Summary of findings tables, grading of the evidence and detailed conclusions of evidence nephrotoxicity surveillance

Who needs nephrotoxicity surveillance?

Outcome: decreased GFR

Chemotherapy

1.1 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1A Risk decreased GFR after ifosfamide (n= 11 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%; RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No ifosfamide adjusted mean 98 (85.00 - 112.00) Ifosfamide ≤ 16000 mg/m² adjusted mean 102 (86.00 - 117.00), p=0.42 Ifosfamide > 16000 mg/m² adjusted mean 88 (73.00 - 103.00), p=0.02	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019**	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* Ifosfamide vs. no ifosfamide HR 24.9 (7.4 - 83.5)	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM;	Cumulative incidence after 35 yr for late-onset kidney	*Odds ratio (95% CI) for late-onset kidney failure* Ifosfamide dose (g/m²) 0.1-59 vs none OR 2.4 (1.3-4.6)	SB: unclear AB: low risk DB: unclear CF: low risk

				Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	failure 1.7% (95% CI 0.1-0.4)	≥60 vs none OR 3.0 (1.0-9.2)	
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95% CI) for CKD stage 3-5* V5 model: OR ifosfamide dose (per 1000 mg/m^2) 1.04 (1.02-1.05) V10 model: OR ifosfamide dose (per 1000 mg/m^2) 1.04 (1.02-1.05) V15 model: OR ifosfamide dose (per 1000 mg/m^2) 1.04 (1.02-1.05) V20 model: OR ifosfamide dose (per 1000 mg/m^2) 1.04 (1.02-1.05)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Cumulative ifosfamide dose (per 10 g/ m²) OR 1.62 (1.44 -1.82) Mutually exclusive treatment group: Ifosfamide only vs. no nephrotoxic therapy OR 38.4 (11.0 - 134.4)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%;	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Ifosfamide vs. no ifosfamide OR 2.9 (1.9 – 4.4) Model cumulative dose: Ifosfamide (mg/m^2) ≤ 12000 vs none OR 1.2 (0.6 – 2.5) 12001 – 42000 vs none OR 3.2 (1.8 – 5.8)	SB: high risk AB: low risk DB: unclear CF: low risk

				Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%		>42000 vs none OR 6.4 (3.4 – 12.2) p-trend 0.006	
	Mudi 2016	130 CCS	Median 2 yr (range NM) after cancer treatment	Ifosfamide: NM, at least 1; Cisplatin: NM, at least 1; Carboplatin NM, at least 1; Nephrectomy: NM, at least 1; RT renal area: NM, at least 1	23/130 (17.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Ifosfamide vs. no ifosfamide OR 5.01 (1.46 - 17.17)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1%; RT renal area: 10.3%	GFR < 90 ml/minute/1.73m² Prevalence NM	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with ifosfamide (yes versus no)* Ifosfamide, p < 0.001 Ifosfamide cumulative dose effect p < 0.001 Ifosfamide by time interaction, p=0.32 Ifosfamide dose by time interaction, p=0.28	SB: low risk AB: low risk DB: unclear CF: low risk
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	39/181 (21.5%) GFR <90 ml/min/1.73m²	*Relative risk (95% CI) for decreased GFR* Ifosfamide dose (g/m²) RR 1.02 (0.99 - 10.04)	SB: low risk AB: low risk DB: unclear CF: low risk

	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* Ifosfamide p-value >0.25 in bivariate analyses, and therefore not included in MV analyses	SB: unclear AB: high risk DB: unclear CF: high risk
	Wu 2023**	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95% CI) for late kidney failure* Ifosfamide vs no ifosfamide RR 2.2 (1.4-4.1)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 6/11, unclear in 3/11, high in 2/11; Attrition bias low in 10/11, high in 1/11; Detection bias unclear in 11/11; Confounding low in 9/11, high in 2/11
Consistency:	0	No important inconsistency, 9 studies show increased risk after ifosfamide, 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in 2 studies (lower bound 95% CI > 2)
Dose-response:	+1	High-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with ifosfamide vs. no ifosfamide. (9 studies significant effect; 2 studies non-significant effect; 72,674 participants; at least 880 events; 11 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study cumulative incidence kidney transplantation; 2 studies cumulative incidence late-onset kidney failure; concerning GFR 6 studies GFR < 90 ml/min/1.73m², 2 studies GFR < 60 ml/min/1.73m²

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; FU, follow-up; GFR, glomerular filtration rate; HD, high-dose; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RR, risk ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

** Overlap in included studies of Dietz 2019, Dieffenbach 2021, and Wu 2023.

1.1 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1B Risk decreased GFR after higher vs. lower ifosfamide dose (n= 8 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%; RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No ifosfamide adjusted mean 98 (85.00 - 112.00) Ifosfamide ≤ 16000 mg/m² adjusted mean 102 (86.00 - 117.00), p=0.42 Ifosfamide > 16000 mg/m² adjusted mean 88 (73.00 - 103.00), p=0.02	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Ifosfamide dose (g/m²) 0.1-59 vs none OR 2.4 (1.3-4.6) ≥60 vs none OR 3.0 (1.0-9.2)	SB: unclear AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: OR ifosfamide dose (per 1000 mg/m²) 1.04 (1.02-1.05) V10 model: OR ifosfamide dose (per 1000 mg/m²) 1.04 (1.02-1.05) V15 model: OR ifosfamide dose (per 1000 mg/m²) 1.04 (1.02-1.05) V20 model: OR ifosfamide dose (per 1000 mg/m²) 1.04 (1.02-1.05)	SB: high risk AB: low risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Cumulative ifosfamide dose (per 10 g/ m²) OR 1.62 (1.44 - 1.82)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Model cumulative dose: Ifosfamide (mg/m²) ≤ 12000 vs none OR 1.2 (0.6 – 2.5) 12001 – 42000 vs none OR 3.2 (1.8 – 5.8) >42000 vs none OR 6.4 (3.4 – 12.2) p-trend 0.006	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1%; RT renal area: 10.3%	GFR < 90 ml/minute/1.73m² Prevalence NM	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with ifosfamide (yes versus no)* Ifosfamide cumulative dose effect p < 0.001 Ifosfamide dose by time interaction, p=0.28	SB: low risk AB: low risk DB: unclear CF: low risk
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%;	39/181 (21.5%) GFR <90 ml/min/1.73m²	*RR (95% CI) for decreased GFR* Ifosfamide dose (g/m²) RR 1.02 (0.99-10.04)	SB: low risk AB: low risk DB: unclear CF: low risk

				RT renal area: 0.01%; HSCT: 0%			
	Wu 2023**	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95% CI) for late kidney failure* Ifosfamide dose (g/m^2) 0.1-59 vs none RR 1.7 (1.0-3.5) ≥60 vs none RR 3.4 (1.2-9.5)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/8, high in 2/8, unclear in 2/8; Attrition bias low in 8/8; Detection bias unclear in 8/8; Confounding low in 8/8
Consistency:	0	No important inconsistency, 7 studies show increased risk after higher ifosfamide dose, 1 study show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found
Dose-response:	+1	High-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors after increasing doses of ifosfamide. (7 studies significant effect; 1 study non-significant effect; 58,309 participants; at least 609 events; 8 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 2 studies late-onset kidney failure, concerning GFR 4 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoetic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.
** Overlap in included patients in studies of Dieffenbach 2021 and Wu 2023.

1.1 C. What is the evidence for dose thresholds for a decreased glomerular filtration rate for CAYA cancer survivors treated with ifosfamide?

Ifosfamide dose (g/m^2)	**Dekkers 2013**	**Dieffenbach 2021**	**Kooijmans 2022**	**Wu 2023**	**Knijnenburg 2012**	**Green 2021**	**Conclusion (range)**

per 1 g/m^2						**OR 1.04 (1.02-1.05)**	n.a.
per 10 g/m^2					**OR 1.62 (1.44-1.82)**		n.a.
1-12 vs. 0			OR 1.2 (0.6 -2.5)				Not significant
1-16 vs. 0	Adjusted mean 102 (86.00 – 117.00) p= 0.42						Not significant
10					**OR 1.62 (1.44-1.82)**	**OR 1.48 (1.22-1.63)**	1.4-1.6 fold
12						**OR 1.60 (1.27-1.80)**	1.6 fold
14						**OR 1.73 (1.32-1.98)**	1.7 fold
1-59 vs. 0		**OR 2.4 (1.3-4.6)**		**RR 1.7 (1.0-3.5)**			1.7-2.4 fold
>16 vs. 0	**Adjusted mean 88 (73.0 – 103.0) p = 0.02**						n.a.
16					**OR 2.16 (1.79-2.61)**	**OR 1.87 (1.37-2.18)**	1.9-2.2 fold
18					**OR 2.38 (1.93-2.94)**	**OR 2.03 (1.43-2.41)**	2.0-2.4 fold
20					**OR 2.62 (2.07-3.31)**	**OR 2.19 (1.49-2.65)**	2.2-2.6 fold
25					**OR 3.35 (2.45-4.47)**	**OR 2.67 (1.64-3.39)**	2.7-3.4 fold
30					**OR 4.25 (2.99-6.03)**	**OR 3.24 (1.81-4.32)**	3.2-4.2 fold
35					**OR 5.41 (3.58-8.13)**	**OR 3.95 (1.99-5.52)**	3.9-5.4 fold
40					**OR 6.89 (4.30-10.97)**	**OR 4.80 (2.21-7.04)**	4.8-6.9 fold
12-42 vs. 0			**OR 3.2 (1.8 – 5.8)**				3.2 fold
>42 vs. 0			**OR 6.4 (3.4 – 12.2)**				6.4 fold
≥60 vs. 0		**OR 3.0 (1.0 – 9.2)**		**RR 3.4 (1.2-9.5)**			3.0-3.4 fold

Conclusions of evidence – high quality

Increased risk of decreased GFR in CAYA cancer survivors after increasing doses of ifosfamide.

Low risk (1.4-1.7 fold) after ifosfamide doses <16 g/m^2 (based on 4 studies: Dekkers 2013, Kooijmans 2022, Knijnenburg 2012, Green 2021)

Moderate to high risk (1.9-4.2 fold) after ifosfamide doses 16-40 g/m^2 (based on 3 studies: Kooijmans 2022, Knijnenburg 2012, Green 2021)

Moderate to high risk (≥3.0-6.9 fold) after ifosfamide doses ≥40 g/m^2 (based on 5 studies: Dieffenbach 2021, Kooijmans 2022, Wu 2023, Knijnenburg 2012, Green 2021)

1.2 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2A Risk decreased GFR after cisplatin (n=8 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No cisplatin adjusted mean 101 (89.00 - 113.00) Cisplatin ≤ 450 mg/m² adjusted mean 96 (82.00 - 109.00), p=0.54 Cisplatin > 450 mg/m² adjusted mean 83 (CI 66.00 - 100.00), p=0.004	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Cisplatin dose (mg/m²) 0.1-499 vs none OR 1.6 (0.8-2.9) ≥500 vs none OR 1.5 (0.7-3.0)	SB: unclear AB: low risk DB: unclear CF: low risk
	Dietz 2019**	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* Cisplatin in univariate analyses p-value >0.10 and therefore not included in MV model	SB: low risk AB: low risk DB: unclear CF: low risk

	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: OR cisplatin dose (per 100 mg/m^2) 1.44 (1.25-1.65) V10 model: OR cisplatin dose (per 100 mg/m^2) 1.44 (1.25-1.65) V15 model: OR cisplatin dose (per 100 mg/m^2) 1.43 (1.24-1.64) V20 model: OR cisplatin dose (per 100 mg/m^2) 1.43 (1.24-1.64)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m^2	*Odds ratio (95% CI) for decreased GFR* Cumulative cisplatin dose (per 100 mg/m^2) OR 1.29 (1.08 - 1.54) Mutually exclusive treatment group: Cisplatin only vs. no nephrotoxic therapy OR 8.9 (1.5 - 54.3)	SB: low risk AB: - GFR: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m^2	*Odds ratio (95% CI) for decreased GFR* Cisplatin vs. no cisplatin OR 1.6 (0.9 – 2.6) Model cumulative dose: Cisplatin (mg/m^2) ≤300 vs none OR 0.3 (0.1 – 0.9) 301-500 vs none OR 1.0 (0.4 – 2.5) >500 vs none OR 7.2 (3.4 – 15.2) p-trend 0.15	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%,	GFR < 90 ml/minute/1.73m^2 Prevalence NM	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with cisplatin (yes versus no)* Cisplatin, p < 0.001	SB: low risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%		Cumulative cisplatin dose effect, p < 0.001 Cisplatin by time interaction, p = 0.005 Cisplatin dose by time interaction, p < 0.001	
	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* Cisplatin p-value >0.25 in bivariate analyses, and therefore not included in MV analyses	SB: unclear AB: high risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/8, high in 2/8, unclear in 2/8; Attrition bias low in 7/8, high in 1/8; Detection bias unclear in 8/8; Confounding low in 7/8, high in 1/8
Consistency:	0	No important inconsistency, 3 studies show increased risk after cisplatin, 2 studies show increased risk after high cumulative dose cisplatin >500 mg/m^2, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, except for one outcome narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	Dose response relationship in four studies, of which three with overlap in included patients
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with cisplatin vs. no cisplatin, especially after cumulative dose >500 mg/m^2. (5 studies significant effect of whom 2 only after exposure to cumulative dose >500 mg/m^2; 3 studies non-significant effect; 46,848 participants; at least 614 events; 8 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study kidney transplantation, 1 study late-onset kidney failure; concerning GFR 4 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; FU, follow-up; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

** Overlap in included patietns of Dietz 2019 and Dieffenbach 2021.

1.2 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2B Risk decreased GFR after higher vs. lower cisplatin dose (n=6 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No cisplatin adjusted mean 101 (89.00 - 113.00) Cisplatin ≤ 450 mg/m² adjusted mean 96 (82.00 - 109.00), p=0.54 Cisplatin > 450 mg/m² adjusted mean 83 (CI 66.00 - 100.00), p=0.004	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Cisplatin dose (mg/m²) 0.1-499 vs none OR 1.6 (0.8-2.9) ≥500 vs none OR 1.5 (0.7-3.0)	SB: unclear AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: OR cisplatin dose (per 100 mg/m²) 1.44 (1.25-1.65) V10 model: OR cisplatin dose (per 100 mg/m²) 1.44 (1.25-1.65) V15 model: OR cisplatin dose (per 100 mg/m²) 1.43 (1.24-1.64) V20 model: OR cisplatin dose (per 100 mg/m²) 1.43 (1.24-1.64)	SB: high risk AB: low risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Cumulative cisplatin dose (per 100 mg/m²) OR 1.29 (1.08 - 1.54)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Model cumulative dose: Cisplatin (mg/m²) ≤300 vs none OR 0.3 (0.1 – 0.9) 301-500 vs none OR 1.0 (0.4 – 2.5) >500 vs none OR 7.2 (3.4 – 15.2) p-trend 0.15	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	GFR < 90 ml/minute/1.73m² Prevalence NM	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with cisplatin (yes versus no)* Cumulative cisplatin dose effect, p < 0.001 Cisplatin dose by time interaction, p < 0.001	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 3/6, high in 2/6, unclear in 1/6; Attrition bias low in 6/6; Detection bias unclear in 6/6; Confounding low in 6/6
Consistency:	0	No important inconsistency, 5 studies show increased risk after high-dose cisplatin, 1 study shows non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	Dose response relationship in four studies of which three with overlap in included patients
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors after increasing dose of cisplatin. (5 studies significant effect; 1study non-significant effect; 32,643 participants; at least 366 events; 6 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study late-onset kidney failure; concerning GFR 3 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; IQR, HSCT, hematopoetic stem cell transplantation; interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.2 C. What is the evidence for dose thresholds for a decreased glomerular filtration rate for CAYA cancer survivors treated with cisplatin?

Cisplatin dose (mg/m^2)	**Dekkers 2013**	**Dieffenbach 2021**	**Kooijmans 2022**	**Knijnenburg 2012**	**Green 2021**	**Conclusion (range)**
per 100 mg/m^2				**OR 1.29 (1.08-1.54)**	**OR 1.44 (1.25-1.65)**	n.a.
200				**OR 1.66 (1.17-2.37)**	**OR 2.07 (1.56-2.72)**	1.7-2.1 fold
300				**OR 2.15 (1.26-3.65)**	**OR 2.99 (1.95-4.49)**	2.2-3.0 fold
1-300 vs. 0			OR 0.3 (0.1 – 0.9)			Not significant
1-450 vs. 0	Adjusted mean 96 (82 – 109), p= 0.54					Not significant
1-499 vs. 0		OR 1.6 (0.8 – 2.9)				Not significant
301-500 vs. 0			OR 1.0 (0.4 – 2.5)			Not significant
>450 vs. 0	**Adjusted mean 83 (66 – 100), p= 0.004**					n.a.
400				**OR 2.77 (1.36-5.62)**	**OR 4.30 (2.44-7.41)**	2.8-4.3 fold
500				**OR 3.57 (1.47-8.66)**	**OR 6.19 (3.05-12.2)**	3.6-6.2 fold
>500 vs. 0			**OR 7.2 (3.4 – 15.2)**			7.2 fold
≥500 vs. 0		OR 1.5 (0.7 – 3.0)				Not significant

Conclusions of evidence – high quality

Increased risk of decreased GFR in CAYA cancer survivors after increasing dose of cisplatin.

Inconclusive evidence for the risk after cisplatin doses <400 mg/m^2 (based on 5 studies: Dekkers 2013, Dieffenbach 2021, Kooijmans 2022, Knijnenburg 2012, Green 2021)
Moderate to high risk (≥2.8-7.2 fold) after cisplatin doses ≥400 mg/m^2 (based on 2 studies: Knijnenburg 2012, Green 2021)
High risk (≥3.6-7.2 fold) after cisplatin doses ≥500 mg/m^2 (based on 3 studies: Kooijmans 2022, Knijnenburg 2012, Green 2021)

1.3 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3A Risk decreased GFR after carboplatin (n= 7 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11% RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No carboplatin adjusted mean 94 (81-106 Carboplatin adjusted mean 98 (81.00 - 115.00), p=0.50	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05 V10 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05 V15 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05 V20 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Cumulative carboplatin dose (per 100 mg/m²) OR 1.03 (1.00 - 1.07) Mutually exclusive treatment group: Carboplatin only vs. no nephrotoxic therapy OR 15.2 (1.5 - 155.5)	SB: low risk AB: low risk DB: unclear CF: low risk

				Nephrectomy: 14.7%; RT renal area: 8.7%			
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Carboplatin vs. no carboplatin OR 1.1 (0.6 – 2.0) Model cumulative dose: Carboplatin (mg/m²) ≤1500 vs none OR 1.1 (0.5 -2.6) 1501-2800 vs none OR 1.1 (0.5 – 3.0) >2800 vs none OR 1.3 (0.9 – 1.9) p-trend 0.90	SB: high risk AB: low risk DB: unclear CF: low risk
	Mudi 2016	130 CCS	Median 2 yr (range NM) after cancer treatment	Ifosfamide: NM, at least 1; Cisplatin: NM, at least 1; Carboplatin NM, at least 1; Nephrectomy: NM, at least 1; RT renal area: NM, at least 1	23/130 (17.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Carboplatin vs. no carboplatin OR 3.25 (0.83 - 12.59)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with carboplatin (yes versus no)* Carboplatin, p < 0.05 Cumulative carboplatin dose effect, p=0.28 Carboplatin by time interaction, p=0.003 Carboplatin dose by time interaction, p=0.26	SB: low risk AB: low risk DB: unclear CF: low risk

	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* Carboplatin p-value >0.25 in bivariate analyses, and therefore not included in MV analyses	SB: unclear AB: high risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/7, high in 2/7 unclear in 1/7; Attrition bias low in 6/7, high in 1/7; Detection bias unclear in 7/7; Confounding low in 5/7, high in 2/7
Consistency:	0	No important inconsistency, 3 studies show increased risk after carboplatin, 4 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	No significant dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with carboplatin vs. no carboplatin. (3 studies significant effect; 4 studies non-significant effect; 8,339 participants; at least 637 events; 7 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: concerning GFR 5 studies GFR < 90 ml/min/1.73m², 2 studies GFR < 60 ml/min/1.73m²

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.3 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3B Risk decreased GFR after higher vs. lower carboplatin dose (n=4 studies)	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%,	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: OR carboplatin dose (per 100 mg/m²) 1.03 (1.00 - 1.06), p<0.05 V10 model: OR carboplatin dose (per 100 mg/m²) 1.03 (1.00 - 1.06), p<0.05	SB: high risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%		V15 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05 V20 model: OR carboplatin dose (per 100 mg/m^2) 1.03 (1.00 - 1.06), p<0.05	
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Cumulative carboplatin dose (per 100 mg/m²) OR 1.03 (1.00 - 1.07)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Model cumulative dose: Carboplatin (mg/m^2) ≤1500 vs none OR 1.1 (0.5 -2.6) 1501-2800 vs none OR 1.1 (0.5 – 3.0) >2800 vs none OR 1.3 (0.9 – 1.9) p-trend 0.90	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1%;	GFR < 90 ml/minute/1.73m² Prevalence NM	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with carboplatin (yes versus no)* Cumulative carboplatin dose effect, p=0.28 Carboplatin dose by time interaction, p=0.26	SB: low risk AB: low risk DB: unclear CF: low risk

		RT renal area: 10.3%
GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 4/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 1 study shows significant effect, one study shows borderline significant effect (p=0.05), two studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size and high total number of events, narrow confidence intervals. Only 1 study reported a significant effect on GFR. Three studies have overlap in patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	No significant dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors after an increasing carboplatin dose. (1 study significant effect, 1 study borderline significant effect (p=0.05), 2 studies non-significant effect; 6,350 participants; at least 319 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: concerning GFR 3 studies GFR < 90 ml/min/1.73m^2 1 study GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoetic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.3 C. What is the evidence for dose thresholds for a decreased glomerular filtration for CAYA cancer survivors treated with carboplatin?

Dose (mg/m^2) vs none	Kooijmans 2022	Knijnenburg 2021	Green 2021	Conclusion (range)
per 100 mg/m^2		**OR 1.03 (1.00 – 1.07)**	**OR 1.03 (1.00 – 1.06)**	n.a.
1-1500	OR 1.1 (0.5 – 2.6)			Not significant
1500		**OR 1.56 (1.00 – 2.76)**	**OR 1.56 (1.00 – 2.40)**	1.6 fold
1501- 2800	OR 1.1 (0.5 – 3.0)			Not significant
2300		**OR 1.97 (1.00 – 4.74)**	**OR 1.97 (1.00 – 3.82)**	1.97 fold
2400		**OR 2.03 (1.00 – 5.07)**	**OR 2.03 (1.00 – 4.05)**	2.0 fold
2800		**OR 2.29 (1.00 – 6.65)**	**OR 2.29 (1.00 – 5.11)**	2.3 fold
>2800	OR 1.3 (0.9 -1.9)			Not significant

Conclusions of evidence – very low quality

Increased risk of decreased GFR in CAYA cancer survivors after an increasing carboplatin dose.

Low risk (<2 fold) after carboplatin doses <2400 mg/m^2 (based on 2 studies: Knijnenburg 2012, Green 2021)

Moderate risk (≥2.0 fold) after carboplatin doses ≥2400 mg/m^2 (based on 2 studies: Knijnenburg 2012, Green 2021)

1.4 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.4A Risk decreased GFR after methotrexate (n= 7 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%, details: intrathecal 29.8%, IV 30.9%, oral 32.8%; Unilateral nephrectomy 11%, RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No MTX adjusted mean 97 (84.00 - 110.00) MTX adjusted mean 95 (81.00 - 109.00), p=0.36	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* MTX vs. no MTX HR 0.6 (0.3 - 1.5)	SB: low risk AB: low risk DB: unclear CF: low risk

	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* HD-methotrexate not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* HD-MTX (yes vs no) (≥ 1 g/m² per course) OR 0.60 (0.19 - 1.85) Mutually exclusive treatment group: HD-MTX only OR 2.0 (0.4 - 11.8)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with HD-MTX* HD-MTX (≥ 1 g/m²/course) vs. no HD-MTX, p=0.91	SB: low risk AB: low risk DB: unclear CF: low risk
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%;	39/181 (21.5%) GFR <90 ml/min/1.73m²	*RR (95% CI) for decreased GFR* MTX p-value 0.6 in univariate analyses, and therefore not included in MV (RR 0.76 (0.27 - 2.15))	SB: low risk AB: low risk DB: unclear CF: low risk

				HSCT: 0%			
	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* MTX p-value >0.25 in bivariate analyses, and therefore not included in MV analyses	SB: unclear AB: high risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 5/7, high in 1/7, unclear in 1/7; Attrition bias low in 6/7, high in 1/7; Detection bias unclear in 7/7; Confounding low in 6/7, high in 1/7
Consistency:	0	No important inconsistency, 7 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		No significant effect of methotrexate on the risk of decreased GFR in CAYA cancer survivors. (7 studies non-significant effect; 20,498 participants; at least 427 events; 4 multivariable analyses and 3 studies not included in MV analyses based on uni-bivariate analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study cumulative incidence kidney transplantation; concerning GFR 4 studies GFR < 90 ml/min/1.73m², 2 studies GFR < 60 ml/min/1.73m²

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HR, hazard ratio; IQR, interquartile range; IV, intravenous; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Mulder 2013.

1.4 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias

1.4B Risk decreased GFR after higher vs. lower methotrexate dose (n= 2 studies)	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* HD-MTX (yes vs no) (≥ 1 g/m² per course) OR 0.60 (0.19 - 1.85) Mutually exclusive treatment group: HD-MTX only vs. no nephrotoxic therapy OR 2.0 (0.4 - 11.8)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with HD-MTX* HD-MTX (≥ 1 g/m²/course) vs. no HD-MTX, p=0.91	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	0	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2					
Consistency:	0	No important inconsistency, 2 studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effects in all studies					
Dose-response:	0	Unclear if dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊕ HIGH					
Conclusion:		No significant effect of methotrexate dose on the risk of decreased GFR in CAYA cancer survivors. (2 studies non-significant effect; 2,564 participants; at least 62 events; 2 multivariable analyses)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

* Overlap in included patients in studies of Knijnenburg 2012 and Mulder 2013.

1.4 C. What is the influence of different routes of administration for methotrexate on the risk of nephrotoxicity in CAYA cancer survivors?

No studies identified investigating the influence of different routes of administration for methotrexate on the risk of decreased GFR in childhood cancer survivors.

1.5 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with nitrosoureas?

No studies identified investigating the risk for nitrosoureas on the risk of decreased GFR in CAYA cancer survivors.

1.5 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of decreased GFR in CAYA cancer survivors.

1.6 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with melphalan?
No studies identified investigating the risk for melphalan on the risk of decreased GFR in CAYA cancer survivors.

1.6 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of melphalan?
No studies identified investigating the risk for melphalan on the risk of decreased GFR in CAYA cancer survivors.

1.7 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7A Risk decreased GFR after cyclophosphamide (n= 7 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No cyclophosphamide Adjusted mean 96 (82.00 - 110.00) Cyclophosphamide < 3500 mg/m² Adjusted mean 96 (83.00 - 110.00), p=0.98 Cyclophosphamide > 3500 mg/m² Adjusted mean 95 (81.00 - 109.00), p=0.74	SB: low risk AB: low risk DB: unclear CF: low risk

	Dietz 2019	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* Cyclophosphamide in univariate analyses p >0.10 and therefore not included in MV model	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* HD-cyclophosphamide not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* HD-cyclophosphamide (yes vs no) (≥1 g/m² per course) OR 7.08 (2.72 - 18.45) Mutually exclusive treatment group: HD-cyclophosphamide only vs no nephrotoxic therapy OR 0.58 (0.07 - 4.47)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%;	226/943 (24.0%)	*Odds ratio (95% CI) for decreased GFR*	SB: high risk AB: low risk

				Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	GFR < 90 ml/minute/1.73m²	HD-cyclophosphamide vs. no HD-cyclophoshamide OR 1.0 (0.6 – 1.7)	DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with HD-cyclophosphamide (yes versus no)* HD-cyclophosphamide (≥ 1 g/m²/ course or a total cumulative dose of ≥ 10 g/m²), p= 0.09 HD-cyclophosphamide by time interaction, p= 0.73	SB: low risk AB: low risk DB: unclear CF: low risk
	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* Cyclophosphamide vs no cyclophosphamide OR 0.69 (0.47 - 1.02)	SB: unclear AB: high risk DB: unclear CF: high risk
GRADE assessment:							

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/7, high in 2/7 unclear in 1/7; Attrition bias low in 6/7, high in 1/7; Detection bias unclear in 7/7; Confounding low in 6/7, high in 1/7
Consistency:	0	No important inconsistency, only 1 out of 7 studies (14.2%) shows significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effects was found in 1 study (lower bound 95% CI >2), but with very wide confidence intervals
Dose-response:	0	Low-quality of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		No significant effect of cyclophosphamide vs no cyclophosphamide on decreased GFR in CAYA cancer survivors after. (1 study significant effect, 6 studies non-significant effect; 21,348 participants; at least 614 events; 5 multivariable analyses and 2 studies not included in MV analyses based on univariate analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study cumulative incidence kidney transplantation; concerning GFR 4 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation;IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.7 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7B Risk decreased GFR after higher versus lower dose of cyclophosphamide (n= 1 study)	Dekkers 2013	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No cyclophosphamide Adjusted mean 96 (82.00 - 110.00) Cyclophosphamide < 3500 mg/m² Adjusted mean 96 (83.00 - 110.00), p=0.98 Cyclophosphamide > 3500 mg/m² Adjusted mean 95 (81.00 - 109.00), p=0.74	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with small number of events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found
Dose-response:	0	Unclear if a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of cyclophosphamide dose on the risk of decreased GFR in CAYA cancer survivors. (1 study non-significant effect; 763 participants; at least 21 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U-ACR, urinary albumin to creatinine ratio; yr, year.

1.8 What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.8 Risk decreased GFR after combination potential nephrotoxic chemotherapy (n= 3 studies)	Dieffenbach 2021	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Ref no ifosfamide or platinum: Platinum agent only OR 1.5 (0.8-2.7) Ifosfamide only OR 2.6 (1.2-5.7) Ifosfamide and platinum agent OR 3.8 (1.8-8.0)	SB: unclear AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%,	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment group: Platinum agents + ifosfamide vs. no nephrotoxic therapy OR 37.9, (10.0 - 144.2)	SB: low risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%			
	Kooijmans 2022*	1033 CCS 500 age- and sex matched controls general population	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment groups: Ifosfamide + HD-cyclophosphamide vs controls OR 1.7 (0.7 – 4.4) Ifosfamide + cisplatin vs controls OR 1.9 (0.8 – 4.5) Ifosfamide + carboplatin vs controls OR 4.0 (1.9 – 8.3) Cisplatin + carboplatin vs controls OR 1.0 (0.1 – 8.5)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	0	Limitations: Selection bias low in 1/3, high in 1/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3					
Consistency:	0	No important inconsistency, 3 studies show a significant effect, but 1 study only for the combination of ifosfamide + carboplatin.					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, large sample size, high total number of events, however in 1 study wide confidence intervals. Two studies have overlap in patients.					
Publication bias:	0	Unlikely					
Effect size:	0	Large magnitude of effect was found in one study (lower bound 95% CI >2), but with very wide confidence intervals.					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with a combination of platinum agents and ifosfamide vs. no nephrotoxic therapy. (3 studies significant effect; 28,005 participants; at least 288 events; 3 multivariable analyses)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; No, number; OR, odds ratio; ref, reference; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
* Overlap in included patients in studies of Knijnenburg 2012 and Kooijmans 2022.

1.9 What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus one of these agents alone?

No studies identified investigating the additive risk for the combination of chemotherapy vs. one of these agents alone on the risk of decreased GFR in CAYA cancer survivors.

Radiotherapy

1.10 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with radiotherapy exposing the renal area?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10A Risk decreased GFR after radiotherapy renal area (n= 9 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2% RT field: abdominal 6.2%, TBI 3.4%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No abdominal RT/nephrectomy adjusted mean 106 (95.00 - 119.00) Abdominal RT adjusted mean 96 (78.00 - 113.00), p =0.09	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Kidney dose from RT (Gy) 0.1-9.9 vs none OR 0.8 (0.5-1.3) 10-14.9 vs none OR 1.6 (0.8-3.3) ≥15 vs none OR 4.0 (2.1-7.4)	SB: unclear AB: low risk DB: unclear CF: low risk
	Dietz 2019**	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM;	Cumulative incidence after 35 yr for kidney transplantation or	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* RT renal area >0-10 Gy vs. none HR 0.4 (0.2 - 0.7)	SB: low risk AB: low risk DB: unclear CF: low risk

				Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	waiting list 0.49% (95% CI 0.36 - 0.62)	>10-15 Gy vs. none HR 1.6 (0.6 - 4.0) 15-20 Gy vs. none HR 3.6 (1.5 - 8.5) >20 Gy vs. none HR 4.6 (1.1 - 19.6)	
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy V5 (per 1%): OR 1.02 (1.01-1.02) V10 (per 1%): OR 1.02 (1.01-1.02) V15 (per 1%): OR 1.01 (1.00-1.02) (p>0.05) V20 (per 1%): OR 1.01 (0.99-1.03)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7% RT field: abdominal 7.1%, TBI 1.5%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Abdominal RT vs. no abdominal RT OR 1.50 (0.62 - 3.63) Mutually exclusive treatment group: RT only vs. no nephrotoxic therapy OR 4.5 (0.5 - 41.7)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%;	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Abdominal RT vs. no abdominal RT OR 1.8 (1.1 – 2.9) Model cumulative dose: Abdominal RT <20 Gy vs none OR 2.5 (1.2 – 5.1)	SB: high risk AB: low risk DB: unclear CF: low risk

				Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%		20-30 Gy vs none OR 1.0 (0.5 – 2.0) >30 Gy vs none OR 2.1 (1.1 – 3.8) p-trend 0.44	
	Mudi 2016	130 CCS	Median 2 yr (range NM) after cancer treatment	Ifosfamide: NM, at least 1; Cisplatin: NM, at least 1; Carboplatin NM, at least 1; Nephrectomy: NM, at least 1; RT renal area: NM, at least 1	23/130 (17.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* RT renal area vs. no RT renal area OR 3.31 (0.55 - 19.98)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3% RT field: abdominal 8.5%, TBI 1.9%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with RT renal area (yes versus no)* RT renal area, p=0.13	SB: low risk AB: low risk DB: unclear CF: low risk
	Wu 2023**	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95% CI) for late kidney failure* Abdominal RT vs. no abdominal RT RR 1.5 (1.0 – 2.3)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	0	Limitations: Selection bias low in 5/9, high in 2/9, unclear in 2/9; Attrition bias low in 9/9; Detection bias unclear in 9/9; Confounding low in 8/9, high in 1/9					

Consistency:	0	No important inconsistency, 5 studies show a significant effect of radiotherapy and 4 studies showed non-significant effects (of which 3 overlap in patients)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events
Publication bias:	0	Unlikely
Effect size:	0	Although 1 study found a large magnitude of effect (lower bound 95% CI > 2), no large magnitude of effects were found in the other studies
Dose-response:	0	Low-quality dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with radiotherapy to the renal area vs. no radiotherapy. (5 studies significant effect; 4 studies non-significant effect; 71,395 participants; at least 593 events; 9 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 2 studies cumulative incidence late-onset kidney failure, 1 study cumulative incidence kidney transplantation, concerning GFR 4 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoetic stem cell transplantation; IQR, interquartile range; mo, months; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RR, risk ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; V, volume; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.
** Overlap in included patients in studies of Dieffenbach 2021, Dietz 2019 and Wu 2023.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10A Risk decreased GFR after TBI (n= 5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2% RT field: abdominal 6.2%, TBI 3.4%	21/763 (2.8%) GFR < 60 ml/minute/1.73m^2	*Adjusted mean (95% CI) for GFR* No TBI adjusted mean 93 (81.00 - 106.00) TBI adjusted mean 99 (83.00 - 115.00), p=0.29	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%;	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* TBI vs. no RT renal area HR 6.9 (2.3 - 21.1)	SB: low risk AB: low risk DB: unclear CF: low risk

				Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%			
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7% RT field: abdominal 7.1%, TBI 1.5%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* TBI vs. no TBI OR 1.72 (0.20 - 15.13)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* TBI vs. no TBI OR 0.8 (0.4 – 1.6)	SB: high risk AB: low risk DB: unclear CF: low risk
	Van Why 1991	64 CCS	Mean 17 mo (range 2 mo - 11 yr)	Ifosfamide: NM, Cisplatin: NM, Carboplatin: NM, Nephrectomy: NM, RT renal area: 61% RT field: TBI 61%	18/64 (28%) after 60 days, 9/64 ((14%) persistent 3 mo - 3 yr GFR < 50 ml/minute/1.73m²	*Logistic regression analysis decreased GFR* Conditioning with TBI, p < 0.05	SB: low risk AB: low risk DB: unclear CF: high risk
GRADE assessment:							
Study design:	+4	Observational studies					

Study limitations:	0	Limitations: Selection bias low in 4/5, high in 1/5; Attrition bias low in 5/5; Detection bias unclear in 5/5; Confounding low in 4/5, high in 1/5
Consistency:	0	No important inconsistency, 2 studies show significant effects, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with TBI vs. no TBI. (2 studies significant effect; 3 studies non-significant effect; 16,441 participants; at least 327 events; 5 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 1 study cumulative incidence kidney transplantation, and concerning GFR 2 studies GFR < 90 ml/min/1.73m^2, 1 study GFR < 60 ml/min/1.73m^2, 1 study GFR < 50 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; mo, months; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.10 B. What is the risk of decreased GFR in CAYA cancer survivors who were treated with higher versus lower dose of radiotherapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10B Risk decreased GFR after higher vs. lower dose of radiotherapy renal area (n= 6 studies)	Dieffenbach 2021*	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Kidney dose from RT (Gy) 0.1-9.9 vs none OR 0.8 (0.5-1.3) 10-14.9 vs none OR 1.6 (0.8-3.3) ≥15 vs none OR 4.0 (2.1-7.4)	SB: unclear AB: low risk DB: unclear CF: low risk

	Dietz 2019*	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* RT renal area >0-10 Gy vs. none HR 0.4 (0.2 - 0.7) >10-15 Gy vs. none HR 1.6 (0.6 - 4.0) 15-20 Gy vs. none HR 3.6 (1.5 - 8.5) >20 Gy vs. none HR 4.6 (1.1 - 19.6)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy V5 (per 1%): OR 1.02 (1.01-1.02) V10 (per 1%): OR 1.02 (1.01-1.02) V15 (per 1%): OR 1.01 (1.00-1.02) (p>0.05) V20 (per 1%): OR 1.01 (0.99-1.03)	SB: high risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Model cumulative dose: Abdominal RT <20 Gy vs none OR 2.5 (1.2 – 5.1) 20-30 Gy vs none OR 1.0 (0.5 – 2.0) >30 Gy vs none OR 2.1 (1.1 – 3.8) p-trend 0.44	SB: high risk AB: low risk DB: unclear CF: low risk

	Poppe 2023	1191 CCS 13 studies included	Mean 8 – 15 years Wilms tumor studies Mean 4 monhs – 16 years TBI studies	WAI 4/13 studies TBI 8/13 studies Partial renal RT 1/13 studies	NA (meta-analysis)	*Risk of kidney dysfunction by RT dose and grade of toxicity according to national kidney foundation (NKF) grades* Total dose if given in 2 Gy per fx (95% CI) predicted to be associated with 5% rates of various levels of toxicity NKF grade ≥1 = 8.5 Gy (7.1 – 10.2) NKF grade ≥2= 10.2 Gy (9.3 – 11.2) NKF grade ≥3= 14.5 (12.2 – 19.0) Conventional Wilms WAI of 10.5 Gy in 6 fx had risks of ≥ grade 2 toxicity 4% and ≥ grade 3 toxicity 1%. Fractionated TBI of 12 Gy had risks of had risks of ≥ grade 2 toxicity 8% and ≥ grade 3 toxicity <3%.	NA (meta-analysis)
	Wu 2023*	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95% CI) for late kidney failure* Mean kidney radiation dose (Gy) 0.1-11.9 vs none RR 1.1 (0.7 – 1.5) ≥12 vs none RR 3.0 (1.7 – 5.3)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study and meta-analysis
Study limitations:	-1	Limitations: Selection bias low in 1/5, high in 2/5, unclear in 2/5; Attrition bias low in 5/5; Detection bias unclear in 5/5; Confounding low in 5/5. One study not applicable (meta-analysis)
Consistency:	0	No important inconsistency; 5 studies show significant effect of radiotherapy dose, 1 study shows non-significant effect for dose-response relationship.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals. Three studies have overlap in patients.
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect was found in one study for dose ≥15Gy (lower bound 95% CI >2)
Dose-response:	0	Low-quality dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors after increasing dose of radiotherapy, especially ≥15 Gy. (5 studies significant effect, 1 study non-significant effect; 69,129 participants; at least 487 events; 5 multivariable analyses and 1 meta-analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease DB, detection bias; HD, high-dose; HSCT, hematopoetic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; NKF, national kidney foundation; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; V, volume; yr, year; WAI, whole abdomen irradiation.
* Overlap in included patients in studies Dieffenbach 2021, Dietz 2019 and Wu 2023.

1.10 C. What is the risk of decreased GFR in CAYA cancer survivors who were treated with radiotherapy exposing one versus both kidneys?
No studies identified investigating the influence of radiotherapy exposing one versus both kidneys on the risk of decreased GFR in CAYA cancer survivors.

1.10 D. What is the evidence for dose thresholds for a decreased glomerular filtration for CAYA cancer survivors treated with radiotherapy exposing the renal area?

RT dose (Gy) vs. 0	Dieffenbach 2021	Dietz 2019	Green 2021	Kooijmans 2022	Wu 2023	Conclusion (range)
0.1-9.9	OR 0.8 (0.5 -1.3)	HR 0.4 (0.2 – 0.7)				Not significant
0.1 -11.9					RR 1.1 (0.7 – 1.5)	Not significant
1-20				**OR 2.5 (1.2 – 5.1)**		2.5 fold
≥5			**OR 1.02 (1.01 – 1.02) per 1% volume**			?
10-14.9	OR 1.6 (0.8 – 3.3)	HR 1.6 (0.6 – 4.0)				Not significant
≥10			**OR 1.02 (1.01 – 1.02) per 1% volume**			?
≥12					**RR 3.0 (1.7 -5.3)**	3.0 fold
15-20		**HR 3.6 (1.5 – 8.5)**				3.6 fold
≥15			OR 1.01 (1.00 – 1.02) per 1% volume			?
≥15	**OR 4.0 (2.1 – 7.4)**					4.0 fold
20-30				OR 1.0 (0.5 – 2.0)		Not significant
≥20			OR 1.01 (0.99 – 1.03) per 1% volume			?
>20		**HR 4.6 (1.1 – 19.6)**				4.6 fold
>30				**OR 2.1 (1.1 – 3.8)**		2.1 fold

Conclusions of evidence – high quality
Increased (moderate to high (≥2.1-4.6 fold)) risk of a decreased GFR in CAYA cancer survivors after increasing doses of radiotherapy, especially after ≥12 Gy.

1.11 What is the influence of the actual portion (e.g., hilum/pelvis vs cortex) of a single kidney irradiated on the risk of decreased GFR in CAYA cancer survivors?

No studies identified investigating the influence of the actual portion of a single kidney irradiated. However, one study identified investigating the volume of a kidney irradiated.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.11 Influence volume of kidney irradiated on risk decreased GFR (n= 1 study)	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy V5 (per 1%): OR 1.02 (1.01-1.02) V10 (per 1%): OR 1.02 (1.01-1.02) V15 (per 1%): OR 1.01 (1.00-1.02) (p-value >0.05) V20 (per 1%): OR 1.01 (0.99-1.03)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size, high total number of events, and narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Low-quality dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors with ≥5 or ≥10 Gy per % volume of kidney irradiated, but no significant effect of ≥15 or ≥20 Gy radiation. (1 study significant effect; 2753 participants; 57 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease DB, detection bias; HD, high-dose; IQR, interquartile range; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; V, volume; yr, year.

Nephrectomy

1.12 A. What is the risk of decreased GFR in CAYA cancer survivors who were treated with nephrectomy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.12A Risk decreased GFR after nephrectomy (n= 10 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX: 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No nephrectomy/no abdominal RT adjusted mean 106 (95.00 -119.00) Nephrectomy/ no abdominal RT, adjusted mean 91 (76.00 - 106.00), p <0.001	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Unilateral nephrectomy vs none OR 1.9 (1.0-3.4)	SB: unclear AB: low risk DB: unclear CF: low risk
	Dietz 2019**	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%;	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* Unilateral nephrectomy vs. no nephrectomy HR 4.2 (2.3 - 7.7)	SB: low risk AB: low risk DB: unclear CF: low risk

				TBI 1.6%			
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V (Gy) Nephrectomy only significantly increased the odds in MV models with volume of kidney irradiated ≥15Gy or ≥20 Gy V15 model: Nephrectomy (yes vs no) OR 3.55 (1.47-8.56) V20 model: Nephrectomy (yes vs no) OR 3.74 (1.56-8.94)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Nephrectomy (yes vs.no) OR 8.56 (3.42 - 21.42) Mutually exclusive treatment group: Nephrectomy only vs. no nephrotoxic therapy OR 19.3 (5.1 - 72.9)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Nephrectomy vs. no nephrectomy OR 3.7 (2.1 – 6.4)	SB: high risk AB: low risk DB: unclear CF: low risk

	Mudi 2016	130 CCS	Median 2 yr (range NM) after cancer treatment	Ifosfamide: NM, at least 1; Cisplatin: NM, at least 1; Carboplatin NM, at least 1; Nephrectomy: NM, at least 1; RT renal area: NM, at least 1	23/130 (17.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Nephrectomy vs. no nephrectomy OR 6.35 (1.84 - 21.89)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with nephrectomy (yes versus no)* Nephrectomy, p < 0.001 Nephrectomy by time interaction, p=0.002 Nephrectomy age at diagnosis, p= 0.29	SB: low risk AB: low risk DB: unclear CF: low risk
	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* Nephrectomy vs. no nephrectomy OR 3.68 (1.05 - 13.72)	SB: unclear AB: high risk DB: unclear CF: high risk
	Wu 2023**	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95%CI) for late kidney failure* Nephrectomy vs. no nephrectomy RR 2.9 (1.7 – 5.0)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment: Study design:	+4 Observational studies, meta-analysis						

Study limitations:	0	Limitations: Selection bias low in 5/10, high in 2/10, unclear in 3/10; Attrition bias low in 9/10, high in 1/10; Detection bias unclear in 10/10; Confounding low in 8/10, high in 2/10
Consistency:	0	No important inconsistency, all studies show significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in three studies (lower bound 95%CI >2)
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with nephrectomy vs. no nephrectomy. (10 studies significant effect ; 72,491 participants; at least 841 events; 10 multivariable analyses)
Comments:		Note differences in outcome definitions used for decreased GFR: 2 studies cumulative incidence late-onset kidney failure; 1 study cumulative incidence kidney transplantation, concerning GFR 5 studies GFR < 90 ml/min/1.73m^2, 2 studies GFR < 60 ml/min/1.73m^2)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; FU, follow-up; GFR, glomerular filtration rate; HD, high-dose; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RR; risk ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

** Overlap in included patients in studies of Dieffenbach 2021, Dietz 2019 and Wu 2023.

1.12b. What is the risk of decreased GFR in CAYA cancer survivors who were treated with unilateral versus partial (unilateral/bilateral) nephrectomy?
No studies identified investigating the influence of unilateral versus partial (unilateral/bilateral) nephrectomy on the risk of decreased GFR in CAYA cancer survivors.

Combination

1.13a. What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus no nephrotoxic therapy?

1.13b. What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus one of these modalities alone?

1.14a. What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.14A Risk decreased GFR after chemotherapy and radiotherapy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment group: RT [1] + chemotherapy[2] vs. no nephrotoxic therapy OR 21.7 (3.6 - 131.9)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	Although this study found a large magnitude of effect (lower bound 95% CI >2), there is only one study included so it's not sure if the effect size is truly large
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with a combination of RT[1] and chemotherapy[2] vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 62 events; 1 multivariable analysis)

Footnote 1: abdominal radiotherapy and/or total body irradiation
Footnote 2: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.14b. What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of chemotherapy and radiotherapy on the risk of decreased GFR in CAYA cancer survivors.

1.15a. What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.15A Risk decreased GFR after chemotherapy and nephrectomy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment group: Nephrectomy + chemotherapy [1] vs. no nephrotoxic therapy OR 108.6 (18.1 - 651.1)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	Although this study found a large magnitude of effect (lower bound 95% CI >2), there is only one study included so it's not sure if the effect size is truly large					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with a combination of nephrectomy and chemotherapy[1] vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 62 events; 1 multivariable analysis)					

Footnote 1: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.15b. What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of chemotherapy and nephrectomy on the risk of decreased GFR in CAYA cancer survivors.

1.16a. What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.16A Risk decreased GFR after radiotherapy and nephrectomy (n= 3 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No nephrectomy/ no abdominal RT adjusted mean 106 (95.00 - 119.00) Nephrectomy and abdominal RT Adjusted mean 90 (74.00 - 106.00), p<0.001	SB: low risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment group: Nephrectomy + RT [1] vs. no nephrotoxic therapy OR 22.0 (6.3 - 77.1)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS 500 age- and sex matched controls general population	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment groups: Nephrectomy + RT abdominal vs controls OR 3.1 (1.8 – 5.3)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment: Study design:	+4	Observational studies					

Study limitations:	0	Limitations: Selection bias low in 2/3; high in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, all studies show significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size, and high total number of events, however some wide confidence intervals. All studies have overlap in patients.
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect was found in one study (lower bound 95% CI >2), but with very wide confidence intervals
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with a combination of nephrectomy and RT to the renal area vs. no nephrotoxic therapy. (3 studies significant effect); 3238 participants; 309 events; 3 multivariable analyses)
Comments:		Note differences in used outcome definitions for decreased GFR: concerning GFR 2 studies GFR < 90 ml/min/1.73m^2, and 1 study GFR < 60 ml/min/1.73m^2

Footnote 1: abdominal radiotherapy and/or total body irradiation

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.16b. What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of radiotherapy and nephrectomy on the risk of decreased GFR in CAYA cancer survivors versus one of these modalities alone.

1.17a. What is the risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.17A Risk decreased GFR after chemotherapy, radiotherapy and nephrectomy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Mutually exclusive treatment group: Nephrectomy + chemotherapy [2] + RT [1] vs. no nephrotoxic therapy OR 125.6, (20.8 - 757.1)	SB: low risk AB: low risk DB: unclear CF: low risk

		Nephrectomy: 14.7%; RT renal area: 8.7%
GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	Although this study found a large magnitude of effect (lower bound 95% CI >2), there is only one study included so it's not sure if the effect size is truly large
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors treated with a combination of nephrectomy, radiotherapy[1] and chemotherapy[2] vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 62 events; 1 multivariable analysis)

Footnote 1: abdominal radiotherapy and/or total body irradiation
Footnote 2: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.17b. What is the additive risk of decreased GFR in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of chemotherapy, radiotherapy and nephrectomy on the risk of decreased GFR in CAYA cancer survivors.

1.18 What is the risk of decreased GFR in CAYA cancer survivors who were treated with stem cell transplant?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.18 Risk decreased GFR after SCT (n= 1 study)	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide:	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95%CI) for decreased GFR* SCT p-value >0.25 in bivariate analyses, and therefore not included in MV analyses	SB: unclear AB: high risk DB: unclear CF: high risk

		62.7%; Nephrectomy: 4.2%; RT renal area: NM
GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-3	Limitations: Selection bias unclear in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size, and high total number of events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of SCT on the risk of decreased GFR in CAYA cancer survivors. (1 study non-significant effect; 1096 participants; 248 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; NM, not mentioned; MTX, methotrexate; MV, multivariable; RT, radiotherapy; SB, selection bias; SCT, stem cell transplantation; yr, year.

Other risk factors

1.19 What is the influence of age at exposure on the risk of decreased GFR in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at ifosfamide treatment on risk decreased GFR (n= 1 study)	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	39/181 (21.5%) GFR <90 ml/min/1.73m^2	*RR (95% CI) for decreased GFR* Age at treatment (years) RR 1.08 (1.00 - 1.17)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (only 1 study)					

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with medium sample size, high total number of events, and narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of age at ifosfamide treatment on the risk of decreased GFR in CAYA cancer survivors. (1 study non-significant effect; 183 participants; 39 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; MV, multivariable; NM, not mentioned; RR, relative risk; RT, radiotherapy; SB, selection bias; yr, year.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at cisplatin treatment on risk decreased GFR (n= 1 study)	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 27 CCS treated with cisplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 100%; Carboplatin: 0%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	11/27 (40%) GFR <90 ml/min/1.73m^2	*Correlation for decreased GFR* After cisplatin, older age at treatment was correlated with lower GFR at 10 years (p = 0.005)	SB: low risk AB: low risk DB: unclear CF: high risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1					
Consistency:	0	Not applicable (only 1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study included with small sample size, high total number of events.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect was found in this study					
Dose-response:	0	Not applicable					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors aged older at cisplatin treatment. (1 study non-significant effect; 27 participants; 11 events; 1 risk analysis)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; MTX, methotrexate; NM, not mentioned; No, number; RT, radiotherapy; SB, selection bias.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at carboplatin treatment on risk decreased GFR (n= 1 study)	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 24 CCS treated with carboplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 100%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	5/24 (21%) GFR <90 ml/min/1.73m^2	*Correlation for decreased GFR* After carboplatin, older age at treatment was correlated with lower GFR at 10 years ($p < 0.03$)	SB: low risk AB: low risk DB: unclear CF: high risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1					
Consistency:	0	Not applicable (only 1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study included with small sample size and small number of events.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect was found in this study					
Dose-response:	0	Not applicable					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors aged older at carboplatin treatment. (1 study non-significant effect; 24 participants; 5 events; 1 risk analysis)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; MTX, methotrexate; NM, not mentioned; No, number; RT, radiotherapy; SB, selection bias.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at HD-MTX and cyclophosphamide treatment on risk decreased GFR (n= 1 study)	Yetgin 2004	116 CCS ALL	Median 35 months (range 18 - 96) after therapy. 48-132 months after diagnosis	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 0%; HD MTX: 100%**, Cyclophosphamide: 91%** Nephrectomy: 0%; RT renal area: 0%	22/116 (19.0%) GFR < 85 ml/minute/1.73m^2	*Risk (95% CI) for decreased GFR* Increased risk for age at diagnosis <2 yr vs ≥ 2 yr old 5.02 (1.58 - 15.89)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							

Study design:	+4	Observational study
Study limitations:	-1	Limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (only 1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with medium sample size, high total number of events, but wide confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors aged <2 yr vs. ≥ 2 yr at time of ALL treatment with HD-MTX and cyclophosphamide. (1 study significant effect; 116 participants; 22 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; MV, multivariable; NM, not mentioned; RT, radiotherapy; SB, selection bias; yr, year.
** Assumption based on treatment protocols.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at exposure on risk decreased GFR (n= 5 studies)	Dietz 2019**	13,139 CCS	Median NM FU until Dec 31 2013	Ifosfamide 0.5%; Cisplatin: 3.4%; Carboplatin: NM; Cyclophosphamide: 44.4%; MTX: 21,6%; Unilateral nephrectomy: 38% of kidney transplant pts; RT renal area: 65.9%; TBI 1.6%	Cumulative incidence after 35 yr for kidney transplantation or waiting list 0.49% (95% CI 0.36 - 0.62)	*Hazard ratio (95% CI) for kidney transplantation or being on waiting list* Age at diagnosis p >0.05, but confounder for other risk factors in MV model	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%;	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Age at initial cancer diagnosis (yr) 4-9 vs 0-3 OR 1.4 (0.9-2.0) 5-14 vs 0-3 OR 0.8 (0.5-1.5) ≥15 vs 0-3 OR 1.7 (0.9-3.3)	SB: unclear AB: low risk DB: unclear CF: low risk

				Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%			
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Age at diagnosis (in years) OR 1.05 (0.97 - 1.13)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Age at diagnosis (in years) OR 1.1 (1.06 - 1.2)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with potentially nephrotoxic therapy* Age at diagnosis, p < 0.0001 An older age at childhood cancer diagnosis was associated with a lower GFR	SB: low risk AB: low risk DB: unclear CF: low risk

				RT renal area: 10.3%		Nephrectomy age at diagnosis, p= 0.29	
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	0	Limitations: Selection bias low in 3/5, high in 1/5, unclear in 1/5; Attrition bias low in 5/5; Detection bias unclear in 5/5; Confounding low in 5/5					
Consistency:	-1	Some inconsistency, 2 studies show significant effect, 3 studies show non-significant effect					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, large sample size, low number of events,. Two studies shows a significant effect, but have overlap in patients.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect was found in all studies					
Dose-response:	0	Not applicable					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors with at an older age at cancer treatment. (2 studies significant effect, 3 studies non-significant effect; 42,266 participants; at least 288 events; 5 multivariable analyses)					
Comments:		Note differences in used outcome definitions for decreased GFR: 1 study late-onset kidney failure; 1 study kidney transplantation; concerning GFR 3 studies GFR < 90 ml/min/1.73m^2					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

** Overlap in included patietns of Dietz 2019 and Dieffenbach 2021.

1.20 What is the influence of sex on the risk of decreased GFR in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.20. Influence sex on risk decreased GFR after nephrotoxic therapy (n= 6 studies)	Dieffenbach 2021	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%;	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Male vs female OR 1.3 (0.9-1.9)	SB: unclear AB: low risk DB: unclear CF: low risk

				RT renal area: 48.4% Anthracycline: 41.0%			
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* Sex not included based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	62/1313 (4.7%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Male vs. female OR 38.4 (11.0 - 134.4)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Female vs. male OR 1.3 (0.9 – 1.9)	SB: high risk AB: low risk DB: unclear CF: low risk

	Mulder 2013*	1122 CCS	Median 21 yr (range 5.0 - 42.0) after cancer diagnosis until last GFR test	Ifosfamide: 13.8%; Cisplatin: 7.8%; Carboplatin: 5.7%; HD MTX: 22.5%, HD cyclophosphamide: 11.9% Nephrectomy: 13.1% RT renal area: 10.3%	Prevalence NM GFR < 90 ml/minute/1.73m²	*Predicted time trends in glomerular dysfunction probability (multivariable logistic regression model) for patients treated with potentially nephrotoxic therapy* Sex effect, p=0.63	SB: low risk AB: low risk DB: unclear CF: low risk
	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%; MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Female vs. male OR 0.65 (0.52 - 0.81)	SB: unclear AB: high risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/6, high in 2/6,unclear in 2/6; Attrition bias low in 5/6, high in 1/6; Detection bias unclear in 6/6; Confounding low in 5/6, high in 1/6
Consistency:	-1	Some inconsistency, 2 studies show significant effect, 4 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect was found in one study (lower bound 95% CI >2), but with very wide confidence intervals
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of decreased GFR in CAYA cancer survivors with male sex vs. female sex. (2 studies significant effect, 4 studies non-significant effect; 32,976 participants; at least 593 events; 6 multivariable analyses)
Comments:		Note differences in used outcome definitions for decreased GFR: 1 study late-onset kidney failure, 4 studies GFR < 90 ml/min/1.73m², 1 study GFR < 60 ml/min/1.73m²

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation;IQR, interquartile range; MTX, methotrexate; MV, multivariable NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
* Overlap in included patients in studies of Knijnenburg 2012, Kooijmans 2022 and Mulder 2013.

1.21 What is the influence of supportive care drugs (e.g., nephrotoxic antibiotics) on the risk of decreased GFR in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.21. Risk decreased GFR after potentially nephrotoxic supportive care drugs next to anticancer treatment (n= 4 studies)	Frisk 2002	40 CCS (26 TBI, 14 no TBI)	Median: 120 mo (group TBI +) Median: 54 mo (group TBI -)	Group TBI +: Ifosfamide: NM, Cisplatin: NM, Carboplatin: NM, MTX: NM, Cyclophosphamide: Yes, exact number NM Nephrectomy: NM, RT: 100%, RT field: TBI 100%	7/26 (27%) GFR < 70 ml/minute/1.73m²	*Bèta (95% CI) for decreased GFR* CCS treated with TBI: Concomitant treatment with aminoglycosides and vancomycin, Beta: 32mL/min/1.73m² (54 - 10), p < 0.01 CCS treated without TBI: Concomitant treatment with aminoglycosides and vancomycin, p=0.22	SB: low risk AB: high risk DB: unclear CF: high risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* V5 model: CNI ever (yes vs no) OR 4.60 (1.48-14.30) V10 model: CNI ever (yes vs no) OR 4.61 (1.42-14.92) V15 model: CNI ever (yes vs no) OR 17.51 (6.16-49.77) V20 model: CNI ever (yes vs no) OR 17.59 (6.18-50.05) Not included in MV model based on Elastic Net statistics: - Current use ACEI - Current use ARB - Aminoglycoside - Doses of abelcet/ambisome - Doses of amphotericin B	SB: high risk AB: low risk DB: unclear CF: low risk

	Van Why 1991	64 CCS	Mean 17 mo (range 2 mo - 11 yr)	Ifosfamide: NM, Cisplatin: NM, Carboplatin: NM, Nephrectomy: NM, RT renal area: 61% RT field: TBI 61%	18/64 (28%) after 60 days, 9/64 ((14%) persistent 3 mo - 3 yr GFR < 50 ml/minute/1.73m²	*Logistic regression analysis decreased GFR* Cyclosporin A use beyond day 60, p < 0.05 Amphotericin B use, p < 0.05	SB: low risk AB: low risk DB: unclear CF: high risk
	Yetgin 2004	116 CCS ALL	Median 35 months (range 18 - 96) after therapy. 48 - 132 months after diagnosis	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 0%; HD MTX: 100%*, Cyclophosphamide: 91%* Nephrectomy: 0%; RT renal area: 0%	22/116 (19.0%) GFR < 85 ml/minute/1.73m²	Use of nephrotoxic antimicrobials (not specified) not associated with adverse renal outcomes in univariate analysis and therefore not included in the MV model.	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 2/4, high in 2/4
Consistency:	0	No important inconsistency, 3 studies show significant effects, 1 study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, large sample size, high total number of events, however most confidence intervals not reported or very wide.
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect was found in 1 study, but with very wide confidence intervals
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	Increased risk of decreased GFR in CAYA cancer survivors treated with TBI and concomitant treatment with aminoglycosides and vancomycin vs. no TBI and concomitant treatment with aminoglycosides and vancomycin. (1 study significant effect for TBI; 1 study non-significant effect aminoglycosides in total cohort; 2793 participants; at least 38 events; 1 multivariable analysis, 1 not included in MV model based on Elastic Net statistics) Increased risk of decreased GFR in CAYA cancer survivors treated with calcineurin inhibitors. (2 studies significant effect; 2,817 participants; 49 events; 2 multivariable analyses) Increased risk of decreased GFR in CAYA cancer survivors treated with amphotericin B. (1 study significant effect, 1 study non-significant effect; 2817 participants; 178 events; 2 multivariable analyses)
Comments:	Note differences in used outcome definitions for decreased GFR: 1 study GFR < 85 ml/min/1.73m^2, 1 study GFR <70 ml/min/1.73m^2, 1 study GFR < 60 ml/min/1.73m^2, study GFR <50 ml/min/1.73m^2

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; ACEI, angiotensin converting enzyme inhibitor; ALL, acute lymphoblastic leukemia; ARB, angiotensin receptor blocker; CCS, childhood cancer survivors; CNI, calineurin inhibitor; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; mo, months; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

1.22 What is the influence of having hypertension on the risk of decreased GFR in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.22. Influence hypertension on risk decreased GFR after treatment potentially nephrotoxic therapy (n= 5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX: 41.8%; Unilateral nephrectomy: 11%; RT renal area: 6.2%	21/763 (2.8%) GFR < 60 ml/minute/1.73m²	*Adjusted mean (95% CI) for GFR* No hypertension, adjusted mean 96 (83.00 - 110.00) Hypertension at time of study, adjusted mean 96 (82.00 - 109.00), p=0.82	SB: low risk AB: low risk DB: unclear CF: low risk
	Dieffenbach 2021**	25,530 CCS	Median 22.4 years (IQR 17.4-28.8)	Ifosfamide: 4.6%; Cisplatin: 9.7%; Carboplatin: NM; Cyclophosphamide: NM; MTX: 19.3%; Unilateral nephrectomy: 7.8%; RT renal area: 48.4% Anthracycline: 41.0%	Cumulative incidence after 35 yr for late-onset kidney failure 1.7% (95% CI 0.1-0.4)	*Odds ratio (95% CI) for late-onset kidney failure* Hypertension during follow-up and no nephrectomy vs none OR 5.9 (3.3-10.5) Hypertension during follow-up and prior nephrectomy vs none OR 14.4 (7.1-29.4)	SB: unclear AB: low risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%,	57/2693 (2.1%) CKD stage 3-5	*Odds ratio (95%CI) for CKD stage 3-5* Hypertension at time of study not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%			
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	226/943 (24.0%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR* Hypertension at time of study vs. no hypertension OR 2.5 (1.6 – 3.9)	SB: high risk AB: low risk DB: unclear CF: low risk
	Wu 2023**	25,483 CCS	Median 22.2 yr (IQR 16.4 - 29.7)	Ifosfamide: 4.6%; Platinum: 9.9%; MTX: NM; Cyclophosphamide: NM; Nephrectomy: 7.2%; RT renal area: 21.0%	204/25,483 (0.8%) Late kidney failure	*Risk ratio (95% CI) for late kidney failure* Hypertension within 5 years of diagnosis vs. no hypertension OR 8.1 (4.3 – 15.6)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 1/5, high in 2/5, unclear in 2/5; Attrition bias low in 4/5, high in 1/5; Detection bias unclear in 5/5; Confounding low in 5/5
Consistency:	0	No important inconsistencies; 4 studies show significant effect, 1 study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, high total number of events, but somewide confidence intervals.
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effects was found in 2 studies (lower bound 95% CI >2)
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE

Conclusion:	Increased risk of decreased GFR in CAYA cancer survivors with hypertension (for both early onset and late onset hypertension). (3 studies significant effect, 2 studies non-significant effect; 55,532 participants; at least 437 events; 5 multivariable analyses)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RR, risk ratio; RT, radiotherapy; SB, selection bias; yr, year; TBI, total body irradiation.
* Overlap in included patients in studies of Dekkers 2013 and Kooijmans 2022.
** Overlap in included patients in studies of Dieffenbach 2021 and Wu 2023.

Outcome: proteinuria

Chemotherapy

1.1 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1A Risk proteinuria after ifosfamide (n= 5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%; RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Ifosfamide ≤ 16000 mg/m² vs. no ifosfamide OR 1.35 (0.34 - 5.33) Ifosfamide >16000 mg/m² vs. no ifosfamide OR 1.49 (0.49 - 4.54)	SB: low risk AB: High risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Ifosfamide not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative ifosfamide dose (per 10 g/m²) OR 1.34 (1.23 - 1.46) Mutually exclusive treatment group: Ifosfamide only vs. no nephrotoxic therapy OR 4.5 (2.44 - 8.31)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Ifosfamide vs. no ifosfamide OR 1.6 (1.01 – 2.4) *Model cumulative doses* Ifosfamide (mg/m²) ≤ 12000 vs none OR 0.6 (0.2 – 1.3) 12001 – 42000 vs none OR 1.9 (1.01 – 3.6) >42000 vs none OR 3.3 (1.7 – 6.2) p-trend 0.11	SB: high risk AB: low risk DB: unclear CF: low risk
	Ramirez 2016	773 CCS	Abnormal urinalysis group: mean 7.2 yr (range 2.9 - 13.3) after cancer diagnosis Normal urinalysis group: mean 7.6 yr (range 2.3 - 21.5) after cancer diagnosis	Ifosfamide: 12.3%; Cisplatin: 14.0%; Carboplatin: 12.0%; MTX: 52.9%, cyclophosphamide: 70.6% Nephrectomy: 39.2%; RT renal area: 28.7%	37/773 (4.8%) ≥ 1+ protein and/or presence of glucose and/or ≥ 5 red blood cells per high power field via urine dipstick or automated analysis	*Odds ratio (95% CI) for abnormal urinalysis* Ifosfamide <30 g/m² vs. no ifosfamide OR 0.5 (0.1 - 4.1) Ifosfamide ≥30 g/m² vs. no ifosfamide OR 6.8 (2.9 - 16.0)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 4/5, high in 1/5; Detection bias unclear in 5/5; Confounding low in 5/5
Consistency:	0	No important inconsistency, 3 studies show increased risk after ifosfamide, 2 studies show non-significant effects

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, , except for one outcome in 1 study narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in 2 studies (lower bound 95% CI > 2)
Dose-response:	+1	High-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with ifosfamide vs. no ifosfamide. (3 studies significant effect; 2 studies non-significant effect; 6,764 participants; 599 events; 4 multivariable analyses and 1 study not included in MV analyses based on Elastic Net statistics)
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 2 studies albuminuria based on dipstick, 1 study abnormal urinalysis

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; FU, follow-up; HD, high-dose; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.1 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1B Risk proteinuria after higher vs. lower ifosfamide dose (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%; RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Ifosfamide ≤ 16000 mg/m² vs. no ifosfamide OR 1.35 (0.34 - 5.33) Ifosfamide >16000 mg/m² vs. no ifosfamide OR 1.49 (0.49 - 4.54)	SB: low risk AB: High risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%,	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative ifosfamide dose (per 10 g/m²) OR 1.34 (1.23 - 1.46)	SB: low risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%			
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* *Model cumulative doses* Ifosfamide (mg/m²) ≤ 12000 vs none OR 0.6 (0.2 – 1.3) 12001 – 42000 vs none OR 1.9 (1.01 – 3.6) >42000 vs none OR 3.3 (1.7 – 6.2) p-trend 0.11	SB: high risk AB: low risk DB: unclear CF: low risk
	Ramirez 2016	773 CCS	Abnormal urinalysis group: mean 7.2 yr (range 2.9 - 13.3) after cancer diagnosis Normal urinalysis group: mean 7.6 years (range 2.3 - 21.5) after cancer diagnosis	Ifosfamide: 12.3%; Cisplatin: 14.0%; Carboplatin: 12.0%; MTX: 52.9%, cyclophosphamide: 70.6% Nephrectomy: 39.2%; RT renal area: 28.7%	37/773 (4.8%) ≥ 1+ protein and/or presence of glucose and/or ≥ 5 red blood cells per high power field via urine dipstick or automated analysis	*Odds ratio (95% CI) for abnormal urinalysis* Ifosfamide <30 g/m² vs. no ifosfamide OR 0.5 (0.1 - 4.1) Ifosfamide ≥30 g/m² vs. no ifosfamide OR 6.8 (2.9 - 16.0)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 3 studies show increased risk after higher ifosfamide dose, 1 stud shows non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, except for one outcome in 1 study narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	Although 1 study found a large magnitude of effect (lower bound 95% CI > 2), no large magnitude of effects were found in the other studies
Dose-response:	+1	High quality evidence of a dose response relationship

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors after increasing doses of ifosfamide. (3 studies significant effect; 1 study non-significant effect; 4,011 participants; 439 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 1 study albuminuria based on dipstick, 1 study abnormal urinalysis

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.1 C. What is the evidence for dose thresholds for proteinuria for CAYA cancer survivors treated with ifosfamide?

Ifosfamide dose (g/m^2)	**Dekkers 2013**	**Kooijmans 2022**	**Ramirez 2016**	**Knijnenburg 2021**	**Conclusion (range)**
per 10 g/m^2				**OR 1.34 (1.23 – 1.46)**	n.a.
1-12 vs. 0		OR 0.6 (0.2 – 1.3)			Not significant
1-16 vs. 0	OR 1.35 (0.34 – 5.33)				Not significant
1-29 vs. 0			OR 0.5 (0.1 – 4.1)		Not significant
12-42 vs. 0		**OR 1.9 (1.01 – 3.6)**			1.9 fold
16				**OR 1.60 (1.39 – 1.83)**	1.6 fold
>16 vs. 0	OR 1.49 (0.49 – 4.54)				Not significant
30				**OR 2.41 (1.86 – 3.11)**	2.4 fold
≥30 vs. 0			**OR 6.8 (2.9 – 16.0)**		6.8 fold
40				**OR 3.2 (2.29 – 4.54)**	3.2 fold
>42 vs. 0		**OR 3.3 (1.7 – 6.2)**			3.3 fold

Conclusions of evidence – high quality

Increased risk of proteinuria in CAYA cancer survivors after increasing doses of ifosfamide.
Low risk (1.6-1.9 fold) after ifosfamide doses <16 g/m^2 (based on 2 studies: Kooijmans 2022, Knijnenburg 2012)
Moderate to high risk (2.4-6.8 fold) after ifosfamide doses 16-30 g/m^2 (based on 2 studies: Ramirez 2016, Knijnenburg 2012)
Moderate to high risk (≥3.2 fold) after ifosfamide doses ≥40 g/m^2 (based on 2 studies: Kooijmans 2022, Knijnenburg 2012)

1.2 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2A Risk proteinuria after cisplatin (n=4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Cisplatin ≤ 450 mg/m² vs. no cisplatin OR 1.73 (0.44 - 6.85) Cisplatin > 450 mg/m² vs. no cisplatin OR 5.19 (1.21 - 22.21)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Cisplatinum not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative cisplatin dose (per 100 mg/m²) OR 0.95 (0.81 - 1.12) Mutually exclusive treatment group: Cisplatin only vs. no nephrotoxic therapy OR 2.20 (0.94- 5.14)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%;	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Cisplatin vs. no cisplatin OR 1.1 (0.6 – 1.9) *Model cumulative doses*	SB: high risk AB: low risk DB: unclear CF: low risk

				HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	Cisplatin (mg/m^2) ≤300 vs none OR 1.1 (0.4 – 2.6) 301-500 vs none OR 0.7 (0.3 – 2.0) >500 vs none OR 1.5 (0.7 – 3.6) p-trend 0.76		
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4					
Consistency:	0	No important inconsistency, 1 study shows increased risk after cisplatin, 3 studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, large sample size and high total number of events. Only 1 study reported a significant effect with wide confidence intervals while other studies with overlap in included patients don't show a significant effect					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effects in all studies					
Dose-response:	0	No clear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Inconclusive evidence for the effect of cisplatin on the risk of proteinuria in CAYA cancer survivors. (1 study significant effect in high-dose category; 3 studies non-significant effect; 5,991 participants; 562 events; 3 multivariable analyses and 1 study not included in MV analyses based on Elastic Net statistics)					
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 2 studies albuminuria based on dipstick					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; FU, follow-up; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.

* Overlap in included patients in studies of Dekkers 2013 and Knijnenburg 2012.

1.2 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2B Risk proteinuria after higher vs. lower cisplatin dose	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2)	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%;	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr	*Odds ratio (95% CI) for albuminuria* Cisplatin ≤ 450 mg/m² vs. no cisplatin OR 1.73 (0.44 - 6.85)	SB: low risk AB: high risk DB: unclear CF: low risk

(n=3 studies)			after cancer diagnosis	Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	(women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	Cisplatin > 450 mg/m² vs. no cisplatin OR 5.19 (1.21 - 22.21)	
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative cisplatin dose (per 100 mg/m²) OR 0.95 (0.81 - 1.12)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* *Model cumulative doses* Cisplatin (mg/m²) ≤300 vs none OR 1.1 (0.4 – 2.6) 301-500 vs none OR 0.7 (0.3 – 2.0) >500 vs none OR 1.5 (0.7 – 3.6) p-trend 0.76	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, 1 study shows increased risk after high-dose cisplatin, 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size and high total number of events, but only 1 study reported a significant effect with wide confidence intervals while other studies with overlap in included patients don't show a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects
Dose-response:	0	No clear dose response relationship

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Inconclusive evidence for the effect of cisplatin dose on the risk of proteinuria in CAYA cancer survivors. (1 study significant effect in high-dose category; 2 studies non-significant effect; 3,238 participants; 402 events; 3 multivariable analyses)
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 1 study albuminuria based on dipstick

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.3 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3A Risk proteinuria after carboplatin (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11% RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Carboplatin vs. no carboplatin OR 2.18 (0.45 - 10.54)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Carboplatin not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative carboplatin dose (per 100 mg/m²) OR 1.02 (1.00 - 1.04) Mutually exclusive treatment group: Carboplatin only vs. no nephrotoxic therapy OR 6.01 (2.21 - 16.35)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Carboplatin vs. no carboplatin OR 1.5 (0.8 – 2.6) *Model cumulative doses* Carboplatin (mg/m²) ≤1500 vs none OR 1.5 (0.6 – 3.6) 1501-2800 vs none OR 1.5 (0.6 – 3.9) >2800 vs none OR 1.4 (0.6 – 3.4) p-trend 0.10	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 1 study shows increased risk after carboplatin 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size and high total number of events, however some wide confidence intervals. Only 1 study reported a significant effect.
Publication bias:	0	Unlikely
Effect size:	0	Although 1 study found a large magnitude of effect (lower bound 95% CI > 2), no large magnitude of effects were found in the other studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding

Quality of evidence: ⊕⊖⊖⊖ VERY LOW

Conclusion: No significant effect of carboplatin on the risk of proteinuria in CAYA cancer survivors.
(1 study significant effect; 3 studies non-significant effect; 5,991 participants; 562 events; 3 multivariable analyses and 1 study not included in MV analyses based on Elastic Net statistics)

Comments: Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 2 studies albuminuria based on dipstick

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.3 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3B Risk proteinuria after higher vs. lower carboplatin dose (n=2 studies)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Cumulative carboplatin dose (per 100 mg/m²) OR 1.02 (1.00 - 1.04)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* *Model cumulative doses* Carboplatin (mg/m²) ≤1500 vs none OR 1.5 (0.6 – 3.6) 1501-2800 vs none OR 1.5 (0.6 – 3.9) >2800 vs none OR 1.4 (0.6 – 3.4) p-trend 0.10	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2					
Consistency:	0	No important inconsistency, both studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					

Precision:	-1	Some imprecision, 2 studies included with large sample size, high total number of events, and narrow confidence intervals. However studies have overlap in patients.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of carboplatin dose on the risk of proteinuria in CAYA cancer survivors. (2 studies non-significant effect;2,475 participants; 336 events; 2 multivariable analyses)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Knijnenburg 2012 and Kooijmans 2022.

1.4 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.4A Risk proteinuria after methotrexate (n= 3 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%, details: intrathecal 29.8%, IV 30.9%, oral 32.8%; Unilateral nephrectomy 11%, RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* MTX vs. no MTX OR 0.94 (0.49 - 2.16)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* HD-methotrexate not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk

				Nephrectomy: 7.4%; RT renal area: 16.0%			
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* HD-MTX (yes vs no) (≥ 1 g/m² per course) OR 1.37 (0.87 - 2.14) Mutually exclusive treatment group: HD-MTX only OR 1.59 (0.94 - 2.66)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		No significant effect of methotrexate on the risk of proteinuria in CAYA cancer survivors. (3 studies non-significant effect; 4,958 participants; 410 events; 2 multivariable analyses and 1 study not included in MV analyses based on Elastic Net statistics)
Comments:		Note differences in outcome definitions used for proteinuria: 1 study U-ACR, 2 studies albuminuria based on dipstick

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HR, hazard ratio; IQR, interquartile range; IV, intravenous; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013 and Knijnenburg 2012.

1.4 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias

1.4B Risk proteinuria after higher vs. lower methotrexate dose (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* HD-MTX (yes vs no) (≥ 1 g/m² per course) OR 1.37 (0.87 - 2.14) Mutually exclusive treatment group: HD-MTX only vs. no nephrotoxic therapy OR 1.59 (0.94 - 2.66)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, narrow confidence intervals. Only 1 study included
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of methotrexate dose on the risk of proteinuria in CAYA cancer survivors. (1 studiy non-significant effect; 1,442 participants; 184 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.4 C. What is the influence of different routes of administration for methotrexate on the risk of proteinuria in CAYA cancer survivors?
No studies identified investigating the influence of different routes of administration for methotrexate on the risk of proteinuria in childhood cancer survivors.

1.5 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of proteinuria in CAYA cancer survivors.

1.5 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of proteinuria in CAYA cancer survivors.

1.6 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with melphalan?

No studies identified investigating the risk for melphalan on the risk of proteinuria in CAYA cancer survivors.

1.6 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of melphalan?
No studies identified investigating the risk for melphalan on the risk of proteinuria in CAYA cancer survivors.

1.7 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7A Risk proteinuria after cyclophosphamide (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Cyclophosphamide < 3500 mg/m² vs. no cyclophosphamide OR 0.54 (0.21 - 1.39) Cyclophosphamide > 3500 mg/m² vs. no cyclophosphamide OR 0.84 (0.35 - 2.00)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* HD-cyclophosphamide not included in MV model based on Elastic Net statistics	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%,	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* HD-cyclophosphamide (yes vs no) (≥ 1 g/m² per course) OR 0.82 (0.43 - 1.57)	SB: low risk AB: low risk DB: unclear CF: low risk

				HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%		Mutually exclusive treatment group: HD-cyclophosphamide only vs no nephrotoxic therapy OR 0.58 (0.07 - 4.47)	
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* HD-cyclophosphamide vs. no HD-cyclophosphamide OR 0.8 (0.4 – 1.4)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4					
Consistency:	0	No important inconsistency, 4 studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, large sample size and high total number of events, narrow confidence intervals.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effects found in all studies					
Dose-response:	0	Unclear if dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of HD-cyclophosphamide (≥ 1 g/m² per course) on the risk of proteinuria in CAYA cancer survivors. (4 studies non-significant effect; 5,991 participants; 562 events; 3 multivariable analyses and 1 study not included in MV analyses based on Elastic Net statistics)					
Comments:		Note differences in outcome definitions used for proteinuria: 1 study cumulative incidence kidney transplantation; concerning GFR 3 studies GFR < 90 ml/min/1.73m², 2 studies GFR < 60 ml/min/1.73m²; and concerning proteinuria 2 studiea U-ACR, 2 studies albuminuria based on dipstick					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.7 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7B Risk proteinuria after higher versus lower dose of cyclophosphamide (n= 1 study)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Cyclophosphamide < 3500 mg/m² vs. no cyclophosphamide OR 0.54 (0.21 - 1.39) Cyclophosphamide > 3500 mg/m² vs. no cyclophosphamide OR 0.84 (0.35 - 2.00)	SB: low risk AB: High risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study included with small number of events.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect was found					
Dose-response:	0	Unclear if a dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		No significant effect of cyclophosphamide dose on the risk of proteinuria in CAYA cancer survivors. (1 study non-significant effect; 763 participants; 66 events; 1 multivariable analysis)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U-ACR, urinary albumin to creatinine ratio; yr, year.

1.8 What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias

1.8 Risk proteinuria after combination potential nephrotoxic chemotherapy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Mutually exclusive treatment group: Platinum agents + ifosfamide vs. no nephrotoxic therapy OR 2.12 (1.03 - 4.63)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size, high total number of events and narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with a combination of platinum agents and ifosfamide vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 184 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.9 What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus one of these agents alone?

No studies identified investigating the additive risk for the combination of chemotherapy vs. one of these agents alone on the risk of proteinuria in CAYA cancer survivors.

Radiotherapy

1.10 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with radiotherapy exposing the renal area?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias

1.10A Risk proteinuria after radiotherapy renal area (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2% RT field: abdominal 6.2%, TBI 3.4%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Abdominal RT no nephrectomy vs. no abdominal RT/nephrectomy OR 3.29 (0.69 - 15.67)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy V5 (per 1%): OR 1.00 (1.00-1.01) V10 (per 1%): OR 1.00 (1.00-1.01) V15 (per 1%): OR 1.01 (1.00-1.02) V20 (per 1%): OR 1.01 (1.00-1.03) All models p-value > 0.05	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7% RT field: abdominal 7.1%, TBI 1.5%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Abdominal RT vs. no abdominal RT OR 1.10 (0.57 - 2.16) Mutually exclusive treatment group: RT only vs. no nephrotoxic therapy OR 2.06 (0.74 - 5.73)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%;	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Abdominal RT vs. no abdominal RT OR 1.6 (0.96 - 2.8) *Model 2 cumulative doses*	SB: high risk AB: low risk DB: unclear CF: low risk

			HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	Abdominal RT <20 Gy vs none OR 1.2 (0.5 – 2.9) 20-30 Gy vs none OR 0.9 (0.3 – 2.1) >30 Gy vs none OR 2.6 (1.4 – 5.0) p-trend 0.001
GRADE assessment:				
Study design:	+4	Observational studies		
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4		
Consistency:	-1	Some inconsistency, three studies show non-significant effects, 1 study shows significant effect for cumulative dose >30 Gy.		
Directness:	0	Results are direct, population and outcomes broadly generalizable		
Precision:	-1	Some imprecision, large sample size and high total number of events, mostly narrow confidence intervals. Only 1 study with a significant effect.		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect in all studies		
Dose-response:	0	Unclear if dose response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖⊖ VERY LOW		
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors after cumulative dose >30 Gy of radiotherapy renal area.. (1 study significant effect for high cumulative dose, 3 studies non-significant effect; 5,991 participants; 562 events; 4 multivariable analyses)		
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 2 studies albuminuria based on dipstick		

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; mo, months; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; V, volume; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10A Risk proteinuria after TBI (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%,	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35	*Odds ratio (95% CI) for albuminuria* TBI vs. no TBI OR 3.28 (0.88 - 12.22)	SB: low risk AB: high risk DB: unclear CF: low risk

				RT renal area: 6.2% RT field: abdominal 6.2%, TBI 3.4%	mg/mmol Cr (women) and > 25 mg/mmol Cr (men)		
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7% RT field: abdominal 7.1%, TBI 1.5%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* TBI vs. no TBI OR 2.73 (0.95 - 7.90)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* TBI vs. no TBI OR 2.3 (1.2 – 4.4)	SB: high risk AB: low risk DB: unclear CF: low risk
	Ramirez 2016	773 CCS	Abnormal urinalysis group: mean 7.2 yr (range 2.9 - 13.3) after cancer diagnosis Normal urinalysis group: mean 7.6 yr (range 2.3 - 21.5) after cancer diagnosis	Ifosfamide: 12.3%; Cisplatin: 14.0%; Carboplatin: 12.0%; MTX: 52.9%, cyclophosphamide: 70.6% Nephrectomy: 39.2%; RT renal area: 28.7%, RT field: abdominal 28.7%, TBI 6.9%	37/773 (4.8%) ≥ 1+ protein and/or presence of glucose and/or ≥ 5 red blood cells per high power field via urine dipstick or automated analysis	*Odds ratio (95% CI) for abnormal urinalysis* TBI vs. no TBI OR 3.0 (1.0 - 8.4),p = 0.04	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 2 studies shows significant effects, 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with TBI vs. no TBI. (2 studies significant effect; 2 studies non-significant effect; 4,011 participants; at least 439 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 1 study albuminuria based on dipstick, 1 study abnormal urinalysis

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; mo, months; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.

* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.10 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with higher versus lower dose of radiotherapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10B Risk proteinuria after higher vs. lower dose of radiotherapy renal area (n= 2 studies)	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy) V5 (per 1%): OR 1.00 (1.00-1.01) V10 (per 1%): OR 1.00 (1.00-1.01) V15 (per 1%): OR 1.01 (1.00-1.02) V20 (per 1%): OR 1.01 (1.00-1.03) All models p-value > 0.05	SB: high risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%;	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* *Model 2 cumulative doses* Abdominal RT <20 Gy vs none OR 1.2 (0.5 – 2.9) 20-30 Gy vs none OR 0.9 (0.3 – 2.1)	SB: high risk AB: low risk DB: unclear CF: low risk

			HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	>30 Gy vs none OR 2.6 (1.4 – 5.0) p-trend 0.001
GRADE assessment:				
Study design:	+4	Observational study		
Study limitations:	-1	Limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2		
Consistency:	0	No important inconsistency, 1 study shows significant effect, 1 study shows non-significant effects		
Directness:	0	Results are direct, population and outcomes broadly generalizable		
Precision:	-1	Some imprecision, large sample size and high total number of events, narrow confidence intervals. Only 1 study reported a significant result.		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ LOW		
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors after cumulative dose >30 Gy of radiotherapy renal area. (1 study significant effect, 1 study non-significant effect; 3,786 participants; 312 events; 2 multivariable analyses) Note differences in outcome definitions used for proteinuria: 1 study U-ACR, 1 study albuminuria based on dipstick		

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; V, volume; yr, year.

1.10 C. What is the risk of proteinuria in CAYA cancer survivors who were treated with radiotherapy exposing one versus both kidneys?
No studies identified investigating the influence of radiotherapy exposing one versus both kidneys on the risk of proteinuria in CAYA cancer survivors.

1.10 D. What is the evidence for dose thresholds for proteinuria for CAYA cancer survivors treated with radiotherapy exposing the renal area?

RT dose (Gy) vs none	Green 2021	Kooijmans 2022
1-20		OR 1.2 (0.5 – 2.9)
≥5	OR 1.00 (1.00 – 1.01) per 1% volume	
≥10	OR 1.00 (1.00 – 1.01) per 1% volume	
≥15	**OR 1.01 (1.00 – 1.02) per 1% volume**	

20-30		OR 0.9 (0.3 – 2.1)
≥20	**OR 1.01 (1.00 – 1.03) per 1% volume**	
>30		**OR 2.6 (1.4 – 5.0)**

Conclusions of evidence – low quality

Increased (moderate (2.6 fold)) risk of proteinuria in CAYA cancer survivors after cumulative dose >30 Gy of radiotherapy to the renal area.

1.11 What is the influence of the actual portion (e.g., hilum/pelvis vs cortex) of a single kidney irradiated on the risk of proteinuria in CAYA cancer survivors?
No studies identified investigating the influence of the actual portion of a single kidney irradiated. However, one study identified investigating the volume of a kidney irradiated.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.11 Influence volume of kidney irradiated on risk proteinuria (n= 1 study)	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* Volume (%) radiated with respectively ≥5 ≥10 ≥15 or ≥20 Gy V5 (per 1%): OR 1.00 (1.00-1.01) V10 (per 1%): OR 1.00 (1.00-1.01) V15 (per 1%): OR 1.01 (1.00-1.02) V20 (per 1%): OR 1.01 (1.00-1.03) All models p-value >0.05	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, only 1 study included with large sample size, high total number of events, and narrow confidence intervals.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Low-quality dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of % volume of kidney irradiated on the risk of proteinuria in CAYA cancer survivors . (1 study non-significant effect; 2753 participants; 160 events; 1 multivariable analysis)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; IQR, interquartile range; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; V, volume; yr, year.

Nephrectomy

1.12 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with nephrectomy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.12A Risk proteinuria after nephrectomy (n= 4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX: 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Nephrectomy/no abdominal RT vs. no nephrectomy/no abdominal RT OR 2.12 (0.21 - 21.21)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* V5 model: Nephrectomy (yes vs. no) OR 2.21 (1.25-3.90) V10 model: Nephrectomy (yes vs. no) OR 2.21 (1.25-3.89) V15 model: Nephrectomy (yes vs. no) OR 2.37 (1.38-4.07) V20 model: Nephrectomy (yes vs. no) OR 2.36 (1.37-4.05)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Nephrectomy (yes vs. no) OR 1.70 (0.97 - 2.96) Mutually exclusive treatment group: Nephrectomy only vs. no nephrotoxic therapy OR 1.55 (0.77 - 3.09)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%;	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Nephrectomy vs. no nephrectomy OR 1.1 (0.6 - 1.9)	SB: high risk AB: low risk DB: unclear CF: low risk

		HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%
GRADE assessment:		
Study design:	+4	Observational studies, meta-analysis
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 1 study shows significant effects, 3 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Some imprecision, large sample size and high total number of events, however some wide confidence intervals. Only 1 study reported a significant effect.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of nephrectomy on the risk of proteinuria in CAYA cancer survivors. (1 study significant effect , 3 studies non-significant effect; 5,991participants; 562 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for proteinuria: 2 studies U-ACR, 2 studies albuminuria based on dipstick, 1 study albuminuria (not defined)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding;; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Knijnenburg 2012 and Kooijmans 2022.

1.12 B. What is the risk of proteinuria in CAYA cancer survivors who were treated with unilateral versus partial (unilateral/bilateral) nephrectomy?
No studies identified investigating the influence of unilateral versus partial (unilateral/bilateral) nephrectomy on the risk of proteinuria in CAYA cancer survivors.

Combination

1.13 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus no nephrotoxic therapy?
1.13 B. What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus one of these modalities alone?

1.14 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.14A Risk proteinuria after chemotherapy and radiotherapy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Mutually exclusive treatment group: RT [1] + chemotherapy [2] vs. no nephrotoxic therapy OR 1.76 (0.49 - 6.29)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, only 1 study included with large sample size, and high total number of events, and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of combined therapy with RT[1] and chemotherapy[2] vs. no nephrotoxic therapy on the risk of proteinuria in CAYA cancer survivors. (1 study non-significant effect; 1442 participants; 184 events; 1 multivariable analysis)

Footnote 1: abdominal radiotherapy and/or total body irradiation
Footnote 2: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.14 B. What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus one of these modalities alone?
No studies identified investigating the additive risk for the combination of chemotherapy and radiotherapy on the risk of proteinuria in CAYA cancer survivors.

1.15 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.15A Risk proteinuria after chemotherapy and nephrectomy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Mutually exclusive treatment group: Nephrectomy + chemotherapy [1] vs. no nephrotoxic therapy OR 6.67 (2.01 - 22.14)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	Although this study found a large magnitude of effects (lower bound 95% CI >2), there is only one study included so it's not sure if the effect size is truly large
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with a combination of nephrectomy and chemotherapy[1] vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 184 events; 1 multivariable analysis)

Footnote 1: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.15 B. What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of chemotherapy and nephrectomy on the risk of proteinuria in CAYA cancer survivors.

1.16 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.16A Risk proteinuria after radiotherapy and nephrectomy (n= 2 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8% Unilateral nephrectomy 11%, RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Nephrectomy and abdominal RT vs. no nephrectomy/ no abdominal RT OR 3.14 (1.02 - 9.69)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Mutually exclusive treatment group: Nephrectomy + RT [1] vs. no nephrotoxic therapy OR 2.01 (0.98 - 4.11)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 1/1, high in 1/1; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, 1 study shows significant effect, 1 study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, and high total number of events. Only one study reported a significant effect. The two studies have overlap in patients.
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect was found in both studies
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with a combination of nephrectomy and RT to the renal area vs. no nephrotoxic therapy. (1 study significant effect, 1 study non-significant); 2205 participants; 250 events; 2 multivariable analyses)
Comments:		Note differences in used outcome definitions for proteinuria: 1 study U-ACR, 1 study albuminuria based on dipstick

Footnote 1: abdominal radiotherapy and/or total body irradiation
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U-ACR, urinary albumin to creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013 and Knijnenburg 2012.

1.16 B. What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?
No studies identified investigating the additive risk for the combination of radiotherapy and nephrectomy on the risk of proteinuria in CAYA cancer survivors versus one of these modalities alone.

1.17 A. What is the risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.17A Risk proteinuria after chemotherapy, radiotherapy and nephrectomy (n= 1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Mutually exclusive treatment group: Nephrectomy + chemotherapy [2] + RT [1] vs. no nephrotoxic therapy OR 5.35 (1.27 - 22.63)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					

Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with a combination of nephrectomy, radiotherapy[1] and chemotherapy[2] vs. no nephrotoxic therapy. (1 study significant effect; 1442 participants; 184 events; 1 multivariable analysis)

Footnote 1: abdominal radiotherapy and/or total body irradiation
Footnote 2: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; MTX, methotrexate; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

1.17 B. What is the additive risk of proteinuria in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?
No studies identified investigating the additive risk for the combination of chemotherapy, radiotherapy and nephrectomy on the risk of proteinuria in CAYA cancer survivors.

1.18 What is the risk of proteinuria in CAYA cancer survivors who were treated with stem cell transplant?
No studies identified investigating the risk for stem cell transplant on the risk of proteinuria in CAYA cancer survivors.

Other risk factors

1.19 What is the influence of age at exposure on the risk of proteinuria in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19 Influence age at exposure on risk proteinuria (n= 3 studies)	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Age at diagnosis (in years) OR 1.02 (0.98 - 1.06)	SB: low risk AB: low risk DB: unclear CF: low risk

	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Age at diagnosis (in years) OR 1.0 (0.9 – 1.03)	SB: high risk AB: low risk DB: unclear CF: low risk
	Ramirez 2016	773 CCS	Abnormal urinalysis group: mean 7.2 yr (range 2.9 - 13.3) after cancer diagnosis Normal urinalysis group: mean 7.6 yr (range 2.3 - 21.5) after cancer diagnosis	Ifosfamide: 12.3%; Cisplatin: 14.0%; Carboplatin: 12.0%; MTX: 52.9%, cyclophosphamide: 70.6% Nephrectomy: 39.2%; RT renal area: 28.7%	37/773 (4.8%) ≥ 1+ protein and/or presence of glucose and/or ≥ 5 red blood cells per high power field via urine dipstick or automated analysis	*Odds ratio (95% CI) for abnormal urinalysis* Age 10-14 years at diagnosis vs. <5 years OR 0.7 (0.3 - 1.4)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, 3 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events, narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in all studies
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		No significant effect of age at diagnosis on the risk of proteinuria in CAYA cancer survivors.. (3 studies non-significant effect; 3,248 participants; 373 events; 3 multivariable analyses)
Comments:		Note differences in used outcome definitions for proteinuria: 1 study U-ACR, 1 study albuminuria based on dipstick and 1 study abnormal urinalysis

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection biasHD, high-dose; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
* Overlap in included patients in studies of Knijnenburg 2012 and Kooijmans 2022.

1.20 What is the influence of sex on the risk of proteinuria in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.20 Influence sex on risk proteinuria after nephrotoxic therapy (n= 3 studies)	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* V5 model: Male vs. female OR 1.43 (1.00-2.04), p=0.05 V10 model: Male vs. female OR 1.43 (1.00-2.04), p =0.05 V15 model: Male vs. female OR 1.42 (1.00-2.03), p=0.05 V20 model: Male vs. female OR 1.41 (0.99-2.01)	SB: high risk AB: low risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	184/1269 (14.5%) Albuminuria based on dipstick	*Odds ratio (95% CI) for albuminuria* Male vs. female OR 0.80 (0.58 - 1.11)	SB: low risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%;	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Female vs. male OR 1.0 (0.6 – 1.4)	SB: high risk AB: low risk DB: unclear CF: low risk

			HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%
GRADE assessment:			
Study design:	+4	Observational studies	
Study limitations:	-1	Limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3	
Consistency:	0	No important inconsistency, 2 studyies show non-significant effect, 1 study shows borderline non-significant effect (p=0.05)_	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	0	No important imprecision, large sample size, and high total number of events, narrow confidence intervals	
Publication bias:	0	Unlikely	
Effect size:	0	No large magnitude of effect was found in both studies	
Dose-response:	0	Not applicable	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⊕⊕⊕⊖ MODERATE	
Conclusion:		No significant effect of sex on the risk of proteinuria in CAYA cancer survivors. (2 studies non-significant effect, 1 study borderline non-significant effect (p=0.05); 5,228 participants; at least 496 events; 3 multivariable analyses)	
Comments:		Note differences in used outcome definitions for proteinuria: 2 studies albuminuria based on dipstick and 1 study U-ACR	

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

* Overlap in included patients in studies of Knijnenburg 2012 and Kooijmans 2022.

1.21 What is the influence of supportive care drugs (e.g., nephrotoxic antibiotics) on the risk of proteinuria in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.21 Risk proteinuria after potentially nephrotoxic supportive care	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%,	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* V5 model: doses of abelcet/ambisome (per dose) OR 1.03 (0.99-1.06) V10 model: doses of abelcet/ambisome (per dose) OR 1.03 (0.99-1.06)	SB: high risk AB: low risk DB: unclear CF: low risk

drugs next to anticancer treatment (n= 1 study)		HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	V15 model: doses of abelcet/ambisome (per dose) OR 1.03 (1.00-1.06), p > 0.05 V20 model: doses of abelcet/ambisome (per dose) OR 1.03 (1.00-1.06), p > 0.05 V5 model: Doses of amphotericin B (per dose) OR 1.02 (1.00-1.04), p < 0.05 V10 model: Doses of amphotericin B (per dose) OR 1.02 (1.00-1.04), p < 0.05 V15 model: Doses of amphotericin B (per dose) OR 1.02 (1.01-1.04) V20 model: Doses of amphotericin B (per dose) OR 1.02 (1.01-1.04) Not included in MV model based on Elastic Net statistics: - Current use ACEI - Current use ARB - Aminoglycoside
GRADE assessment:			
Study design:	+4	Observational studies	
Study limitations:	-1	Limitations: Selection high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1	
Consistency:	0	Not applicable (1 study)	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	-1	Some imprecision, large sample size, high total number of events, however only 1 study included.	
Publication bias:	0	Unlikely	
Effect size:	0	No large magnitude of effect was found	
Dose-response:	0	Not applicable	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⊕⊕⊖⊖ LOW	
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors treated with amphotericin B. (1 study significant effect; 2,753 participants; 160 events; 1 multivariable analysis). No significant effect of abelcet/ambisome, current use ACEI, ARB or aminoglycoside on the risk of proteinuria in CAYA cancer survivors. (1 study non-significant effect; 2,753 participants; 160 events; 1 multivariable analysis or not included in MV analyses based on Elatic Net Statistics).	

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HD, high-dose; mo, months; MTX, methotrexate; MV, multivariable; No, number; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

1.22 What is the influence of having hypertension on the risk of proteinuria in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.22 Influence hypertension on risk proteinuria after treatment potentially nephrotoxic therapy (n= 3 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX: 41.8%; Unilateral nephrectomy: 11%; RT renal area: 6.2%	56/496 (11.3%) Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) 10/496 (2.0%) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	*Odds ratio (95% CI) for albuminuria* Hypertension at time of study vs. no hypertension OR 1.71 (0.86 - 3.40)	SB: low risk AB: high risk DB: unclear CF: low risk
	Green 2021	2753 CCS	Median 23.2 yr (IQR 17.6-29.7) after cancer diagnosis	Ifosfamide: 7.1%; Cisplatin: 8.0%; Carboplatin: 4.9%; HD MTX: 27.1%, HD cyclophosphamide: 33.9% Nephrectomy: 7.4%; RT renal area: 16.0%	160/2693 (5.9%) Proteinuria A2-A3 (based on dipstick)	*Odds ratio (95%CI) for proteinuria A2-A3* V5 model: Hypertension at time of study grade ≥2 vs <2 OR 2.62 (1.81-3.79) V10 model: Hypertension at time of study grade ≥2 vs <2 OR 2.62 (1.81-3.79) V15 model: Hypertension at time of study grade ≥2 vs <2 OR 2.63 (1.82-3.81) V20 model: Hypertension at time of study grade ≥2 vs <2 OR 2.61 (1.80-3.77)	SB: high risk AB: low risk DB: unclear CF: low risk
	Kooijmans 2022*	1033 CCS	Median 25.6 yr (IQR 21.1 – 30.1)	Ifosfamide: 29.1%; Cisplatin: 17.0%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 27.0%; Nephrectomy: 26.3%; RT renal area: 17.4%; TBI: 8.3% HSCT: 9.3%	152/943 (16.4%) Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol)	*Odds ratio (95% CI) for albuminuria* Hypertension at time of study vs. no hypertension OR 1.9 (1.2 – 3.1)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistencies; 2 studies shows significant effect, 1 study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of proteinuria in CAYA cancer survivors with hypertension. (2 studies significant effect, 1 study non-significant effect; 4,549 participants; 378 events; 3 multivariable analyses)
Comments:		Note differences in used outcome definitions for proteinuria: 2 studies U-ACR, 1 study albuminuria based on dipstick

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MTX, methotrexate; MV, multivariable; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U-ACR, urinary albumin to creatinine ratio; yr, year.

* Overlap in included patients in studies of Dekkers 2013 and Kooijmans 2022.

Outcome: tubular dysfunction

Chemotherapy

1.1a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1A Risk tubular dysfunction after ifosfamide (n= 5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX: 41.8%; Unilateral nephrectomy: 11%; RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Ifosfamide < 16000 mg/m² vs. no Ifosfamide OR 1.34 (0.48 - 3.76) Ifosfamide >16000 mg/m² vs. no Ifosfamide OR 6.19 (2.45 - 15.67)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5)	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%;	17/572 (3.0%) Hypophosphatemia	*Odds ratio (95% CI) for hypophosphatemia* Cumulative ifosfamide dose (per 10 g/m²) OR 1.02 (0.82 - 1.27)	SB: low risk AB:

			after cancer diagnosis	HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	(serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	Mutually exclusive treatment group: Ifosfamide only vs. no nephrotoxic therapy OR 1.32 (0.22 - 7.89) *Odds ratio (95% CI) for hypomagnesemia* Cumulative ifosfamide dose (per 10 g/m²) OR 1.08 (0.87 - 1.34) Mutually exclusive treatment group: Ifosfamide only vs. no nephrotoxic therapy OR 5.53 (0.42 - 72.94)	- Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Ifosfamide vs. no ifosfamide OR 0.3 (0.1 – 0.7) *Odds ratio (95% CI) for tubular potassium loss* Ifosfamide vs. no ifosfamide OR 2.4 (1.2-4.7) *Odds ratio (95% CI) for tubular phosphate loss* Ifosfamide vs. no ifosfamide OR 2.3 (1.2 – 4.3) *Odds ratio (95% CI) for LMWP* Ifosfamide vs. no ifosfamide OR 2.8 (2.0 – 4.1)	SB: high risk AB: low risk DB: unclear CF: low risk
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7)	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%;	38/156 (24%) Reduced TmP/GFR	*β (SE) for reduced TmP/GFR* Ifosfamide dose (g/m²) β -0.0028, SE 0.001, p =0.02	SB: low risk AB: low risk DB: unclear

			after cancer treatment	MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%			CF: low risk
	Stohr 2007b	593 sarcoma CCS	Median 19 mo (range 8 - 36) after cessation of therapy	Ifosfamide: 100%; Cisplatin: 36.6%; Carboplatin: 14.2%; MTX: NM; Nephrectomy: 0%; RT renal area: 10.6%	27/593 (4.6%) Tubulopathy (Having at least 2 out of 3 criteria: - hypophosphatemia - glucosuria - proteinuria At least at 2 consecutive examinations 4 weeks apart)	*Hazard ratio (95% CI) for tubulopathy* Cumulative ifosfamide dose (24 - 60 g/m^2) vs. ifosfamide dose (≤ 24 g/m^2) HR 5.6 (0.7 - 45.4) Cumulative ifosfamide dose (>60 g/m^2) vs. ifosfamide dose (≤ 24 g/m^2) HR 18.6 (2.4 - 143.2)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/5, high in 1/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5; Confounding low in 5/5
Consistency:	0	No important inconsistency, 3 studies show increased risk after HD-ifosfamide or increasing dose, other study show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in 2 studies (95% CI > 2)
Dose-response:	0	Low-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of tubular dysfunction in CAYA cancer survivors treated with ifosfamide vs. no ifosfamide. (4 studies significant effect; 1 study non-significant effect; 4,005 participants; at least 219 events; 5 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study tubulopathy including hypophosphatemia, glucosuria and/or proteinuria, 1 study reduced TmP/GFR, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HR, hazard ratio; mo, month; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; SE, standard error; TmP/GFR, renal tubular threshold for phosphate; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022, and Knijnenburg 2012.

1.1b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1B Risk tubular dysfunction after higher versus lower dose ifosfamide (n= 5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%; RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Ifosfamide < 16000 mg/m² vs. no Ifosfamide OR 1.34 (0.48 - 3.76) Ifosfamide >16000 mg/m² vs. no Ifosfamide OR 6.19 (2.45 - 15.67)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Cumulative ifosfamide dose (per 10 g/m²) OR 1.02 (0.82 - 1.27) *Odds ratio (95% CI) for hypomagnesemia* Cumulative ifosfamide dose (per 10 g/m²) OR 1.08 (0.87 - 1.34)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%;	45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss	*Odds ratio (95% CI) for tubular potassium loss* Ifosfamide ≤12 g/m² vs none OR 3.7 (1.2 – 11.7) Ifosfamide 12-42 g/m² vs none OR 2.4 (0.9 – 6.4)	SB: high risk AB: low risk DB: unclear CF: low risk

				Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	187/931 (20.1%) LMWP	Ifosfamide >42 g/m^2 vs none OR 3.7 (1.3 – 10.7) p-trend among exposed= 0.56 *Odds ratio (95% CI) for tubular phosphate loss* Ifosfamide ≤12 g/m^2 vs none OR 1.6, 95%CI 0.6 – 4.5 Ifosfamide 12-42 g/m^2 vs none OR 2.4, 95%CI 1.0 – 5.9 Ifosfamide >42 g/m^2 vs none OR 4.1, 95%CI 1.6 – 10.4 p-trend among exposed= 0.39 *Odds ratio (95% CI) for LMWP* Ifosfamide ≤12 g/m^2 vs none OR 1.2 (0.6 – 2.2) Ifosfamide 12-42 g/m^2 vs none OR 2.5 (1.4 – 4.4) Ifosfamide >42 g/m^2 vs none OR 8.2 (4.7 – 14.4) p-trend among exposed= 0.03	
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	38/156 (24%) Reduced TmP/GFR	*β (SE) for reduced TmP/GFR* Ifosfamide dose (g/m^2) β -0.0028, SE 0.001, p =0.02	SB: low risk AB: low risk DB: unclear CF: low risk
	Stohr 2007b	593 sarcoma CCS	Median 19 mo (range 8 - 36) after cessation of therapy	Ifosfamide: 100%; Cisplatin: 36.6%; Carboplatin: 14.2%; MTX: NM; Nephrectomy: 0%; RT renal area: 10.6%	27/593 (4.6%) Tubulopathy (Having at least 2 out of 3 criteria: - hypophosphatemia - glucosuria - proteinuria At least at 2 consecutive	*Hazard ratio (95% CI) for tubulopathy* Cumulative ifosfamide dose (24-60 g/m^2) vs. ifosfamide dose (≤ 24 g/m^2) HR 5.6 (0.7 - 45.4) Cumulative ifosfamide dose (>60 g/m^2) vs. ifosfamide dose (≤ 24 g/m^2) HR 18.6 (2.4 - 143.2)	SB: low risk AB: low risk DB: unclear CF: low risk

		examinations 4 weeks apart)
GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 4/5, high in 1/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5; Confounding low in 5/5
Consistency:	0	No important inconsistency, 4 studies show increased risk after HD-ifosfamide or increasing dose, other study show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in 3 studies (95% CI > 2)
Dose-response:	0	Low-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of tubular dysfunction in CAYA cancer survivors exposed to higher doses of ifosfamide. (4 studies significant effect; 1 study non-significant effect; 4,005 participants; at least 257 events; 5 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study tubulopathy including hypophosphatemia, glucosuria and/or proteinuria; 1 study reduced TmP/GFR, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HR, hazard ratio; Mg, magnesium; mo, months; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; SE, standard error; TmP/GFR, renal tubular threshold for phosphate; U- β2MCR, Urinary β2-microglobulin creatinine ratio; ; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.2a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2A Risk tubular dysfunction after cisplatin (n=5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Cisplatin < 450 mg/m² vs. no cisplatin OR 0.58 (0.15 - 2.26) Cisplatin > 450 mg/m² vs. no cisplatin OR 0.52 (0.08 - 3.29)	SB: low risk AB: high risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Cumulative cisplatin dose (per 100 mg/m²) OR 1.00 (0.77 - 1.30) Mutually exclusive treatment group: Cisplatin only vs. no nephrotoxic therapy OR 1.21 (0.19 - 7.69) *Odds ratio (95% CI) for hypomagnesemia* Cumulative cisplatin dose (per 100 mg/m²) OR 1.66 (1.34 - 2.05) Mutually exclusive treatment group: Cisplatin only vs. no nephrotoxic therapy OR 96.31 (12.68 - 731.36)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Cisplatin vs. no cisplatin OR 10.1 (3.9 – 26.0) Model 2: Cisplatin ≤300 mg/m² vs none OR 5.7 (1.7 – 18.9) Cisplatin 301-500 mg/m² vs none OR 8.1 (2.5 – 25.8) Cisplatin >500 mg/m² vs none OR 22.9 (7.7 – 68.2) p-trend among exposed= 0.45 *Odds ratio (95% CI) for tubular potassium loss* Cisplatin vs. no cisplatin OR 3.5 (1.6 -7.5) Model 2:	SB: high risk AB: low risk DB: unclear CF: low risk

						Cisplatin ≤300 mg/m^2 vs none OR 1.0 (0.2 – 5.3) Cisplatin 301-500 mg/m^2 vs none OR 1.8 (0.4 – 7.5) Cisplatin >500 mg/m^2 vs none OR 17.7 (6.2 – 50.4) p-trend among exposed= 0.84 *Odds ratio (95% CI) for tubular phosphate loss* Cisplatin vs. no cisplatin OR 1.2 (0.5 – 2.8) Model 2: Cisplatin ≤300 mg/m^2 vs none OR 0.8 (0.2 – 3.9) Cisplatin 301-500 mg/m^2 vs none OR 0.5 (0.1 – 3.6) Cisplatin >500 mg/m^2 vs none OR 3.6 (1.2 – 10.9) p-trend among exposed= 0.85 *Odds ratio (95% CI) for LMWP* Cisplatin vs. no cisplatin OR 0.8 (0.5 – 1.3) Model 2: Cisplatin ≤300 mg/m^2 vs none OR 1.2 (0.5 – 2.5) Cisplatin 301-500 mg/m^2 vs none OR 1.0 (0.4 – 2.3) Cisplatin >500 mg/m^2 vs none OR 1.3 (0.6 – 2.9) p-trend among exposed= 0.18	
	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Cisplatin (cumulative dose g/m^2) 0.108 (0.005-0.211)	SB: high risk AB: low risk DB: unclear CF: high risk

	Stohr 2007a	435 sarcoma CCS	Median 23 mo (range 0 - 59) after cessation of therapy	Ifosfamide: 94.3%; Cisplatin: 36.3%; Carboplatin: 13.8%; MTX: NM Nephrectomy: NM; RT renal area: 12.2%	30/339 (8.9%) after +/- 6 months cessation of therapy 9/286 (3.1%) last examination Hypomagnesemia (serum Mg < 0.7 mmol/L or receiving Mg supplementation)	*Adjusted mean (95% CI) for magnesium* Cisplatin (yes vs no) adjusted mean (95% CI): First examination[1] yes 0.77 (0.74 - 0.81), no 0.82 (0.80 - 0.84) Last examination yes 0.82 (0.79 - 0.85), no 0.86 (0.84 - 0.88) Overall effect p < 0.05, interaction with time[2] p > 0.05	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/5, high in 2/5, unclear in 1/5; Attrition bias low in 2/5, high in 3/5; Detection bias unclear in 5/5; Confounding low in 4/5, high in 1/5
Consistency:	0	No important inconsistency, 3 studies show increased risk of hypomagnesemia after cisplatin, 1 study for tubular potassium loss, 1 study for NGAL/creatinine ratio, for other outcomes studies show non-significant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	No important imprecision, large sample size and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	2 studies found a large magnitude of effect (lower bound 95% CI >2)
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of tubular dysfunction in CAYA cancer survivors treated with cisplatin vs. no cisplatin. (Hypomagnesemia 3 studies significant effect; tubular potassium loss & - phosphate loss 1 study significant effect; NGAL/creatinine ratio 1 study significant effect; other outcomes 2 studies non-significant effect; 3,724 participants; at least 222 events; 5 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study mean serum magnesium, 1 study NGAL/creatinine ratio, 1 study tubular electrolyte losses and LMWP

Footnote 1: the first examination took place approximately 6 months after cessation of therapy. The last examination took place at a median follow-up of 23 months.
Footnote 2: A non-significant P-value of ''interaction with time'' means that the effect of a particular factor does not differ between the two examinations.
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, IQR, interquartile range; magnesium; mo, month; MTX, methotrexate; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.2b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2B Risk tubular dysfunction after higher vs. lower cisplatin dose (n=5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Cisplatin < 450 mg/m² vs. no cisplatin OR 0.58 (0.15 - 2.26) Cisplatin > 450 mg/m² vs. no cisplatin OR 0.52 (0.08 - 3.29)	SB: low risk AB: high risk DB: unclear CF: low risk
	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Cisplatin (cumulative dose g/m²) 0.108 (0.005-0.211)	SB: high risk AB: low risk DB: unclear CF: high risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS	*Odds ratio (95% CI) for hypophosphatemia* Cumulative cisplatin dose (per 100 mg/m²) OR 1.00 (0.77 - 1.30) *Odds ratio (95% CI) for hypomagnesemia* Cumulative cisplatin dose (per 100 mg/m²) OR 1.66 (1.34 - 2.05)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk

					receiving a Mg supplement)		
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Cisplatin ≤300 mg/m^2 vs none OR 5.7 (1.7 – 18.9) Cisplatin 301-500 mg/m^2 vs none OR 8.1 (2.5 – 25.8) Cisplatin >500 mg/m^2 vs none OR 22.9 (7.7 – 68.2) p-trend among exposed= 0.45 *Odds ratio (95% CI) for tubular potassium loss* Cisplatin ≤300 mg/m^2 vs none OR 1.0 (0.2 – 5.3) Cisplatin 301-500 mg/m^2 vs none OR 1.8 (0.4 – 7.5) Cisplatin >500 mg/m^2 vs none OR 17.7 (6.2 – 50.4) p-trend among exposed= 0.84 *Odds ratio (95% CI) for tubular phosphate loss* Cisplatin ≤300 mg/m^2 vs none OR 0.8 (0.2 – 3.9) Cisplatin 301-500 mg/m^2 vs none OR 0.5 (0.1 – 3.6) Cisplatin >500 mg/m^2 vs none OR 3.6 (1.2 – 10.9) p-trend among exposed= 0.85 *Odds ratio (95% CI) for LMWP* Cisplatin ≤300 mg/m^2 vs none OR 1.2 (0.5 – 2.5) Cisplatin 301-500 mg/m^2 vs none OR 1.0 (0.4 – 2.3)	SB: high risk AB: low risk DB: unclear CF: low risk

						Cisplatin >500 mg/m^2 vs none OR 1.3 (0.6 – 2.9) p-trend among exposed= 0.18	
	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 27 CCS treated with cisplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 100%; Carboplatin: 0%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	10/27 (17%) Hypomagnesemia (Serum Mg <0.75 mmol/L < 2 yr, <0.70 ≥ 2 years)	*Correlation for hypomagnesemia* Higher cisplatin dose was not associated with lower Mg at 10 years (p>0.05)	SB: low risk AB: low risk DB: unclear CF: high risk
GRADE assessment:							
Study design:	+4	Observational studies					
Study limitations:	-1	Limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5; Confounding low in 3/5, high in 2/5					
Consistency:	0	No important inconsistency, 3 studies show increased risk after increasing cisplatin dose, other studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, large sample size, high total number of events, but some wide confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	Large magnitude of effects in one study, but with very wide confidence intervals					
Dose-response:	0	Low-quality evidence of a dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of hypomagnesemia and deviant NGAL/creatinine ratio in CAYA cancer survivors exposed to higher doses of cisplatin. No significant effects of higher cisplatin doses on other tubular outcomes. (hypomagnesemia 2 studies significant effect; 1 study non-significant; NGAL/creatinine ratio 1 study significant effect; other outcomes 3 studies non-significant effect; 3,652 participants; at least 202 events; 5 risk analyses)					
Comments:		Note differences in outcome definitions used for tubular dysfunction: 2 studies hypomagnesemia, 1 study hypophosphatemia, 1 study U-β2MCR, 1 study NGAL/creatinine ratio, 1 study tubular electrolyte losses and LMWP					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; IQR, interquartile range; Mg, magnesium; MTX, methotrexate; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U-ACR, urinary albumin to creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.3a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias

1.3A Risk tubular dysfunction after carboplatin (n=4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-ß2MCR* Carboplatin vs. no carboplatin OR 2.93 (0.68 - 12.64)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Cumulative carboplatin dose (per 100 mg/m²) OR 1.00 (0.92 - 1.07) *Odds ratio (95% CI) for hypomagnesemia* Cumulative carboplatin dose (per 100 mg/m²) OR 0.97 (0.87 - 1.07)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%;	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss	*Odds ratio (95% CI) for tubular magnesium loss* Carboplatin vs. no carboplatin OR 1.2 (0.4 – 3.4 *Odds ratio (95% CI) for tubular potassium loss* Carboplatin vs. no carboplatin OR 1.6 (0.7 -3.8)	SB: high risk AB: low risk DB: unclear CF: low risk

				RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	187/931 (20.1%) LMWP	Model 2: Carboplatin ≤1500 mg/m^2 vs none OR 1.1 (0.2 – 5.7) Carboplatin 1501-2800 mg/m^2 vs none OR 0.6 (0.1 – 5.2) Carboplatin >2800 mg/m^2 vs none OR 5.1 (1.7 – 15.8) p-trend among exposed= 0.04 *Odds ratio (95% CI) for tubular phosphate loss* Carboplatin vs. no carboplatin OR 1.5 (0.7 – 3.3) *Odds ratio (95% CI) for LMWP* Carboplatin vs. no carboplatin OR 1.2 (0.7 – 2.0)	
	Stohr 2007a	435 sarcoma CCS	Median 23 mo (range 0 - 59) after cessation of therapy	Ifosfamide: 94.3%; Cisplatin: 36.3%; Carboplatin: 13.8%; MTX: NM Nephrectomy: NM; RT renal area: 12.2%	30/339 (8.9%) after +/- 6 months cessation of therapy 9/286 (3.1%) last examination Hypomagnesemia (serum Mg < 0.7 mmol/L or receiving Mg supplementation)	*Adjusted mean (95% CI) for magnesium* Carboplatin (yes vs no) adjusted mean (95%CI): First examination[1] yes 0.78 (0.74 - 0.81), no 0.82 (0.80- 0.84) Last examination yes 0.82 (0.79 - 0.86), no 0.86 (0.83 - 0.88) Overall effect p < 0.05, interaction with time[2] p > 0.05	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 2/4, high in 1/4, unclear in 1/3; Attrition bias low in 1/4, high in 3/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, 1 study shows significant effect, 1 study only significant effect for high doses, 2 studies show non-significant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, high total number of events, and narrow confidence intervals; however, only 1 study reported a significant effect on magnesium levels, and one study for tubular potassium loss after high doses
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in all studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	Increased risk of lower (but not necessarily abnormal) magnesium in CAYA cancer survivors treated with carboplatin vs. no carboplatin, and increased risk of tubular potassium loss after carboplatin dose >2800 mg/m2. (1 study significant effect magnesium, 1 study significant effect potassium loss, 2 studies non-significant effect; 3,664 participants; 222 events; 4 multivariable analyses)
Comments:	Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study mean serum magnesium, 1 study tubular electrolyte losses and LMWP

Footnote 1: the first examination took place approximately 6 months after cessation of therapy. The last examination took place at a median follow-up of 23 months.
Footnote 2: A non-significant P-value of ''interaction with time'' means that the effect of a particular factor does not differ between the two examinations.
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; mo, month; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.3b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3B Risk tubular dysfunction after higher vs. lower carboplatin (n=3 studies)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Cumulative carboplatin dose (per 100 mg/m²) OR 1.00 (0.92 - 1.07) *Odds ratio (95% CI) for hypomagnesemia* Cumulative carboplatin dose (per 100 mg/m²) OR 0.97 (0.87 - 1.07)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk

	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular potassium loss* Carboplatin ≤1500 mg/m^2 vs none OR 1.1 (0.2 – 5.7) Carboplatin 1501-2800 mg/m^2 vs none OR 0.6 (0.1 – 5.2) Carboplatin >2800 mg/m^2 vs none OR 5.1 (1.7 – 15.8) p-trend among exposed= 0.04 *Odds ratio (95% CI) for tubular phosphate loss* Carboplatin ≤1500 mg/m^2 vs none OR 1.6 (0.5 – 5.5) Carboplatin 1501-2800 mg/m^2 vs none OR 2.8 (1.0 – 7.9) Carboplatin >2800 mg/m^2 vs none OR 0.7 (0.2 – 3.5) p-trend among exposed= 0.74 *Odds ratio (95% CI) for LMWP* Carboplatin ≤1500 mg/m^2 vs none OR 1.3 (0.6 – 2.7) Carboplatin 1501-2800 mg/m^2 vs none OR 1.8 (0.9 – 3.9) Carboplatin >2800 mg/m^2 vs none OR 1.0 (0.4 – 2.3) p-trend among exposed= 0.06	SB: high risk AB: low risk DB: unclear CF: low risk
	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 24 CCS treated with carboplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 100%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	4/24 (17%) Hypomagnesemia (Serum Mg <0.75 mmol/L < 2 yr, <0.70 ≥ 2 years)	*Correlation for hypomagnesemia* Higher carboplatin dose was not associated with lower Mg at 10 years (p>0.05)	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3
Consistency:	0	No important inconsistency, 1 study shows significant effect, other studies show non-significant effects

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Some imprecision, large sample size, and narrow confidence intervals. Only 1 study reported a significant effect with low number of events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of tubular potassium loss in CAYA cancer survivors exposed to high doses (>2800 mg/m²) of carboplatin. (1 study significant effect, 2 studies non-significant effect; 2,529 participants; at least 66 events; 3 risk analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 2 studies hypomagnesemia, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NA, not applicable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Kooijmans 2022 and Knijnenburg 2012.

1.4a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.4A Risk tubular dysfunction after methotrexate (n=4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%, details: intrathecal 277 (29.8%), IV 236 (30.9%), oral 250 (32.8%); Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* MTX vs. no MTX OR 1.07 (0.59 - 1.92)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a	*Odds ratio (95% CI) for hypophosphatemia* HD-MTX (≥ 1 g/m² per course) vs. no HD-MTX OR 0.34 (0.07 - 1.76) Mutually exclusive treatment group: HD-MTX only (≥ 1 g/m² per	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear

				Nephrectomy: 14.7%; RT renal area: 8.7%	phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	course) vs. no nephrotoxic therapy OR 0.58 (0.10 - 3.46) *Odds ratio (95% CI) for hypomagnesemia* HD-MTX (≥ 1 g/m² per course) vs. no HD-MTX OR 1.32 (0.43 - 4.05) Mutually exclusive treatment group: HD-MTX only (≥ 1 g/m² per course) vs. no nephrotoxic therapy OR 2.17 (0.17 - 27.61)	CF: low risk
	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Methotrexate not included in MV model based on univariate analysis (p>0.05)	SB: high risk AB: low risk DB: unclear CF: high risk
	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	38/156 (24%) Reduced TmP/GFR	*β (SE) for reduced TmP/GFR* Methotrexate not included in MV model based on univariate analysis: β 0.0049, SE 0.046, p=0.9	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 2/4, high in 2/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4
Consistency:	0	No important inconsistency, all studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, and high total number of events,
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in both studies
Dose-response:	0	Unclear if dose response relationship

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of methotrexate on the risk of tubular dysfunction in CAYA cancer survivors. (4 studies non-significant effect; 2,448 participants; at least 185 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia; 1 study reduced TmP/GFR; 1 study NGAL/creatinine ratio

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; IQR, interquartile range; Mg, magnesium; MTX, methotrexate; MV, multivariable; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; SE, standard error; TmP/GFR, renal tubular threshold for phosphate; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs; versus yr, year.

* Overlap in included patients in studies of Dekkers 2013 and Knijnenburg 2012.

1.4b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of methotrexate?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.4B Risk tubular dysfunction after higher vs. lower dose methotrexate (n=2 studies)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* HD-MTX (≥ 1 g/m² per course) vs. no HD-MTX OR 0.34 (0.07 - 1.76) Mutually exclusive treatment group: HD-MTX only (≥ 1 g/m² per course) vs. no nephrotoxic therapy OR 0.58 (0.10 - 3.46) *Odds ratio (95% CI) for hypomagnesemia* HD-MTX (≥ 1 g/m² per course) vs. no HD-MTX OR 1.32 (0.43 - 4.05) Mutually exclusive treatment group: HD-MTX only (≥ 1 g/m² per course) vs. no nephrotoxic therapy OR 2.17 (0.17 - 27.61)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk

	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	38/156 (24%) Reduced TmP/GFR	*β (SE) for reduced TmP/GFR* Methotrexate not included in MV model based on univariate analysis: β 0.0049, SE 0.046, p=0.9	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias high in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, and high total number of events, however some wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of methotrexate dose on the risk of tubular dysfunction in CAYA cancer survivors. (2 studies non-significant effect; 1,625 participants; at least 55 events; 2 multivariable analyses)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; SE, standard error; TmP/GFR, renal tubular threshold for phosphate; yr, year.

1.4c. What is the influence of different routes of administration for methotrexate on the risk of tubular dysfunction in CAYA cancer survivors?
No studies identified investigating the influence of different routes of administration for methotrexate on the risk of tubular dysfunction in CAYA cancer survivors.

1.5a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of tubular dysfunction in CAYA cancer survivors.

1.5b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of tubular dysfunction in CAYA cancer survivors.

1.6a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with melphalan?
No studies identified investigating the risk for melphalan on the risk of tubular dysfunction in CAYA cancer survivors.

1.6b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of melphalan?
No studies identified investigating the risk for melphalan on the risk of tubular dysfunction in CAYA cancer survivors.

1.7a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7A Risk tubular dysfunction after cyclophosphamide (n=4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Cyclophosphamide < 3500 mg/m² vs. no cyclophosphamide OR 1.09 (0.56 - 2.15) Cyclophosphamide > 3500 mg/m² vs. no cyclophosphamide OR 1.61 (0.81 - 3.20)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* HD-cyclophosphamide (≥1 g/m² per course) vs. no HD-cyclophosphamide OR 0.63 (0.08 - 5.22) *Odds ratio (95% CI) for hypomagnesemia* HD-cyclophosphamide (≥ 1 g/m² per course) vs. no HD-cyclophosphamide OR 2.98 (0.92 - 9.63)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk

	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magesium loss* HD-cyclophosphamide* vs none OR 0.5 (0.2 – 1.8) *Odds ratio (95% CI) for tubular potassium loss* HD-cyclophosphamide* vs none OR 0.5 (0.1 – 1.5) *Odds ratio (95% CI) for tubular phosphate loss* HD-cyclophosphamide* vs none OR 0.8 (0.4 – 1.9) *Odds ratio (95% CI) for LMWP* HD-cyclophosphamide* vs none OR 0.8 (0.5 – 1.3) *≥10 g/m² in total or ≥1 g/m² per course	SB: high risk AB: low risk DB: unclear CF: low risk
	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Cyclophosphamide not included in MV model based on univariate analysis (p>0.05)	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, high in 2/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4
Consistency:	0	No important inconsistency, all studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No imprecision, large sample size, high total number of events, and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in both studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE

Conclusion:	No significant effect of cyclophosphamide on the risk of tubular dysfunction in CAYA cancer survivors. (4 studies non-significant effect; 3,289 participants; at least 192 events; 4 multivariable analyses)
Comments:	Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia; 1 study NGAL/creatinine ratio, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; IQR, interquartile range; Mg, magnesium; MTX, methotrexate; MV, multivariable; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.7b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of cyclophosphamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.7B Risk tubular dysfunction after higher vs. lower dose of cyclophosphamide (n=2 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Cyclophosphamide < 3500 mg/m² vs. no cyclophosphamide OR 1.09 (0.56 - 2.15) Cyclophosphamide > 3500 mg/m² vs. no cyclophosphamide OR 1.61 (0.81 - 3.20)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71	*Odds ratio (95% CI) for hypophosphatemia* HD-cyclophosphamide (≥1 g/m² per course) vs. no HD-cyclophosphamide OR 0.63 (0.08 - 5.22) *Odds ratio (95% CI) for hypomagnesemia* HD-cyclophosphamide (≥ 1 g/m² per course) vs. no HD-cyclophosphamide OR 2.98 (0.92 - 9.63)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk

					mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)		
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magesium loss* HD-cyclophosphamide* vs none OR 0.5 (0.2 – 1.8) *Odds ratio (95% CI) for tubular potassium loss* HD-cyclophosphamide* vs none OR 0.5 (0.1 – 1.5) *Odds ratio (95% CI) for tubular phosphate loss* HD-cyclophosphamide* vs none OR 0.8 (0.4 – 1.9) *Odds ratio (95% CI) for LMWP* HD-cyclophosphamide* vs none OR 0.8 (0.5 – 1.3) *≥10 g/m² in total or ≥1 g/m² per course	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias high in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, all studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No imprecision, large sample size, high total number of events, and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in both studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of cyclophosphamide dose on the risk of tubular dysfunction in CAYA cancer survivors. (3 studies non-significant effect; 3,229 participants; at least 192 events; 3 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; vs, versus; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.8 What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.8 Risk tubular dysfunction after combination potential nephrotoxic chemotherapy (n=1 study)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Mutually exclusive treatment group: Platinum agents + ifosfamide vs. no nephrotoxic therapy OR 1.71 (0.34 - 8.76) *Odds ratio (95% CI) for hypomagnesemia* Mutually exclusive treatment group: Platinum agents + ifosfamide vs. no nephrotoxic therapy OR 75.53 (9.75 - 584.89)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	NA (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study included with large sample size, and high total number of events, however wide confidence intervals					

Publication bias:	0	Unlikely
Effect size:	0	Although this study found a large magnitude of effect (lower bound 95% CI >2), there is only one study included so it's not sure if the effect size is truly large
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of hypomagnesemia in CAYA cancer survivors after treatment with a combination of platinum agents and ifosfamide vs. no nephrotoxic therapy. No significant effect of platinum agents and ifosfamide on hypophosphatemia.(1 study (non-)significant effect; 1,442 participants; at least 17 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NA, not applicable; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; vs, versus; yr, year.

1.9 What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus one of these agents alone?
No studies identified investigating the additive risk for the combination of chemotherapy vs. one of these agents alone on the risk of tubular dysfunction in CAYA cancer survivors.

Radiotherapy
1.10a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with radiotherapy exposing the renal area?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10A Risk tubular dysfunction after radiotherapy (n=5 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%, RT field: abdominal 6.2%, TBI 3.4%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Abdominal RT vs. no abdominal RT OR 1.12 (0.23 - 5.55)	SB: low risk AB: high risk DB: unclear CF: low risk

	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%, RT field: abdominal 7.1%, TBI 1.5%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Abdominal RT vs. no abdominal RT OR 1.16 (0.11 - 12.47) *Odds ratio (95% CI) for hypomagnesemia* Abdominal RT vs. no abdominal RT OR 0.30 (0.06 - 1.47)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022*	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Abdominal radiotherapy vs none OR 1.0 (0.4 – 1.7) *Odds ratio (95% CI) for tubular potassium loss* Abdominal radiotherapy vs none OR 1.9 (0.7 – 5.2) *Odds ratio (95% CI) for tubular phosphate loss* Abdominal radiotherapy vs none OR 1.3 (0.5 – 3.9) *Odds ratio (95% CI) for LMWP* Abdominal radiotherapy vs none OR 1.2 (0.7 – 2.0)	SB: high risk AB: low risk DB: unclear CF: low risk

	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Abdominal radiotherapy not included in MV model based on univariate analysis (p>0.05)	SB: high risk AB: low risk DB: unclear CF: high risk
	Stohr 2007a	435 sarcoma CCS	Median 23 mo (range 0 - 59) after cessation of therapy	Ifosfamide: 94.3%; Cisplatin: 36.3%; Carboplatin: 13.8%; MTX: NM Nephrectomy: NM; RT renal area: 12.2%, RT field: abdominal 12.2%	8.9% after +/- 6 months cessation of therapy 9/286 (3.1%) last examination Hypomagnesemia (serum Mg < 0.7 mmol/L or receiving Mg supplementation)	*Adjusted mean (95% CI) for magnesium* Abdominal RT (yes vs no) adjusted mean (95%CI) First examination[1] yes 0.79 (0.75 - 0.83), no 0.80 (0.79-0.82) Last examination yes 0.84 (0.80 - 0.88), no 0.84 (0.82 - 0.86) Overall effect p > 0.05, interaction with time[2] p > 0.05	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 2/5, high in 2/5, unclear in 1/5; Attrition bias low in 2/5, high in 3/5; Detection bias unclear in 5/5; Confounding low in 4/5, high in 1/5
Consistency:	0	No important inconsistency, all studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events, and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in both studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of radiotherapy exposing the kidneys on the risk of tubular dysfunction in CAYA cancer survivors. (5 studies non-significant effect; 3,724 participants; at least 201 events; 5 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study adjusted mean magnesium; 1 study NGAL/creatinine ratio, 1 study tubular electrolyte losses and LMWP

Footnote 1: the first examination took place approximately 6 months after cessation of therapy. The last examination took place at a median follow-up of 23 months.
Footnote 2: A non-significant P-value of ''interaction with time'' means that the effect of a particular factor does not differ between the two examinations.

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; IQR, interquartile range; Mg, magnesium; mo, month; MTX, methotrexate; MV, multivariable; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.10A Risk tubular dysfunction after TBI (n=2 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%, RT field: abdominal 6.2%, TBI 3.4%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* TBI vs. no TBI OR 0.48 (0.12 - 1.96)	SB: low risk AB: high risk DB: unclear CF: low risk
	Kooijmans 2022	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* TBI vs none OR 0.9 (0.2 – 4.6) *Odds ratio (95% CI) for tubular potassium loss* TBI vs none OR 0.8 (0.2 – 3.8) *Odds ratio (95% CI) for tubular phosphate loss* TBI vs none OR 1.1 (0.3 – 3.0) *Odds ratio (95% CI) for LMWP* TBI vs none OR 1.1 (0.6 – 2.0)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-2	Limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2					
Consistency:	0	No important inconsistency, both studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, large sample size, high total number of events, and narrow confidence intervals					

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in both studies
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of TBI on the risk of tubular dysfunction in CAYA cancer survivors. (2 studies non-significant effect; 1,787 participants; at least 175 events; 2 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; MTX, methotrexate; NM, not mentioned; OR, odds ratio; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.

1.10b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of radiotherapy?
No studies identified investigating the influence of higher versus lower dose of radiotherapy on the risk of tubular dysfunction in CAYA cancer survivors.

1.10c. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with radiotherapy exposing one versus both kidneys?
No studies identified investigating the influence of radiotherapy exposing one versus both kidneys on the risk of tubular dysfunction in CAYA cancer survivors.

1.11 What is the influence of the actual portion (e.g., hilum/pelvis vs cortex) of a single kidney irradiated on the risk of tubular dysfunction in CAYA cancer survivors?
No studies identified investigating the influence of the actual portion of a single kidney irradiated on the risk of tubular dysfunction in CAYA cancer survivors.

Nephrectomy
1.12a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with nephrectomy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.12A Risk tubular dysfunction after nephrectomy (n=4 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Nephrectomy vs. no nephrectomy OR 1.69 (0.67 - 4.31)	SB: low risk AB: high risk DB: unclear CF: low risk

				RT renal area: 6.2%			
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Nephrectomy vs. no nephrectomy OR 0.70 (0.06 - 8.26) Mutually exclusive treatment group: Nephrectomy only vs. no nephrotoxic therapy OR 2.12 (0.20 - 22.39) *Odds ratio (95% CI) for hypomagnesemia* Nephrectomy vs. no nephrectomy OR 17.46 (4.63 - 65.79) Mutually exclusive treatment group: Nephrectomy only vs. no nephrotoxic therapy OR 121.85 (15.97 - 929.97)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Nephrectomy vs none OR 1.2 (0.4 – 3.7) *Odds ratio (95% CI) for tubular potassium loss* Nephrectomy vs none OR 0.6 (0.2 – 2.1) *Odds ratio (95% CI) for tubular phosphate loss* Nephrectomy vs none OR 1.2 (0.5 – 2.9) *Odds ratio (95% CI) for LMWP* Nephrectomy vs none OR 0.7 (0.4 – 1.2)	SB: high risk AB: low risk DB: unclear CF: low risk

	Latoch 2021	60 solid tumors CCS	Median 8.35 yr (IQR 4.95-12.55)	Ifosfamide: 20%; Cisplatin: 26.7%; Carboplatin: NM; Cyclophosphamide: 31.7%; MTX: 8.3% Nephrectomy: NM; RT renal area: 31.7%	NA	*Coefficient (95% CI) for NGAL/creatinine ratio* Nephrectomy (no vs yes) 5.009 (-47.18-147.3)	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, high in 2/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4
Consistency:	0	No important inconsistency, 1 study shows significant effect, 3 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size, high total number of events, but some wide confidence intervals. Only 1 study reported a significant effect.
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect was found in one study, but with very wide confidence intervals
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of tubular dysfunction in CAYA cancer survivors after nephrectomy vs no nephrectomy. (1 study significant effect; 3 studies non-significant effect; 3,289 participants; at least 192 events; 4 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypophosphatemia and hypomagnesemia, 1 study NGAL/creatinine ratio. 1 study tubular electrolyte losses and LMWP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; IQR, interquartile range; Mg, magnesium; MTX, methotrexate; NM, not mentioned; NA, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022 and Knijnenburg 2012.

1.12b. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with unilateral versus partial (unilateral/bilateral) nephrectomy?
No studies identified investigating the influence of unilateral versus partial (unilateral/bilateral) nephrectomy on the risk of tubular dysfunction in CAYA cancer survivors.

Combination

1.13a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus no nephrotoxic therapy?
1.13b. What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus one of these modalities alone?

1.14a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus no nephrotoxic therapy?
1.14b. What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus one of these modalities alone?
No studies identified investigating the risk for the combination of chemotherapy and radiotherapy on the risk of tubular dysfunction in CAYA cancer survivors.

1.15a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus no nephrotoxic therapy?
1.15b. What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus one of these modalities alone?
No studies identified investigating the risk for the combination of chemotherapy and nephrectomy on the risk of tubular dysfunction in CAYA cancer survivors.

1.16a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.16A Risk tubular dysfunction after radiotherapy and nephrectomy (n=2 studies)	Dekkers 2013*	763 CCS	Median 18.3 yr (range 5.0-58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Nephrectomy and abdominal RT vs. no nephrectomy and abdominal RT OR 1.31 (0.43 - 3.99)	SB: low risk AB: high risk DB: unclear CF: low risk
	Knijnenburg 2012*	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%,	36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years	*Odds ratio (95% CI) for hypomagnesemia* Mutually exclusive treatment group: Nephrectomy + RT [1] vs. no nephrotoxic therapy OR 14.80 (2.25 - 97.12)	SB: low risk AB: high risk DB: unclear CF: low risk

			HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)
GRADE assessment:				
Study design:	+4	Observational studies		
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias high in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2		
Consistency:	0	No important inconsistency, 1 study shows significant effect, 1 study shows non-significant effect		
Directness:	0	Results are direct, population and outcomes broadly generalizable		
Precision:	-2	Important imprecision, large sample size, high total number of events, but some wide confidence intervals. Only 1 study reported a significant effect.		
Publication bias:	0	Unlikely		
Effect size:	0	Large magnitude of effect was found in one study, but with very wide confidence intervals		
Dose-response:	0	Not applicable		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ VERY LOW		
Conclusion:		Increased risk of hypomagnesemia in CAYA cancer survivors after combination therapy of nephrectomy and radiotherapy exposing the kidneys vs. no nephrotoxic therapy. No significant effect after combination therapy of nephrectomy and radiotherapy on other tubular outcomes. (hypomagnesemia 1 study significant effect; other outcome 1 study non-significant effect; 2,205 participants; 157 events; 2 multivariable analyses)		
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study U-β2MCR, 1 study hypomagnesemia		

Footnote 1: abdominal radiotherapy and/or total body irradiation

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.

* Overlap in included patients in studies of Dekkers 2013 and Knijnenburg 2012.

1.16b. What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?

No studies identified investigating the additive risk for the combination of radiotherapy and nephrectomy on the risk of tubular dysfunction in CAYA cancer survivors versus one of these modalities alone.

1.17a. What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?

1.17b. What is the additive risk of tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?

No studies identified investigating the risk for the combination of chemotherapy, radiotherapy and nephrectomy on the risk of tubular dysfunction in CAYA cancer survivors.

1.18 What is the risk of tubular dysfunction in CAYA cancer survivors who were treated with stem cell transplant?
No studies identified investigating the risk for stem cell transplant on the risk of tubular dysfunction in CAYA cancer survivors.

Other risk factors

1.19 What is the influence of age at exposure on the risk of tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19 Influence age at ifosfamide treatment on risk tubular dysfunction (n=1 study)	Oberlin 2009	183 pediatric sarcoma survivors	Median 10.3 yr (range 5 - 10.7) after cancer treatment	Ifosfamide: 100%; Cisplatin: 0%; Carboplatin: 0%; MTX: some, number NM; Nephrectomy: 0%; RT renal area: 0.01%; HSCT: 0%	38/156 (24%) Reduced TmP/GFR	*β (SE) for reduced TmP/GFR* Age at treatment (yr) β -0.0047, SE 0.0033, p= 0.2	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (only 1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, small sample size and only 1 study included.					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Not applicable					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of age at ifosfamide treatment on the risk of tubular dysfunction in CAYA cancer survivors. (1 study non-significant effect; 183 participants; 38 events; 1 multivariable analysis)					

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; HSCT, hematological stem cell transplantation; MTX, methotrexate; NM, not mentioned; RT, radiotherapy; SB, selection bias; SE, standard error; TmP/GFR, renal tubular threshold for phosphate; yr, year.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19 Influence age at exposure on risk tubular dysfunction after potentially nephrotoxic therapy (n=3 studies)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Age at diagnosis (in years) OR 1.10 (0.98 - 1.24) *Odds ratio (95% CI) for hypomagnesemia* Age at diagnosis (in years) OR 1.05 (0.96 - 1.16)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	*Odds ratio (95% CI) for tubular magnesium loss* Age at diagnosis (in years) OR 1.0 (0.97 – 1.1) *Odds ratio (95% CI) for tubular potassium loss* Age at diagnosis (in years) OR 1.1 (0.99 – 1.1) *Odds ratio (95% CI) for tubular phosphate loss* Age at diagnosis not included in MV model based on univariate analyses. *Odds ratio (95% CI) for LMWP*	SB: high risk AB: low risk DB: unclear CF: low risk

						Age at diagnosis not included in MV model based on univariate analyses.	
	Stohr 2007b	593 sarcoma CCS	Median 19 mo (range 8 - 36) after cessation of therapy	Ifosfamide: 100%; Cisplatin: 36.6%; Carboplatin: 14.2%; MTX: NM; Nephrectomy: 0%; RT renal area: 10.6%	27/593 (4.6%) Tubulopathy (Having at least 2 out of 3 criteria: - hypophosphatemia - glucosuria - proteinuria At least at 2 consecutive examinations 4 weeks apart)	*Hazard ratio (95% CI) for tubulopathy* Age at diagnosis <4 years vs ≥ 4 years HR 8.7 (3.5 - 21.8)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	0	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	0	No important inconsistency, 1 study shows significant effect, 2 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, large sample size, high total number of events, but some wide confidence intervals and only one study showing a significant effect
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect was found in one study, but with wide confidence intervals
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of tubular dysfunction in CAYA cancer survivors aged younger at cancer diagnosis (<4 years) vs. older (≥4 years) after potentially nephrotoxic therapy. (1 study significant effect, 2 studies non-significant effect; 3,059 participants; at least 89 events; 3 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study hypophosphatemia and hypomagnesemia, 1 study tubulopathy, 1 study tubular electrolyte losses and LWMP

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; HR, hazard ratio; Mg, magnesium; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Dekkers 2013, Kooijmans 2022, and Knijnenburg 2012.

1.20 What is the influence of sex on the risk of tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.20 Influence of sex on risk tubular dysfunction after potentially nephrotoxic therapy (n=2 studies)	Knijnenburg 2012	1442 CCS	Median 12.1 yr (range 7.8 - 17.5) after cancer diagnosis	Ifosfamide: 14.0%; Cisplatin: 7.8%; Carboplatin: 7.7%; HD MTX: 25.5%, HD cyclophosphamide: 8.6% Nephrectomy: 14.7%; RT renal area: 8.7%	17/572 (3.0%) Hypophosphatemia (serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement) 36/534 (8.8%) Hypomagnesemia (serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement)	*Odds ratio (95% CI) for hypophosphatemia* Male sex vs. female sex OR 0.36 (0.12 - 1.05) *Odds ratio (95% CI) for hypomagnesemia* Male sex vs. female sex OR 0.97 (0.46 - 2.05)	SB: low risk AB: - Phosphate: high risk - Magnesium: high risk DB: unclear CF: low risk
	Kooijmans 2022	1024 CCS	Median 25.5 yr (IQR 21.4 – 30.3)	Ifosfamide: 27.2%; Cisplatin: 17.1%; Carboplatin: 14.7%; MTX: 0%; HD-cyclophosphamide: 17.1%; Nephrectomy: 25.8%; RT renal area: 17.1%; TBI: 8.4% HSCT: 9.3%	56/999 (5.6%) tubular magnesium loss 45/1003 tubular potassium loss 55/997 (5.5%) tubular phosphate loss 187/931 (20.1%) LMWP	Sex not included in MV models based on univariate analyses.	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment: Study design: +4 Observational studies Study limitations: -2 Limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2							

Consistency:	0	No important inconsistency, both studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, and high total number of events and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of sex on the risk of tubular dysfunction in CAYA cancer survivors after treatment with potentially nephrotoxic therapy. (2 studies non-significant effects; 2,466 participants; at least 62 events; 2 multivariable analyses)
Comments:		Note differences in outcome definitions used for tubular dysfunction: 1 study hypophosphatemia and hypomagnesemia, 1 study tubular electrolyte losses and LMWP.

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; HD, high-dose; Mg, magnesium; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.
* Overlap in included patients in studies of Kooijmans 2022 and Knijnenburg 2012.

1.21 What is the influence of supportive care drugs (e.g., nephrotoxic antibiotics) on the risk of tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?
No studies identified investigating the influence of supportive care drugs on the risk of tubular dysfunction in CAYA cancer survivors.

1.22 What is the influence of having hypertension on the risk of tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.22 Influence hypertension on risk tubular dysfunction after treatment potentially nephrotoxic (n=1 study)	Dekkers 2013	763 CCS	Median 18.3 yr (range 5.0 - 58.2) after cancer diagnosis	Ifosfamide: 10%; Cisplatin: 7%; Carboplatin: 2%; Cyclophosphamide: 39.9%; MTX 41.8%; Unilateral nephrectomy 11% RT renal area: 6.2%	130/496 (26.2%) U-β2MCR ≥ 0.04 mg/mmol Cr	*Odds ratio (95% CI) for U-β2MCR* Hypertension at time of study vs. no hypertension OR 2.05 (1.17 - 3.61)	SB: low risk AB: high risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	NA (1 study)					

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size, and high total number of events and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of tubular dysfunction in CAYA cancer survivors with hypertension vs. no hypertension. (1 study significant effect; 763 participants; 130 events; 1 multivariable analysis)

Footnote 1: abdominal radiotherapy and/or total body irradiation

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; Cr, creatinine; DB, detection bias; MTX, methotrexate; NM, not mentioned; No, number; OR, odds ratio; RT, radiotherapy; SB, selection bias; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.

Outcome: combined glomerular & tubular dysfunction

Chemotherapy

1.1a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1A Risk combined glomerular & tubular dysfunction after ifosfamide (n= 1 study)	Arga 2015	33 CCS of solid tumors	Median 56 months (range 12 - 174), mean 48 months after treatment	Ifosfamide: 36%; Cisplatin: 100%; Carboplatin: NM; Cyclophosphamide: at least 1; MTX: NM; Unilateral nephrectomy: NM; RT renal area: 21%	12/33 (36.4%) eGFR <90 ml/min/1.73m^2 12/33 (36.4%) hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Odds ratio (95% CI) for development nephrotoxicity* Ifosfamide dose (g/m^2) OR 1.108 (1.02 - 1.2) *Odds ratio (95% CI) for severity of nephrotoxicity* Ifosfamide dose (g/m^2) OR 1.166 (1.07 - 1.33)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					

Precision:	-1	Some imprecision, only 1 study included with relative small sample size, but high total number of events, and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Low-quality evidence of a dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of combined glomerular & tubular dysfunction in CAYA cancer survivors after ifosfamide. (1 study significant effect; 33 participants; 12 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; OR, odds ratio; RT, radiotherapy; SB, selection bias.

1.1b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of ifosfamide?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.1B Risk combined glomerular & tubular dysfunction after higher versus lower dose ifosfamide (n= 1 study)	Arga 2015	33 CCS of solid tumors	Median 56 months (range 12 - 174), mean 48 months after treatment	Ifosfamide: 36%; Cisplatin: 100%; Carboplatin: NM; Cyclophosphamide: at least 1; MTX: NM; Unilateral nephrectomy: NM; RT renal area: 21%	12/33 (36.4%) eGFR <90 ml/min/1.73m^2 12/33 (36.4%) hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Odds ratio (95% CI) for development nephrotoxicity* Ifosfamide dose (g/m^2) OR 1.108 (1.02-1.2) *Odds ratio (95% CI) for severity of nephrotoxicity* Ifosfamide dose (g/m^2) OR 1.166 (1.07-1.33)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, only 1 study included with relative small sample size, but high total number of events, and small confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effects were found in this study					
Dose-response:	0	Low-quality evidence of a dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⨁⨁⨀⨀ LOW					
Conclusion:		Increased risk of combined glomerular & tubular dysfunction in CAYA cancer survivors after increasing dose of ifosfamide.					

	(1 study significant effect; 33 participants; 12 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; OR, odds ratio; RT, radiotherapy; SB, selection bias.

1.2a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2A Risk combined glomerular & tubular dysfunction after cisplatin (n=1 study)	Arga 2015	33 CCS of solid tumors	Median 56 months (range 12 - 174), mean 48 months after treatment	Ifosfamide: 36%; Cisplatin: 100%; Carboplatin: NM; Cyclophosphamide: at least 1; MTX: NM; Unilateral nephrectomy: NM; RT renal area: 21%	12/33 (36.4%) eGFR <90 ml/min/1.73m^2 12/33 (36.4%) hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Odds ratio (95% CI) for development nephrotoxicity* Cisplatin dose (g/m^2) OR 1.001 (0.99 – 1.08) *Odds ratio (95% CI) for severity of nephrotoxicity* Cisplatin dose (g/m^2) OR 1.010 (0.93 – 1.017)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with relative small sample size, but high total number of events, and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of cisplatin on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors. (1 study non-significant effect; 33 participants; 12 events; 1 multivariable analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; OR, odds ratio; RT, radiotherapy; SB, selection bias.

1.2b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of cisplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.2B Risk combined glomerular & tubular dysfunction after higher vs. lower cisplatin dose (n=2 studies)	Arga 2015	33 CCS of solid tumors	Median 56 months (range 12 - 174), mean 48 months after treatment	Ifosfamide: 36%; Cisplatin: 100%; Carboplatin: NM; Cyclophosphamide: at least 1; MTX: NM; Unilateral nephrectomy: NM; RT renal area: 21%	12/33 (36.4%) eGFR <90 ml/min/1.73m^2 12/33 (36.4%) hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Odds ratio (95% CI) for development nephrotoxicity* Cisplatin dose (g/m^2) OR 1.001 (0.99 – 1.08) *Odds ratio (95% CI) for severity of nephrotoxicity* Cisplatin dose (g/m^2) OR 1.010 (0.93 – 1.017)	SB: unclear AB: low risk DB: unclear CF: low risk
	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 27 CCS treated with cisplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 100%; Carboplatin: 0%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	11/27 (40%) GFR <90 ml/min/1.73m^2 10/27 (17%) Hypomagnesemia 10/27 (37%) Nephrotoxicity score based on GFR and serum Mg	*Correlation for nephrotoxicity score* Higher cisplatin dose rate (>40 mg/m2/day) was not associated with higher Ns at 10 years (p>0.05)	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/1, high in 1/2
Consistency:	0	No important inconsistency, both studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, both studies have a relative small sample size, but high total number of events, and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Unclear if dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of cisplatin dose on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors. (2 studies non-significant effect; 96 participants; 22 events; 2 risk analyses)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; Ns, nephrotoxicity score; OR, odds ratio; RT, radiotherapy; SB, selection bias.

1.3a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with carboplatin?
No studies identified investigating the risk for carboplatin on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.3b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of carboplatin?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.3B Risk combined glomerular & tubular dysfunction after higher vs. lower carboplatin dose (n= 1 study)	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 24 CCS treated with carboplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 100%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	5/24 (21%) GFR <90 ml/min/1.73m^2 4/24 (17%) Hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Correlation for nephrotoxicity score* Higher carboplatin dose was associated with higher Ns at 10 years (p< 0.008)	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	Not applicable (only 1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with small sample size and small number of events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	Low-quality dose response relationship
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of combined glomerular & tubular dysfunction in CAYA cancer survivors after increasing dose of carboplatin. (1 study significant effect; 24 participants; 5 events; 1 risk analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; Ns, nephrotoxicity score; RT, radiotherapy; SB, selection bias.

1.4a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with methotrexate?
No studies identified investigating the risk for methotrexate on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.4b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of methotrexate?
No studies identified investigating the risk for methotrexate on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors

1.4c. What is the influence of different routes of administration for methotrexate on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors?
No studies identified investigating the influence of different routes of administration for methotrexate on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.5a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.5b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of nitrosoureas?
No studies identified investigating the risk for nitrosoureas on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.6a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with melphalan?
No studies identified investigating the risk for melphalan on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.6b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of melphalan?
No studies identified investigating the risk for melphalan on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.7a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with cyclophosphamide?
No studies identified investigating the risk for cyclophosphamide on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.7b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of cyclophosphamide?
No studies identified investigating the risk for cyclophosphamide on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.8 What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus no nephrotoxic therapy?

No studies identified investigating the risk for the combination of chemotherapeutic agents on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.9 What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapeutic agents versus one of these agents alone?
No studies identified investigating the additive risk for the combination of chemotherapeutic agents on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

Radiotherapy
1.10a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with radiotherapy exposing the renal area?
No studies identified investigating the risk for radiotherapy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.10b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with higher versus lower dose of radiotherapy?
No studies identified investigating the influence of higher versus lower dose of radiotherapy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.10c. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with radiotherapy exposing one versus both kidneys?
No studies identified investigating the influence of radiotherapy exposing one versus both kidneys on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.11 What is the influence of the actual portion (e.g., hilum/pelvis vs cortex) of a single kidney irradiated on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors?
No studies identified investigating the influence of the actual portion of a single kidney irradiated on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

Nephrectomy
1.12a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with nephrectomy?
No studies identified investigating the risk for nephrectomy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.12b. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with unilateral versus partial (unilateral/bilateral) nephrectomy?
No studies identified investigating the influence of unilateral versus partial (unilateral/bilateral) nephrectomy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

Combination
1.13a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus no nephrotoxic therapy?
1.13b. What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of chemotherapy, radiotherapy exposing the renal area, and/or nephrectomy versus one of these modalities alone?
No studies identified investigating the (additive) risk for the combination therapy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.14a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus no nephrotoxic therapy?
1.14b. What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and radiotherapy exposing the renal area versus one of these modalities alone?
No studies identified investigating the (additive) risk for the combination of chemotherapy and radiotherapy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.15a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus no nephrotoxic therapy?
1.15b. What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy and nephrectomy versus one of these modalities alone?
No studies identified investigating the (additive) risk for the combination of chemotherapy and nephrectomy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.16a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?
1.16b. What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?

No studies identified investigating the (additive) risk for the combination of radiotherapy and nephrectomy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.17a. What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus no nephrotoxic therapy?
1.17b. What is the additive risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with a combination of potential nephrotoxic chemotherapy, radiotherapy exposing the renal area and nephrectomy versus one of these modalities alone?
No studies identified investigating the risk for the combination of chemotherapy, radiotherapy and nephrectomy on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.18 What is the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with stem cell transplant?
No studies identified investigating the risk for stem cell transplant on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

<u>Other risk factors</u>
1.19 What is the influence of age at exposure on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19. Influence age at exposure cisplatin on risk combined glomerular & tubular dysfunction (n=2 studies)	Arga 2015	33 CCS of solid tumors	Median 56 months (range 12 - 174), mean 48 months after treatment	Ifosfamide: 36%; Cisplatin: 100%; Carboplatin: NM; Cyclophosphamide: at least 1; MTX: NM; Unilateral nephrectomy: NM; RT renal area: 21%	12/33 (36.4%) eGFR <90 ml/min/1.73m^2 12/33 (36.4%) hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Odds ratio (95% CI) for development nephrotoxicity* Age at treatment (years) OR 0.768 (0.6-0.98) *Odds ratio (95% CI) for severity of nephrotoxicity* Age at treatment (years) OR 0.737 (0.497-0.952)	SB: unclear AB: low risk DB: unclear CF: low risk
	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group:	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 100%; Carboplatin: 0%; MTX: 12.7%; Nephrectomy: NM;	11/27 (40%) GFR <90 ml/min/1.73m^2 10/27 (17%) Hypomagnesemia	*Correlation for nephrotoxicity score* After cisplatin, older age at treatment was correlated with higher Ns at 10 years (p = 0.02)	SB: low risk AB: low risk DB: unclear CF: high risk

		27 CCS treated with cisplatin only	RT renal area: 4.8%;	10/27 (37%) Nephrotoxicity score based on GFR and serum Mg

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Important inconsistency, 2 studies show conflicting results
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, both studies have relative small sample size, but high total number of events, and small confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		It is unclear whether there is an increased risk of age for combined glomerular & tubular dysfunction in CAYA cancer survivors treated with cisplatin due to inconsistencies between published studies. (2 studies significant effect; 96 participants; 22 events; 2 risk analyses)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; Ns, nephrotoxicity score; OR, odds ratio; RT, radiotherapy; SB, selection bias.

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
1.19 Influence age at exposure carboplatin on risk combined glomerular & tubular dysfunction (n=1 study)	Skinner 2009	63 CCS treated with platinum. Mutually exclusive treatment group: 24 CCS treated with carboplatin only	Median 10.3 yr (range 9.0 – 10.3) after cancer treatment	Ifosfamide: 0%; Cisplatin: 0%; Carboplatin: 100%; MTX: 12.7%; Nephrectomy: NM; RT renal area: 4.8%;	5/24 (21%) GFR <90 ml/min/1.73m^2 4/24 (17%) Hypomagnesemia Nephrotoxicity score based on GFR and serum Mg	*Correlation for nephrotoxicity score* After carboplatin treatment, older age was not associated with higher Ns at 10 years (p>0.05).	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	NA (only 1 study)

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with small sample size and total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effects were found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of age on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors treated with carboplatin (1 study non-significant effect; 63 participants; 5 events; 1 risk analysis)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; Mg, magnesium; MTX, methotrexate; NM, not mentioned; N, number; Ns, nephrotoxicity score; RT, radiotherapy; SB, selection bias.

1.20 What is the influence of sex on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer therapy?
No studies identified investigating the influence of sex on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.21 What is the influence of supportive care drugs (e.g., nephrotoxic antibiotics) on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?
No studies identified investigating the influence of supportive care drugs on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

1.22 What is the influence of having hypertension on the risk of combined glomerular and tubular dysfunction in CAYA cancer survivors who were treated with potentially nephrotoxic anticancer treatment?
No studies identified investigating the influence of hypertension on the risk of combined glomerular & tubular dysfunction in CAYA cancer survivors.

When should surveillance be initiated and at what frequency should surveillance be performed?

Outcome: glomerular dysfunction

2.1 When does the glomerular function start to change in CAYA cancer survivors compared to controls?

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Start change	Risk of bias
2.1 Glomerular dysfunction CCS with nephrotoxic therapy	Cozzi 2013	72 unilateral renal tumor CCS	First evaluation: Pre-op Second evaluation:	NM Preop no significant differences were	GFR < 90 at last follow-up Group A: 1 (8.3%), mean	The longitudinal analysis of eGFR in relation to age showed that patients undergoing nephrectomy experience a progressive decrease of renal function that parallels the physiological decline of renal function in	SB: low risk AB: low risk DB: unclear

compared to controls* (n= 3 studies)		Group A= 12 pts < 30 yr old who underwent NSS Group B= 42 pts < 30 yr old who underwent nephrectomy Group C= 18 pts ≥ 30 yr old who underwent nephrectomy Controls Subjects with two healthy kidneys from Rowe [1]	1st - 2nd -3rd - 4th- 5th decade Outcome: Change in eGFR	found between groups in mean eGFR	eGFR 109.8 ± 18.4 SD Group B: 18 (42.8%), mean eGFR 95.1 ± 18.5 SD Group C: 14 (77.8%), mean eGFR 76.1 ± 16.3 SD	subjects with two healthy kidneys. However, the mean ± SEM value of eGFR in patients with an age between 45 and 54 years was significantly lower than that of normal subjects (70.28 ± 6.1 vs. 128.1 ± 1.6; P<0.001)	
	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis Outcomes: 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	Mean eGFR 132 (range 130.5 - 133.6) Mean eGFR controls 139 (range 137.0 - 141.1)	Mean eGFR 95.2 (range 92.2 - 97.9) Mean eGFR controls 100.2 (range 98.1 - 102.3)	Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (p < 0.001), but there were no differences in time trends between the two groups (p = 0.11)	SB: low risk AB: low risk DB: unclear
	Dietz 2019	13,139 CCS	Linkage of CCSS cohort to OPTN database to obtain	NA	NA	Cumulative incidence 35 yr after cancer diagnosis for kidney transplantation or being on waiting list = 0.49%, 95% CI 0.36 - 0.62.	SB: low risk AB: low risk DB: unclear

		data regarding solid organ (kidney) transplantation from Oct 1, 1987 until Dec 31, 2013 <u>Outcome</u> Solid organ (kidney) transplantation
GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	0	Limitations: Selection bias low risk in 3/3, Attrition bias low in 3/3; Detection bias unclear in 3/3
<u>Consistency:</u>	0	No important inconsistency
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	0	No important imprecision, large sample size and long follow-up period
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	Not applicable
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		CAYA cancer survivors treated with nephrotoxic therapy have a progressive decrease of GFR that parallels the physiological decline of GFR also seen in healthy subjects or CCS without nephrotoxic therapy. However, they have a decreased mean GFR compared to controls (range follow-up 1st – 5th decade) (3 studies; 14,333 participants)

* The study of Dietz 2019 was included despite no comparison with controls was made, because it was assumed that kidney transplantation is not needed in healthy individuals.
Footnote 1: Rowe et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J. Gerontol 1976;31:155-163
Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; DDS, Denys-Drash syndrome; (e)GFR, (estimated) glomerular filtration rate; ESRD, end stage renal disease; FU, follow-up; GU, hypospadias/cryptorchism; NA, not applicable; NSS, nephron sparing surgery; OPTN, The Organ Procurement and Transplantation Network; pts, patients; SB, selection bias; SD, standard deviation; SEM, standard error of mean; WAGR, Wilms tumor-aniridia syndrome; WT, Wilms tumor; yr, year.

2.2 Is acute renal toxicity a risk factor for long-term glomerular dysfunction in CAYA cancer survivors?

Outcome	Study	No. of participants described cohort	Follow up (median/mean, range) yr	Nephrotoxic therapy	Events	Effect size	Risk of bias
2.2 Acute renal toxicity risk factor long-term	Park 2019	1096 CCS	Median 5 yr (range 2.26 - 6.16) after cancer diagnosis	Ifosfamide: 18.7%; Cisplatin: 28.2%; Carboplatin: 30.6%;	248/1096 (22.6%) GFR < 90 ml/minute/1.73m²	*Odds ratio (95% CI) for decreased GFR*	SB: unclear AB: high risk DB: unclear

glomerular dysfunction (n= 1 study)		MTX: 38.8%; Cyclophosphamide: 62.7%; Nephrectomy: 4.2%; RT renal area: NM	Comparison creatinine levels first yr after diagnosis versus 5 yr after diagnosis	Initial eGFR at diagnosis < 60 ml/min/1.73m^2 vs > 60 ml/min/1.73m^2 OR 1.80 (1.08 - 2.95) AKI episodes during cancer treatment: 1 time vs. no AKI OR 1.04 (0.72 - 1.50) 2-3 times vs. no AKI OR 1.19 (0.77 - 1.82) ≥ 4 times vs. no AKI OR 2.12 (1.09 - 4.03) AKI stage & time point at first onset of AKI p > 0.25 in bivariate analyses and therefore not included in MV model	CF: high risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-2	Limitations: Selection bias unclear in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect was found in this study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of glomerular dysfunction in CAYA cancer survivors with eGFR <60 vs. >60 ml/min/1.73m^2 at the time of childhood cancer diagnosis and in those having a history of ≥ 4 AKI episodes vs. no AKI episodes during cancer treatment. (1 study significant effect; 1096 participants; 248 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; AKI, acute kidney injury; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; (e)GFR, (estimated) glomerular filtration rate; DB, detection bias; MTX, methotrexate; MV, multivariable; NM, not mentioned; OR, odds ratio; RT, radiotherapy; SB, selection bias; yr, year.

2.3a Does the risk of developing glomerular dysfunction change (increase or decrease) over time in CAYA cancer survivors?

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Change GFR (increase/decrease)	Change over time	Risk of bias
2.3a Change over time glomerular dysfunction for	Cozzi 2005*	26 survivors of unilateral renal tumor (16	Yearly measurements for total 9 years	NA	NA	Decrease	Significant increase of mean serum creatinine SDS in total group with increasing	SB: low risk AB: low risk DB: unclear

survivors treated with nephrectomy or NSS (n=5 studies)		nephrectomy, 10 NSS)					postoperative follow up ($p < 0.05$), $r^2 = 0.49$. For each year of postoperative follow up 5/16 (31%) CCS with nephrectomy and 2/10 (20%) CCS with NSS had higher serum creatinine SDS	
	Cozzi 2012*	25 renal tumor CCS	First evaluation: at diagnosis Second evaluation: At last follow-up. Mean (SD): group UN: 148.6 mo (48.5), group NSS: 147.9 mo (48.5) postoperative Measurement every 2 yr <u>Outcome:</u> change in eGFR	Group UN with stage 2 CKD (n=8) eGFR 75.70 ± 25.5 Group UN with stage 1 CKD (n=7) eGFR 81.16 ± 24.74 Group NSS (n=10) eGFR 88.74 ± 26.74 No significant differences in eGFR at diagnosis among the 3 groups.	Group UN with stage 2 CKD (n=8) eGFR 79.49 ± 3.9 Group UN with stage 1 CKD (n=7) eGFR 102.3 ± 3.6 Group NSS (n=10) eGFR 107.41 ± 14.39	Increase	Group UN with stage 2 CKD Slope 1.35 - 2.04, $p > 0.05$, r^2 0.05 Group UN with stage 1 CKD Slope 0.30 - 2.93, $p < 0.05$, r^2 0.65 Group NSS (n=10) Slope 0.71 - 2.44, $p < 0.05$, r^2 0.81 At last follow-up significant difference UN with stage 2 CKD vs. stage 1 CKD: 79.49 ± 3.9 vs 102. 3± 3.6, $p < 0.05$. UN had a significant lower mean eGFR compared to NSS at last follow up.	SB: low risk AB: low risk DB: unclear
	Cozzi 2013*	72 unilateral renal tumor CCS <u>Group A</u>= 12 pts < 30 yr old who underwent NSS <u>Group B</u>= 42 pts < 30 yr old who underwent nephrectomy <u>Group C</u>= 18 pts ≥ 30 yr old who underwent nephrectomy	First evaluation: Pre-op Second evaluation: 1^{st} - 2^{nd} -3^{rd} - 4^{th}- 5^{th} decade <u>Outcome:</u> Change in eGFR	NM Preop no significant differences were found between mean eGFR	GFR < 90 at last follow-up Group A: 1 (8.3%), mean eGFR 109.8 ± 18.4 SD Group B: 18 (42.8%), mean eGFR 95.1 ± 18.5 SD Group C: 14 (77.8%), mean	1^{st} and 2^{nd} decade significant increase NSS group, not for UN group. 3^{rd} - 4^{th} and 5^{th} decade significant decrease UN group	Group A preop - 1^{st} - 2^{nd} decade: Slope 0.28 to 1.55, r^2= 0.99, p=0.03 (significant increase eGFR) Group B preop - 1^{st} - 2^{nd} decade: Slope -8.80 to 9.40, r^2= 0.51, p=0.74 Group C 3^{rd} - 4^{th} - 5^{th} decade: Slope -1.28 to -0.47, r^2= 0.99, p=0.02 (significant decrease in eGFR) <u>Comparison with healthy subjects</u>	SB: high risk AB: low risk DB: unclear

					eGFR 76.1 ± 16.3 SD		The longitudinal analysis of eGFR in relation to age showed that patients undergoing nephrectomy experience a progressive decrease of renal function that parallels the physiological decline of renal function in subjects with two healthy kidneys	
	Cozzi 2017*	36 unilateral renal tumor CCS	First evaluation: Pre-op Second evaluation: Last evaluation ≥ 13 yr post-op <u>Outcome</u> Change in eGFR	*Group without PRD (n=19)* eGFR 110.5 ± 17.9 SD *Group with PRD (n=17)* eGFR 66.7 ± 17.4 SD	*Group without PRD* eGFR 103.0 ± 20.8 SD *Group with PRD* eGFR 96.2 ± 19.1 SD	Without PRD: non-significant decrease With PRD: increase	*Nephrectomy* - pts with PRD: Significant eGFR increase over time after puberty, slope 0.095 to 1.785 (p=0.03) - pts without PRD: Non-significant eGFR decline, slope -1.832 to 0.827 (p=0.4) *NSS* - pts with PRD: Significant eGFR increase over time after puberty, slope 1.973 to 5.871 (p=0.002) - pts without PRD: Non-significant eGFR decline, slope -1.497 to 1.253 (p=0.83)	SB: low risk AB: low risk DB: unclear
	Janeczko 2015	50 Wilms tumor survivors	First evaluation: end of treatment Second evaluation: 6 - 12 - 24 months <u>Outcome</u>: abnormal GFR depending on age	*Age 12 -13 months* EoT: 6 *Age >2 years* EoT: 17	*Age 12 - 13months* 6 months: 2 12 months: 1 24 months: 0 *Age >2 years* 6 months: 17 12 months: 20 24 months: 7	Decrease	NM	SB: unclear AB: low risk DB: unclear

GRADE assessment:

<u>Study design:</u>	+4	Longitudinal cohort studies or studies investigating cumulative incidence
<u>Study limitations:</u>	-1	Limitations: Selection bias low in 3/5, unclear in 1/5, high in 1/5; Attrition bias low in 5/5; Detection bias unclear in 5/5
<u>Consistency:</u>	-1	Some inconsistency between studies (3 studies show decreased GFR, 2 studies show increased GFR)
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-1	Some imprecision, medium sample size and long follow-up period. 5 studies have possible overlap in included patients.
<u>Publication bias:</u>	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		1. GFR decreases over time in CAYA cancer survivors treated with nephrectomy until at least the 5th decade since the end of cancer treatment. (2 studies significant effect, 2 studies non-significant effect, 1 study significance unclear; 209 participants) 2. GFR increases in CAYA cancer survivors treated with NSS for at least two decades since the end of cancer treatment. (2 studies significant effect, 97 participants) 3. GFR increases in CAYA cancer survivors with PRD treated with nephrectomy or NSS until at least 13 years since end of treatment. (1 study significant effect, 36 participants)

* Possible overlap in patients between Cozzi 2005, Cozzi 2012, Cozzi 2013 and Cozzi 2017.

Abbreviations: 95% CI, 95% confidence interval; CAYA, childhood, adolescent and young adult; ; CCSS, childhood cancer survivor study; CCS, childhood cancer survivors; CF, confounding; CKD, chronic kidney disease; DB, detection bias; eGFR, estimated glomerular filtration rate; EoT, end of therapy; ESRD, end stage renal disease; FU, follow-up; GFR, glomerular filtration rate; mo, month; NA, not applicable; NM, not mentioned; NSS, nephron sparing surgery; OPTN, The Organ Procurement and Transplantation Network; post-op, post-operative; preop, pre-operative; PRD, pre-operative renal dysfunction; pts, patients; SB, selection bias; SD, standard deviation; SDS, standard deviation score; TBI, total body irradiation; UN, unilateral nephrectomy; WT, Wilms tumor; yr, year.

2.3b What is the timing of such change?

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Change GFR (increase/decrease)	Change over time	Risk of bias
2.3b Change over time glomerular dysfunction for survivors treated with BMT (n=3 studies)	Frisk 2002	40 CCS treated with autologous BMT (26 TBI+, 14 TBI-)	First evaluation: before BMT Second evaluation: 6 months post BMT Outcome: change in GFR	TBI+: GFR 124 (range 114 - 134) TBI-: GFR 129 (range 117 - 143)	TBI+: GFR 99 (range 82 - 115) TBI-: GFR 121 (range 105 - 136)	Initial decrease followed by partial improvement	Significant decrease in GFR during 6 months follow-up in TBI+ group ($p<0.001$), not in TBI- group. 7 pts in TBI+ group (27%) developed chronic renal impairment, in all pts the lowest GFR was recorded 6 months after BMT (mean 56, range 38 - 67). After improving to some extent the GFR stabilized to reduced level. The mean GFR after median of 60 months (range 67 - 85) was 76 ml/min/1.73m^2	SB: low risk AB: high risk DB: unclear
	Grönroos 2007	187 CCS treated with BMT (169 allogenic, 18 autologous)	First evaluation: before BMT Second evaluation: 1 year post BMT	Total cohort GFR 114± 39, ERPF 586± 222 Group 1*:	Total cohort GFR 85± 26, ERPF 508± 189 Per group NM	Initial decrease followed by partial improvement	Total cohort: both GFR and ERPF reduced 1 year after BMT compared to pre-BMT ($p < 0.0001$), and compared to 1 year GFR of controls ($p < 0.001$)	SB: low risk AB: low risk DB: unclear

		Controls: 50 healthy children	<u>Outcome:</u> change in GFR and ERPF	GFR 108 ± 33, ERPF 590 Group 2**: GFR 114 ± 38, ERPF 574 Group 3***: GFR 130 ± 50, ERPF 587 Controls: GFR 116 ± 11, ERPF 611 Group 1 had lower GFR compared to controls (p=0.02) * hematological malignancies ** AA & FA *** non-malignant			GFR was decreased significantly in all groups, ERPF only in group 1 (hematological malignancies) 3 years after transplantation a slight recovery in GFR after the initial fall was seen (P=0.04), after which it remained stable Renal impairment post BMT: 3 yr 31%, 7 yr 11% and 10 yr 23%	
	Patzer 2001	44 CCS treated with BMT (20 allogenic, 24 autologous) *Group A*= 41 CCS with normal renal function prior to BMT	First evaluation: Before BMT Second evaluation: 1 year post BMT 2 years post BMT <u>Outcome:</u> change in GFR	*Group A, median (range)* Before: 130 (range 73-217)	*Group A, median (range)* 1 year: 123 (range 68 - 185) 2 years: 105 (range 81 - 177) Significantly	Decrease	GFR significantly decreased at 1 and 2 years compared to before BMT	SB: low risk AB: high risk DB: unclear

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	-1	Limitations: Selection bias low in 3/3; Attrition bias low in 1/3, high in 2/3; Detection bias unclear in 3/3
<u>Consistency:</u>	0	No important inconsistency; 3 studies show significant decrease
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-1	Some imprecision, medium sample size and relative short follow-up period
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding

Quality of evidence:	⊕⊕⊖⊖ LOW
Conclusion:	GFR decreases early after treatment after which partial improvement and stabilisation occurs until at least 3 years since end of cancer treatment in CAYA cancer survivors treated with BMT. (3 studies significant effect, 271 participants)

Abbreviations: 95% CI, 95% confidence interval; AA, aplastic anemia; AB, attrition bias; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplantation; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; ERPF, effective renal plasma flow; FA, Fanconi anemia; GFR, glomerular filtration rate; NA, not applicable; NM, not mentioned; pts, patients; SB, selection bias; SD, standard deviation; TBI, total body irradiation; yr, year.

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Change GFR (increase/decrease)	Change over time	Risk of bias
2.3b Change over time glomerular dysfunction for CAYA cancer survivors (n=5 studies)	Brock 1991	40 CCS (neuroblastoma, germ cell tumor, hepatoblastoma, osteogenic sarcoma)	First evaluation: end of treatment Second evaluation: Median 2 yr 6 mo after end of treatment <u>Outcome:</u> GFR (measured by 51Cr-EDTA clearance)	GFR median 74 (range 13 to 184) GFR >80: 16/40 (40%) GFR 60-80: 13/40 (32.5%) GFR < 60: 11/40 (27.5%)	GFR Median 90 (range 27 to 135) GFR > 80: 23/40 (57.5%) GFR 60 - 80: 15/40 (37.5%) GFR <60: 2/40 (5%)	Increase	Compared to EoT, GFR at FU increased in all but 4 patients GFR improved at 1, 2 and 4 year FU with respect to EoT GFR ($p < 0.05$) CCS with EoT GFR 60-80 had better chance of regaining GFR 80 at median FU time than CCS with EoT GFR <60 ($p< 0.01$)	SB: low risk AB: low risk DB: unclear
	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	Mean eGFR 132 (range 130.5 - 133.6) Mean eGFR controls 139 (range 137.0 - 141.1)	Mean eGFR 95.2 (range 92.2 - 97.9) Mean eGFR controls 100.2 (range 98.1 - 102.3)	Decrease	GFR declined in both groups during follow up, $p < 0.001$. The differences in GFR between both groups were highly significant ($P < 0.001$), but the differences in time trends were not ($P = 0.04$)	SB: low risk AB: low risk DB: unclear

	Grönroos 2008	28 CCS (ALL and lymphoma)	First evaluation: pre-treatment Second evaluation: at follow-up (median 6.0 years, range 1.0 -10.0) <u>Outcome:</u> change in iGFR	Mean iGFR 136.7 (range 87 - 237) Mean GFR by Schwartz 109.4 (range 79.5 - 152.3)	Mean iGFR 113.9 (SD 24.2, range 75.7 - 185.6) iGFR ≥ 115 n=11 (39%) iGFR 90 - 114 n=14 (50%) iGFR ≤ 89 n=3 (11%)	Decrease	The iGFR declined significantly with increasing follow-up time (p=0.02) In subgroup of 17 pts with isotope GFR measurement pre-treatment and during follow-up the mean iGFR dropped from 136.7 (pre-treatment) to 118.8 (follow-up), but not significantly	SB: unclear AB: low risk DB: unclear
	Skinner 2009	63 CCS treated with platinum	First evaluation: End of treatment Second evaluation: 1 year and 10 years post treatment <u>Outcome:</u> GFR change over time	Normal GFR >90 and median (range) *Cisplatin alone* End: 40%, median 84 (18 - 197) *Carboplatin alone* End: 80%, median 120 (68 - 207) *Cisplatin and carboplatin* End: 80%, median 91 (45 - 160)	Normal GFR >90 and median (range) *Cisplatin alone* 1 year: 62%, median 98 (25 - 130) 10 years: 60%, median 96 (29 - 142) *Carboplatin alone* 1 year: 81%, median 109 (63 - 161) 10 years: 79%, median 110 (66 - 171) *Cisplatin and carboplatin* 1 year: 75%, median 93 (55 - 131) 10 years: 55%, median 92 (66 - 135)	Considerable inter-individual patient variability	There was no significant change with time in any of the measures of nephrotoxicity in any treatment group, nor in the proportion with clinically significant complications or ongoing treatment with supplements.	SB: low risk AB: low risk DB: unclear

	Skinner 2010	25 CCS treated with ifosfamide	First evaluation: end of treatment Second evaluation: 1 year and 10 years post treatment Outcome: GFR change over time	GFR<60= 0%	GFR <60 1 year: 4% 10 years: 13%	Considerable interpatient variability	GFR change over time: End - 1 year: -17.5 (-24.5, -11.5), p = 0.006 End - 10 years: -11.5 (-21.0, 1.5), p= 0.22 1 year - 10 years: 5.5 (-2.0, 12.0), p=0.13 There was considerable interpatient variability in the severity of renal toxicity and in changes with time (GFR)	SB: low risk AB: low risk DB: unclear

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	0	Limitations: Selection bias low in 4/5, unclear in 1/5; Attrition bias low in 5/5; Detection unclear in 5/5
Consistency:	-1	Important inconsistency; 2 studies show significant decrease, 1 study significant increase, 2 studies show non-significant results
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, long follow-up period, but majority of studies small sample size
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		It is unclear whether the trajectory of GFR changes over time in in CAYA cancer survivors because published studies are incomparable with respect to treatment. (2 studies significant decrease, 1 study significant increase, 2 studies considerable interpatient variability; 1278 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; eGFR, estimated glomerular filtration rate; EoT, end of therapy; FU, follow-up; GFR, glomerular filtration rate; iGFR, isotope glomerular filtration rate; mo, month; NA, not applicable; NM, not mentioned; post-op, pts, patients; SB, selection bias; SD, standard deviation; yr, year.

2.4 What are predictors for change of risk over time in glomerular dysfunction in CAYA cancer survivors?

Summary of findings per possible predictor.

Ifosfamide

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Ifosfamide as predictor for change over time glomerular dysfunction (n= 2 studies)	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	GFR declined in both groups during follow up, p < 0.001. The differences in GFR between both groups were highly significant (P < 0.001), but the differences in time trends were not (P = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1-5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (P < 0.001), but there were no differences in time trends between the two groups (P = 0.11)	<u>Linear effects model:</u> Ifosfamide by time interaction p=0.08, Ifosfamide dose by time interaction p=0.09 No significantly different GFR pattern over time for CCS treated with and without ifsofamide	SB: low risk AB: low risk DB: unclear CF: low risk
	Skinner 2010	25 CCS treated with ifosfamide	First evaluation: end of treatment Second evaluation: 1 year and 10 years post treatment	GFR change over time: End - 1 year: -17.5 (-24.5, -11.5), p = 0.006 End - 10 years: -11.5 (-21.0, 1.5), p = 0.22 1 year - 10 years: 5.5 (-2.0, 12.0), p = 0.13	No correlation between cumulative ifosfamide dose and GFR at any timepoint	SB: low risk AB: low risk DB: unclear CF: high risk

		Outcome: GFR change over time	There was considerable interpatient variability in the severity of renal toxicity and in changes with time (GFR)

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of participants.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		No significant effect of ifosfamide dose on the change of glomerular function over time in CAYA cancer survivors. (2 studies non-significant effect; 1147 participants)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; SB, selection bias.

Cisplatin

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Cisplatin as predictor for change over time glomerular dysfunction (n= 2 studies)	Brock 1991	40 CCS (neuroblastoma, germ cell tumor, hepatoblastoma, osteogenic sarcoma)	First evaluation: end of treatment Second evaluation: Median 2 yr 6 mo after end of treatment Outcome: GFR (measured by 51Cr-EDTA clearance)	Compared to EoT, GFR at FU increased in all but 4 patients GFR improved at 1, 2 and 4 year FU with respect to EoT GFR ($p < 0.05$) CCS with EoT GFR 60 - 80 had better chance of regaining GFR 80 at median FU time than CCS with EoT GFR <60 ($p < 0.01$)	No association between GFR and total cisplatin dose	SB: low risk AB: low risk DB: unclear CF: unclear
	Mulder 2013	1122 CCS of miscellaneous malignancies	First evaluation: 5 years after diagnosis	GFR declined in both groups during follow up, $p < 0.05$. The differences in GFR	Linear effects model: Cisplatin by time interaction $p < 0.001$, cisplatin dose by time interaction $p < 0.001$	SB: low risk AB: low risk DB: unclear

		Controls: 251 CCS treated without nephrotoxic therapy	Second evaluation: 35 years after diagnosis Outcomes: 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	between both groups were highly significant (P < 0.001), but the differences in time trends were not (P = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (P < 0.001), but there were no differences in time trends between the two groups (P = 0.11)	Higher deterioration rate in CCS with higher doses of cisplatin vs. lower doses up to 25 years after diagnosis	CF: low risk

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	0	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 1/2, unclear in 1/2
Consistency:	0	No important inconsistency, 1 study shows significant effects, 1 study shows non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of participants. Only 1 study reported a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		More rapid deterioration rate of GFR in CAYA cancer survivors treated with higher vs. lower cisplatin doses up to 25 years after diagnosis. (1 study significant effect, 1 study non-significant effect; 1162 participants)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; EoT, end of treatment; FU, follow-up; GFR, glomerular filtration rate; mo, month; SB, selection bias; yr, year.

Carboplatin

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Carboplatin as predictor for change over time glomerular dysfunction (n= 1 study)	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	GFR declined in both groups during follow up, p < 0.05. The differences in GFR between both groups were highly significant (P < 0.001), but the differences in time trends were not (P = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1- 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (p < 0.001), but there were no differences in time trends between the two groups (p = 0.11)	<u>Linear effects model:</u> Carboplatin by time interaction p = 0.24, carboplatin dose by time interaction p = 0.06	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort study
<u>Study limitations:</u>	0	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; confounding low in 1/1

Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with large sample size
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODDERATE
Conclusion:		No significant effect of carboplatin dose on the change of glomerular function over time in CAYA cancer survivors. (1 study non-significant effect; 1122 participants)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; SB, selection bias.

Methotrexate

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Methotrexate as predictor for change over time glomerular dysfunction (n= 2 studies)	Grönroos 2008	28 CCS (ALL and lymphoma)	First evaluation: pre-treatment Second evaluation: at follow-up (median 6.0 years, range 1.0 - 10.0) Outcome: change in iGFR	The iGFR declined significantly with increasing follow-up time (p = 0.02) In subgroup of 17 pts with isotope GFR measurement pre-treatment and during follow-up the mean iGFR dropped from 136.7 (pre-treatment) to 118.8 (follow-up), but not significantly	No significant influence on change of iGFR by dose of MTX (5 or 8 g/m^2) and cumulative MTX dose	SB: unclear AB: low risk DB: unclear CF: low risk
	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis Outcomes: 1. Comparison mean GFR with controls	GFR declined in both groups during follow up, p < 0.05. The differences in GFR between both groups were highly significant (P < 0.001), but the differences in time trends were not (P = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis	Linear effects model: HD-MTX (>1 g/m^2/course) by time interaction p = 0.17	SB: low risk AB: low risk DB: unclear CF: low risk

		2. Linear random effects model continuous GFR 3. Logistic regression model (GFR <90)	CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant ($p < 0.001$), but there were no differences in time trends between the two groups ($p = 0.11$)

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	0	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 2/2
Consistency:	0	No important inconsistency, 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of participants.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		No significant effect of HD-methotrexate (>5 g/m^2) on the change of glomerular function over time in CAYA cancer survivors. (2 studies non-significant effect; 1150 participants)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; iGFR, isotope glomerular filtration rate; MTX, methotrexate; SB, selection bias.

Nitrosoureas

No studies identified.

Melphalan

No studies identified.

Cyclophosphamide

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Cyclophosphamide as predictor for change over time glomerular dysfunction (n= 3 studies)	Grönroos 2007	187 CCS treated with BMT (169 allogenic, 18 autologous) Controls: 50 healthy children	First evaluation: before BMT Second evaluation: 1 year post BMT <u>Outcome:</u> change in GFR and ERPF	Total cohort: both GFR and ERPF reduced 1 year after BMT compared to pre-BMT ($p < 0.0001$), and compared to 1 year GFR of controls ($p < 0.001$) GFR was decreased significantly in all groups, ERPF only in group 1 (hematological malignancies) 3 years after transplantation a slight recovery in GFR after the initial fall was seen ($P=0.04$) , after which it remained stable Renal impairment post BMT: 3 yr 31%, 7 yr 11% and 10 yr 23%	No differences in GFR or ERPF in pts treated with/without cyclo before BMT and during follow up	SB: low risk AB: low risk DB: unclear CF: high risk
	Janeczko 2015	50 Wilms tumor survivors	First evaluation: end of treatment Second evaluation: 6 - 12 - 24 months <u>Outcome</u>: abnormal GFR depending on age	NM	No difference over time between cyclo/carbo and non-cyclo/carbo	SB: unclear AB: low risk DB: unclear CF: high risk
	Mulder 2013	1122 CCS of miscellaneous malignancies	First evaluation: 5 years after diagnosis	GFR declined in both groups during follow up, $p < 0.05$. The differences in GFR	<u>Linear effects model:</u> HD-cyclophosphamide by time interaction, $p = 0.006$	SB: low risk AB: low risk DB: unclear

		Controls: 251 CCS treated without nephrotoxic therapy	Second evaluation: 35 years after diagnosis Outcomes: 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR < 90)	between both groups were highly significant (P < 0.001), but the differences in time trends were not (p = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (p < 0.001), but there were no differences in time trends between the two groups (p = 0.11)	CCS treated with and without HD-cyclophosphamide showed different GFR time trends, although differences were small	CF: low risk

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; confounding low in 1/3, high in 2/3
Consistency:	0	No important inconsistency, 1 study shows significant effects, 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of participants. Only 1 study reported a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Modest differences in rate of GFR deterioration between survivors treated with HD- (≥1 g/m^2/course or a total cumulative dose of ≥10 g/m^2) vs. non-HD-cyclophosphamide.

(1 study significant effect, 2 studies non-significant effect; 1359 participants)

Abbreviations: AB, attrition bias; BMT, bone marrow transplantation; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; carbo, carboplatin; CF, confounding; cyclo, cyclophosphamide; DB, detection bias; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; HD, high-dose; NM, not mentioned; SB, selection bias.

Radiotherapy renal area

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 RT renal area as predictor for change over time glomerular dysfunction (n= 2 studies)	Grönroos 2007	187 CCS treated with BMT (169 allogenic, 18 autologous) Controls: 50 healthy children	First evaluation: before BMT Second evaluation: 1 year post BMT <u>Outcome:</u> change in GFR and ERPF	Total cohort: both GFR and ERPF reduced 1 year after BMT compared to pre-BMT ($p < 0.0001$), and compared to 1 year GFR of controls ($p < 0.001$) GFR was decreased significantly in all groups, ERPF only in group 1 (hematological malignancies) 3 years after transplantation a slight recovery in GFR after the initial fall was seen ($p = 0.04$) , after which it remained stable Renal impairment post BMT: 3 yr 31%, 7 yr 11% and 10 yr 23%	In the TBI + group, the fall in GFR and ERPF after BMT was more profound than in the TBI- group at all time points ($p = 0.02$)	SB: low risk AB: low risk DB: unclear CF: high risk

	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR < 90)	GFR declined in both groups during follow up, p < 0.05. The differences in GFR between both groups were highly significant (p < 0.001), but the differences in time trends were not (p = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (p < 0.001), but there were no differences in time trends between the two groups (p = 0.11)	<u>Linear effects model:</u> RT kidney region by time interaction p = 0.04 (p <0.01 was considered significant)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 1/2, high in 1/2
<u>Consistency:</u>	0	No important inconsistency, 1 study shows significant effect for TBI, 1 study shows non-significant effects
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-1	Some imprecision, high total number of participants. Only 1 study reported a significant effect
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding

Quality of evidence:	⊕⊕⊖⊖ LOW
Conclusion:	Higher deterioration rate of GFR and ERPF in CAYA cancer survivors treated with TBI vs. no TBI. No significant effect of RT on the kidney region on the change of glomerular function over time in CAYA cancer survivors. (1 study significant effect, 1 study non-significant effect; 1309 participants)

Abbreviations: AB, attrition bias; BMT, bone marrow transplantation; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; RT, radiotherapy; SB, selection bias; TBI, total body irradiation.

Nephrectomy

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Nephrectomy as predictor for change over time in glomerular dysfunction (n= 2 studies)	Janeczko 2015	50 Wilms tumor survivors	First evaluation: end of treatment Second evaluation: 6 - 12 - 24 months <u>Outcome</u>: abnormal GFR depending on age	NM	No difference over time between nephrectomy and NSS	SB: unclear AB: low risk DB: unclear CF: high risk
	Mulder 2013	1122 CCS of miscellaneous malignancies Controls: 251 CCS treated without nephrotoxic therapy	First evaluation: 5 years after diagnosis Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR < 90)	GFR declined in both groups during follow up, $p < 0.05$. The differences in GFR between both groups were highly significant ($p < 0.001$), but the differences in time trends were not ($p = 0.04$) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis	<u>Linear effects model:</u> Nephrectomy by time interaction $p = 0.26$,	SB: low risk AB: low risk DB: unclear CF: low risk

		CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant ($p < 0.001$), but there were no differences in time trends between the two groups ($p = 0.11$)
GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, 2 studies show non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of participants. Only 1 study reported a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant effect of nephrectomy on the change of glomerular function over time in CAYA cancer survivors. (2 studies non-significant effect; 1172 participants)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; NM, not mentioned; NSS, nephron sparing surgery; SB, selection bias.

HSCT

No studies identified.

Age at treatment

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Age at treatment as predictor for change over	Mulder 2013	1122 CCS of miscellaneous malignancies	First evaluation: 5 years after diagnosis	GFR declined in both groups during follow up, $p < 0.05$. The differences in GFR between both groups were highly significant ($p < 0.001$),	Linear effects model: Nephrectomy age at diagnosis $p = 0.002$ Faster decline in GFR in CCS nephrectomized at an older vs. younger age	SB: low risk AB: low risk DB: unclear CF: low risk

time glomerular dysfunction (n= 3 studies)		Controls: 251 CCS treated without nephrotoxic therapy	Second evaluation: 35 years after diagnosis <u>Outcomes:</u> 1. Comparison mean GFR with controls 2. Linear random effects model continuous GFR 3. Logistic regression model (GFR < 90)	but the differences in time trends were not (p = 0.04) Mean glomerular dysfunction probability (95% CI) At 15 years after diagnosis CCS treated with nephrotoxic therapy 5.4% (4.0 - 7.4) CCS treated without nephrotoxic therapy 1.7% (0.1 - 5.2) At 35 years after diagnosis CCS treated with nephrotoxic therapy 26.4% (20.6 - 33.0) CCS treated without nephrotoxic therapy 6.6% (4.4 - 9.6) These differences were highly significant (p < 0.001), but there were no differences in time trends between the two groups (p = 0.11)		
	Skinner 2010	25 CCS treated with ifosfamide	First evaluation: end of treatment Second evaluation: 1 year and 10 years post treatment <u>Outcome:</u> GFR change over time	GFR change over time: End - 1 year: -17.5 (-24.5, -11.5), p = 0.006 End - 10 years: -11.5 (-21.0, 1.5), p = 0.22 1 year - 10 years: 5.5 (-2.0, 12.0), p = 0.13 There was considerable interpatient variability in the severity of renal toxicity and in changes with time (GFR)	No correlation between age at treatment and GFR at any timepoint	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; confounding low in 1/2, high in 1/2

Consistency:	0	No important inconsistency, 1 study show significant effect for age nephrectomy, 1 study shows non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of participants. Only 1 study reported a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Faster decline in GFR in CAYA cancer survivors treated with nephrectomy at an older vs. younger age. (1 study significant effect, 1 study non-significant effect; 1147 participants)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; HR, hazard ratio; SB, selection bias.

Sex

No studies identified.

Other predictors

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Other predictors for change over time glomerular dysfunction (n= 2 studies)	Grönroos 2008	28 CCS (ALL and lymphoma)	First evaluation: pre-treatment Second evaluation: at follow-up (median 6.0 years, range 1.0 - 10.0) Outcome: change in iGFR	The iGFR declined significantly with increasing follow-up time (p = 0.02) In subgroup of 17 pts with isotope GFR measurement pre-treatment and during follow-up the mean iGFR dropped from 136.7 (pre-treatment) to 118.8 (follow-up), but not significantly	No significant influence on change of iGFR by simultaneous use of amphotericin B, vancomycin or gentamycin.	SB: unclear AB: low risk DB: unclear CF: low risk
	Patzer 2001	44 CCS treated with BMT (20 allogenic, 24 autologous) *Group A*= 41 CCS with normal renal	First evaluation: Before BMT Second evaluation: 1 year post BMT 2 years post BMT	GFR significantly decreased at 1 and 2 years compared to before BMT	No significant differences with respect to: - acute renal failure within 30 days after HSCT vs no doubling of creatinine - initial disease - type of conditioning (TBI or not) - kind of HSCT (allo vs auto) - presence of GVHD at time of investigation	SB: low risk AB: high risk DB: unclear CF: high risk

		function prior to BMT	Outcome: change in GFR

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-2	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, small total number of participants.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of the following predictors on the change of glomerular dysfunction over time in CAYA cancer survivors: simultaneous use of amphotericin B, vancomycin or gentamycin; acute renal failure within 30 days after HSCT vs no doubling of creatinine, type of HSCT (allo vs auto), presence of GVHD at time of investigation. (2 studies non-significant effect; 72 participants)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; allo, allogenic; auto, autologous; BMT, bone marrow transplantation; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; GFR, glomerular filtration rate; GVHD, graft versus host disease; HSCT, hematological stem cell transplantation; iGFR, isotope glomerular filtration rate; pts, patients; SB, selection bias; TBI, total body irradiation.

Outcome: tubular dysfunction

2.1 When does the tubular function start to change in CAYA cancer survivors compared to controls?

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Start Change	Risk of bias
2.1 Start change tubular dysfunction (n= 1 study)	Rossi 1999	75 CCS treated with ifosfamide	First evaluation: End of first year Second evaluation: End of second year Outcome 1. Fanconi syndrome	Reduced amino acid reabsorption Cumulative probability 18% Impaired phosphate reabsorption	Reduced amino acid reabsorption Cumulative probability 28% Impaired phosphate reabsorption	Fanconi syndrome Total cumulative probability 9.6% (SD 4.3%) This occurred up to 3 years off therapy Generalized subclinical tubulopathies Total cumulative probability 17% (SD 4.5%) This developed within the first 2 years off therapy only Reduced amino acid reabsorption Cumulative probabilities:	SB: unclear AB: low risk DB: unclear

		2. Generalized subclinical tubulopathies 3. Reduced amino acid reabsorption 4. Impaired phosphate reabsorption	Cumulative probability 8%	Cumulative probability 14%	End of first year: 18% End of second year: 28% Total 38.3% (SD 8.5%) Impaired phosphate reabsorption Cumulative probabilities: End of first year: 8% End of second year: 14% Total 30.6% (SD 8.9%)

GRADE assessment:		
Study design:	+4	Longitudinal cohort study
Study limitations:	-1	Limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included with medium number of patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		In CAYA cancer survivors treated with ifosfamide, the risk of tubular dysfunction increases over time until at least 3 years following therapy (1 study; 75 participants)

Abbreviations: AB, attrition bias; DB, detection bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; NA, not applicable; SB, selection bias; SD, standard deviation.

2.2 Is acute renal toxicity a risk factor for long-term tubular dysfunction in CAYA cancer survivors?
No studies identified investigating acute renal toxicity as a risk factor for long-term tubular dysfunction in CAYA cancer survivors.

2.3a Does the risk of developing tubular dysfunction change (increase or decrease) over time in CAYA cancer survivors?
2.3b What is the timing of such change?

PICO	Study	No. of participants	Timing / outcome	1st evaluation	2nd evaluation	Change tubular function (increase/decrease)	Change over time	Risk of bias

2.3a Change over time tubular dysfunction (n= 5 studies)	Janeczko 2015	50 WT survivors	First evaluation: Beginning treatment End of treatment Second evaluation: 6 months 12 months 24 months <u>Outcome</u> Serum sodium Serum potassium Serum phosphate	<u>Sodium</u> *Decreased* Beginning treatment: 39% EoT: 17% *Increased* Beginning treatment: 0% EoT: 0% <u>Potassium</u> *Decreased* Beginning treatment: 4% EoT: 2% *Increased* Beginning treatment: 12% EoT: 4% <u>Phosphate</u> *Decreased* Beginning treatment: 46% EoT: 27% *Increased* Beginning treatment: 12% EoT: 32%	<u>Sodium</u> *Decreased* 6 months: 21% 12 months: 6% 24 months: 0% *Increased* 6 months: 0% 12 months: 2% 24 months: 0% <u>Potassium</u> *Decreased* 6 months: 0% 12 months: 0% 24 months: 3% *Increased* 6 months: 19% 12 months: 25% 24 months: 12% <u>Phosphate</u> *Decreased* 6 monhts: 57% 12 months: 18% 24 monhts: 22% *Increased* 6 months: 14% 12 months: 27% 24 months: 22%	<u>Sodium</u> No statistical analyses performed <u>Potassium</u> No statistical analyses performed <u>Phosphate</u> No statistical analyses performed	Conclusion authors: the deterioration of kidney function in most cases is not serious	SB: unclear AB: low risk DB: unclear
	Patzer 2001	44 CCS treated with BMT (20 allogenic, 24 autologous) *Group A*= 41 CCS with normal renal function prior to BMT	First evaluation: Before BMT Second evaluation: 1 year post BMT 2 years post BMT <u>Outcome:</u> change in:	*Group A, median (range)* <u>TP/Cl_{cr}</u> Before: 1.21 (0.51 -1.75)	*Group A, median (range)* <u>TP/Cl_{cr}</u> 1 year: 1.11 (0.56 - 1.64) 2 years: 1.08 (0.53 -1.44)	<u>TP/Cl_{cr}</u> Decreased <u>α1-mg</u> Stable <u>β-NAG</u> Decreased	1. TP/Cl_{cr} significantly decreased at 1 and 2 years compared to before 2. α1-mg no significant differences	SB: low risk AB: high risk DB: unclear

			1. TP/Cl_{cr} (mmol/l) 2. α1-mg (mg/mmol creat) 3. β-NAG (U/mmol creat)	<u>α1-mg</u> Before: 0.98 (0.02 -9.9) <u>β-NAG</u> Before: 0.45 (0.16 -1.7)	<u>α1-mg</u> 1 year: 0.66 (0.03 - 23.2) 2 years: 0.63 (0.03 -17.12) <u>β-NAG</u> 1 year: 0.27 (0.05 - 1.4) 2 years: 0.22 (0.06 -1.13)		3. β-NAG significantly decreased at 1 and 2 years compared to before	
	Skinner 2010*	25 CCS treated with ifosfamide	First evaluation: end of treatment Second evaluation: 1 year and 10 years post treatment <u>Outcome</u> Serum phosphate Serum bicarbonate Tmp/GFR	Percentage normal <u>Phosphate</u> EoT: 78% EoT: 78% 1 yr: 72% <u>Bicarbonate</u> EoT: 65% EoT: 65% 1 yr: 64% <u>Tmp/GFR</u> EoT: 52% EoT: 52% 1 yr: 50%	Percentage normal <u>Phosphate</u> 1 yr: 78%, p=1.0 10 yr: 91%, p=0.38 10 yr: 92%, p=0.13 <u>Bicarbonate</u> 1yr: 61%, p=1.0 10 yr: 74%, p=0.73 10 yr: 72%, p=0.77 <u>Tmp/GFR</u> 1 yr: 52%, p=1.0 10 yr: 33%, p=0.39 10 yr: 38%, p=0.58	<u>Phosphate</u> Decrease (not significant) <u>Bicarbonate</u> Increase (not significant) <u>TmP/GFR</u> Stable	<u>Serum phosphate</u> End - 1 year: 0.00 (-0.09, 0.09), p = 1.0 End - 10 years: -0.20 (-0.36, 0.0), p = 0.38 1 year - 10 years: -0.17 (-0.29, 0.01), p = 0.13 <u>Serum bicarbonate</u> End - 1 year: 0.00 (-2.0, 1.5), p = 1.0 End - 10 years: 2.0 (0.5, 3.5), p = 0.73 1 year - 10 years: 2.0 (0.0, 4.0), p = 0.77 <u>Tmp/GFR</u> End - 1 year: 0.5 (-1.0, 1.0), p = 1.0 End - 10 years: 0.0 (-1.5, 1.0), p = 0.45 1 year - 10 years: -0.5 (-2.0, 0.5), p = 0.51 <u>Electrolyte supplementation:</u> End of treatment: 32% (phosphate 28%, potassium 8%) 1 yr: 24% (phosphate 24%, additional bicarbonate,	SB: low risk AB: low risk DB: unclear

		potassium, calcium and 1α-cholecalciferol in 4%) 10 yr: 0% End vs 10 years p = 0.008, 1 vs 10 years p = 0.03 At end of treatment: higher cumulative ifosfamide dose correlated to increased tubular toxicity (lower phosphate (p = 0.03) and bicarbonate (p = 0.002)). An increase in cumulative ifosfamide dose of 36 g/m2 was associated with a fall in phosphate of 0.14 (95% CI 0.02-0.25) mmol/L, and in bicarbonate of 1.18 (0.53 - 1.82) mmol/L. At 1 year: higher ifosfamide dose correlated to lower phosphate (p = 0.02) and renal tubular threshold (P=0.008). At 10 years: no correlation between ifosfamide dose and nephrotoxicity (p = 0.85, 0.69 and 0.79, respectively, for phosphate, bicarbonate, renal tubular threshold). An increase in ifosfamide dose of 36 g/m^2 was associated with much smaller falls in phosphate (0.009 mmol/L) and bicarbonate (0.17 mmol/L) with 95% CI phosphate -0.081 to 0.098 and bicarbonate -0.70 to 1.04.

	Skinner 2009*	63 CCS treated with platinum	First evaluation: End of treatment Second evaluation: 1 year and 10 years post treatment <u>Outcome:</u> 1. Hypocalcemia 2. Hypomagnesemia	<u>Normal calcium and median (range)</u> *Cisplatin alone* End: 90%, median 2.45 (2.02 - 2.60) *Carboplatin alone* End: 100%, median 2.42 (2.25 - 2.59) *Cisplatin and carboplatin* End: 100%, median 2.39 (2.18 - 2.61) <u>Normal Magnesium and median (range)</u> *Cisplatin alone* End: 48%, median 0.68 (0.32 - 0.93) *Carboplatin alone*	<u>Normal calcium and median (range)</u> *Cisplatin alone* 1 year: 100%, median 2.47 (2.19 - 2.66) 10 years: 100%, median 2.38 (2.18 - 2.53) *Carboplatin alone* 1 year: 100%, median 2.48 (2.34 - 2.58) 10 years: 100%, median 2.39 (2.28 - 2.59) *Cisplatin and carboplatin* 1 year: 100%, median 2.46 (2.24 - 2.55) 10 years: 100%, median 2.36 (2.23 - 2.53) <u>Normal Magnesium and median (range)</u> *Cisplatin alone* 1 year: 50%, median 0.70 (0.44 - 0.95) 10 years: 63%, median 0.73 (0.37 - 0.83) *Carboplatin alone*	Considerable inter-individual patient variability	There was no significant change with time in any of the measures of nephrotoxicity in any treatment group, nor in the proportion with clinically significant complications or ongoing treatment with supplements.	SB: low risk AB: low risk DB: unclear

				End: 74%, median 0.77 (0.42 - 0.89) *Cisplatin and carboplatin* End: 55%, median 0.74 (0.62 - 0.98)	1 year: 73%, median 0.78 (0.51 - 0.90) 10 years: 83%, median 0.77 (0.54 - 0.94) *Cisplatin and carboplatin* 1 year: 92%, median 0.80 (0.69 - 0.89) 10 years: 91%, median 0.81 (0.68 - 0.92)			
	Stohr 2007	435 CCS of sarcoma treated with platinum derivates Controls: CCS not treated with platinum derivates	First evaluation: end of treatment Second evaluation: 1 yr 2 yr 3 yr <u>Outcome</u> Hypomagnesemia	<u>Hypomagnesemia</u> EoT: 8.9%	<u>Hypomagnesemia</u> Last examination: 3.1%	<u>Magnesium</u> Improved first year, stable thereafter	Serum magnesium increased during the first year after therapy and remained stable thereafter. This was confirmed in 74 patients who had three yearly examinations during 2 years of follow-up: statistically significant increase in serum magnesium by 0.03 mmol/L (95% CI 0.01 - 0.06 mmol/L) in the first year and remained unchanged thereafter.	SB: unclear AB: high risk DB: unclear

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	0	Limitations: Selection bias low in 3/5, unclear in 2/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5
<u>Consistency:</u>	0	No important inconsistency, all studies used different outcome measures of tubular dysfunction and are not comparable
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, except for one study small sample sizes. Studies used different outcomes. For outcomes with a significant effect, this was reported by only 1 study
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW

Conclusion:	Hypomagnesemia occurs at low levels 1 year after therapy and remains stable up to at least 3 years after platinum therapy in CAYA cancer survivors. (1 study significant; 435 participants) The need for supplementation of phosphate and potassium decreases over time and may no longer be needed in CAYA cancer survivors at 10 years after ifosfamide treatment (1 study significant, 25 participants) Increasing ifosfamide dose is associated with statistically significant falls in phosphate and bicarbonate levels at the end of treatment, but not 10 years later. (1 study significant effect, 25 participants) No significant changes over time for other tubular outcomes including serum sodium, calcium, bicarbonate, α1-mg, and TmP/GFR . (4 studies non-significant; 182 participants)
Comments:	Note differences in outcome definitions used for tubular dysfunction: 2 studies serum magnesium; 2 studies serum phosphate; 1 study serum sodium, potassium; 1 study TP/CL_{cr}, α1-mg, β-NAG; 1 study serum bicarbonate, TmP/GFR; 1 study serum calcium.

Abbreviations: α1-mg, α1-microglobuline; β-NAG, β-N-acetylglucosaminidase; AB, attrition bias; BMT, bone marrow transplantation; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; creat, creatinine; EoT, end of treatment; NM, not mentioned; SB, selection bias; Tmp/GFR, renal tubular threshold for phosphate; TP/Cl_{cr}, tubular phosphate reabsorption; WT, Wilms tumor; yr, year.

* No overlap in included patients in studies of Skinner 2009 and Skinner 2010.

2.4 What are predictors for change of risk over time in tubular dysfunction in CAYA cancer survivors?

PICO	Study	No. of participants	Timing / outcome	Change over time	Predictors	Risk of bias
2.4 Predictors for change over time tubular function (n= 2 studies)	Patzer 2001	44 CCS treated with BMT (20 allogenic, 24 autologous) *Group A* = 41 CCS with normal renal function prior to BMT	First evaluation: Before BMT Second evaluation: 1 year post BMT 2 years post BMT <u>Outcome:</u> change in: 1. TP/Cl_{cr} (mmol/l) 2. α1-mg (mg/mmol creat) 3. β-NAG (U/mmol creat)	1. TP/Cl_{cr} significantly decreased at 1 and 2 years compared to before 2. α1-mg no significant differences 3. β-NAG significantly decreased at 1 and 2 years compared to before	TP/Cl_{cr} and α1-mg: No significant differences with respect to earlier ifosfamide therapy, type of HSCT (allo vs auto), use of RT, occurrence of acute renal insufficiency, presence of chronic GVHD, CyA therapy 1 year after HSCT	SB: low risk AB: high risk DB: unclear CF: high risk

	Stohr 2007	435 CCS of sarcoma Controls: CCS not treated with platinum derivates	First evaluation: end of treatment Second evaluation: 1 yr 2 yr 3 yr <u>Outcome</u> Hypomagnesemia	Serum magnesium increased during the first year after therapy and remained stable thereafter. This was confirmed in 74 patients who had three yearly examinations during 2 years of follow-up: statistically significant increase in serum magnesium by 0.03 mmol/L (95% CI 0.01 - 0.06 mmol/L) in the first year and remained unchanged thereafter.	Cisplatin by time interaction, p = 0.78 Carboplatin by time interaction, p = 0.59 Abdominal RT by time interaction, p = 0.76	SB: unclear AB: high risk DB: unclear CF: low risk longitudinal analysis, high risk other analysis

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	-2	Limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias high in 2/2; Detection bias unclear in 2/2; confounding high in 2/2
<u>Consistency:</u>	0	No important inconsistency, 2 studies show non-significant effects
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-1	Important imprecision, small sample sizes.
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of predictors (including ifosfamide, cisplatin, carboplatin, abdominal RT, type of HSCT (allo vs auto), occurrence of acute renal insufficiency, presence of chronic GVHD, CyA therapy 1 year after HSCT) on the change of tubular function over time. (2 studies non-significant effects, 479 participants)
Comments:		Note differences in used outcome definitions for tubular dysfunction: 1 study TP/CL_{cr}, α1-mg, β-NAG; 1 study serum magnesium; 1 study serum phosphate, bicarbonate, TmP/GFR.

Abbreviations: α1-mg, α1-microglobuline; β-NAG, β-N-acetylglucosaminidase; AB, attrition bias; allo, allogeneical; auto, autologous; BMT, bone marrow transplantation; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; creat, creatinine; CyA, cyclosporine; DB, detection bias; GVHD, graft versus host disease; HSCT, hematological stem cell transplantation; RT, radiotherapy; SB, selection bias; Tmp/GFR, renal tubular threshold for phosphate; TP/Cl_{cr}, tubular phosphate reabsorption.

What surveillance modality should be used?

3.1 What methods are available to detect an abnormal GFR? What is the diagnostic value of GFR equations versus filtration of an exogenous filtration marker in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
3.1 Diagnostic value of GFR equations for detecting glomerular dysfunction (n= 5 studies)	Green 2020	40 WT survivors 35 non-cancer controls	Non RT average 26.9 yrs RT average 30.1 yrs	1. CKD-EPI 2012 creatinine based 2. CKD-EPI 2012 creatinine + cystatin C based 3. ^{99m}Tc DTPA plasma clearance 4. 24-hour creatinine clearance	NA	<u>Correlation estimates</u> Plasma ^{99m}Tc clearance did not correlate with eGFR using the creatinine only equations for either unirradiated (Pearson r = 0.323; P = 0.177) or irradiated (Pearson r = 0.284; p = 0.254) patients. Plasma ^{99m}Tc clearance did correlate well with the eGFR using the creatinine + cystatin C equations among unirradiated (Pearson r = 0.488; p = 0.034) and irradiated (Pearson r = 0.558; p = 0.020) survivors. 24-hour urine creatinine clearance did not correlate with plasma ^{99m}Tc clearance among either the unirradiated (Pearson r=0.120; P = 0.625) or the irradiated (Pearson r=0.252; P = 0.314) WT participants.	SB: low risk IB: NA RB: NA VB: low risk AB: low risk
	Stefanowicz 2011*	32 survivors of unilateral WT	Mean 9.3 yrs (SD 5.4) Median 7.7. yrs (range 0.3 - 20)	1. ^{99}Tc-DTPA clearance 2. Old Schwartz formula 3. New Schwartz formula 4. Filler formula	NA	<u>Mean GFR in mL/min/1.73m² (SD)</u> 1. ^{99}Tc-DTPA clearance: mean: 94.3 (SD 10.24) 2. old Schwartz formula: mean: 122.3 (SD 19.92) 3. new Schwartz formula: mean: 94.3 (SD 10.2) 4. Filler formula: mean: 129.8 (SD 23.9) <u>Comparison</u> ^{99}Tc-DPTA vs old Schwartz p < 0.001 ^{99}Tc-DPTA vs new Schwartz p = 0.55 ^{99}Tc-DPTA vs Filler p < 0.001 Old Schwartz vs New Schwartz vs. p < 0.0001 Old Schwartz vs Filler (p = 0.26) New Schwartz vs Filler p < 0.0001 <u>Correlation rate</u> 99Tc-DTPA vs old Schwartz 0.33 (p < 0.05) 99Tc-DTPA vs new Schwartz 0.33 (p < 0.05) 99Tc-DTPA vs Filer formula 0.44 (p < 0.05) 99Tc-DTPA vs serum cystatin C 0.51 (p < 0.05)	SB: unclear IB: NA RB: NA VB: low risk AB: low risk
GRADE assessment: <u>Study design:</u>	+4	Cohort studies					

Study limitations:	-1	Some limitations: Selection bias low in 1/5, unclear in 4/5; Index test bias NA in 5/5; Reference test bias NA in 5/5; Verification bias low in 5/5; Attrition bias low in 5/5.
Consistency:	0	No important inconsistency of the correlation between different GFR equations across the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, low total number of patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		- Correlation rate Plasma ^{99m}Tc clearance vs CKD-EPI 2012 creatinine only unirradiated (Pearson *r* = 0.323) and irradiated (Pearson *r* = 0.284). (1 study, 40 participants) - Correlation rate Plasma ^{99m}Tc clearance vs CKD-EPI 2012 creatinine + cystatin C unirradiated (Pearson *r* = 0.488) and irradiated (Pearson *r* = 0.558). (1 study, 40 participants) - Correlation rate 99Tc-DTPA vs old Schwartz (creatinine) = 0.33 (Pearson's or Spearman's r) (1 study, 32 participants) - Correlation rate 99Tc-DTPA vs new Schwartz (creatinine + cystatin C) = 0.33 (Pearson's or Spearman's r) (1 study, 32 participants) - Correlation rate 99Tc-DTPA vs Filer formula (cystatin C) = 0.44 (Pearson's or Spearman's r) (1 study, 32 participants)

Abbreviations: ^{99}Tc-DPTA, diethylene-triamine-pentaacetate; AB, attrition bias; CAPA, Caucasian and Asian pediatric and adult subjects CAYA, childhood, adolescent and young adult; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; IB, index test bias; MDRD, modification of diet in renal disease; NA, not applicable; RB, reference test bias; RT, radiotherapy; SB, selection bias; SD, standard deviation; URA, unilateral renal agnesia; VB, verification bias; WT, Wilms tumor; yrs, years.
* Possible overlap in included patients in studies of Stefanowicz 2011 and Stefanowicz 2012.

No guidelines including recommendations regarding GFR in **children**.

Summary of guidelines including recommendations regarding GFR in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
KDIGO 2024	In adults at risk for CKD, we recommend using creatinine-based estimated glomerular filtration rate (eGFRcreat). If cystatin C is available, the GFR category should be estimated from the combination of creatinine and cystatin C (creatinine and cystatin C–based estimated glomerular filtration rate [eGFRcreat-cys])*	Strong	Moderate
	We recommend using a validated GFR estimating equation to derive GFR from serum • filtration markers (eGFR) rather than relying on the serumfiltration markers alone (1D) (	Strong	Very low
	We recommend using eGFRcreat-cys in clinical situations when eGFRcreat is less accurate and GFR affects clinical decision-making	Strong	Low
SIGN 2008	Where an assessment of GFR is required prediction equations should be used in preference to 24-hour urine creatinine clearance or serum creatinine alone.	Not graded	Low

CARI 2012	CKD screening should include both a urine test for albuminuria and a blood test for serum creatinine to determine an eGFR.	Strong	Low
CKD UK 2006	There is **no** need to collect 24-hour urine samples to measure creatinine clearance in primary care.	Not graded	Moderate
	Kidney function in patients with CKD should be assessed by formula-based estimation of GFR, preferably using the 4-variable Modification of Diet in Renal Disease (MDRD) equation: GFR (mL/min/1.73m2) = 186 x {[serum creatinine (µmol/L)/88.4] -1.154} x age (years) - 0.203 x 0.742 if female and x 1.21 if African American.	Not graded	Moderate
	The same criteria should be used for assessment of kidney function in older people as in younger people. "Age-adjusted" reference ranges for GFR are **not** recommended.	Not graded	Moderate
ESC/ESH 2018	Serum-creatinine, eGFR and urine albumin/creatinine ratio should be measured in all hypertensive patients	Strong	Moderate
DELGADO 2021	For US adults (.85% of whom have normal kidney function), we recommend immediate implementation of the CKD-EPI creatinine equation refit without the race variable in all laboratories in the United States	Not graded	Not graded
	We recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in adults who are at risk for or have CKD, because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone. If ongoing evidence supports acceptable performance, the CKD-EPI eGFR–cystatin C (eGFRcys) and eGFR creatinine–cystatin C (eGFRcr-cys_R) refit without the race variables should be adopted to provide another first-line test, in addition to confirmatory testing.	Not graded	Not graded

** This also applies for children at risk for CKD, no different pediatric considerations.*

Recommendation: methods to detect an abnormal GFR

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u>	
No general guidelines in children identified.	
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (5 general adult guideline)	
Where an assessment of GFR is required prediction equations should be used in preference to serum creatinine or cystatin C alone.	Evidence-based guidelines[1,2,3,4]
There is no need to collect 24-hour urine samples to measure creatinine clearance in primary care.	Evidence-based guidelines[2,4]
We suggest using creatinine-based estimated glomerular filtration rate (eGFRcreat). If cystatin C is available, the GFR category should be estimated from the combination of creatinine and cystatin C (creatinine and cystatin C–based estimated glomerular filtration rate [eGFRcreat-cys])as the combination of both markers is more accurate.	Evidence-based guidelines[1,5]

We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions.	Evidence-based guidelines[1]

Abbreviations: CKD, chronic kidney disease; creat, creatinine; CKD-EPI, chronic kidney disease epidemiology collaboration; cystatin C; (e)GFR, (estimated) glomerular filtration rate.
Abbreviations: CKD, chronic kidney disease; creat, creatinine; CKD-EPI, chronic kidney disease epidemiology collaboration; cystatin C; (e)GFR, (estimated) glomerular filtration rate.
[1] *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group*. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2024; 105 (Suppl 4S):S117-S314[2] *Scottish Intercollegiate Guidelines Network (SIGN).* Diagnosis and management of chronic kidney disease, a national clinical guideline. 2008. Available at www.**sign**.ac.uk/guidelines/published/numlist.html
[3] *Toussaint N et al*. CARI Guidelines. Screening for early chronic kidney disease. Early Chronic Kidney Disease. 2012: 1-32
[4] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7
[5] *Delgado et al.* A unifying approach for GFR estimation: Recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. 2021;32:2994-3015

3.2 What methods are available to detect glomerular proteinuria?
No studies identified in CAYA cancer survivors.

No guidelines including recommendations regarding glomerular proteinuria in **children**.

Summary of guidelines including recommendations regarding glomerular proteinuria in **adults**.

Recommendation 1: methods to detect glomerular proteinuria

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
KDIGO 2024	We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases a first void in the morning midstream sample is preferred): (i) urine ACR, or (ii) reagent strip urinalysis for albumin and ACR with automated reading. If measuring urine protein, use the following measurements: (i) urine protein-to-creatinine ratio (PCR), (ii) reagent strip urinalysis for total protein with automated reading, or (iii) reagent strip urinalysis for total protein with manual reading.	Not graded	Not graded
	Use more accurate methods when albuminuria is detected using less accurate methods. • Confirm reagent strip positive albuminuria and/or proteinuria by quantitative laboratory measurement and express as a ratio to urine creatinine wherever possible (i.e., quantify the ACR or PCR if initial semiquantitative tests are positive). • Confirm ACR ≥30 mg/g (≥3 mg/mmol) on a random untimed urine with a subsequent first morning void in the morning midstream urine sample.	Not graded	Not graded
SIGN 2008	In patients with diabetes, ACR may be used to exclude diabetic nephropathy	Not graded	Moderate
	ACR is recommended for detecting and monitoring diabetic nephropathy	Not graded	Moderate

	In patient groups with a high prevalence of proteinuria without diabetes PCR may be used to exclude chronic kidney disease	Not graded	Low
	Dipstick proteinuria (≥1+) can be used to identify patients at risk of subsequent endstage renal disease and cardiovascular disease.	Not graded	Expert opinion
	Urine dipstick testing cannot be used reliably in isolation to diagnose the presence or absence of proteinuria	Not graded	Expert opinion
CARI 2012	We recommend a ACR measurement in a first void specimen. When not possible or practical, a random urine specimen is recommended.	Strong	Low
CKD UK 2006	A positive dipstick test (1+ or greater) should result in a urine sample (preferably early morning) being sent to the laboratory for confirmation by measurement of the total PCR or ACR (depending on local practice). Simultaneously, a midstream sample should be sent for culture to exclude urinary tract infection.	Not graded	Moderate
	Urine albumin should be measured using a laboratory method in an early morning (preferred) or random mid-stream urine sample and expressed as an ACR. If dipsticks designed to detect urinary albumin are used, positive tests should be followed by laboratory confirmation.	Not graded	Moderate
ESC/ESH 2018	Serum-creatinine, eGFR and ACR should be measured in all hypertensive patients	Strong	Moderate

Abbreviations: ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio

Recommendation 2: timing of sample

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
CARI 2012	ACR preferably on the first morning urine, although a random urine is acceptable.	Not graded	Not graded
KDIGO 2024	In all cases a first void in morning midstream urine sample is preferred	Not graded	Not graded
	If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.	Not graded	Not graded
CARI 2012	We recommend a ACR measurement in a first void specimen. When not possible or practical, a random urine specimen is recommended.	Strong	Low
	We recommend that a positive ACR screening test should be repeated on 1-2 occasions over a period of three months to confirm persistence of albuminuria. If the first positive ACR is a random spot, then repeat tests should ideally be first morning void specimens.	Strong	Expert opinion
CKD UK 2006	There is no need to perform 24 hour urine collections for the quantitation of proteinuria in primary care.	Not graded	Moderate
	A positive dipstick test (1+ or greater) should result in a urine sample (preferably early morning)	Not graded	Moderate
	PCR >45 mg/mmol or ACR of >30 mg/mmol should be considered as positive tests for proteinuria. Positive tests for proteinuria should be followed by tests to exclude postural proteinuria, by analysis of an early morning urine sample, unless this has already been done.	Not graded	Moderate
	An ACR >2.5 mg/mmol in a male or >3.5 mg/mmol in a female is consistent with microalbuminuria. ACR above, or equal to, this cut-off should have urine samples sent to the laboratory on two further occasions (ideally within one to three months) for albumin estimation. Patients demonstrating persistently elevated ACR in one or both of these further samples have microalbuminuria.	Not graded	Not graded

Abbreviations: ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine-ratio.

Recommendation 1: methods to detect glomerular proteinuria

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u>	
No general guidelines in children identified.	
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (5 general adult guideline)	
For testing of proteinuria the preferred test is urine ACR or PCR.	Evidence-based guidelines[1,2,3,4]
Other tests beside ACR or PCR, that can be used to test for proteinuria (in order of preference) - reagent strip urinalysis for albumin and ACR with automated reading.- reagent strip urinalysis for total protein with automated reading; - reagent strip urinalysis for total protein with manual reading.	Evidence-based guidelines[1]
In patient groups with a high prevalence of proteinuria without diabetes PCR may be used to exclude chronic kidney disease.	Evidence-based guidelines[2]
A positive dipstick test cannot be used reliable in isolation and should result in a quantitative laboratory measurement by measurement of PCR or ACR.	Evidence-based guidelines[1,2,5]

Abbreviations: ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio.

[1] *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group*. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., 2024; 105 (Suppl 4S):S117-S314

[2] *Scottish Intercollegiate Guidelines Network (SIGN).* Diagnosis and management of chronic kidney disease, a national clinical guideline. 2008. Available at www.sign.ac.uk/guidelines/published/numlist.html

[3] *Toussaint N et al.* CARI Guidelines. Screening for early chronic kidney disease. Early Chronic Kidney Disease. 2012: 1-32

[4] *Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021-3104 doi:10.1093/eurheartj/ehy339

[5] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7

Recommendation 2: timing of sample

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u>	
No general guidelines in children identified.	
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (4 general adult guideline)	
In all cases an early morning urine sample is preferred.	Evidence-based guidelines[1,2,3,4]

When an early morning urine sample is not possible, a random sample urine is acceptable.	Evidence-based guidelines[1,3]
If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.	Evidence-based guidelines[2]
A positive ACR screening test should be repeated on 1-2 occasions over a period of one to three months to confirm persistence of albuminuria (early morning urine sample).	Evidence-based guidelines[3,4]

Abbreviations: ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio.

[1] *Johnson et al.* CARI Guidelines. Diagnosis, classification and staging of chronic kidney disease. Early Chronic Kidney Disease. 2012:1-31

[2] *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group*. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., 2024; 105 (Suppl 4S):S117-S314

[3] *Toussaint N et al*. CARI Guidelines. Screening for early chronic kidney disease. Early Chronic Kidney Disease. 2012: 1-32

[4] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7

3.3 What methods are available to detect tubular proteinuria?
No studies identified in CAYA cancer survivors.'

No guidelines including recommendations regarding tubular proteinuria in **children**.

No guidelines including recommendations regarding tubular proteinuria in **adults**.

3.4 What methods are available to detect electrolyte disturbance?
No studies identified in CAYA cancer survivors.
No studies or guidelines identified investigating available methods to detect electrolyte disturbance in CAYA cancer survivors or the general population.

3.5 What methods are available to detect an abnormal blood pressure?
No studies identified in CAYA cancer survivors.
Summary of guidelines including recommendations regarding methods to detect an abnormal blood pressure in **children and adolescents**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
HYPERTENSION CANADA 2017	BP may be measured with a mercury sphygmomanometer, aneroid sphygmomanometer, or oscillometric device	Not graded	Expert opinion
	Abnormal oscillometric values should be confirmed with auscultation	Not graded	Low

AAP 2017	Oscillometric devices may be used for BP screening in children and adolescents. When doing so, providers should use a device that has been validated in the pediatric age group. If elevated BP is suspected on the basis of oscillometric readings, confirmatory measurements should be obtained by auscultation.	Strong	Moderate
	Use the standardized technique for measuring BP by auscultation to obtain accurate BP values.	Not graded	Expert opinion
	When an oscillometric BP reading is elevated, obtain repeat readings, discard the first reading, and average subsequent readings to approximate auscultatory BP.	Not graded	Expert opinion
	Wrist and forearm BP measurements should not be used in children and adolescents for the diagnosis or management of hypertension.	Not graded	Expert opinion
	ABPM should be performed by using a standardized approach with monitors that have been validated in a pediatric population, and studies should be interpreted by using pediatric normative data	Moderate	Low
ESH 2016	If hypertension is detected by the oscillometric method, it must be confirmed by the auscultatory one.	Not graded	Not graded
	HBPM for 6-7 days, with duplicate morning and evening measurements is recommended	Not graded	Not graded

Abbreviations: ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure monitoring; BP, blood pressure.

Summary of guidelines including recommendations regarding methods to detect an abnormal blood pressure in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ADA 2017	Patients found to have an elevated BP (≥140/90 mmHg) should have BP confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension.	Not graded	Moderate
NICE 2019	When considering a diagnosis of hypertension, measure BP in both arms. • If the difference in readings between arms is more than 15 mmHg, repeat the measurements. • If the difference in readings between arms remains more than 15 mmHg on the second measurement, measure subsequent blood pressures in the arm with the higher reading.	Not graded	Not graded
	If BP measured in the clinic is 140/90 mmHg or higher: • Take a second measurement during the consultation. • If the second measurement is substantially different from the first, take a third measurement. • Record the lower of the last two measurements as the clinic BP	Not graded	Not graded
	When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension.	Not graded	Not graded
	When using HBPM to confirm a diagnosis of hypertension, ensure that: • for each BP recording, two consecutive measurements are taken, at least 1minute apart and with the person seated **and** • BP is recorded twice daily, ideally in the morning and evening **and** • BP recording continues for at least 4 days, ideally for 7 days.	Not graded	Not graded

	• Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension.		
ASH/ISH 2014	BP can be measured by either a conventional sphygmomanometer using a stethoscope or by an automated electronic device. The electronic device, if available, is preferred because it provides more reproducible results than the older method and is not influenced by variations in technique or by the bias of the observers. If the auscultatory method is used, the first and fifth Korotkoff sounds (the appearance and disappearance of sounds) will correspond to the systolic and diastolic BP.	Not graded	Not graded
	Arm cuffs are preferred. Cuffs that fit on the finger or wrist are often inaccurate and should, in general, not be used.	Not graded	Not graded
	It is important to ensure that the correct size of the arm cuff is used (in particular, a wider cuff in patients with large arms [>32 cm circumference]).	Not graded	Not graded
	At the initial evaluation, BP should be measured in both arms; if the readings are different, the arm with the higher reading should be used for measurements thereafter.	Not graded	Not graded
	It can be helpful to measure BP at home. If available, the electronic device is simpler to use and is probably more reliable than the sphygmomanometer. The average of BP measured over 5 to 7 days, if possible in duplicate at each measurement, can be a useful guide for diagnostic and treatment decisions.	Not graded	Not graded
ACC/AHA 2018	Proper methods are recommended for accurate measurement and documentation of BP in order to diagnose and manage high BP.	Strong	Expert opinion
	Out-of-office measurements are recommended to confirm the diagnosis of hypertension.	Strong	High
ESC/ESH 2018	Initial BP should be measured in both arms and further measurements should be taken from the arm with the highest BP.	Strong	High, low
	The diagnosis of hypertension should be based on: • repeated office measurements on more than one visit, except when hypertension is severe (e.g., grade 3). At each visit three BP measurement should be recorded, 1-2 min apart, and additional measurements should be performed if the first two readings differ >10 mmHg. The patient's BP is the average of the last two BP readings.	Strong	Low
	• Or out-of-office measurements with ABPM or HBPM, provided that these measurements are logistically and economically feasible.	Strong	Low
ISH 2020	Usually 2-3 office visits at 1-4 weeks intervals (depending on the BP level) are required to confirm the diagnosis of hypertension. The diagnosis might be made on a single visit, if BP is ≥ 180/110 mmHg and evidence of CVD.	Not graded	Not graded
	If possible and available, the diagnosis of hypertension should be confirmed by out-of-office BP measurement.	Not graded	Not graded

Abbreviations: ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; BP, blood pressure.

Recommendation: methods available to detect an abnormal blood pressure

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (3 general pediatric guidelines)	
Office BP may be measured with a mercury sphygmomanometer, aneroid sphygmomanometer, or oscillometric device.	Evidence-based guidelines[1]
When an oscillometric BP reading is elevated, obtain repeat readings, discard the first reading, and average subsequent readings to approximate auscultatory BP.	Evidence-based guidelines[2]
Abnormal oscillometric values should be confirmed with auscultation.	Evidence-based guidelines[1,2.3]
Wrist and forearm BP measurements should not be used in children and adolescents for the diagnosis or management of hypertension.	Evidence-based guidelines[2]
ABPM should be performed by using a standardized approach with monitors that have been validated in a pediatric population, and studies should be interpreted by using pediatric normative data.	Evidence-based guidelines[2]
When HBPM is used to confirm a diagnosis of hypertension, monitoring for 6-7 days, with duplicate morning and evening measurements is recommended.	Evidence-based guidelines[3]
For the different methods of BP measurement, it is recommended using a proper standardized approach for accurate measurement and documentation of BP, which is provided in more detail in the original guidelines.	Evidence-based guidelines[1,2.3]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (6 general adult guidelines)	
BP can be measured by either a conventional sphygmomanometer using a stethoscope or by an automated electronic device. The electronic device, if available, is preferred because it provides more reproducible results than the older method and is not influenced by variations in technique or by the bias of the observers. If the auscultatory method is used, the first and fifth Korotkoff sounds (the appearance and disappearance of sounds) will correspond to the systolic and diastolic BP.	Evidence-based guidelines[4]
Initial BP should be measured in both arms and further measurements should be taken from the arm with the highest BP.	Evidence-based guidelines[4,5,6]
Arm cuffs are preferred. Cuffs that fit on the finger or wrist are often inaccurate and should, in general, not be used.	Evidence-based guidelines[4]
Patients found to have an elevated BP should have repeated office measurements on more than one visit. At each visit three BP measurement should be recorded.	Evidence-based guidelines[5,6,7,8]

The diagnosis of hypertension might only be made on a single visit, when hypertension is severe (e.g., grade 3).	Evidence-based guidelines[6,8]
If possible and available, the diagnosis of hypertension should be confirmed by out-of-office BP measurement (ABPM or HBPM).	Evidence-based guidelines[6,8,9]
When HBPM is used to confirm a diagnosis of hypertension, monitoring for 4-7 days, with duplicate morning and evening measurements is recommended.	Evidence-based guidelines[4,5]
When ABPM is used to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours. Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension.	Evidence-based guidelines[5]
For the different methods of BP measurement, it is recommended using a proper standardized approach for accurate measurement and documentation of BP, which is provided in more detail in the original guidelines.	Evidence-based guidelines[4,5,6,7,8,9]

Abbreviations: ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; BP, blood pressure.

[1]*Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[2]*Dionne et al.* Hypertension Canada Guideline Committee. Hypertension Canada's 2017 Guidelines for the Diagnosis, Assessment, Prevention and Treatment of Pediatric Hypertension. Canadian Journal of Cardiology 2017; 33: 577-585

[3]*Lurbe et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887-920

[4]*Weber et al.* Clinical practice guideline for the management of hypertension in the community, a statement by the American Society of Hypertension and the International Society of Hypertension. The Journal of Clinical Hypertension. 2014;16:14-26

[5]*NICE.* Hypertension in adults: diagnosis and Management. Clinical guideline. Published: 24 August 2011, www.nice.org.uk/guidance/cg127. Last updated August 2019.

[6]*Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021-3104 doi:10.1093/eurheartj/ehy339

[7]*De Boer et al.* American Diabetes Association. Diabetes and Hypertension: A position statement by the American Diabetes Association. Diabetes Care. 2017;40:1273-1284

[8]*Unger et al.* International Society of Hypertension. Global hypertension practice guideline. Hypertension. 2020;75:1334-57

[9]*Whelton PK et al.* The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71:e13-e115. DOI: 10.1161/HYP.0000000000000065

3.6 What is the diagnostic value of ambulatory or home blood pressure monitoring versus office blood pressure measurement in CAYA cancer survivors at risk for nephrotoxicity?

No studies identified investigating the diagnostic value of different blood pressure methods in CAYA cancer survivors.
Summary of guidelines including recommendations regarding indications for ABPM or HBPM in **children and adolescents**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
AAP 2017	ABPM should be performed for confirmation of hypertension in children and adolescents with office BP measurements in the elevated BP category for 1 year or more or with stage 1 hypertension over 3 clinic visits.	Moderate	Low
	Routine performance of ABPM should be strongly considered in children and adolescents with high-risk conditions to assess hypertension severity and determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage. High-risk conditions include secondary hypertension, CKD or structural renal abnormalities, T1DM, T2DM, solid-organ transplant, obesity, OSAS, aortic coarctation (repaired), genetic syndromes associated with hypertension, treated hypertensive patients, and patients born prematurely.	Moderate	Moderate
	Children and adolescents with suspected WCH should undergo ABPM. Diagnosis is based on the presence of mean SBP and DBP <95th percentile and SBP and DBP load <25%.	Strong	Moderate
	ABPM may be used to assess treatment effectiveness in children and adolescents with hypertension, especially when clinic BP and/or HBPM indicate insufficient BP response to treatment.	Moderate	Moderate
	Regardless of apparent control of BP with office measures, children and adolescents with CKD and a history of hypertension should have BP assessed by ABPM at least yearly to screen for MH.	Strong	Moderate
	HBPM should not be used to diagnose hypertension, MH, or WCH but may be a useful adjunct to office and ABPM after hypertension has been diagnosed.	Moderate	Low
ESH 2016	Especially in children, 24-h ABPM should be recommended to confirm hypertension before starting antihypertensive treatment, to avoid treating with drugs children with WCH. See table 1 for other recommendations.	Not graded	Not graded
	HBPM values correlates closely with daytime ABPM values and has superior reproducibility to office BP, similar to that of ABPM. Indications for use: • All patients receiving antihypertensive medication • Suspicion of WCH Conditions where strict BP control is mandatory (high-risk patients)	Not graded	Not graded

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; MH, masked hypertension; OSAS, obstructive sleep apnea syndrome; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WCH, white coat hypertension.

Table 1. **Recommendations for 24-h ambulatory blood pressure monitoring**

During the process of diagnosis
Confirm hypertension before starting antihypertensive drug treatment to avoid treatment of white-coat hypertension
Target organ damage (LVH and microalbuminuria) and office BP normal (masked hypertension)
DM1 and DM2
CKD
Renal, liver or heart transplant

Severe obesity with or without sleep-disordered breathing Hypertensive response during the treadmill test Discrepancy between office BP and home BP
During antihypertensive drug treatment Evaluate for apparent drug-resistant hypertension Assessment of BP control in children with target organ damage Symptoms of hypotension
Clinical trials
Other clinical conditions Autonomic dysfunction Suspicion of catecholamine-secreting tumors

Abbreviatons: BP, blood pressure; CKD, chronic kidney disease; DM1, type 1 diabetes; DM2, type 2 diabetes; LVH, left ventricular hypertrophy.

Summary of guidelines including recommendations regarding indications for ABPM or HBPM in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ADA 2017	All hypertensive patients with diabetes should have HBPM to identify WCH.	Not graded	Moderate
NICE 2019	If the clinic BP is 140/90 mmHg or higher, offer ABPM to confirm the diagnosis of hypertension.	Not graded	Not graded
	If a person is unable to tolerate ABPM, offer HBPM to confirm the diagnosis of hypertension.	Not graded	Not graded
	Consider ABPM or HBPM, in addition to clinic BP measurements for people with hypertension identified as having WCH or MH.	Not graded	Not graded
NICE QS 2013	People with suspected hypertension* are offered ABPM to confirm a diagnosis of hypertension. Rationale: ABPM is the most accurate method for confirming a diagnosis of hypertension, and its use should reduce unnecessary treatment in people who do not have true hypertension. ABPM has also been shown to be superior to other methods of multiple BP measurement for predicting BP-related clinical events. * Suspected hypertension is a clinic BP of 140/90 mmHg or higher without a confirmed diagnosis of hypertension	Not graded	Not graded
	ABPM may not be suitable for everyone, for example people with particular learning or physical disabilities. Some people may be unable to tolerate ABPM and some people may decline it. HBPM should be offered as an alternative to ABPM in such cases. If a person is unable to tolerate ABPM, HBPM is a suitable alternative to confirm the diagnosis of hypertension.	Not graded	Not graded
ASH/ISH 2014	If WCH is suspected, consider getting HBPM to check this possibility. Another approach is to use ABPM, if it is available.	Not graded	Not graded
ACC/AHA 2018	In adults with an untreated SBP greater than 130 mm Hg but less than 160 mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is reasonable to screen for the presence of WCH by using either daytime ABPM or HBPM before diagnosis of hypertension.	Moderate	Moderate

	In adults with WCH, periodic monitoring with either ABPM or HBPM is reasonable to detect transition to sustained hypertension.	Moderate	Low
	In adults being treated for hypertension with office BP readings not at goal and HBPM readings suggestive of a significant WCH, confirmation by ABPM can be useful.	moderate	Low
	In adults with untreated office BPs that are consistently between 120 mm Hg and 129 mm Hg for SBP or between 75 mm Hg and 79 mm Hg for DBP, screening for MH with HBPM or ABPM is reasonable.	moderate	Moderate
	In adults on multiple-drug therapies for hypertension and office BPs within 10 mm Hg above goal, it may be reasonable to screen for WCH with HBPM or ABPM.	Weak	Low
	In adults being treated for hypertension with elevated HBPM readings suggestive of uncontrolled MH, confirmation of the diagnosis by ABPM might be reasonable before intensification of antihypertensive drug treatment.	Weak	Expert opinion
	It may be reasonable to screen for uncontrolled MH with HBPM in adults being treated for hypertension and office readings at goal, in the presence of target organ damage or increased overall CVD risk.	Moderate	Expert opinion
ESC/ESH 2018	To identify MH and WCH, ABPM or HBPM are recommended.		1A
ISH 2020	Out-of-office BP measurement is often necessary for the accurate diagnosis of hypertension and for treatment decisions. In untreated or treated subjects with office BP classified as high-normal BP or grade 1 hypertension (systolic 130-159 mm Hg and/or diastolic 85-99 mm Hg), the BP level needs to be confirmed using HBPM or ABPM.	Not graded	Not graded

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; MH, masked hypertension; SBP, systolic blood pressure; WCH, white coat hypertension.

Recommendation: indications for ABPM or HBPM

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (2 general pediatric guidelines)	
ABPM should be recommended to confirm hypertension before starting antihypertensive treatment, to avoid treating with drugs children with WCH.	Evidence-based guidelines[1,2]
HBPM can be used <u>after</u> hypertension have been diagnosed for the following indications: • All patients receiving antihypertensive medication • Suspicion of WCH • Conditions where strict BP control is mandatory (high-risk patients)	Evidence-based guidelines[1,2]
Children and adolescents with suspected WCH should undergo ABPM.	Evidence-based guidelines[1]
ABPM may be used to assess treatment effectiveness in children and adolescents with hypertension, especially when clinic BP and/or HBPM indicate insufficient BP response to treatment.	Evidence-based guidelines[1]

Regardless of apparent control of BP with office measures, children and adolescents with CKD and a history of hypertension should have BP assessed by ABPM at least yearly to screen for MH.	Evidence-based guidelines[1]
Routine performance of ABPM should be strongly considered in children and adolescents with high-risk conditions to assess hypertension severity and determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage. High-risk conditions include secondary hypertension, CKD or structural renal abnormalities, T1DM, T2DM, solid-organ transplant, obesity, OSAS, aortic coarctation (repaired), genetic syndromes associated with hypertension, treated hypertensive patients, and patients born prematurely.	Evidence-based guidelines[1,2]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (7 general adult guidelines)	
If hypertension is suspected offer ABPM to confirm the diagnosis of hypertension.	Evidence-based guidelines[3,4,5]
If a person is unable to tolerate ABPM, HBPM is a suitable alternative to confirm the diagnosis of hypertension.	Evidence-based guidelines[3,4,5]
If MH or WCH is suspected, ABPM or HBPM are recommended.	Evidence-based guidelines[3,6,7,8,9]
In adults with WCH, periodic monitoring with either ABPM or HBPM is reasonable to detect transition to sustained hypertension.	Evidence-based guidelines[7]
In adults being treated for hypertension with office BP readings not at goal and HBPM readings suggestive of a significant WCH, confirmation by ABPM can be useful.	Evidence-based guidelines[7]
In adults being treated for hypertension with elevated HBPM readings suggestive of uncontrolled MH, confirmation of the diagnosis by ABPM might be reasonable before intensification of antihypertensive drug treatment.	Evidence-based guidelines[7]

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; HBPM, home blood pressure monitoring; MH, masked hypertension; OSAS, obstructive sleep apnea syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WCH, white coat hypertension.

[1]*Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[2]*Lurbe et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887-920

[3]*NICE.* Hypertension in adults: diagnosis and Management. Clinical guideline. Published: 24 August 2011, www.nice.org.uk/guidance/cg127. Last updated August 2019.

[4]*NICE.* Hypertension in adults, Quality standard, Published: 20 March 2013, www.nice.org.uk/guidance/qs2

[5]*Unger et al.* International Society of Hypertension. Global hypertension practice guideline. Hypertension. 2020;75:1334-57

[6]*Weber et al.* Clinical practice guideline for the management of hypertension in the community, a statement by the American Society of Hypertension and the International Society of Hypertension. The Journal of Clinical Hypertension. 2014;16:14-26

[7]*Whelton PK et al.* The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017

[8]*Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021-3104 doi:10.1093/eurheartj/ehy339
[9]*De Boer et al.* American Diabetes Association. Diabetes and Hypertension: A position statement by the American Diabetes Association. Diabetes Care. 2017;40:1273-1284

What should be done when abnormalities are identified?

4.1 When should CAYA cancer survivors be referred to a nephrologist?

No studies or guidelines identified investigating when to refer CAYA cancer survivors to a nephrologist.
Summary of guidelines including recommendations in the **general population** in **children**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
HYPERTENSION CANADA 2017	If the BP is at the 95th percentile or greater, BP should be staged. Stage 1 is defined by BP between the 95th and 99th percentiles plus 5 mmHg. Stage 2 is defined by BP > the 99th percentile plus 5 mmHg.	Not graded	Expert opinion
	If BP is Stage 1, BP measurements should be repeated on 2 more occasions within 1 month; if hypertension is confirmed, evaluation or appropriate referral should be initiated with 1 month or both.	Not graded	Expert opinion
	If BP goals are not achieved with standard dose monotherapy for > 6 months, children should be referred to an expert in pediatric hypertension.	Not graded	Expert opinion
AAP 2017	Adolescents with elevated BP or hypertension (whether they are receiving antihypertensive treatment) should typically have their care transitioned to an appropriate adult care provider by 22 year of age. There should be a transfer of information regarding hypertension etiology and past manifestations and complications of the patient's hypertension.	Not graded	Expert opinion

Abbreviations: BP, blood pressure.

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
CARI 2012	We recommend referral to a specialist renal service or nephrologist in the following situations:		
	i. Stage 4 and 5 CKD of any cause (eGFR < 30mL/min/1.73m^2).	Strong	Low
	ii. Persistent significant albuminuria (UACR ≥ 30 mg/mmol, approx equivalent to UPCR ≥ 50 mg/mmol, or UP excretion ≥ 500 mg/24 hours).	Strong	Low
	iii. Consistent decline in eGFR from a baseline of < 60 ml/min/1.73 m^2 (a decline > 5 ml/min/1.73 m^2 over a 6-month period, confirmed on at least 3 separate readings).	Strong	Low
	We suggest referral to a specialist renal service or nephrologist in the following situations:		
	i. Glomerular hematuria with macroalbuminuria.	Moderate	Low
	ii. CKD and hypertension that is hard to get to target despite at least 3 anti-hypertensive agents.	Moderate	Low

	We suggest discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist.	Moderate	Expert opinion
	Once a referral has been made and a plan jointly agreed, routine follow-up could take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, we recommend that criteria for future referral or re-referral should be specified.	Strong	Expert opinion
CKD UK 2006	Non-diabetic patients with early morning urine protein:creatinine ratio >100 mg/mmol (approximately 1 g/24 h or 2+) should be referred to a nephrology service for consideration of kidney biopsy.	Not graded	Not graded
	Non-diabetic patients with early morning protein:creatinine ratio 45-100 mg/mmol *without hematuria* should be considered to have CKD and entered into a CKD disease management programme, with referral only if other criteria for referral are met.	Not graded	Not graded
	Patients with both hematuria and proteinuria (protein:creatinine ratio >45 mg/mmol) should be referred to a nephrology service for investigation irrespective of GFR.	Not graded	Not graded

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; UP, urinary protein; UPCR, urine protein to creatinine ratio.

Recommendations: when to refer to a nephrologist

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (2 general pediatric guidelines)	
Children should be referred to a nephrologist when hypertension is confirmed on 3 occasions within 1 month.	Evidence-based guidelines[1]
Children should be referred to a nephrologist if blood pressure goals are not achieved with standard dose monotherapy for >6 months.	Evidence-based guidelines[1]
Adolescents with hypertension should be transitioned to adult care by 22 years of age.	Evidence-based guidelines[2]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (2 general adult guidelines)	
Adults with persistent proteinuria (urinary protein:creatinine ratio > 50-100 mg/mmol) should be referred to a nephrologist.	Evidence-based guidelines[3,4]
Adults having hematuria with albuminuria should be referred to a nephrologist.	Evidence-based guidelines[3,4]
Adults with stage 4 or 5 CKD should be referred to a nephrologist.	Evidence-based guidelines[3]
Adults with persistent decline in eGFR from baseline of < 60 ml/min/1.73m^2 (a decline > 5 ml/min/1.73 m^2 over a 6-month period, confirmed on at least 3 separate readings) should be referred to a nephrologist.	Evidence-based guidelines[3]

Adults with a combination of CKD and hypertension that is hard to target despite at least 3 anti-hypertensive agents should be referred to a nephrologist	Evidence-based guidelines[3]

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[1] *Dionne et al.* Hypertension Canada Guideline Committee. Hypertension Canada's 2017 Guidelines for the Diagnosis, Assessment, Prevention and Treatment of Pediatric Hypertension. Canadian Journal of Cardiology 2017; 33: 577-585

[2] *Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[3] *Johnson et al.* CARI guidelines. When to refer for specialist renal care. Early chronic kidney disease. 2012: 1-13

[4] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7

4.2 When and how should electrolyte supplementation be considered?

No studies or guidelines identified investigating electrolyte supplementation in CAYA cancer survivors.
No guidelines identified regarding electrolyte supplementation in the **general population** in **children**. Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
HOORN 2013	In case of hypokalemia potassium chloride is the preferred supplementation. If there is concurrent acidosis potassium bicarbonate, citrate or acetate can be given. Potassium phosphate can be given if there is concurrent hypophosphatemia.	Not graded	Not graded
	We recommend that less severe cases of hypokalemia (usually serum potassium 2.5-3.5 mmol/l) can be treated with oral potassium supplementation either as liquid or as tablet.	Not graded	Not graded
	We recommend that symptomatic hypokalemia should be treated intravenously and, in severe cases, may require a central venous catheter and continuous ECG monitoring.	Not graded	Not graded
	We recommend in hypokalemia due to renal potassium loss, that a potassium-sparing diuretic may be added as treatment such as amiloride or spironolactone.	Not graded	Not graded
	We recommend magnesium supplementation complementary to potassium supplementation when hypomagnesemia is present.	Not graded	Not graded

Recommendations: when and how should electrolyte supplementation be considered

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u>
No general guidelines in children identified.
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (1 general adult guideline)

In case of hypokalemia potassium chloride is the preferred supplementation. If there is concurrent acidosis potassium bicarbonate, citrate or acetate can be given. Potassium phosphate can be given if there is concurrent hypophosphatemia.	Evidence-based guidelines[1]
Less severe cases of hypokalemia (usually serum potassium 2.5-3.5 mmol/l) can be treated with oral potassium supplementation either as liquid or as tablet	Evidence-based guidelines[1]
Symptomatic hypokalemia should be treated intravenously and, in severe cases, may require a central venous catheter and continuous ECG monitoring.	Evidence-based guidelines[1]
In hypokalemia due to renal potassium loss, a potassium-sparing diuretic may be added as treatment such as amiloride or spironolactone.	Evidence-based guidelines[1]
Magnesium supplementation complementary to potassium supplementation should be added when hypomagnesemia is present.	Evidence-based guidelines[1]

[1] *Hoorn et al.* Dutch guideline for the management of electrolyte disorders – 2012 revision. The Netherlands Journal of Medicine. 2013;71:153-165

4.3 What is the evidence for treatment with angiotensin converting enzyme (ACEi) or angiotensin receptor blocking (ARB) agent in CAYA cancer survivors with proteinuria?

No randomized controlled trials identified investigating the use of ACEi or ARB in CAYA cancer survivors.

Summary of guidelines including recommendations in the **general population** in **children and adolescents**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
AAP 2017	Children and adolescents with the combination of CKD, hypertension, and proteinuria should be treated with an ACEi or ARB.	Strong	Moderate
ESH 2016	In a child with hypertension associated with diabetes mellitus and microalbuminuria, or with the combination of CKD and proteinuria, an ACEi or ARB is the most appropriate first line agent because of their antiproteinuric effect.	Not graded	Not graded

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE

ADA 2017	An ACEi or ARB, at the maximum tolerated dose is the recommended first-line treatment for hypertension in patients with diabetes and urine albumin-to-creatinine ≥300 mg/g creatinine (high) or 30-299 mg/g creatinine (moderate).	Not graded Not graded	High Moderate
JNC8 2014	In patients aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEi or ARB to improve kidney outcomes.	Moderate	Moderate
NICE 2019	Do not combine an ACE inhibitor with an ARB to treat hypertension.	Not graded	Not graded
CARI 2012	We recommend that either ACEi or ARBs should be used as first line therapy in adults with non-diabetic kidney disease.	Strong	Moderate
	We recommend that combination therapy with both an ACEi and ARB should be avoided	Strong	Low
	We recommend that either an ACEI or ARBs should be used as first line therapy in adults with diabetic kidney disease.	Strong	High
SIGN 2008	Patients with the combination of CKD and type 1 diabetes with microalbuminuria should be treated with an ACEi irrespective of blood pressure.	Not graded	High
	Patients with the combination of CKD and type 2 diabetes with microalbuminuria should be treated with an ACEi or an ARB irrespective of blood pressure.	Not graded	High
	ACEi's and ARB are the agents of choice to reduce proteinuria in patients without diabetes but who have the combination of CKD and proteinuria.	Not graded	High
	ACEi's and/or ARB should be used as agents of choice in patients *(with or without diabetes)* with CKD and proteinuria *(≥ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol)* in order to reduce the rate of progression of CKD.	Not graded	High
DIABETES CANADA 2018	For people with CVD or CKD, including albuminuria, or with CV risk factors in addition to diabetes and hypertension, an ACEi or an ARB is recommended as initial therapy.	Strong	High
CKD UK 2006	Many patients will need more than 2 drugs to achieve optimal control. ACEi's should be included in the regimen for all patients with proteinuria (urine protein:creatinine ratio > 100 mg/mmol), diabetic patients with microalbuminuria, and for patients with heart failure; ARBs may be used as alternatives to ACEi's.		1
ASH/ISH 2014	Do not combine ACEi's with ARB's; each of these drug types is beneficial in patients with kidney disease, but in combination they may actually have adverse effects on kidney function.	Not graded	Not graded
ACC/AHA 2018	In adults with the combination of hypertension and CKD stage 3 or stage 1/2 with albuminuria (>300 mg/g creatinine) treatment with ACEi is reasonable to slow kidney disease progression.	Moderate	Moderate
	In adults with the combination of hypertension and CKD stage 3 or stage 1/2 with albuminuria (>300 mg/g creatinine), treatment with an ARB may be reasonable if an ACEi is not tolerated.	Weak	Expert opinion
ESC/ESH 2018	RAS blockers (i.e., ACEi and ARB) are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.	Strong	High
	A combination of two RAS blockers is not recommended in patients with CKD.	Not to do	High

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV(D), cardiac vascular (disease); RAS, renin aldosterone system.

Recommendations: treatment with ACE inhibitor or angiotensin receptor blocking (ARB) agent in patients with proteinuria

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (2 general pediatric guidelines)	
Children and adolescents with the combination of CKD, hypertension, and proteinuria should be treated with an ACEi or ARB because of their antiproteinuric effect.	Evidence-based guidelines[1,2]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (10 general adult guidelines)	
In adults with the combination of hypertension and albuminuria, treatment with an ACEi is recommended to slow kidney disease progression.	Evidence-based guidelines[3,4,5,6,7]
In adults with the combination of hypertension and CKD treatment with an ACEi is recommended to slow kidney disease progression.	Evidence-based guidelines[6,8,9]
ACEi's or ARB's should be used as agents of choice in patients *(with or without diabetes)* with the combination of CKD and proteinuria in order to reduce the rate of progression of CKD.	Evidence-based guidelines[10]
An ARB may be used as alternative to an ACEi.	Evidence-based guidelines[3,4,5,6,7,8,9,10]
Combination therapy with both an ACEi and ARB should be avoided.	Evidence-based guidelines[7,9,11,12]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

[1] *Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[2] *Lurbe et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887-920

[3] *de Boer et al.* American Diabetes Association. Diabetes and Hypertension: A position statement by the American Diabetes Association. Diabetes Care. 2017;40:1273-1284

[4] *Tobe et al.* Diabetes Canada Clinical Practice Guidelines Expert Committee. Treatment of hypertension. Canadian Journal of Diabetes. 2018:S186-189.

[5] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7

[6] *Whelton PK et al.* The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71:e13-e115

[7] *Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021–3104 doi:10.1093/eurheartj/ehy339

[8] *James et al.* Evidence-based guideline for the management of high blood pressure in adults. Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5): 507-520

[9] *Phoon et al.* CARI guidelines. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: antihypertensive agents. Early chronic kidney disease. 2012; 1-24

[10] *Scottish Intercollegiate Guidelines Network (SIGN).* Diagnosis and management of chronic kidney disease, a national clinical guideline. 2008. Available at www.**sign**.ac.uk/guidelines/published/numlist.html

[11] *NICE.* Hypertension in adults: diagnosis and Management. Clinical guideline. Published: 24 August 2011, http://www.nice.org.uk/guidance/cg127. Last updated august 2019.

[12] *Weber et al.* Clinical practice guideline for the management of hypertension in the community, a statement by the American Society of Hypertension and the International Society of Hypertension. The Journal of Clinical Hypertension. 2014;16:14-26.

4.4 Does blood pressure treatment influence the trajectory of renal dysfunction in CAYA cancer survivors?

No studies identified investigating the influence of blood pressure treatment on the trajectory of renal dysfunction in CAYA cancer survivors.
Summary of guidelines including recommendations in the **general population** in **children and adolescents**.

Recommendation 1: type of treatment

GUIDELINE	RECOMMENDATIO	STRENGTH	LEVEL OF EVIDENCE
ESH 2016	In a child with hypertension associated with diabetes mellitus and microalbuminuria, or with the combination of CKD and proteinuria, an ACEi or ARB is the most appropriate first line agent because of their antiproteinuric effect.	Not graded	Not graded
AAP 2017	Children and adolescents with the combination of CKD, hypertension, and proteinuria should be treated with an ACEi or ARB.	Strong	Moderate

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

Recommendation 2: target blood pressure

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
AAP 2017	Children or adolescents with both CKD and hypertension should be treated to lower 24-hour MAP <50th percentile by ambulatory blood pressure monitoring.	Strong	Moderate
ESH 2016	Strict BP control leads to a decrease in proteinuria and a slowing of the progression of CKD in children. It appears appropriate to target BP to the 75th percentile in children with non-proteinuric CKD and to below the 50th percentile in children with proteinuria of any degree with close monitoring of creatinine	Not graded	Not graded

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; MAP, mean arterial pressure.

Summary of guidelines including recommendations in the **general population** in **adults**.

Recommendation 1: type of treatment

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
JNC8 2014	In patients aged ≥ 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes.	Moderate	Moderate
SIGN 2008	ACEi's and/or ARB should be used as agents of choice in patients *(with or without diabetes)* with CKD and proteinuria *(≥ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol)* in order to reduce the rate of progression of CKD.	Not graded	High
	Non-dihydropyridine calcium channel blockers should be considered in patients with the combination of CKD and proteinuria who are intolerant of ACEi or ARB	Not grated	High

NICE 2019	Do not combine an ACEi with an ARB to treat hypertension.	Not graded	Not graded
ASH/ISH 2014	Do not combine ACEi's with ARB's; each of these drug types is beneficial in patients with kidney disease, but in combination they may actually have adverse effects on kidney function	Not graded	Not graded
ACC/AHA 2018	In adults with hypertension and CKD stage 3 or stage 1/2 with albuminuria (> 300 mg/g creatinine) treatment with ACEi is reasonable to slow kidney disease progression	Moderate	Moderate
	In adults with hypertension and CKD stage 3 or stage 1/2 with albuminuria (> 300 mg/g creatinine), treatment with ARB may be reasonable if an ACEi is not tolerated	Weak	Low
	After kidney transplantation, it is reasonable to treat patients with hypertension with a calcium antagonist on the basis of improved GFR and kidney survival	Moderate	Moderate
ESC/ESH 2018	RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria	Strong	Strong
	A combination of two RAS blockers is not recommended in patients with CKD	Not to do	High

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; RAS, renine aldosterone system.

Recommendation 2: target blood pressure

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
CARI 2012	We recommend BP ≤130/80 in people with micro- or macroalbuminuria (UACR > 3.5 mg/mmol in women, UACR > 2.5 mg/mmol in men)	Strong	Moderate
SIGN 2008	Blood pressure should be controlled to slow the deterioration of GFR and reduce proteinuria. Patients with ≥ 1 g/day of proteinuria *(approximately equivalent to a protein/creatinine ratio of 100 mg/mmol)* should have a target maximum systolic blood pressure of 130 mmHg.	Not graded	High
CKD UK 2006	The threshold for initiation and subsequent adjustment of antihypertensive therapy should be 140/90 mm Hg for patients without proteinuria, and 130/80 for those with urine protein:creatinine ratio > 100 mg/mmol	Not graded	Moderate
	Antihypertensive therapy should be adjusted to achieve blood pressure < 130/80, or < 125/75 mm Hg for those with urine protein:creatinine ratio > 100 mg/mmol.	Not graded	Moderate
ACC/AHA 2018	Adults with the combination of hypertension and CKD should be treated to a BP goal of < 130/80 mmHg	Strong	Moderate, expert opinion
	After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal of < 130/80 mm Hg	Moderate	Moderate, expert opinion
ESC/ESH 2018	In patients with diabetic or non-diabetic CKD it is recommended to lower SBP to a range of 130-139 mmHg	Strong	High

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; BP, blood pressure; UACR, urine albumin to creatinine ratio.

Recommendation 1: influence of type of blood pressure treatment on the trajectory of renal dysfunction

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (2 general pediatric guidelines)

Children and adolescents with the combination of CKD, hypertension, and proteinuria should be treated with an ACEi or ARB because of their antiproteinuric effect.	Evidence-based guidelines[1,2]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (6 general adult guidelines)	
In adults with CKD and proteinuria antihypertensive treatment should include an ACEi or ARB to slow kidney disease progression.	Evidence-based guidelines[3,4,5,6]
Do not combine an ACEi with ARB. The combination may have adverse effects on kidney function.	Evidence-based guidelines[6,7,8]
Calcium antagonist should be considered in patients with the combination of CKD and proteinuria who are intolerant of ACEi or ARB.	Evidence-based guidelines[4]
After kidney transplantation, it is reasonable to treat patients with hypertension with a calcium antagonist on the basis of improved GFR and kidney survival.	Evidence-based guidelines[5]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate.

[1] *Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[2] *Lurbe et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887-920

[3] *James et al.* Evidence-based guideline for the management of high blood pressure in adults. Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5): 507-520

[4] *Scottish Intercollegiate Guidelines Network (SIGN).* Diagnosis and management of chronic kidney disease, a national clinical guideline. 2008. Available at www.sign.ac.uk/guidelines/published/numlist.html

[5] *Whelton PK et al.* The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71:e13-e115

[6] *Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021–3104 doi:10.1093/eurheartj/ehy339

[7] *NICE.* Hypertension in adults: diagnosis and Management. Clinical guideline. Published: 24 August 2011, www.nice.org.uk/guidance/cg127. Last updated august 2019.

[8] *Weber et al.* Clinical practice guideline for the management of hypertension in the community, a statement by the American Society of Hypertension and the International Society of Hypertension. The Journal of Clinical Hypertension. 2014;16:14-26.

Recommendation 2: influence of target blood pressure on the trajectory of renal dysfunction

Overall conclusions recommendations in existing clinical practice guidelines in <u>children</u> (2 general pediatric guidelines)	
In children with the combination of proteinuric CKD and hypertension strict BP control (below < 50th percentile) leads to a decrease in proteinuria and a slowing of the progression of CKD.	Evidence-based guidelines[1,2]
Overall conclusions recommendations in existing clinical practice guidelines in <u>adults</u> (5 general adult guidelines)	

Adults with the combination of hypertension and proteinuria (UPCR > 100 mg/mmol) should be treated to achieve BP ≤ 130/80 mg/mmol to slow the deterioration of GFR and reduce proteinuria.	Evidence-based guidelines[3,4,5]
Adults with the combination of hypertension and CKD should be treated to a systolic BP goal of < 130-139 mmHg.	Evidence-based guidelines[6,7]
After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal of < 130/80 mmHg.	Evidence-based guidelines[6]

Abbreviations: CKD, chronic kidney disease; BP, blood pressure.

[1] *Flynn et al.* American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140:e20171904

[2] *Lurbe et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887-920

[3] *Phoon et al.* CARI guidelines. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: antihypertensive agents. Early chronic kidney disease. 2012; 1-24

[4] *Scottish Intercollegiate Guidelines Network (SIGN).* Diagnosis and management of chronic kidney disease, a national clinical guideline. 2008. Available at www.sign.ac.uk/guidelines/published/numlist.html

[5] *Vanholder et al.* Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. Nephrol Dial Transplant. 2006;21:1776-7

[6] *Whelton PK et al.* The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71:e13-e115

[7] *Williams et al.* The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021–3104 doi:10.1093/eurheartj/ehy339

Appendix L. Legend level of evidence included guidelines.

	STRENGTH RECOMMENDATION			LEVEL OF EVIDENCE		
GUIDELINE	**Label**	**Definition by article**	**Definition used for IGHG**	**Label**	**Definition by article**	**Definition used for IGHG**
AAP 2017		Strong	Strong	A	Intervention: Well-designed and conducted trials, meta-analyses on applicable populations Diagnosis: independent gold standard studies of applicable populations	High
		Moderate	Moderate	B	Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate
		Weak (low-quality of evidence)	Weak	C	Single or few observational studies or multiple studies with inconsistent findings or major limitations	Low
		Weak (balance of benefit and harm)	Weak	D	Expert opinion, case reports, reasoning from first principles	Expert opinion
		No recommendation can be made	No recommendation can be made	X	Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Not applicable
ACC/AHA 2018	1	Strong	Strong	A	High-quality evidence from more than 1 RCT; Meta-analyses of high-quality RCTs; One or more RCT corroborated by high-quality registry studies	High
	2a	Moderate	Moderate	B-R	Moderate (randomized) Moderate-quality evidence from 1 or more RCTs; Meta-analyses of moderate-quality RCTs	Moderate
	2b	Weak	Weak	B-NR	Moderate (non-randomized) Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; Meta-analyses of such studies	Moderate
	3	No benefit – moderate	Not to do	C-LD	Low (limited data) Randomized or nonrandomized observational or registry studies with limitations of design or execution;	Low

					Meta-analyses of such studies; Physiological or mechanistic studies in human subjects	
	4	Harm – strong	Not to do	C-EO	Low (expert opinion)	Expert opinion
ADA 2017				A	Clear or supporting evidence from well conducted, generalizable RCTs that are adequately powered, including: well-conducted single- or multicenter trial, meta-analysis that incorporated quality ratings in the analysis.	High
				B	Supportive evidence from well-conduced cohort studies (prospective study or registry, meta-analysis of cohort studies) or case-control study	Moderate
				C	Supportive evidence from poorly controlled or uncontrolled trials (RCT with 1 or more major or 3 or more methodological flaws, observational study with high potential bias), case-series, or conflicting evidence	Low
				E	Expert consensus or clinical experience	Expert opinion
CARI 2012	1	No definition described	Strong	A	No definition described	High
	2	No definition described	Moderate	B	No definition described	Moderate
				C	No definition described	Low
				D	No definition described	Expert opinion
CKD UK 2006				1	Meta-analyses, systematic reviews of RCT or RCT	High
				2	Systematic reviews of case-control or cohort studies, or case-control or cohort studies	Moderate
				3	Non-analytic studies, e.g., case reports, case series	Low
				3DA	Observational diagnostic accuracy (DA) instead of non-analytic studies	Moderate
				4	Expert opinion (in the absence of any of the above)	Expert opinion
DIABETES CANADA 2018	1A	No definition described	Strong	A	No definition described	High
ESC/ESH 2018	1	Recommended	Strong	A	Multiple RCT or meta-analyses	High
	2a	Should be recommended	Moderate	B	Single RCT or large non-randomized studies	Moderate

	2b	May be considered	Weak	C	Expert opinion, small studies, retrospective cohort studies, registries	Low
	3	Not recommended	Not to do			
HYPERTENSION CANADA 2017				A	RCT (or systematic reviews of RCT) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes	High
				B	RCT, systematic reviews or prespecified subgroup analyses of RCT that have lower precision, or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes	Moderate
				C	Trials that have lower levels of internal validity and/or precision, or trials reporting invalidated surrogate outcomes, or results from non-randomized observational studies	Low
				D	Low-powered imprecise studies or expert opinion	Expert opinion
JNC8 2014	A	Strong	Strong	High	Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies	High
	B	Moderate	Moderate	Moderate	RCTs with minor limitations affecting confidence in, or applicability of, the results; Well-designed, well-executed non–randomized controlled studies and well-designed, well-executed observational studies; Well-conducted meta-analyses of such studies	Moderate
	C	Weak	Weak	Low	RCTs with major limitations; Non–randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results;	Low

					Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports); Physiological studies in humans; Meta-analyses of such studies	
	D	Against	Not to do			
	E	Expert opinion	Expert opinion			
	N	No recommendation for or against (net benefit unclear)	No recommendation can be made			
KDIGO 2024	1	Strong	Strong	A	High	High
	2	Moderate	Moderate	B	Moderate	Moderate
				C	Low	Low
				D	Very low	Expert opinion
SIGN 2008				A	At least one meta-analysis systematic review, or RCT rated as high-quality with a very low risk of bias and directly applicable to the target population; Body of evidence from well-conducted meta-analyses, systematic reviews or RCTs with low risk of bias	High
				B	Body of evidence from high-quality systematic reviews of case control or cohort studies; Extrapolated evidence from high-quality of well-conducted meta-analyses, systematic reviews or RCTs with low risk of bias	Moderate
				C	Body of evidence from well conducted case control or cohort studies with low risk of bias; Extrapolated evidence from high-quality systematic reviews of case control or cohort studies	Moderate
				D	Non-analytic studies; Extrapolated evidence from well-conducted case-control or cohort studies	Low
				E	Expert opinion	Expert opinion

Abbreviations: DA, diagnostic accuracy; IGHG, international guideline harmonization group; RCT, randomized controlled trial.

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