Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Nephrotoxic Medications

High Risk Nephrotoxins		**Moderate Risk Nephrotoxins**	
Acyclovir	IVIG	Accupril	Hydrochlorothiazide
Amikacin	Ketorolac	Aminocaproic acid	Linezolid
Amphotericin B	Lomustine	Aspirin	Lisinopril
Cidofovir	Meloxicam	Bevacizumab	Lithium
Cisplatin	Mercaptopurine	Bumetanide	Losartan
Colistimethate	Mesalamine	Celecoxib	Methocarbamol
Cyclophosphamide	Methotrexate	Chlorothiazide	Mitoxantrone
Cyclosporine	Naproxen	Daptomycin	Nelarabine
Fludarabine	Neomycin	Enalapril	Phenylephrine
Gentamicin	Sirolimus	Enalaprilat	Piperacillin/tazobactam
Hydroxyurea	Streptomycin	Etravirine	Ramipril
Ibuprofen	Tacrolimus	Everolimus	Spironolactone
Ifosfamide	Tobramycin	Foscarnet	Trimethoprim/ sulfamethoxazole
Imatinib	Vancomycin	Furosemide	Valacyclovir
Indomethacin		Gabapentin	Valganciclovir
		Ganciclovir	Valsartan
		Glipizide	

eTable 2. Primary Diagnoses of the Primary Cohort

Primary Diagnosis	N
Atrioventricular Septal Defect	120
Ventricular Septal Defect	103
Tetralogy of Fallot	90
Atrial Septal Defect	75
Coarctation of the Aorta	47
Partial Anomalous Pulmonary Venous Return	27
Double Outlet Right Ventricle	22
Aortic Stenosis	21
Cardiomyopathy	16
Subaortic stenosis	16
Vascular Rings	12
Other Single Ventricle Anomalies	10
Anomolous Coronary Artery	9
Complex Congenital Heart Disease	9
Congenital heart disease NOS	9
Double Chamber Right Ventricle	9
Total Anomalous Pulmonary Venous Return	7
Transposition of the Great Arteries	7
Ebstein's Anomaly	6
Pulmonary Valvar Stenosis	6
Tricuspid Atresia	6
AP window	4
Interrupted Aortic Arch	4
Supravalvar Aortic Stenosis	4
Cardiac disease NOS	3
Aortic arch hypoplasia	2
Arrhythmia	2
Critical Pulmonary Stenosis	2
Double Inlet Left Ventricle	2
Mitral valve stenosis	2
Patent Ductus Arteriosus	2
Pulmonary Atresia	2
Pulmonary artery sling	2
Rheumatic carditis	2
Cleft Mitral Valve	1
Cor Tritriatum	1
Hypoplastic Left Heart Syndrome	1
Intracardiac Mass	1
Mitral valve prolaspe	1
Truncus Arteriosus	1

eTable 3. Primary Diagnoses of the Validation Cohort

Primary Diagnoses	N
Ventricular Septal Defect	54
Atrial Septal Defect	51
Atrioventricular Septal Defect	39
Tetralogy of Fallot	26
Coarctation of the Aorta	18
Patent Ductus Arteriosus	18
Coronary Anomaly	17
Cardiomyopathy	13
Partial Anomalous Pulmonary Venous Connection	9
Partial Anomalous Pulmonary Venous Return	9
Aortic Insufficiency	7
Double Outlet Right Ventricle	7
Vascular Ring	7
Aortic Stenosis	6
Arrhythmia Necessitating Pacemaker	5
Pulmonary Atresia	5
Ebstein's Anomaly	4
Pericardial Effusion	4
Cardiac Tumor	3
Double Inlet Left Ventricle	3
Sinus of Valsalva Aneurysm	3
Total Anomalous Pulmonary Venous Connection	3
Mitral Regurgitation	2
Pulmonary Stenosis	2
Transposition of the Great Arteries	2
Tricuspid Atresia	2
Anomalous Pulmonary Venous Connection	1
Aortic Aneurysm	1
Cardiac Assist Device Complication	1
Cardiac Tamponade	1
Cor Triatriatum	1
Hypoplastic Aortic Arch	1
Hypoplastic Left Heart Syndrome	1
Interrupted Aortic Arch	1
Mitral Atresia	1
Pericardial Cyst	1
Pulmonary Embolism	1
Pulmonary Insufficiency	1
Scoliosis	1
Tricuspid Regurgitation	1

eTable 4. Clinical Characteristics of Acetaminophen Exposed vs Unexposed in the Primary and Validation Cohorts[a]

Variable	Primary Cohort (n=666)			Validation Cohort (n=333)		
	No Acet (n=72)	**Acet** (n=594)	**Unadjusted *P* value**	**No Acet** (n=18)	**Acet** (n=315)	**Unadjusted *P* value**
Age, median (IQR), mo	3.8 (2.0-9.7)	7.4 (4.2-47.1)	<0.001	55.6 (2.7-220.1)	14.0 (4.0-143.6)	0.81
Female Sex, No. (%)	35 (49)	293 (49)	0.91	8 (44)	164 (52)	0.53
Weight, median (IQR), kg	4.7 (3.8-8.1)	7.4 (5.3-14.9)	<0.001	15.7 (4.4-75.0)	9.2 (4.8-44.5)	0.5
Serum Creatinine, median (IQR), mg/dL						
Preoperative baseline	0.31 (0.21-0.42)	0.35 (0.25-0.45)	0.1	0.55 (0.30-1.08)	0.30 (0.20-0.60)	0.017
Postoperative peak	0.61 (0.49-0.77)	0.52 (0.45-0.64)	0.004	1.00 (0.60-1.37)	0.50 (0.40-0.80)	<0.001
Number of Postoperative Serum Creatinines, median (IQR)	8 (6-10)	6 (4-8)	<0.001	N/A	N/A	N/A
CPB Time, median (IQR), min[b]	110 (75-165)	85 (57-119)	<0.001	112 (10-160)	94 (40-148)	0.58
RDW, median (IQR), %[c]	14.9 (13.7-16.3)	13.5 (12.8-14.6)	<0.001	16.1 (15.2-19.0)	14.6 (13.5-16.2)	0.008
Postoperative hypotension, No. (%)	63 (88)	455 (77)	0.036	15 (83)	144 (46)	0.002
High Risk Nephrotoxins, No. (%)			0.22			0.54
0	46 (64)	304 (51)		7 (39)	117 (37)	
1	22 (31)	243 (41)		10 (56)	140 (44)	
2	4 (6)	43 (7)		1 (6)	46 (15)	
≥3	0 (0)	4 (1)		0 (0)	12 (4)	
Moderate Risk Nephrotoxins, No. (%)			0.041			0.85
0	7 (10)	23 (4)		0 (0)	8 (3)	
1	36 (50)	262 (44)		2 (11)	33 (10)	
2	25 (35)	237 (40)		7 (39)	101 (32)	
≥3	4 (6)	72 (12)		9 (50)	173 (55)	
RACHS Score, No. (%)[d]			<0.001			0.66
1	9 (13)	134 (24)		2 (22)	86 (33)	
2	19 (28)	237 (42)		5 (56)	107 (41)	
≥3	40 (59)	197 (35)		2 (22)	71 (27)	

Abbreviations: CPB, Cardiopulmonary Bypass; RDW, Red (Cell) Distribution Width; RACHS - Risk Adjustment for Congenital Heart Surgery; N/A – Not available.
SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4.

[a] *P* values from the univariate Wilcoxon rank-sum test for continuous variables and from the univariate Pearson chi-square test for categorical variables. [b] Time available for 665 in the primary cohort and all 333 of the validation cohort.
[c] Value available for 613 in the primary cohort and 329 in the validation cohort.
[d] Score available for 636 in the primary cohort and 273 in the validation cohort.

eTable 5. Bias-Corrected Adjusted Odds Ratios from Sensitivity Analysis of Unmeasured Confounding Effects

		OR_{UY}									
		1.5	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**	**4.5**	**5.0**	**5.5**	**6.0**
OR_{UE}	**1.5**	2.53 (1.29, 4.95)	2.46 (1.26, 4.81)	2.40 (1.23, 4.70)	2.36 (1.21, 4.62)	2.33 (1.19, 4.55)	2.30 (1.17, 4.50)	2.28 (1.16, 4.45)	2.26 (1.15, 4.41)	2.24 (1.14, 4.38)	2.22 (1.14, 4.35)
	2.0	2.48 (1.27, 4.85)	2.37 (1.21, 4.63)	2.28 (1.16, 4.46)	2.21 (1.13, 4.32)	2.15 (1.10, 4.21)	2.10 (1.08, 4.12)	2.06 (1.05, 4.04)	2.03 (1.04, 3.97)	2.00 (1.02, 3.91)	1.97 (1.01, 3.86)
	2.5	2.43 (1.24, 4.75)	2.28 (1.16, 4.46)	2.17 (1.11, 4.24)	2.08 (1.06, 4.07)	2.01 (1.03, 3.93)	1.95 (1.00, 3.82)	1.91 (0.97, 3.73)	1.86 (0.95, 3.65)	1.83 (0.94, 3.58)	1.80 (0.92, 3.52)
	3.0	2.38 (1.22, 4.66)	2.21 (1.13, 4.32)	2.08 (1.06, 4.07)	1.98 (1.01, 3.88)	1.90 (0.97, 3.73)	1.84 (0.94, 3.60)	1.79 (0.91, 3.50)	1.74 (0.89, 3.41)	1.71 (0.87, 3.34)	1.67 (0.86, 3.27)
	3.5	2.35 (1.20, 4.59)	2.15 (1.10, 4.21)	2.01 (1.03, 3.93)	1.90 (0.97, 3.73)	1.82 (0.93, 3.56)	1.75 (0.90, 3.43)	1.70 (0.87, 3.32)	1.65 (0.84, 3.23)	1.61 (0.82, 3.15)	1.58 (0.81, 3.09)
	4.0	2.31 (1.18, 4.53)	2.10 (1.08, 4.12)	1.95 (1.00, 3.82)	1.84 (0.94, 3.60)	1.75 (0.90, 3.43)	1.68 (0.86, 3.29)	1.63 (0.83, 3.18)	1.58 (0.81, 3.09)	1.54 (0.79, 3.01)	1.50 (0.77, 2.94)
	4.5	2.29 (1.17, 4.48)	2.06 (1.05, 4.04)	1.91 (0.97, 3.73)	1.79 (0.91, 3.50)	1.70 (0.87, 3.32)	1.63 (0.83, 3.18)	1.57 (0.80, 3.07)	1.52 (0.78, 2.97)	1.48 (0.75, 2.89)	1.44 (0.74, 2.82)
	5.0	2.26 (1.16, 4.43)	2.03 (1.04, 3.97)	1.86 (0.95, 3.65)	1.74 (0.89, 3.41)	1.65 (0.84, 3.23)	1.58 (0.81, 3.09)	1.52 (0.78, 2.97)	1.47 (0.75, 2.87)	1.43 (0.73, 2.79)	1.39 (0.71, 2.72)
	5.5	2.24 (1.15, 4.39)	2.00 (1.02, 3.91)	1.83 (0.94, 3.58)	1.71 (0.87, 3.34)	1.61 (0.82, 3.15)	1.54 (0.79, 3.01)	1.48 (0.75, 2.89)	1.43 (0.73, 2.79)	1.39 (0.71, 2.71)	1.35 (0.69, 2.64)
	6.0	2.30 (1.18, 4.50)	2.07 (1.06, 4.04)	1.89 (0.97, 3.70)	1.75 (0.90, 3.43)	1.64 (0.84, 3.22)	1.55 (0.79, 3.04)	1.48 (0.76, 2.89)	1.42 (0.72, 2.77)	1.36 (0.70, 2.66)	1.31 (0.67, 2.57)

Each cell contains the bias-corrected adjusted odds ratio (OR) and 95% confidence interval (in parentheses) based upon a hypothetical confounder with the indicated OR_{UY} [ORs between an unmeasured confounder (*U*) and AKI risk (*Y*)] and OR_{UE} [ORs between an unmeasured confounder and acetaminophen exposure (*E*)]. Light gray shaded values indicate results maintaining statistical significance at the indicated OR_{UY} and OR_{UE}. Dark gray shading indicates the threshold value for both OR_{UY} and OR_{UE} required for the 95% confidence interval to include the null value, 1, indicating being sensitive to the hypothetical unobserved confounder (actual value 3.07 for OR_{UY} and OR_{UE}).

eAppendix. Supplemental Sensitivity Analysis of Unmeasured Confounding Effects on the Association of Acetaminophen Exposure and Acute Kidney Injury Risk

Background

In any retrospective observational study, a causal link between the exposure and the outcome cannot be definitively proven. In our study, we observed an association between acetaminophen exposure and reduced risk of the outcome of acute kidney injury (AKI). In our analyses, we included subset analyses and adjustment for several covariates in an attempt to control for confounding, defined as factors that are associated with both the exposure and outcome, as confounding can lead to spurious associations. In our subset analyses and adjusted analyses, our observed association between acetaminophen exposure and reduced risk for AKI remained statistically significant. However, even after adjusting for potential observed confounders, there remains a possibility of residual confounding, as our covariates may fail to capture all factors associated with acetaminophen exposure and AKI.

Several methods have been developed to perform sensitivity analysis for the effects of unmeasured confounding. One approach is to calculate the bias due to hypothetical unmeasured confounders with various values of parameters, then correct for that bias to find the "true" association between the exposure and the outcome. Another approach is to find how strong an unmeasured confounder would have to be, in terms of its association to the exposure and the outcome, to "explain away" the observed association (i.e., to make the 95% confidence intervals (CI) include the null value, or 1). To address the possibility of unmeasured confounding in our study, we performed sensitivity analyses using both strategies. In these analyses, we sought to determine if bias-correcting our findings based on a hypothetical covariate with stronger association to both the exposure and the outcome than any of our ascertained covariates would render our findings statistically insignificant. Furthermore, we sought to define the strength of association to the exposure and outcome required for a hypothetical confounder to make our findings statistically insignificant.

Methods

For these sensitivity analyses, we defined acetaminophen exposure as a binary variable (i.e., no acetaminophen vs. any acetaminophen). We expressed the odds ratios (OR) for susceptibility to AKI based on the increased risk for those with no acetaminophen exposure [i.e., patients who received no acetaminophen were 2.63 (95% CI, 1.34-5.15) times more likely to develop AKI that those with ≥1 dose of acetaminophen, after adjusting for potential (measured) confounders such as age at surgery, surgery bypass time, the risk adjustment for congenital heart surgery (RACHS) score,[1] red cell distribution width, hypotension and use of nephrotoxic co-medications]. As a note, the observed OR of 2.63 for binary acetaminophen exposure is approximately equivalent to that for weight-adjusted acetaminophen dose of 60 mg/kg, which is the dose halfway between the low and high dose acetaminophen thresholds in Figure 1. In other words, patients who received ≥1 dose of acetaminophen were 62% (OR=0.38, 95% CI, 0.19-0.74) less likely to develop AKI compared to those who received no acetaminophen.

We used the methods developed by VanderWeels and Arah and Lin et al. to calculate the bias due to unmeasured confounders and correct the observed OR and 95% CI, where a bias-corrected 95% CI including the null value of 1 indicates the observation is no longer statistically significant.[2,3] Specifically, we first developed an example of a hypothetical unmeasured confounder, assuming its strength to be equal to the strongest confounder observed in our data, and calculated the bias factors across various values of prevalence for the confounder in those with and without acetaminophen exposure. Based on this, we calculated the bias-corrected OR and 95% CI for our association of acetaminophen exposure to AKI. Second, we calculated the bias factor at various values of strength for the association of hypothetical confounders to find the ORs that would make the bias-corrected result include the null.

Results

In the primary cohort, we identified a range of magnitude of confounding effects on the exposure and the outcome. The ORs between the observed confounders and acetaminophen exposure (i.e., patients with no acetaminophen compared to with ≥1 acetaminophen dose) ranged from 0.18 to 3.02. The OR between the observed confounders and the outcome of AKI ranged from 0.73 to 2.38. The strongest measured confounder was RACHS score. Compared to patients with low RACHS score of 1, patients with RACHS score ≥3 were 3.02 times more likely to have no acetaminophen, and also had 2.38-fold increased risk for AKI. Assuming that the strength of an unmeasured confounder has similar magnitude as RACHS score, we calculated the bias factor at various values of prevalence of the confounder, and corrected the observed OR of 2.63 (95% CI, 1.34-5.15). The bias-corrected OR was 2.09 (95% CI, 1.07-4.09) under the worst-case scenario, which was obtained at the prevalence of an unmeasured confounder of 0.56 in the no acetaminophen group and 0.3 in the ≥1 acetaminophen dose group.

For the second sensitivity analysis, we used various values of parameters including extreme values to determine when the study inference could be changed to include the null value, indicating our data were sensitive to that degree of unmeasured confounding. **eTable 5** presents the sensitivity analysis results with various values of the ORs between an unmeasured confounder (*U*) and acetaminophen exposure (*E*), OR_{UE}, and the ORs between an unmeasured confounder and AKI risk (*Y*), OR_{UY}. Highlighted in gray are the potential unmeasured confounding effects for which the bias-corrected ORs for the association between AKI and acetaminophen exposure remain statistically significant (i.e., each 95% CI does not include 1). As shown in **eTable 5**, when values of OR_{UE} and OR_{UY} both exceed 3.0 (dark gray highlight, actual value 3.07), the study inference would be sensitive to this unobserved confounder.

Discussion

In our first sensitivity analysis, the bias-corrected 95% CI did not include the null. Thus inclusion of some hypothetical confounder (currently unmeasured) with similar strength to our strongest measured confounder would not change the study inference. Our second sensitivity analysis indicated that a hypothetical confounder must be associated with >3 fold increased odds of receiving no acetaminophen as compared to receiving ≥1 acetaminophen dose and also must also have >3 fold increased odds of AKI risk to explain away our observed OR of 2.63 for AKI and acetaminophen exposure. That is, the joint minimum strength of association that an unmeasured confounder must have with acetaminophen exposure and AKI is >3.07 to make the 95% CI include the null.

In order for an unmeasured variable to be a confounder, it must be associated with both the exposure (acetaminophen) and the outcome (AKI). In this study, patients with no acetaminophen exposure had several indicators of more severe illness than those with one or more acetaminophen dose, including longer cardiopulmonary bypass time, higher red cell distribution width, and higher RACHS scores. These same variables are associated with increased risk for AKI, making them (measured) confounders. It is possible that there are additional variables that are associated with both acetaminophen exposure and AKI. For example, the Pediatric Risk of Mortality III (PRISM III) score is a mortality risk model for pediatric intensive care unit patients.[4] This variable is not available for our study cohort, but may be associated with the likelihood of acetaminophen exposure, as the sickest patients would be expected, based on our data, to have the lowest exposure rates. The association of PRISM III score and AKI has been assessed. In one study of 252 pediatric intensive care unit patients, higher PRISM III score was associated with AKI with an OR of 1.21 (95% CI 1.11-1.31) after adjusting for age, infection, sepsis, shock, cardiac disease, and mechanical ventilation.[5] Based on the sensitivity analyses, even if PRISM III score was associated with the outcome of AKI with an OR of 1.5 and was associated with an OR of 6.0 for acetaminophen exposure (nearly double the OR observed for RACHS score and acetaminophen exposure), our study findings would remain statistically significant with adjustment for this variable. While no analysis can completely rule out a significant impact of unmeasured confounding, we believe it is unlikely that an additional unmeasured variable has sufficient strength of association to both the exposure and outcome to make our findings statistically insignificant.

In summary, under a wide range of OR_{UY} and OR_{UE}, our study conclusions are not sensitive to unmeasured confounders. For typical values reported in observation studies in the range of 1.2 to 3, our study conclusion is robust.

References

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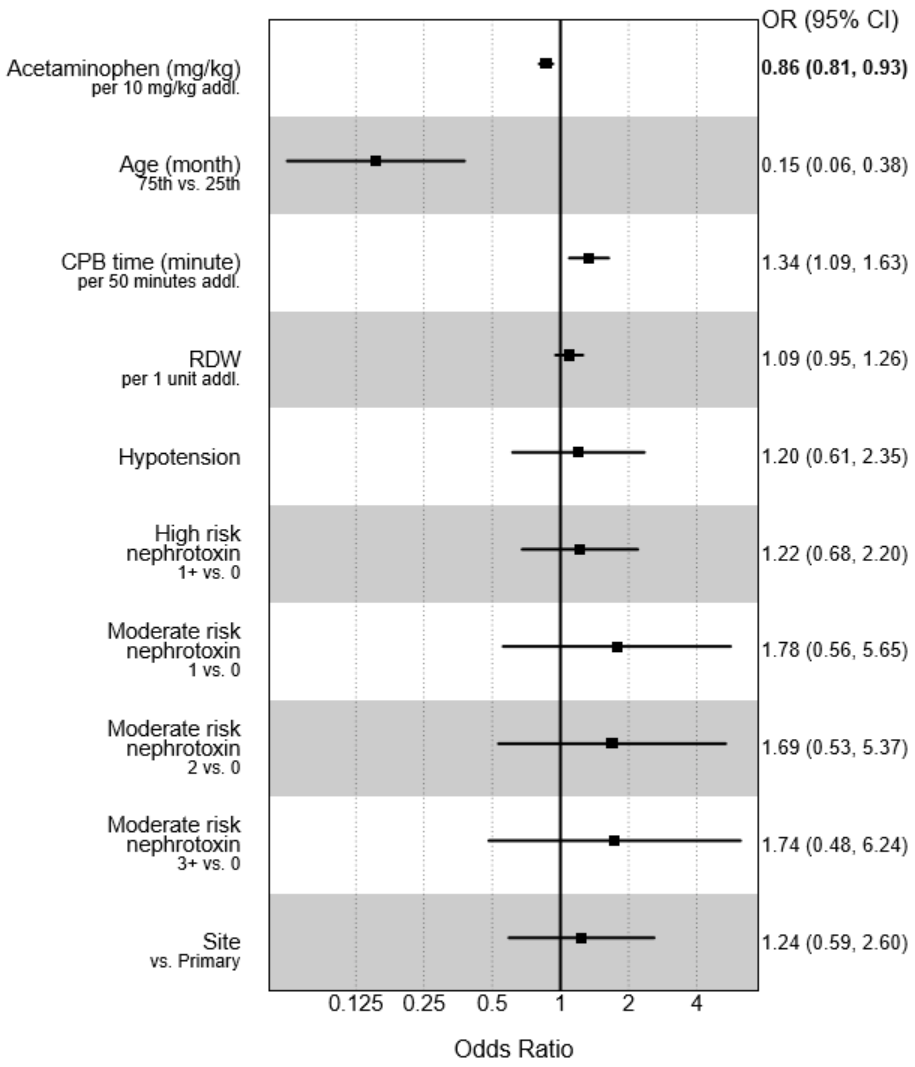
eFigure. Subgroup Analysis of RACHS Score ≥3



eFigure. Subgroup Analysis of RACHS Score ≥3. Shown are the ORs and the 95% CI for each of the clinical variables in the multiple logistic model for association to AKI in the subgroup of individuals with RACHS score ≥3 from both clinical sites. ORs are for weight-adjusted acetaminophen dose (per additional 10 mg/kg); Age (75th vs. 25th percentile for each cohort); CPB time (per additional 50 minutes); RDW (per additional 1%); Hypotension (present vs. absent); High risk nephrotoxins (one or more vs. none); Moderate risk nephrotoxins (one, two, and three or more vs. none); and Site (validation vs. primary). Point estimates and 95% CI are listed to the right of each plot. AKI – Acute kidney injury. OR – Odds ratio. CI – Confidence interval. CPB – Cardiopulmonary bypass. RDW – Red cell distribution width. RACHS – Risk Adjustment for Congenital Heart Surgery.