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Impact of Ambient Particulate Matter (PM) Exposure of Lung Donors and Recipients on Bronchiolitis Obliterans Syndrome (BOS) and Mortality after Lung Transplant (LT)

Presenter: Thomas Egan

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All authors: No relationships to disclose

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Impact of Ambient Particulate Matter (PM) Exposure of Lung Donors and Recipients on Bronchiolitis Obliterans Syndrome (BOS) and Mortality after Lung Transplant (LT)

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Introduction

The impact of traffic air pollution on bronchiolitis obliterans syndrome and mortality after lung transplantation

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Thorax 2011;66:784-54. doi: 10.1136/thx.2010.155192

ABSTRACT

Background Approximately half of all patients who underwent a lung transplantation suffer from bronchiolitis obliterans syndrome (BOS), the clinical correlate of chronic rejection, within 5 years after transplantation. This prevalence is much higher than for other solid organ transplantations, possibly due to the lung's direct contact with the environment. The authors assessed the association between proximity of the home to major roads and BOS and mortality in a cohort of patients after lung transplantation.

Methods The authors calculated hazard ratios for BOS and mortality in relation to proximity of the home to major roads, adjusting for relevant covariables, in 288 patients after lung transplantation at the Leuven University Hospital between 1997 and 2009 and with follow-up until August 2009. Inflammatory parameters in plasma and bronchoalveolar lavage were assessed in 207 patients.

Results During follow-up, 117 (41%) patients developed BOS and 61 (21%) died. Patients who lived within 171 m of a major road (lowest tertile) were 2.06 (95% CI 1.39 to 3.05) times more likely to develop BOS and 2.20 (1.25 to 3.86) times more likely to die than patients living farther away. The adjusted hazard ratios of BOS and mortality were 0.57 and 0.72 for each 10-fold increase in distance from major roads. Proximity to a major road was inversely associated with plasma C-reactive protein levels, neutrophil percentage and interleukin-6 concentration in bronchoalveolar lavage.

Conclusion Traffic-related air pollution appears to constitute a serious risk of BOS and mortality after lung transplantation.

colonisation by *Pseudomonas*, lymphocytic bronchitis/bronchiolitis and gastro-oesophageal reflux have been added as risk factors.[3–7] These risk factors act via neutrophilic airway inflammation, suggesting that activation of the innate immune system is a trigger of BOS. Many inhaled air pollutants also give rise to activation of the innate immune system.[8 9] Moreover, air pollution exposure exerts adverse health effects, especially in patients with cardiopulmonary diseases,[10–12] and can aggravate chronic inflammatory lung disorders.[13 14] A substantial proportion of ambient air pollution results from the combustion of fossil fuels by vehicle traffic.[15]

As the lung is in direct contact with the environment, the authors hypothesised that air pollution may be a risk factor for BOS and mortality after lung transplantation. The incidence of BOS and mortality was assessed in a large cohort of well characterised and closely monitored patients after lung transplantation in relation to their exposure to (traffic-related) air pollution, as measured by the proximity of their home to a major road.

METHODS

Study design

This study considered patients who had had a lung transplant between 1 January 1997 and 31 December 2008 with long-term follow-up at UZ Leuven. Of these 403 transplantations, the authors excluded 22 patients living outside Belgium, 24 patients who died within 3 months after transplantation, 29 patients in whom BOS could not be

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“In view of the epidemiological evidence about the cardiopulmonary effects of particulate air pollution, the lack of effect of PM_{10} was unexpected.”

Conclusion Traffic-related air pollution appears to constitute a serious risk of BOS and mortality after lung transplantation.

Purpose

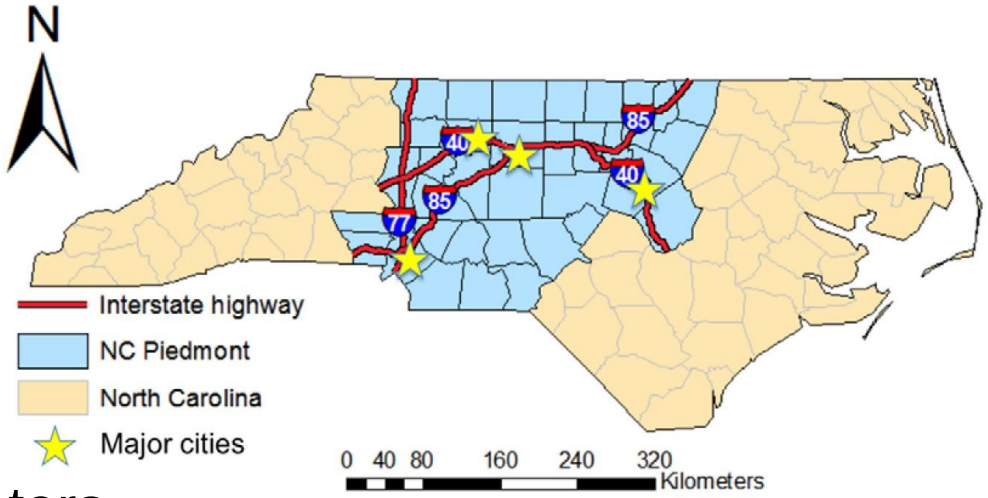
- We investigated the impact of **$PM_{2.5}$ concentration** ($\mu g/m^3$) exposure of ***both*** donors and recipients on **BOS** and **mortality** after LT in the United States.

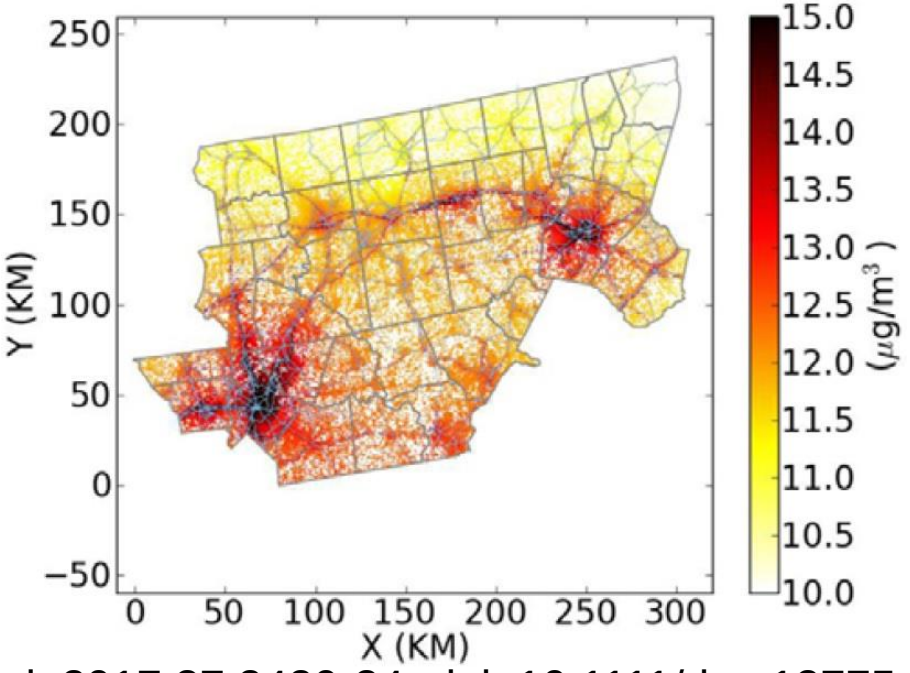
Methods

- We used the **United Network for Organ Sharing** (UNOS**) Standard Transplant Analysis and Research** (STAR) **database** - acquired with data up to June 30, 2017 - to identify home zip codes for LT donors and recipients, and follow-up information for recipients between 2005 and 2015.
- We used zip codes as a surrogate for different areas, and calculated the **average ambient $PM_{2.5}$ conc** associated with donor and recipient residences one year prior to LT.

Methods

- UNC Institute for the Environment (https://ie.unc.edu) hosts an EPA-funded Center for Community Modeling and Analyses System (CMAS) since 2002.
- UNC-IE has access to and develops multiple national datasets on measured and modeled air quality parameters in the Continental U.S. by Geocodes dating back to 2002
- We used **zip codes** of residence at the time of LT as a surrogate for donor and recipient residences (addresses not available).
- **$PM_{2.5}$ µg/m³ conc** 1 year prior to LT were estimated by mapping each zip code to a census tract, using a crosswalk from HUD*, downscaled from a 12 x 12-km sq grid resolution detailed chemistry-transport model application using a Bayesian space-time downscaler, then fused with surface observations.





Chang S et. al. Risk Anal. 2017;37:2420-34. doi: 10.1111/risa.12775

*https://www.huduser.gov/portal/datasets/usps_crosswalk.html

Methods

- **Cox proportional hazards regression** and **Kaplan-Meier curves** were used to assess the impact of $PM_{2.5}$ conc exposure during the year before LT on the incidence of BOS and all-cause mortality.
- **Average $PM_{2.5}$ conc** was classified into different exposure categories:
  - **Low** (<8 μg/m^3)
  - **Medium** (8-12 μg/m^3)
  - **High** (>12 μg/m^3)

Results

- **17,760 donor/recipient pairs** were included in the analysis.
- Median **follow-up** was **1,101** (IQR 511-2073, range 1-4448) days.
- Median 1-year **$PM_{2.5}$ conc** was **10.24 µg/m³** (IQR 8.85-11.81, range 3.72-19.03).

	Low (<8 µg/m³)	Medium (8-12 µg/m³)	High (>12 µg/m³)
Total N, %	2529 (14%)	11145 (63%)	4086 (23%)
Recipient characteristics			
Age at transplant, med (IQR)	60 (51–65)	59 (49-64)	58 (48-63)
Male, n (%)	1522 (60)	6632 (60)	2354 (58)
BMI at transplant, med (IQR)	25 (21-29)	25 (21-29)	25 (21-29)
Status at transplant, n (%)			
Hospitalized, ICU	314 (12)	1198 (11)	320 (8)
Hospitalized, not ICU	173 (7)	1080 (10)	283 (7)
Not hospitalized	2042 (81)	8867 (80)	3483 (85)
Life support at transplant, n (%)			
Ventilator	200 (8)	788 (7)	252 (6)
ECMO	81 (3)	327 (3)	50 (1)
Double lung transplant, n (%)	1710 (68)	7512 (67)	2545 (62)
Ischemic time, hours, med (IQR)	5.0 (4.1-6.2)	4.9 (3.9-6.1)	5.0 (3.9-6.1)
Donor characteristics			
Age, med (IQR)	32 (22-46)	32 (22-47)	32 (21-46)
Male, n (%)	1569 (62)	6702 (60)	2426 (59)
History of cigarette use, n (%)	238 (10)	1070 (10)	578 (14)
Cause of death, n (%)			
Anoxia	429 (17)	1803 (17)	491 (12)
CVA/stroke	833 (34)	3833 (25)	1495 (37)
Head trauma	1199 (48)	5152 (47)	1967 (49)
CNS tumor	19 (1)	77 (1)	39 (1)

Abbreviations: med; median; IQR, interquartile range; CVA, cerebrovascular event; CNS, central nervous system

Results

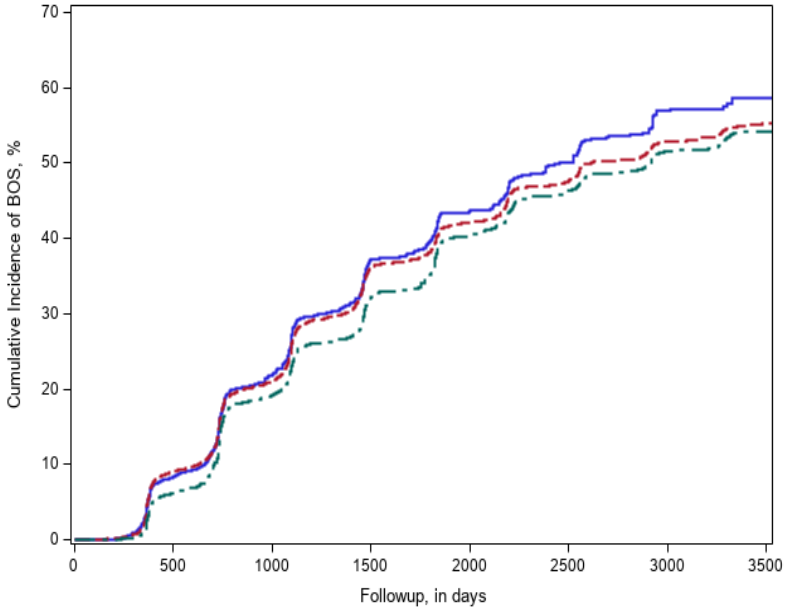


Figure 1:
Cumulative incidence of BOS

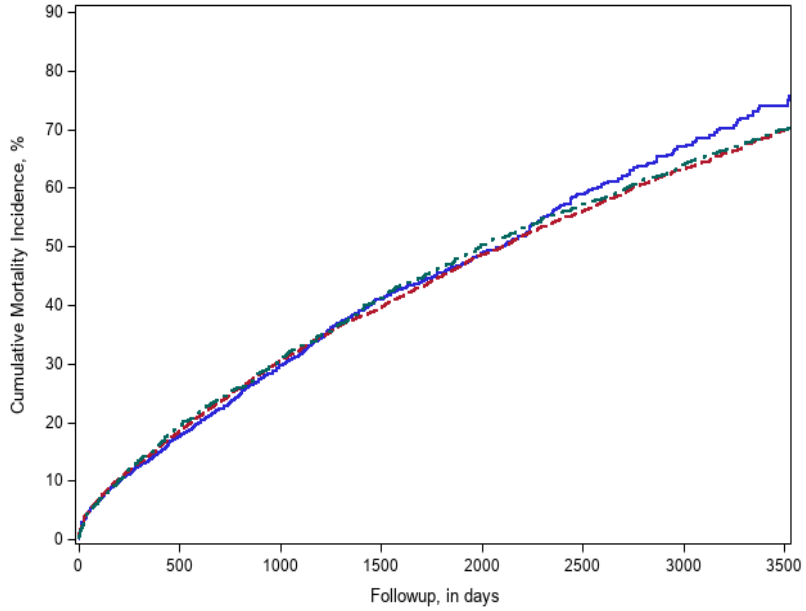


Figure 2:
Cumulative incidence of mortality

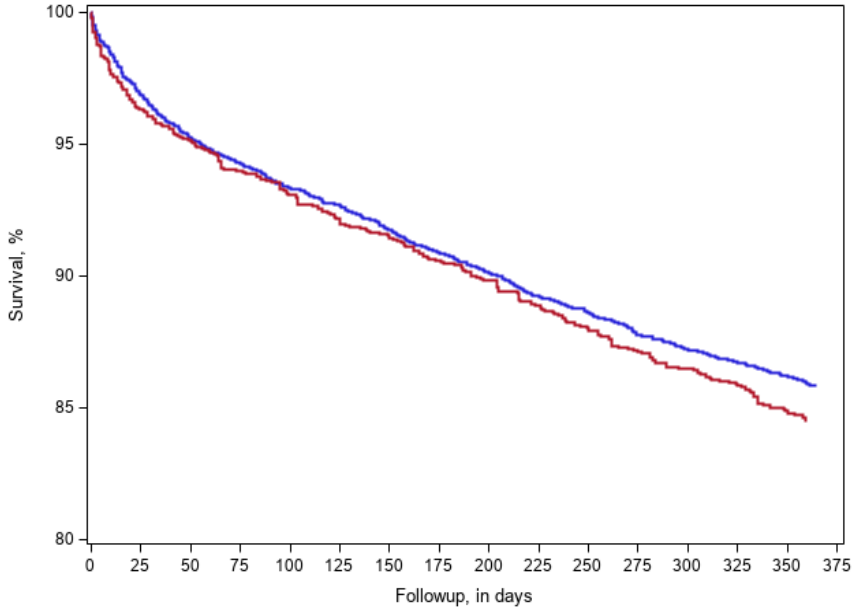


Figure 3:
1-year mortality after LT

Blue: < 8 µg/m³ Red: 8 - 12 µg/m³ Green: > 12 µg/m³

Results

- ↑ $Pm_{2.5}$ donor exposure was associated with ↑ risk of early death (p=0.09).
- Curiously, ↑ $Pm_{2.5}$ recipient exposure was associated with ↓ risk of BOS.
- Like the Leuven study, $Pm_{2.5}$ does not impair LT outcomes.

	Donor Exposure		Recipient Exposure	
	HR (95% CI)[a]	p-value	HR (95% CI)[a]	p-value
1-year mortality				
Low (<8 μg/m^3)	ref	-	ref	-
Medium (8-12 μg/m^3)	1.09 (0.95, 1.24)	0.24	1.06 (0.92, 1.22)	0.41
High (>12 μg/m^3)	1.16 (0.98, 1.38)	0.09	1.08 (0.89, 1.31)	0.45
Long-term mortality				
Low (<8 μg/m^3)	ref	-	ref	-
Medium (8-12 μg/m^3)	0.99 (0.91, 1.07)	0.73	0.95 (0.88, 1.03)	0.23
High (>12 μg/m^3)	0.99 (0.90, 1.09)	0.84	0.97 (0.88, 1.08)	0.59
Long-term BOS[b]				
Low (<8 μg/m^3)	ref	-	ref	-
Medium (8-12 μg/m^3)	0.97 (0.91, 1.04)	0.41	0.94 (0.88, 1.00)	0.06
High (>12 μg/m^3)	0.97 (0.90, 1.05)	0.44	0.87 (0.80, 0.94)	0.0004

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Inverse-probability of treatment weights were used to account for potential confounding; weights included recipient age, gender, race/ethnicity, primary payer, total days on waitlist, single vs. double lung transplant, status at transplant (ICU, hospitalized, at home), life support (ventilator and ECMO), recipient and donor cigarette history, donor cause of death, and year of transplant.

[b] Mortality was treated as a competing risk.

Limitations

- Addresses were not available for donors or recipients, just zip code of residence at the time of LT.
- Donor zip codes were likely more reliable than recipient zip codes as a place of residence.
- For this analysis, we assumed
  - Donors lived in their zip code for the year before being a donor.
  - Only one year of donor exposure to $PM_{2.5}$ conc.
  - Recipients stayed in their place of residence after LT.
  - Only $PM_{2.5}$ conc prior to LT was used for the entire survival duration.

Epidemiological time series studies of $PM_{2.5}$ and daily mortality and hospital admissions: a systematic review and meta-analysis

Atkinson RW, *et al*. *Thorax* 2014;**69**:660–665. doi:10.1136/thoraxjnl-2013-204492

Key messages

What is the key question?

- Is there convincing and consistent evidence worldwide that short-term exposure to outdoor fine particulate matter (particles with a median aerodynamic diameter <2.5 μm ($PM_{2.5}$)) air pollution is associated with increased risk of death and emergency admission to hospital?

What is the bottom line?

- We found evidence for adverse health effects of short-term exposure to $PM_{2.5}$ across a range of important health outcomes, diseases and age groups with substantial variation between different regions of the world that needs explanation.

An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe

Ruttens D, et al. Eur Respir J. 2017;49:1600484. doi: 10.1183/13993003.00484-2016.

n = 5707 LT recipients. ↑ CLAD risk → Proximity to roads, Pm10 ? small impact .

Ambient Air Pollution and Mortality After Cardiac Transplantation

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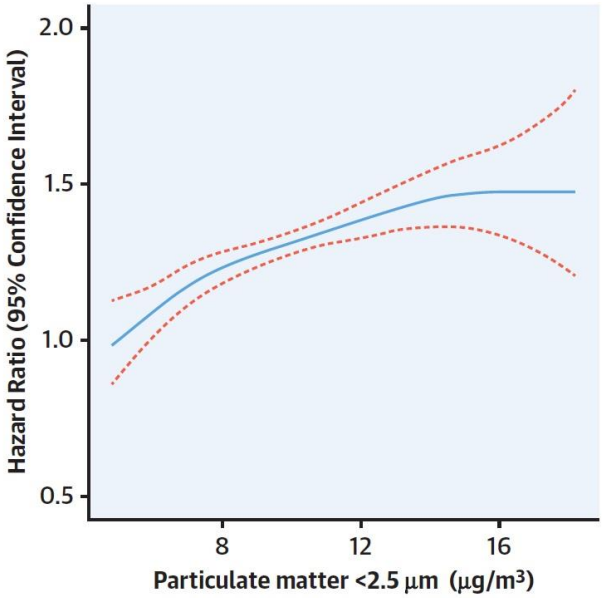
J Am Coll Cardiol 2019:74;3026-3035. doi: 10.1016/j.jacc.2019.09.066



Conclusions

- **$PM_{2.5}$** does **not** appear to increase long-term risk of **BOS** or **mortality** after LT.
- Donor $PM_{2.5}$ exposure may have a small effect on one-year mortality after LT.
- $PM_{2.5}$ conc is not the only characteristic of air quality; there may be other factors influencing risk.

Future Directions

- Evaluate impact of $PM_{2.5}$ conc over time for recipients.
- Determine location of recipients after LT.
  - Contact a sample of LT centers to query recipient location.
- Analyze impact of other pollutants on BOS and post-LT mortality.
- If air quality impacts chronic rejection after LT, look at air quality impact on other organs.

Acknowledgments

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