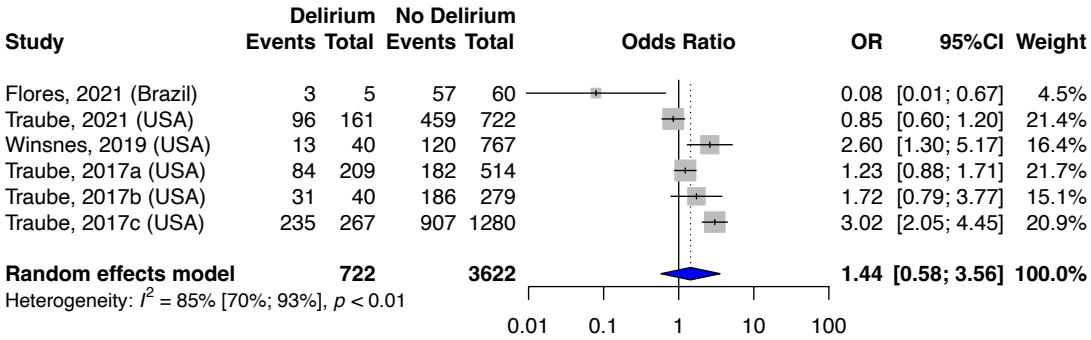
Vasoactive medication

Study	Delirium Events	Delirium Total	No Delirium Events	No Delirium Total	OR	95%CI	Weight
Yontem, 2021 (Turkey)	7	14	30	128	3.27	[1.06; 10.06]	13.2%
Flores, 2021 (Brazil)	3	5	55	60	0.14	[0.02; 1.02]	7.0%
Gupta, 2020 (USA)	11	19	23	76	3.17	[1.13; 8.91]	14.1%
Staveski, 2020 (USA)	40	73	28	108	3.46	[1.84; 6.51]	18.2%
Patel, 2017 (USA)	94	95	67	99	44.90	[5.99; 336.71]	7.0%
Traube, 2017a (USA)	60	209	61	514	2.99	[2.00; 4.47]	20.3%
Traube, 2017c (USA)	61	267	48	1280	7.60	[5.06; 11.41]	20.3%
Random effects model		**682**		**2265**	**3.68**	**[1.17; 11.60]**	**100.0%**

Heterogeneity: I^2 = 79% [56%; 90%], $p < 0.01$

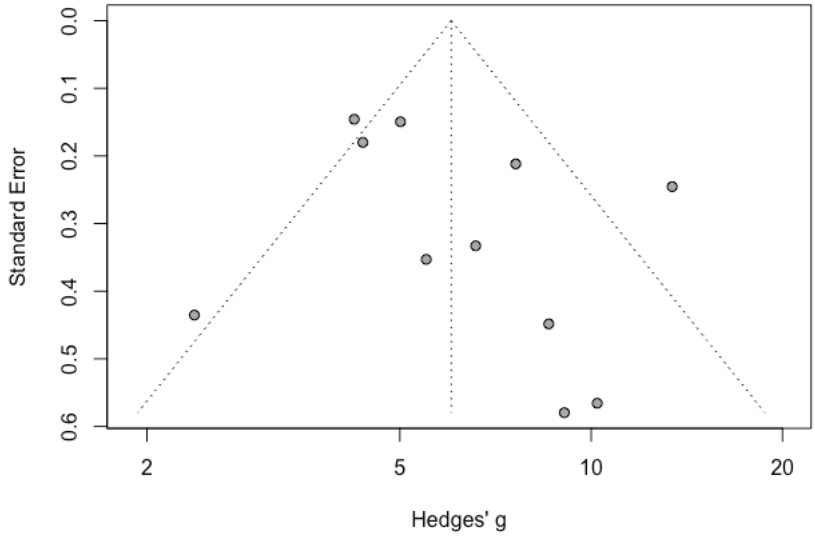


Anticholinergic drugs



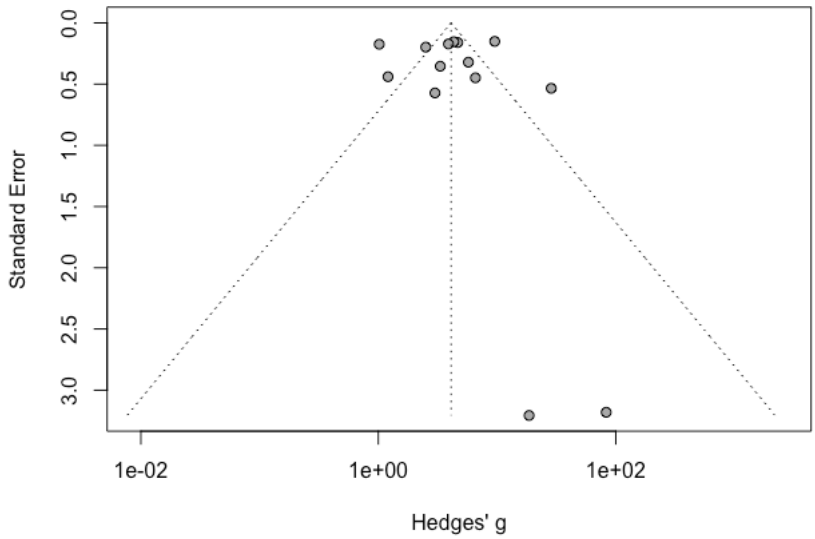
SDC 7 – Funnel plots

Mechanical ventilation



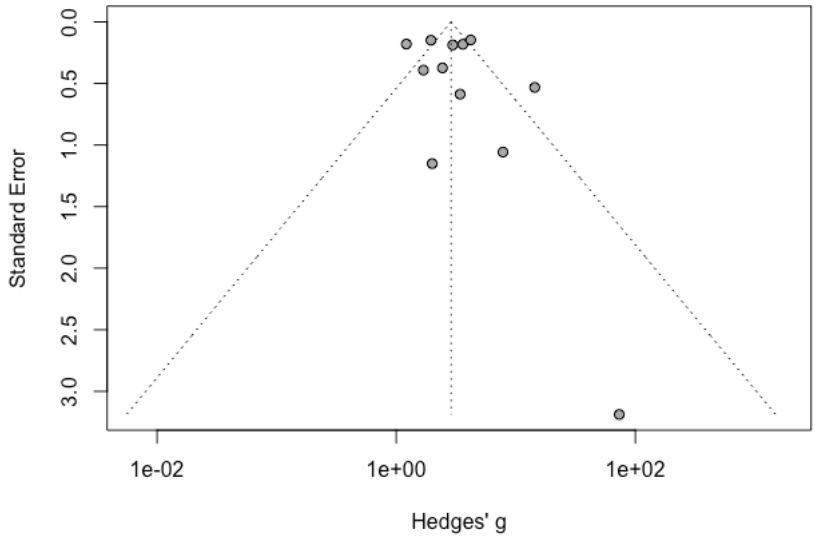
Egger's test: 1.338; p=0.270

Benzodiazepines



Egger's test: 0.419; p=0.805

Opioids



Egger's test: 0.807; p=0.488