IMPACT OF DONOR SMOKING HISTORY ON KIDNEY TRANSPLANT RECIPIENT OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

- It is hypothesized that kidney donor smoking history may lead to worse transplant outcomes.
  - Extrapolated from studies in **native kidney disease** where smoking is a well-established risk factor for small vessel kidney disease, nodular glomerulosclerosis, proteinuria, or lower eGFR.
  - Smoking history in **kidney donors and transplant recipients** also correlate with worse post-donation and post-transplant outcomes[1-11].

- **Aim: To better understand possible impacts of any versus no donor smoking history on adult or pediatric kidney-alone transplant recipient outcomes of allograft failure, allograft function, or mortality, we systematically identified, critically appraised, and summarized the available literature since 2000.**

Methods

- Searched databases MEDLINE (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews (Ovid), and Cochrane Central Register of Controlled Trials (Ovid) from **2000-2023** to capture the modern era of immunosuppression.
- **Two independent systematic reviewers** screened title/abstract and did full-text review with data extraction and risk of bias assessment with the Risk of Bias in Non-randomized Studies – of Exposure (ROBINS-E) tool.
- Exposure:
  - **Donor smoking history** was dichotomized as "yes" or "no" and quantified when possible.
- Outcomes:
  - Co-primary outcomes were **death-censored graft failure (DCGF) and all-cause graft failure (ACGF).**
  - Secondary exploratory outcomes were donor kidney histologic scoring (interstitial fibrosis (IF), tubular atrophy (TA), vascular intimal thickening (VIT), glomerulosclerosis (GS)), delayed graft function (DGF), serum creatinine (Cr), estimated glomerular filtration rate (eGFR), and mortality.
- Analytic methods:
  - **Meta-analysis** was done if there were at least two studies that were sufficiently homogeneous (clinically and statistically), and we utilized an inverse variance, **random-effects model** (Der Simonian and Laird).
  - Statistical heterogeneity of pooled effect estimate was assessed by visual forest plot inspection, I^2 statistic, and τ^2 statistic.
  - Quality of evidence was assessed by Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group recommendations.
  - Subgroup analysis was done by donor type. Sensitivity analysis included only studies with adjusted analyses.

Results

- From 1785 citations, we included **17 studies**.
  - Published from 2005 to 2023, with data spanning 1987 to 2023 and sample sizes ranging from 100 to 156,069 patients. 6 studies included both adult and pediatric patients, 10 studies included only adults, and 1 included only pediatric patients.
  - One study was 'low risk' of bias for DGF outcome; all other studies had 'some concerns' for bias in all outcomes.

- Donor smoking history ascertainment was by retrospective chart review in 5 studies, registry databases in 8 studies, self-reported by living donors in 2 studies, or unclear in 2 studies. Smoking history was documented in 9 to 59% of donors and did not differ among studies in deceased or living donors.

- Donor smoking was associated with **modest increases in DCGF** (HR 1.05 (95% CI: 1.01, 1.09); I2 = 0%; low quality of evidence), predominantly in deceased donors, and **ACGF** in adjusted analyses (HR 1.12 (95% CI: 1.06, 1.19); I2 = 20%; very low quality of evidence).

- Pooled analyses did not demonstrate any meaningfully increased risk for recipients of kidney donors who smoked when outcomes of binary DCGF, binary ACGF, mortality as a time-to-event outcome, histologic changes (arteriolar hyalinosis, glomerulosclerosis), or eGFR at 3-6 months post-transplant, were assessed.

Figure 1. Forest plot for time to death-censored graft failure.

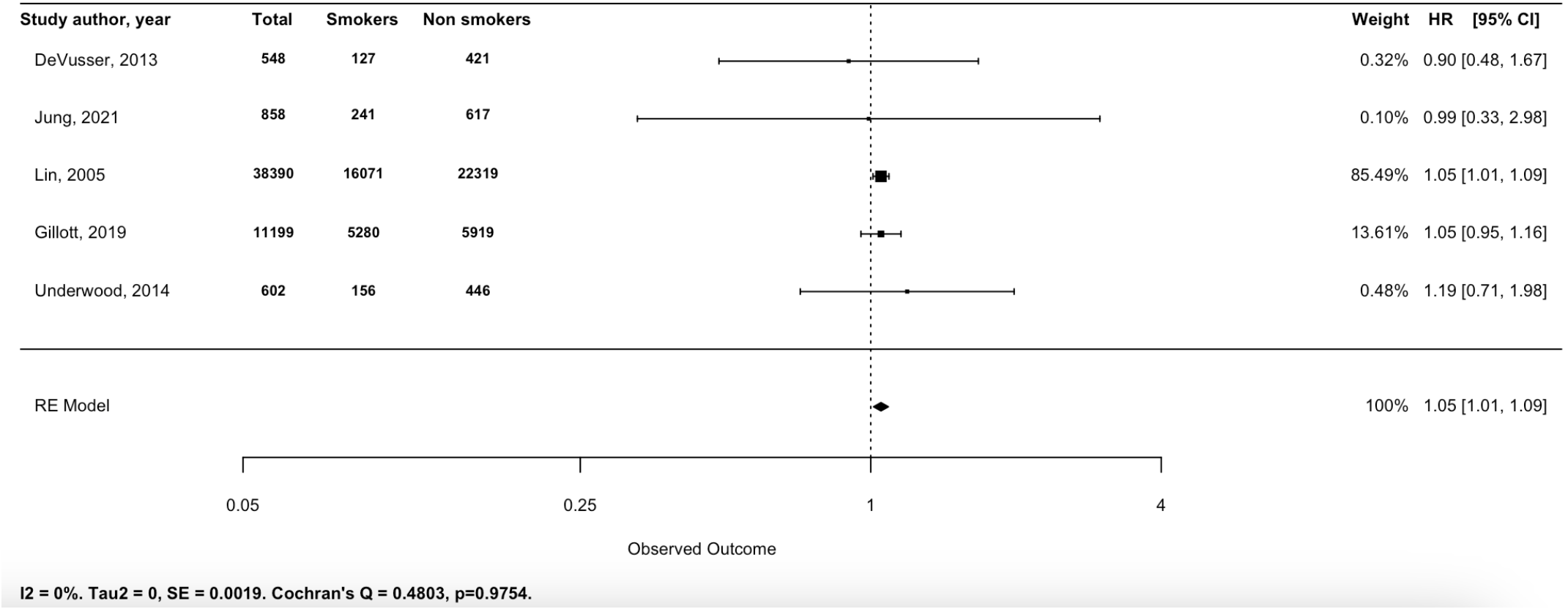

Table 1. Summary of findings

Outcome		Type of outcome	Pooled effect estimate (95% CI)	Heterogeneity	Number of patients (studies)	GRADE
DCGF		Time to event	HR 1.05 (1.01, 1.09)	I^2 = 0% (low)	51597 (5 studies)	Low
		Binary	OR 1.18 (0.90, 1.56)	I^2 = 92.7% (high)	42937 (5 studies) (6 cohorts)	Very low
ACGF		Time to event	HR 1.04 (1.00, 1.08)	I^2 = 23.8% (unclear)	168126 (3 studies)	Very low
		Binary	OR 1.03 (0.84, 1.26)	I^2 = 85.5% (high)	22646 (3 studies)	Very low
		Binary	RR 1.03 (0.87, 1.23)	I^2 = 94.9% (high)	142343 (3 studies)	Very low
Mortality		Time to event	HR 1.23 (0.96, 1.59)	I^2 = 88.5% (high)	51049 (4 studies)	Very low
Histo	IF	Binary	Not estimable	N/A	N/A	N/A
	TA	Binary	Not estimable	N/A	N/A	N/A
	AH	Binary	OR 0.96 (0.15, 6.13)	I^2 = 93% (high)	654 (2 studies)	Low
	VIT	Binary	Not estimable	N/A	N/A	N/A
	GS	Binary	OR 1.02 (0.74, 1.42)	I^2 = 0% (low)	654 (2 studies)	Low
DGF		Binary	Not estimable	N/A	N/A	N/A
Cr		Continuous	Not estimable	N/A	357 (2 studies)	N/A
eGFR		Continuous	Mean diff 1.71mL/min (95% CI: -5.17, +1.75)	I^2 = 0% (low)	205 (2 studies)	Low
BPAR		Binary	Not estimable	N/A	N/A	N/A

Strengths and Limitations

- Strengths of this review were robust systematic review methodology adherent to known guidelines and standards, broad search terms, multiple relevant databases, few restrictions to the search strategy, a clinically important question, and sensitivity analyses.

- Limitations included aggregate-level data, unmeasured confounders in cohort studies, and measurement error in donor smoking history due to recall error, incomplete data capture, erroneous documentation, or inappropriate classification.

Conclusions

- This systematic review and meta-analysis identified that any kidney donor smoking history was associated with modestly increased risk of death-censored graft failure and all-cause graft failure.
  - The principal finding was that kidney donor smoking history was associated with 5% increased risk of death-censored graft failure as a time-to-event outcome in both unadjusted and adjusted analyses, and this relationship persisted among deceased donors but not living donors.

- Few studies explored impacts of donor smoking on recipient outcomes of mortality, DGF, kidney function, or early kidney histologic changes.

- This review emphasizes the need for continued research, standardized reporting, and thoughtful consideration in clinical decision-making on kidney utilization.

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