Health Effects of Nitrogen Dioxide

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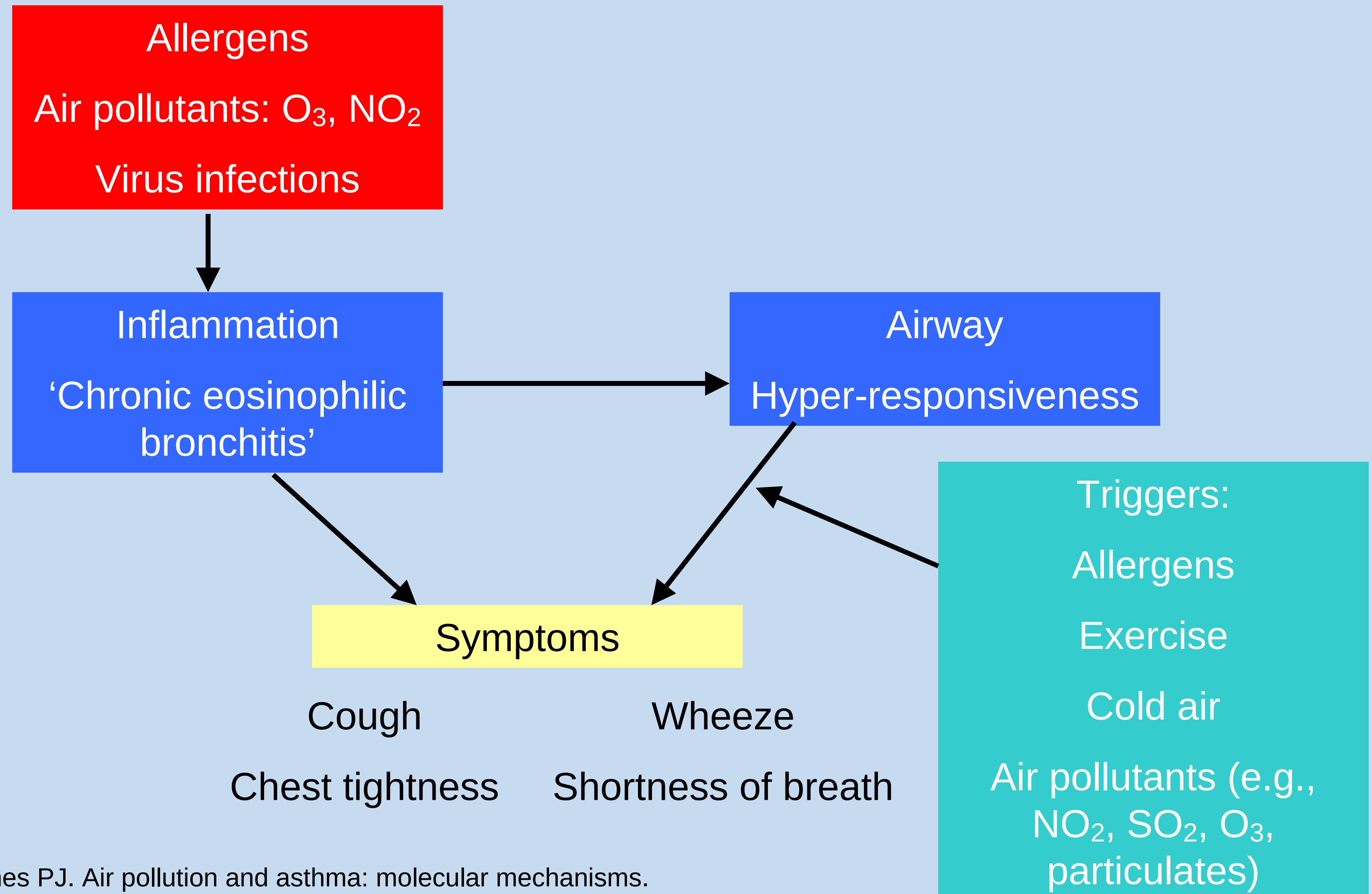
Focus

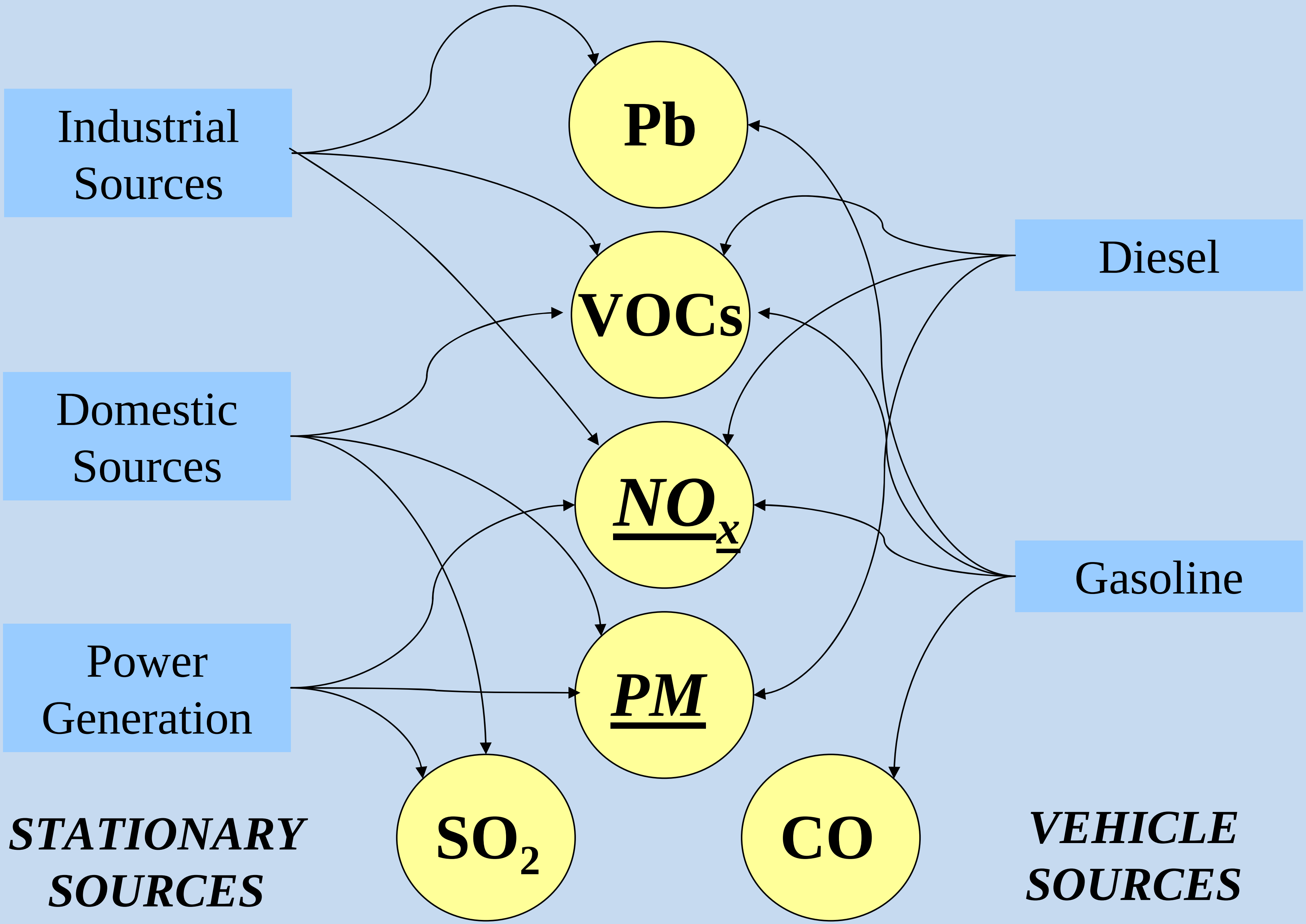
- Epidemiologic studies of human health
- Studies from North America, Europe, Australia
- Where possible, details from Canadian studies

Mechanisms of Health Effects of NO_2

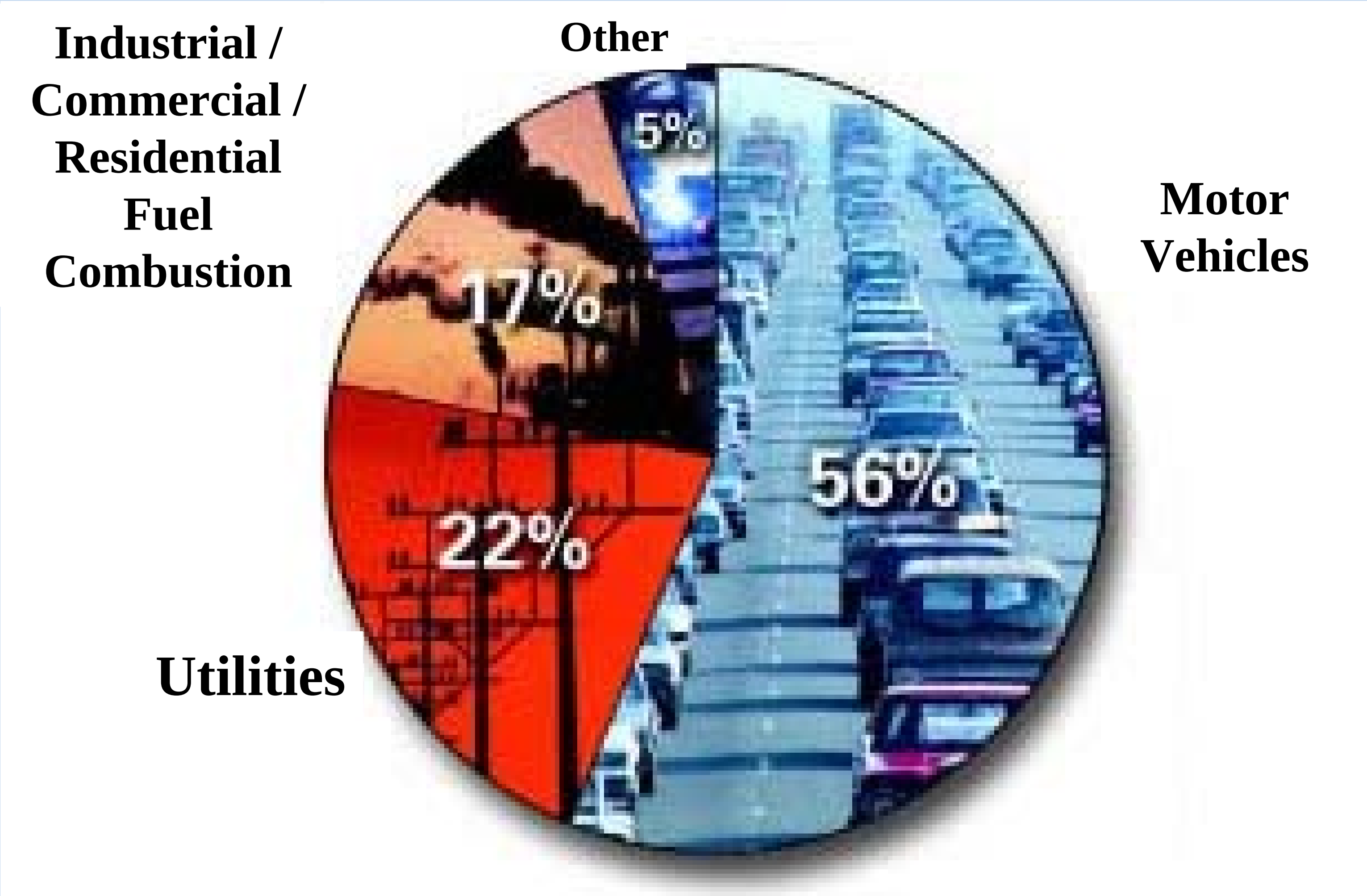


From: Barnes PJ. Air pollution and asthma: molecular mechanisms. *Molecular Medicine Today*. 1995;1(3):149-155.

Major Outdoor Sources of Air Pollution



NO_x Sources



Source: US EPA

Major ***Indoor*** Sources

- Gas Appliances
- Gas Space Heaters
- Kerosene Space Heaters
- Tobacco Combustion
- From Outdoor Air – traffic

Exposure to NO_2: What health effects would cause concern?

- Death
- Serious acute illness
- Chronic illness

Exposure to NO_2: Epidemiology of health effects

- Death – Mortality studies
- Serious acute illness – Patterns of hospital admissions
- Chronic illness – Incidence and prevalence of asthma

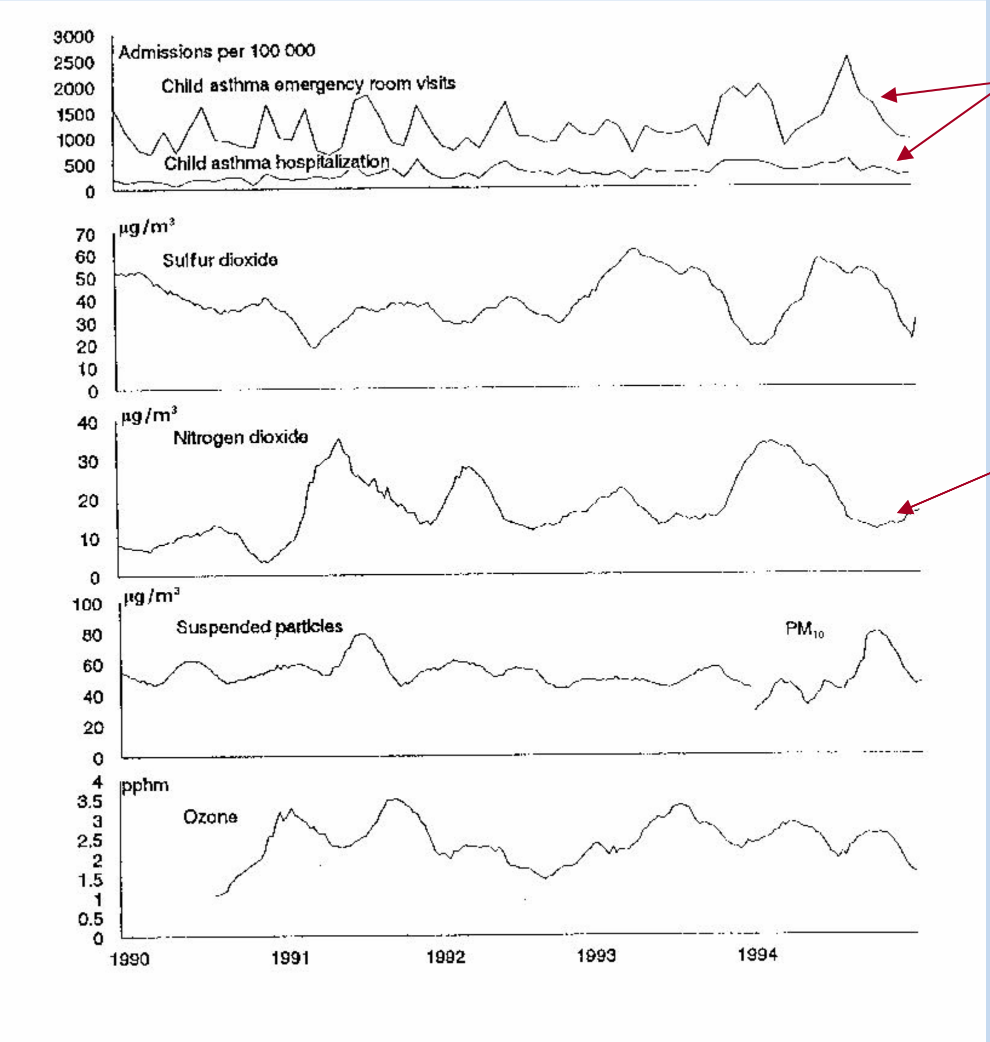
Interpretation of epidemiologic studies of NO_2 and health effects: Cautions

- Contaminants - NO_2 found in complex mixtures and often highly correlated with other pollutants
- Exposure assessment – measurements averaged from central sites may misclassify personal exposure
- Sources - Indoor and outdoor sources of NO_2 rarely considered together
- Other risk factors - NO_2 exposure often confounded by other risk factors associated with low SES

Health effects of NO_2:

Mortality studies

Time trends in air-pollution levels and health outcomes



Health outcomes

Nitrogen dioxide

From: Chew *et al.* Association of ambient air-pollution levels with acute asthma exacerbation among children in Singapore. *Allergy* 1999;54:320-329.

Epidemiologic studies reporting associations of Nitrogen dioxide or Particulates with mortality (all causes, cardiopulmonary or respiratory).

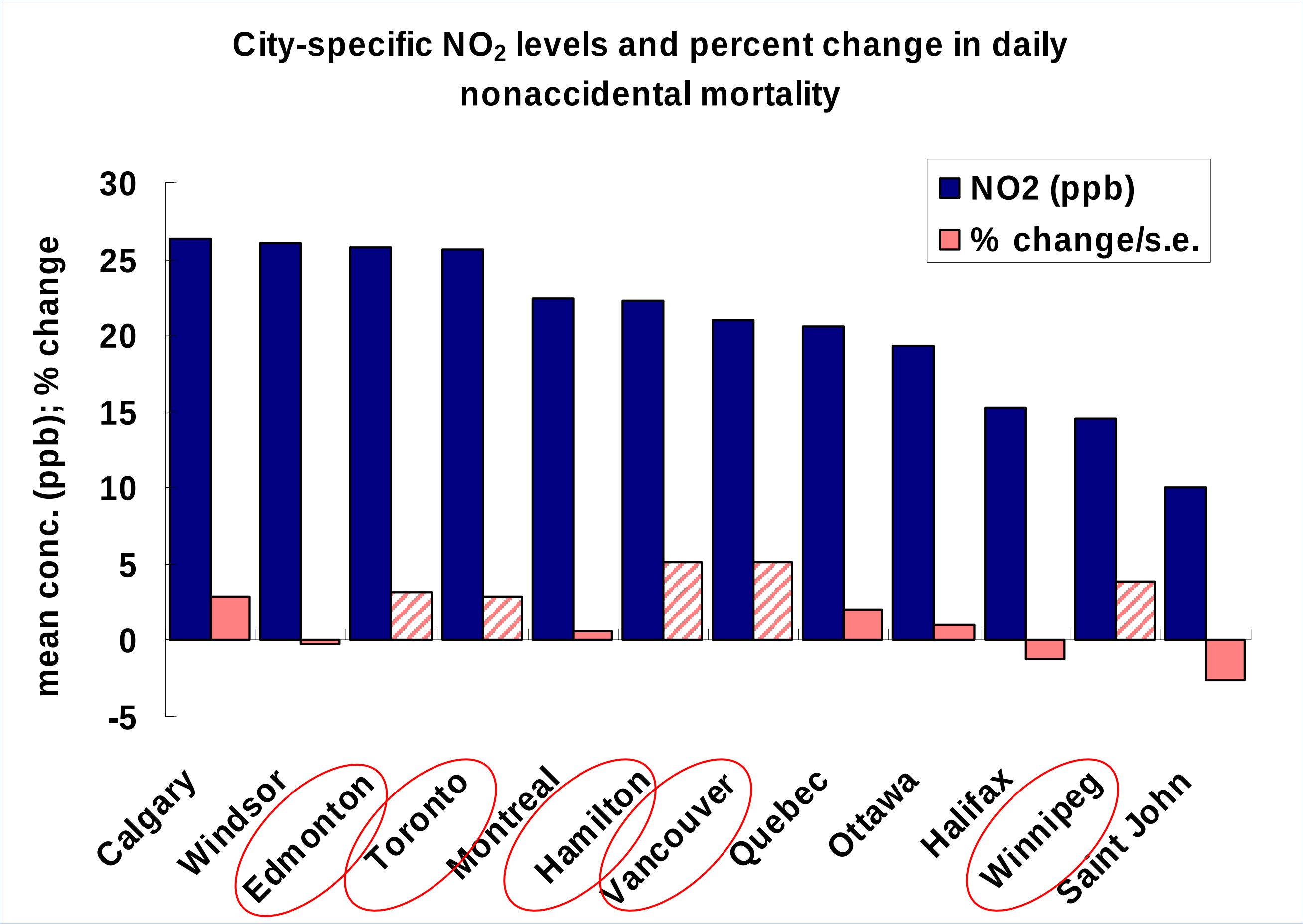
			Significant result (✓)	
Author	**Year**	**Study Location**	**PM_{10}**	**NO_2**
Ponka *et al.*	1998	Helsinki	✓	
Michelozzi *et al.*	1998	Rome	✓	✓
Samet *et al.*	2000	20 US cities	✓	
Roemer & van Wijnen	2001	Amsterdam		✓
Vedal *et al.*	2003	Vancouver		✓
Samoli *et al.*	2003	9 European cities		✓
Burnett *et al.*	2004	12 Canadian cities		✓
Scoggins *et al.*	2004	Aukland		✓
Penttinen *et al.*	2004	Helsinki	✓	

NO_2 Standards

Standard	US EPA	Canada	WHO
Outdoor			
Annual average	53 ppb (100 $\mu g/m^3$)	53 ppb (100 $\mu g/m^3$)	21 ppb (40 $\mu g/m^3$)
24-Hour average		106 ppb (200 $\mu g/m^3$)	
1-Hour average		213 ppb (400 $\mu g/m^3$)	106 ppb (200 $\mu g/m^3$)
Indoor		53 ppb (100 $\mu g/m^3$)	

Annual NO_2 concentrations significantly associated with mortality in epidemiologic studies

City	Mean ppb (μg/m³)	Median ppb (μg/m³)
Rome	53 (99)	51 (96)
Amsterdam		
background	24 (46)	23 (44)
traffic sites	54 (101)	69 (130)
Vancouver	16 (30)	17 (32)



Mean NO_2 concentration (ppb) and percentage change (ratio of percent change to standard error) in daily non-accidental mortality associated with a 22.4-ppb change in 3-day moving average concentration of NO_2 based on data from each of 12 study cities (1998-2000). (Significant % change indicated by striped bar.)

Data from Burnett et al. "Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities" *Archives of Environ Health* 2004;59:228-236.

Health effects of NO_2:

Hospitalization studies

Hospital Admissions for Cardiovascular Disease

Author	Year	Study Location	Disease	NO_2 Sig. result (✓)	Other Sig. Pollutants
Morgan *et al.*	1998	Sydney	Heart disease	✓	
Burnett *et al.*	1999	Toronto	Several diagnoses	✓	PM, CO, O_3
Linn *et al.*	2000	Los Angeles	Cardiovascular	✓	PM, CO, O_3
Petroeschevsky *et al.*	2001	Brisbane	Cardiovascular	no	
Mann *et al.*	2002	Southern California	Ischemic heart disease	✓	CO
Grazvleviciene *et al.*	2004	Kaunas, Lithuania	Myocardial infarction (MI)	✓	
Llorca *et al.*	2005	Torrelavega, Spain	Cardiac	✓	PM
von Klot *et al.*	2005	5 European cities	MI readmission	✓	PM

Hospital Admissions for Respiratory Disease

Author	Year	Study Location	Disease	NO_2 Sig. result (✓)	Other Sig. Pollutants
Walters *et al.*	1995	West Midlands, UK	Respiratory < age 5	✓	
Morgan *et al.*	1998	Sydney	Asthma - Children	✓	
			COPD - adults	✓	PM
Burnett *et al.*	1999	Toronto	Respiratory	✓	PM, CO, O_3
Linn *et al.*	2000	Los Angeles	Pulmonary	✓	PM
Fusco *et al.*	2001	Rome	Total respiratory	✓	CO
			Acute respiratory	✓	O_3
			Asthma - children	✓	
Petroeschevsky *et al.*	2001	Brisbane	Respiratory	**no**	PM, O_3
			Asthma	**no**	PM, O_3
Migliaretti *et al.*	2004	Turin	Asthma < age 15	✓	PM
Llorca *et al.*	2005	Torrelavega, Spain	Respiratory	✓	

Percentage Increase in Hospital Admissions Attributable to an Increase in Pollution Based on Multiple-pollutant Regression Models.

Disease	Ambient air pollutants					All pollutants
	PM	CO	NO_2	SO_2	O_3	
Asthma	4	4	-	-	5	13
Obstructive lung disease	4	3	-	-	6	13
Respiratory infection	6	-	4	-	4	14
Dysrythmias	3	7	-	-	3	13
Heart failure	-	4	7	-	-	11
Ischemic heart disease	-	-	8	1	-	9

From: Burnett et al. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health1999;54(2):130-139.

Conclusions

NO_2 exposure (at levels common currently in Alberta) is associated with:

- increased mortality
- increased hospital admissions for
  - cardiovascular disease
  - respiratory disease
  - asthma

Health effects of NO_2:

Asthma studies

Children's Health Study (US)

- 12 communities in southern California selected for variability in air pollution
- Children enrolled:
  - 493 with asthma
  - 653 with wheeze, no asthma
  - 2,211 with no wheeze, no asthma
- Exposure: measured in the 12 communities and averaged for 12 months

From: McConnell *et al. Environ Health Persp* 1999;107:757-760.

Children's Health Study (US)

Results

Among asthmatics:

- NO_2 (per increase of 24 ppb) associated with 2 ½ times the likelihood of respiratory symptoms
- $PM_{2.5}$ (per increase of 15 $\mu g/m^3$) associated with 2 ½ times the likelihood of respiratory symptoms and bronchitis

From: McConnell *et al. Environ Health Persp* 1999;107:757-760.

School Study (France)

- 108 schools in 6 French cities
- Children enrolled:
  - 6,672 ages 9 - 11
- Exposure: measured at each school and averaged for 3 years

From: Morand *et al. Clin Exper Allergy* 2005;35:1279-1287.

School Study (France)
Results

- NO_2 (per increase of 10 μg/m^3) associated with 23% increase in allergic symptoms
- O_3 (per increase of 10 μg/m^3) associated with 27% increase in allergic symptoms

From: Morand *et al. Clin Exper Allergy* 2005;35:1279-1287.

Toronto Hospital Admissions for Asthma (Canada)

• 7,319 children ages 6 – 12 admitted to Toronto hospitals for asthma

• Exposure: averaged for up to 7 days before admission compared to control periods before and after

From: Lin *et al. J Epidemiol Commun Health* 2003;57:50-55.

Toronto Hospital Admissions for Asthma (Canada)

Results

- NO_2 (per increase of 11 ppb) associated with 10% increase in hospital admissions
- CO (per increase of 0.5 ppm) associated with 7% increase in hospital admissions

From: Lin *et al. J Epidemiol Commun Health* 2003;57:50-55.

Yale Center for Perinatal, Pediatric and Environmental Epidemiology

- Summary of studies of environmental factors in the development and severity of asthma in children
- Results related NO_2
- New study (**S**tudy of **T**raffic, **A**ir Quality and **R**espiratory Health [**STAR**])

Funded by the US National Institute of Environmental Health Sciences (*NIEHS)*

Yale Childhood Asthma Study

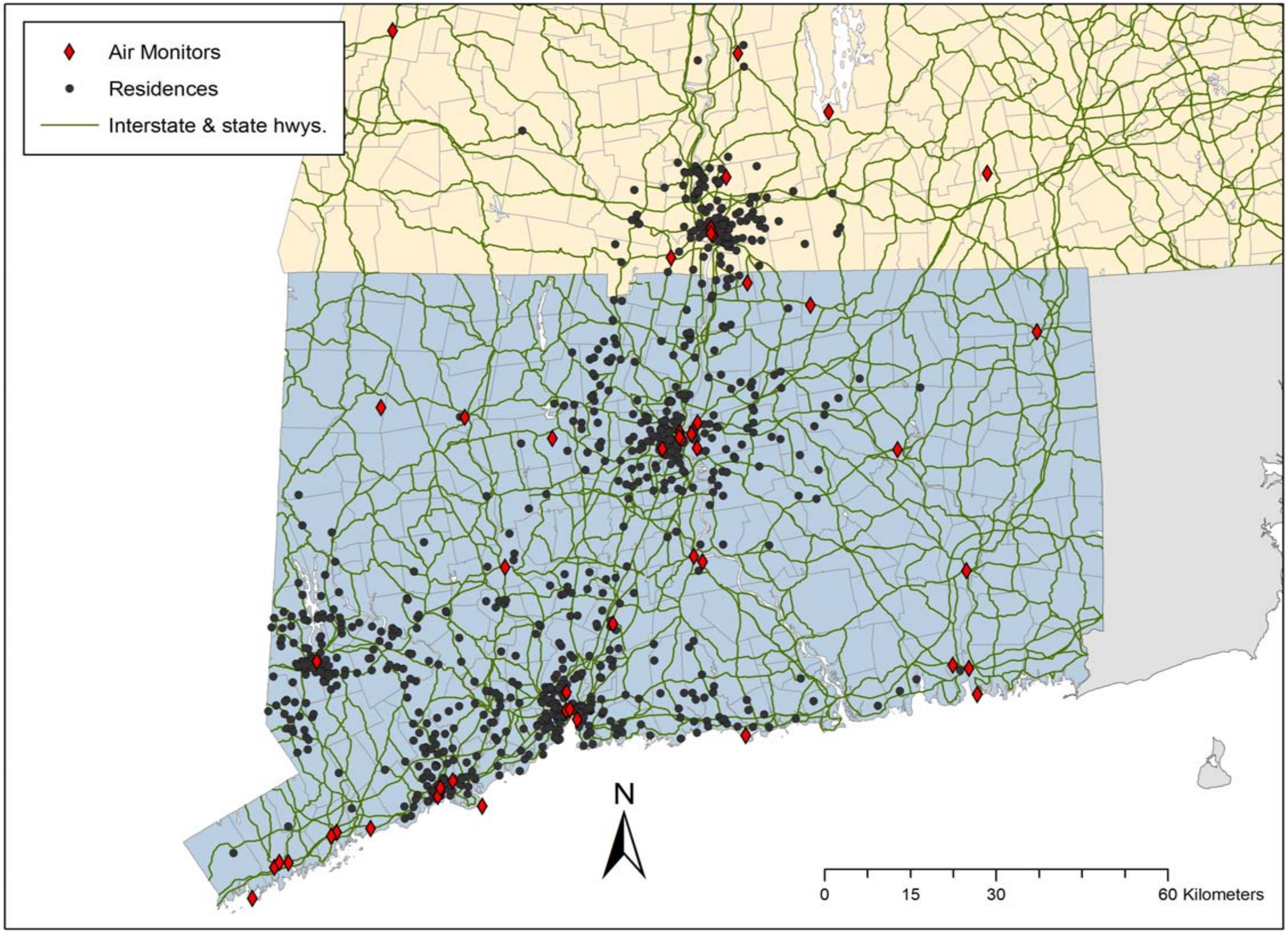
- Prospective cohort
- Mothers recruited from women delivering at 5 area hospitals (> 33,000 deliveries)
- Enrolled: 1,002 families in Connecticut and Southwestern Massachusetts
- Eligible families had

  newborn infant

  child with physician-diagnosed asthma

*** subject in cohort**

*** subject pool for 12-month follow-up Study of Asthma Severity**



Map of study region for Yale Childhood Asthma Study (CHAS) showing subject residence (black dots), location of ambient air monitors (red diamonds), interstate and state highways (green lines).

Initial Home Visit

- Interview with mother to obtain demographic data, information about pregnancy, home and family characteristics

- Dust collection to measure allergens:
  Dustmite (*Der p, Der f)*
  Cat (*Fel d)*
  Dog (*Can f)*

- Airborne mold sample to measure:
  Total mold count
  Cladosporium
  Penicillium

- Air Quality sample to measure:
  NO2
  Nicotine (in smoking homes)

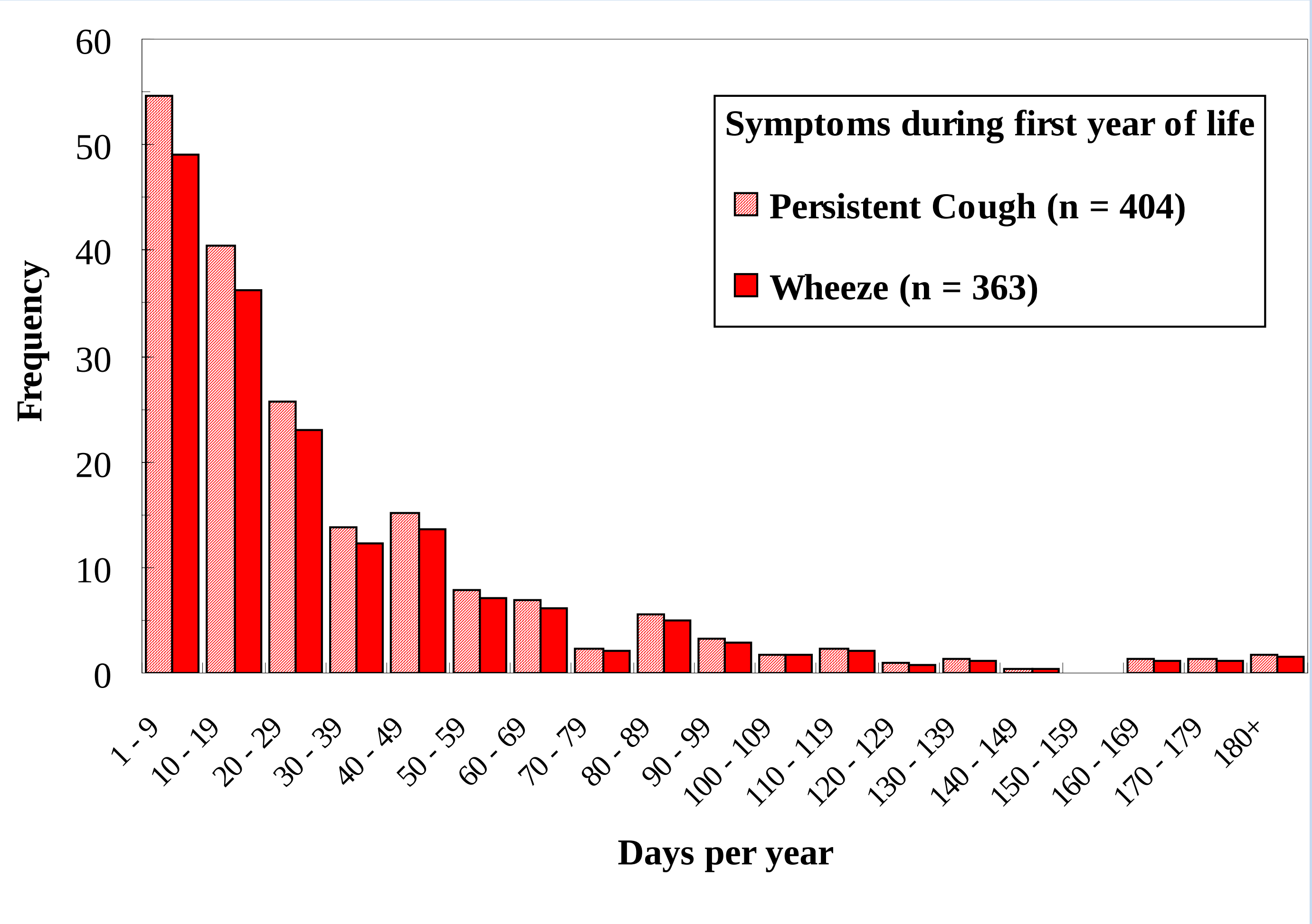
Follow-up Interviews

- Mothers were interviewed by phone every 3 months for the first three years to collect data on monthly symptoms, asthma diagnosis and medication use

- After age 3, mothers were interviewed annually to obtain data.

- Asthma diagnosis reported by the mother was confirmed by contacting the child’s pediatrician.

Results for Index Infant

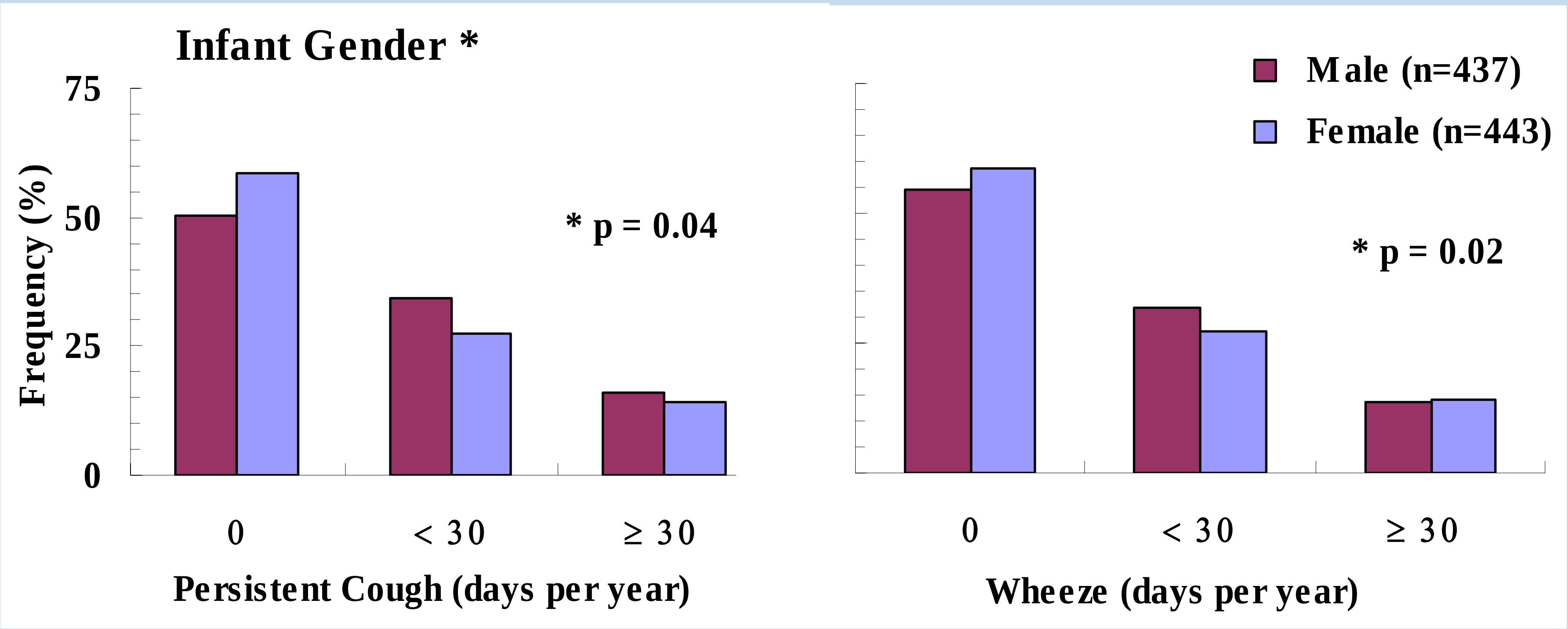


Rate of respiratory symptoms per year for infants who experienced any wheeze (41% of 880) or persistent cough (46%) in the first year of life.

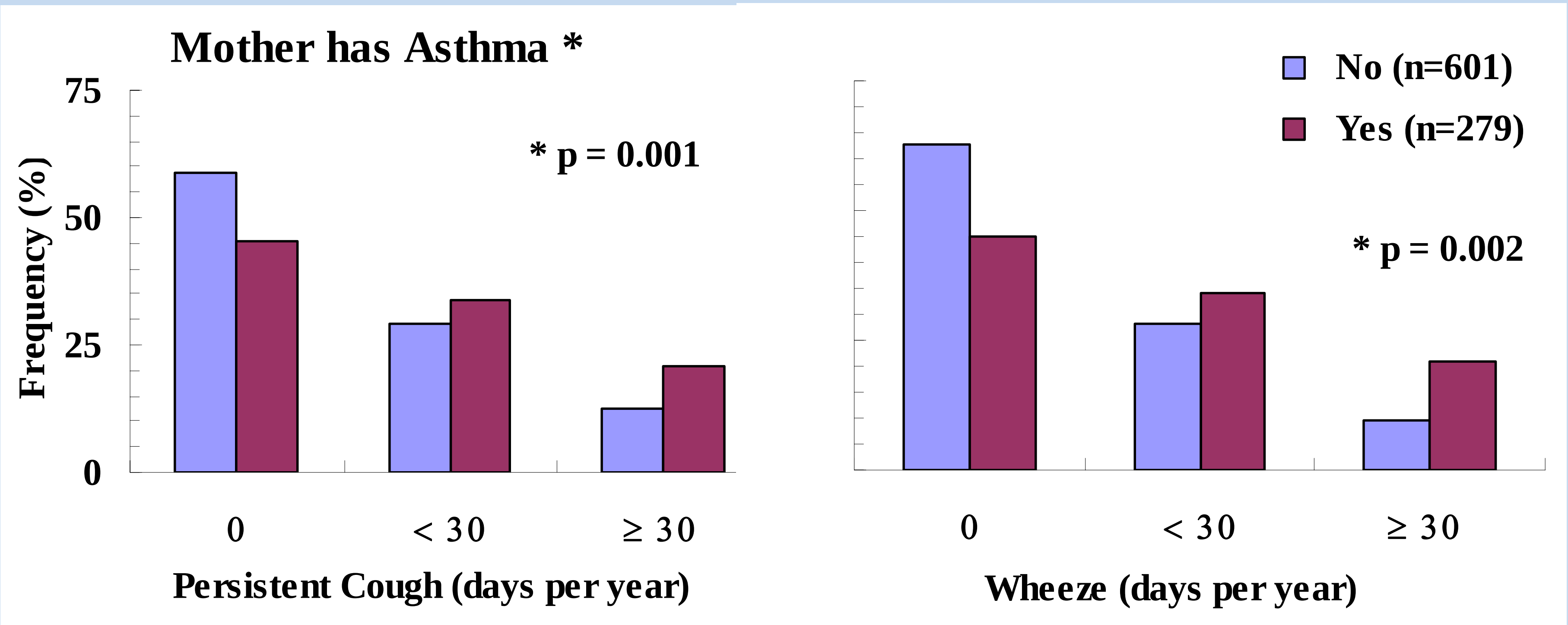
Approximately one-third of the infants who experienced symptoms had the equivalent of 30 or more days of wheeze (27.5%) or persistent cough (34.9%).

Infant respiratory symptoms in the first year of life associated with:

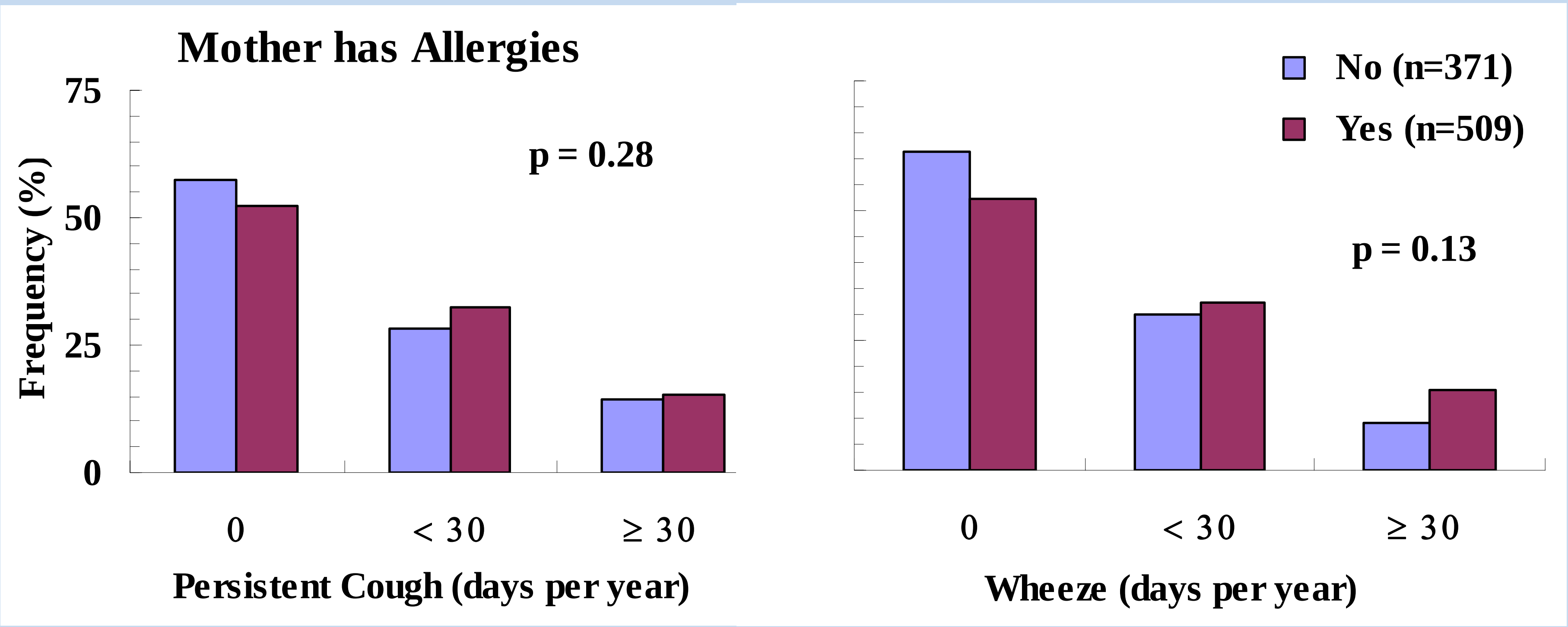
- Infant’s gender
- Mother’s asthma
- Mother’s allergy



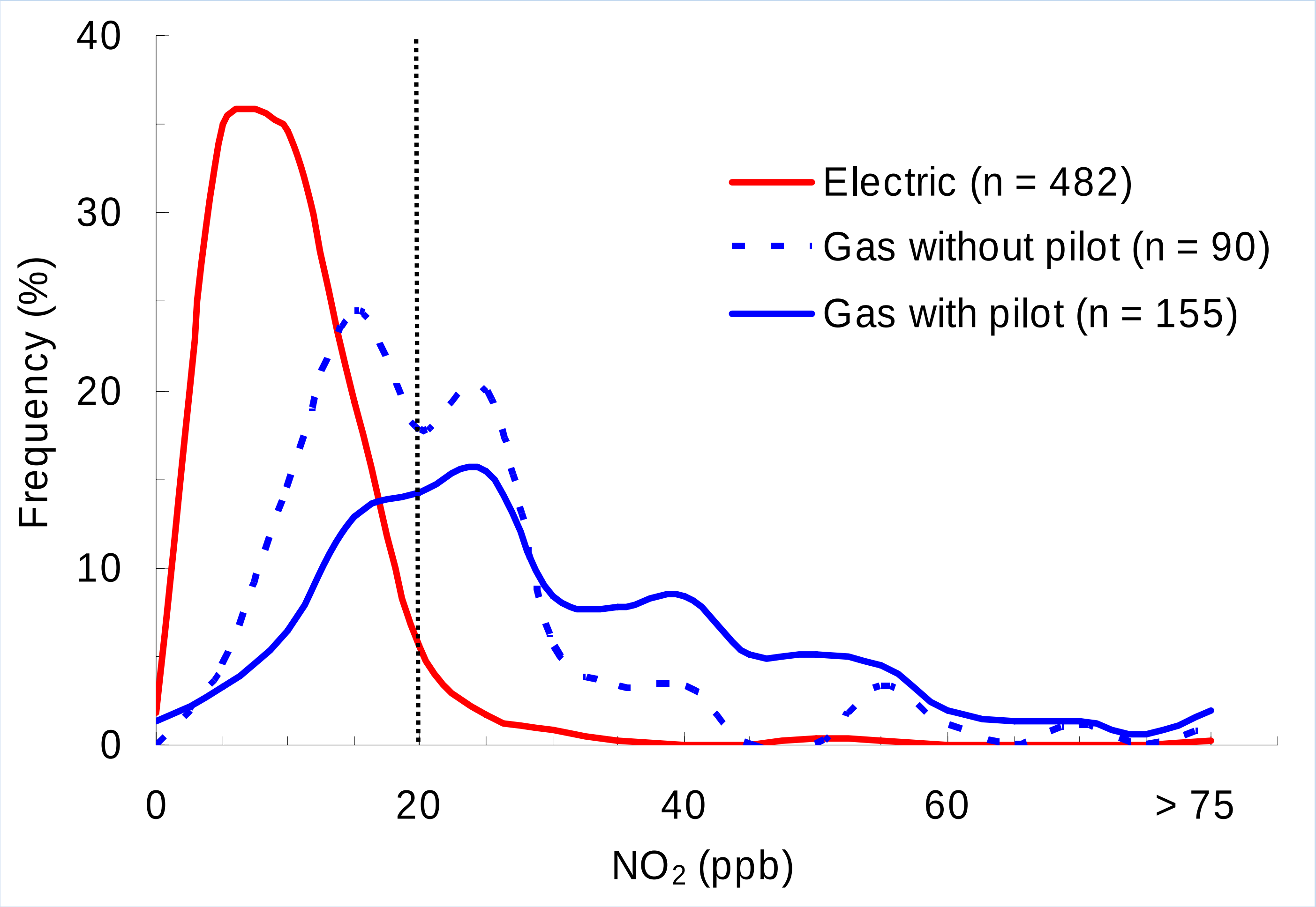
Gent et al. *Environmental Health Perspectives* 2002;110:A781-A786.



Gent et al. *Environmental Health Perspectives* 2002;110:A781-A786.



Gent et al. *Environmental Health Perspectives* 2002;110:A781-A786.



Measured levels of NO_2: Distribution by cooking appliance. Dotted line at 20 ppb indicates the 80th percentile of the overall distribution of NO_2.

Infant Cohort, 1st year of life: Indoor NO_2

Adjusted[1] rate ratios (aRR and 95% confidence intervals), showing the increase in the frequency of days with wheeze, persistent cough and shortness of breath, with increasing NO_2 concentrations for children from homes sampled in autumn/winter and in spring/summer separately, southern New England, USA, 1996-1998.

			Wheeze aRR (95% CI)	Persistent cough aRR (95% CI)	Shortness of breath aRR (95% CI)
autumn/winter (n=283)	NO_2	1st quartile	1.00	1.00	1.00
		2nd quartile	0.76 (0.42-1.36)	1.18 (0.68-2.06)	**2.27 (1.04- 4.95)***
		3rd quartile	0.58 (0.29-1.19)	**1.86 (1.01-3.42)***	**3.74 (1.60- 8.73)****
		4th quartile	1.48 (0.68-3.22)	**2.42 (1.19-4.92)***	**4.79 (1.81-12.67)****
spring/ summer (n=322)	NO_2	1st quartile	1.00	1.00	1.00
		2nd quartile	**1.73 (1.04-2.88)***	0.92 (0.59-1.42)	1.33 (0.72-2.46)
		3rd quartile	**1.71 (1.02-2.89)***	1.41 (0.92-2.16)	1.49 (0.80-2.78)
		4th quartile	1.70 (0.92-3.13)	1.50 (0.88-2.57)	**2.20 (1.01-4.80)***

[1] Rate ratio, adjusted for parental asthma diagnosis, ethnic background, maternal education level, smoking in the home, day care, living in an apartment, the presence of siblings, and the other contaminant

* $p<0.05$

** $p<0.01$

1st quartile < 5.0 ppb

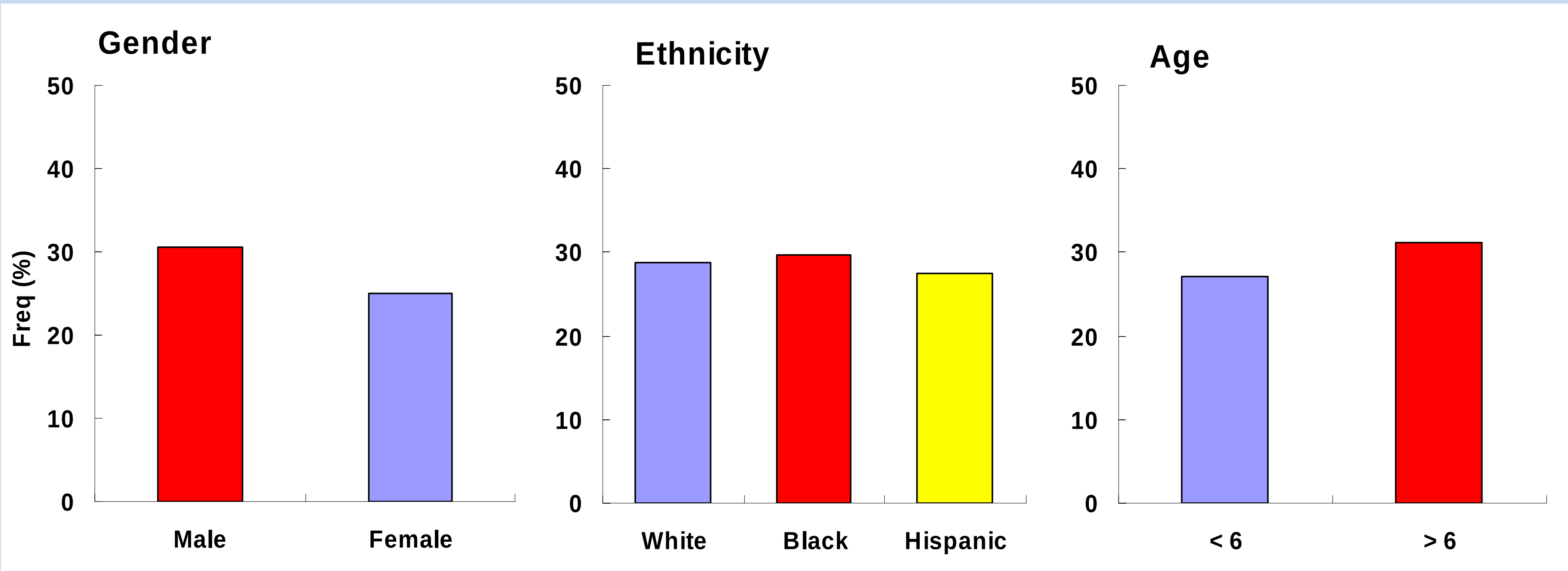
2nd quartile 5.1 – 9.8 ppb

3rd quartile 9.9 – 17.4 ppb

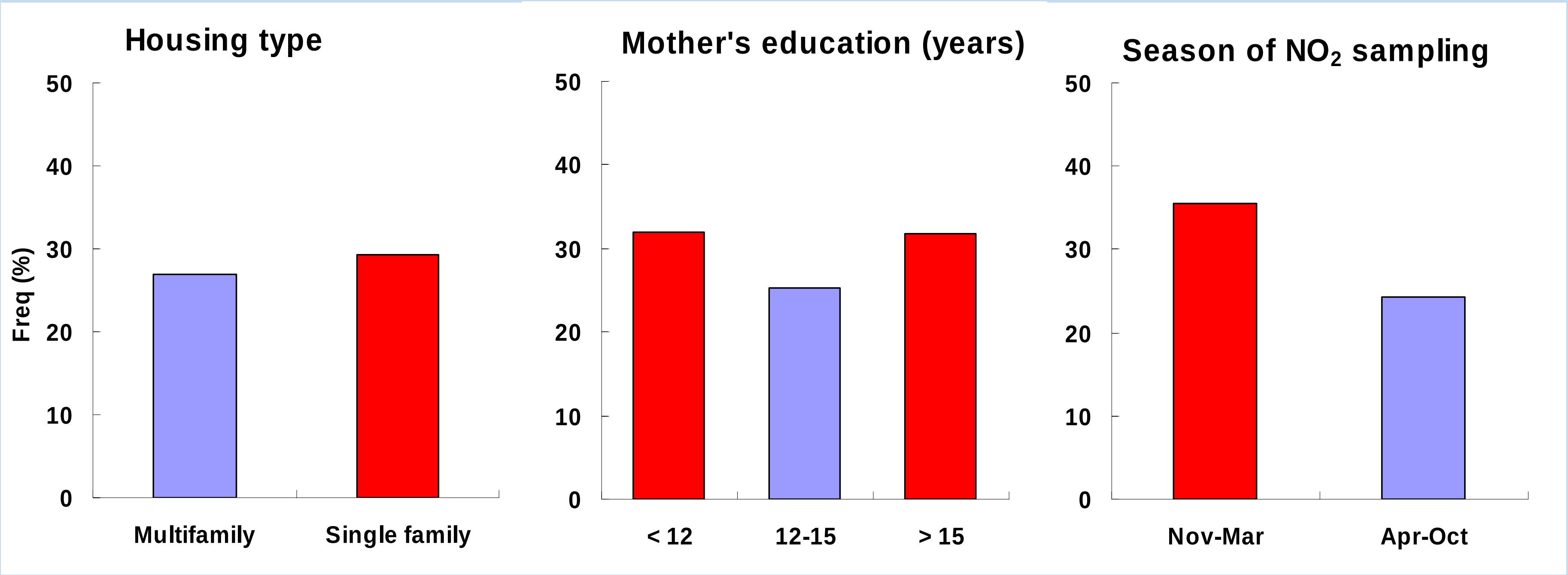
4th quartile > 17.4 ppb

van Strien, et al. 2004 *Epidemiology*;15:471-478.

Results for Asthmatic Sibling

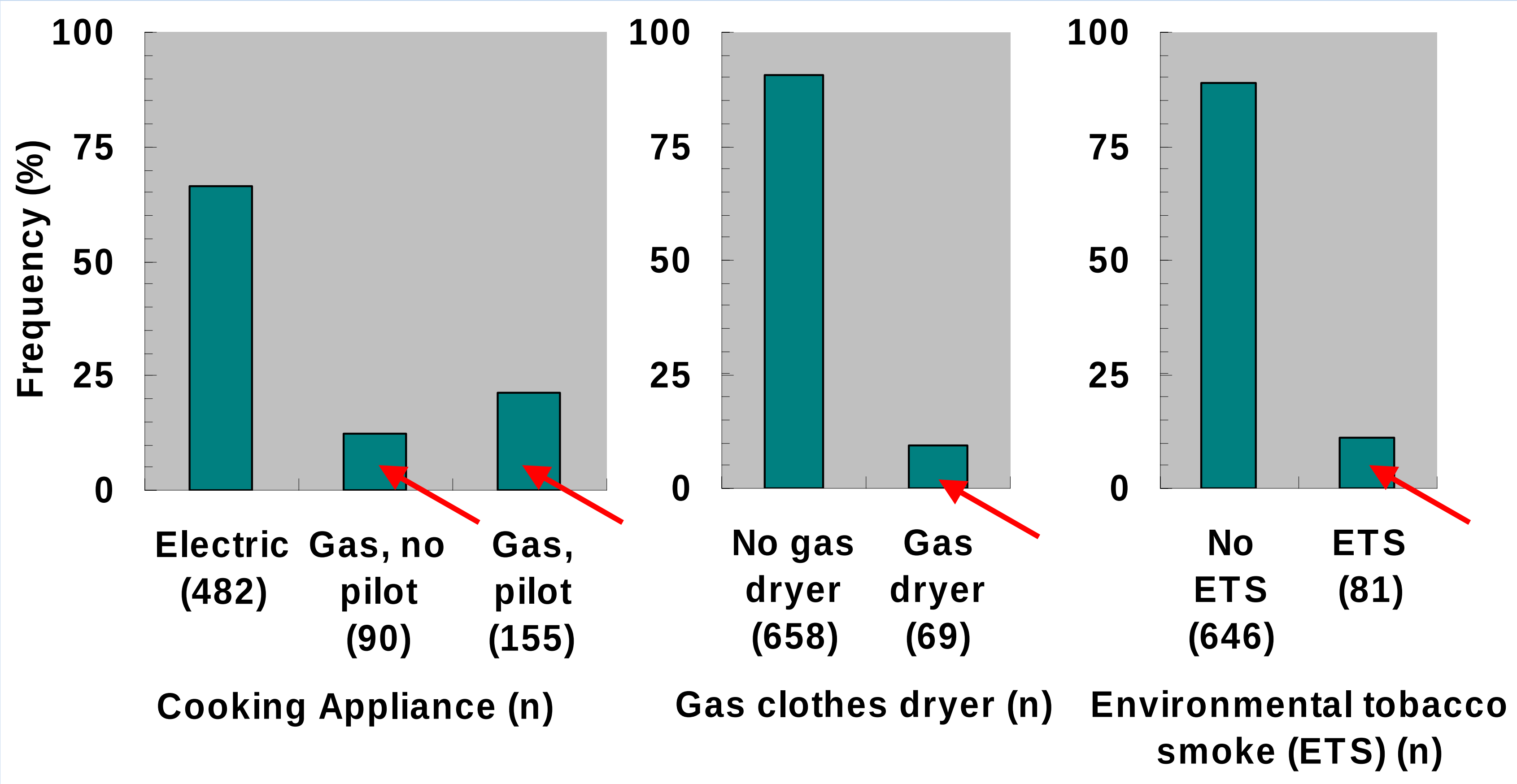


Frequency (%) of wheezing by gender, ethnicity, age.



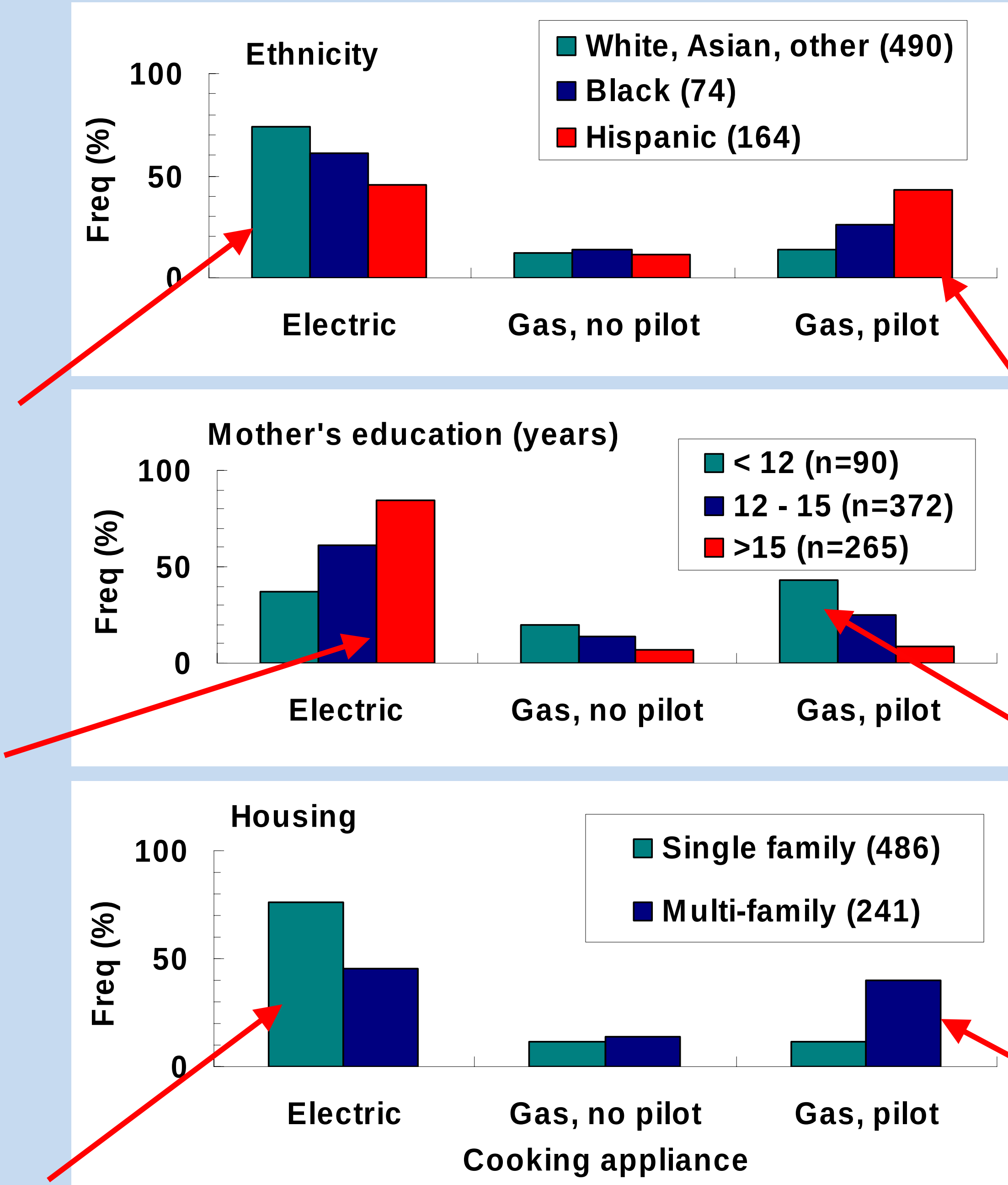
Frequency (%) of wheezing by housing type, mother’s level of education, season of nitrogen dioxide sampling

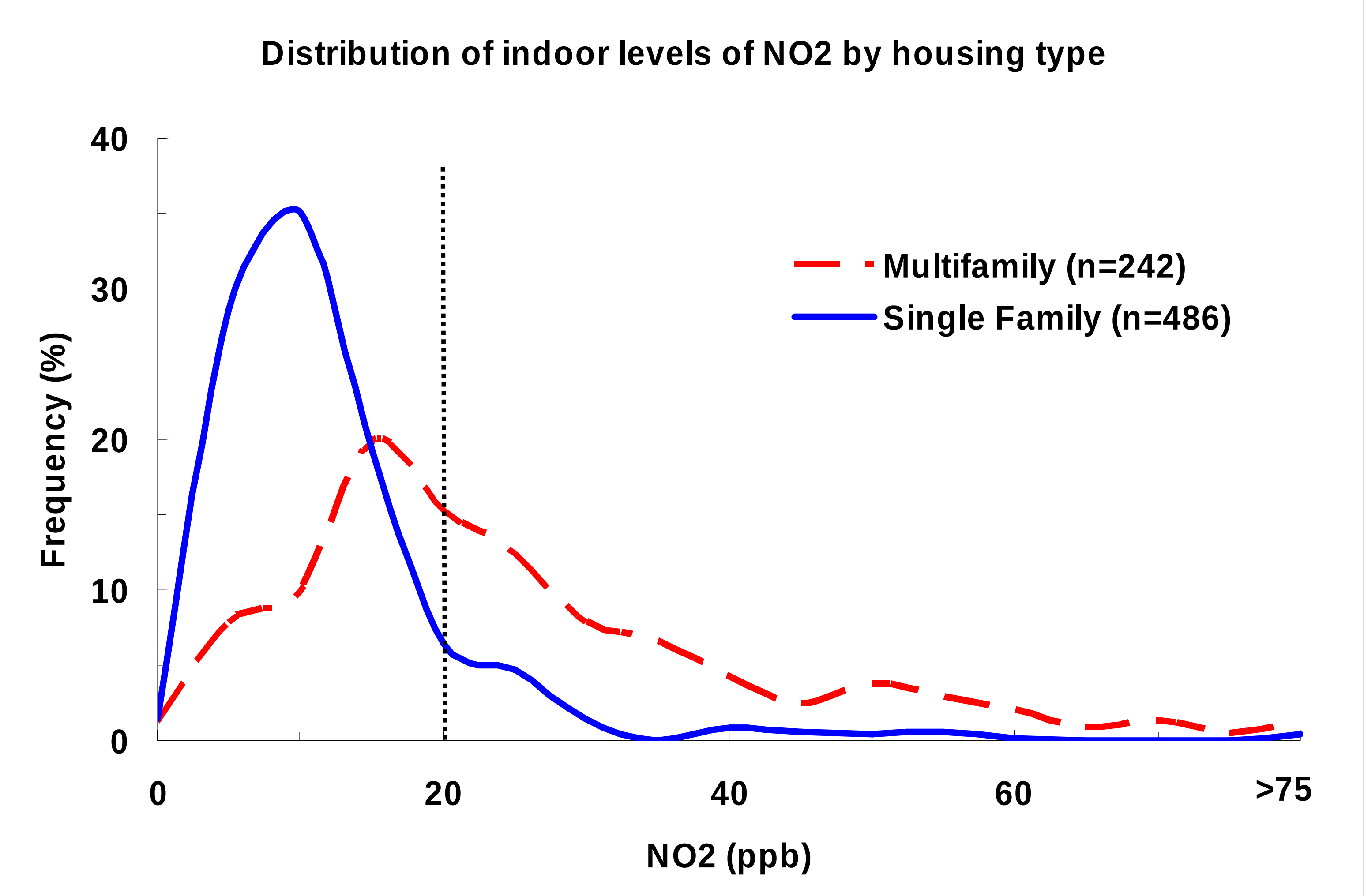
- NO_2 exposure from household sources:
    - Gas stoves
    - Gas dryers
    - Tobacco smoker in the home



Distribution of household sources of NO_2 among study families (n = 728)

Socioeconomic factors associated with cooking appliance use





Measured levels of NO_2: Distribution by housing type. Dotted line at 20 ppb indicates the 80th percentile of the overall distribution of NO_2.

Estimates of odds ratios and 95% confidence intervals from logistic regression models for household sources of NO_2, related to respiratory symptoms in the month before sampling (Southern New England, 1998-2000)

Factors	Wheeze OR (95% CI)	Persistent cough OR (95% CI)	Shortness of breath OR (95% CI)	Chest tightness OR (95% CI)
Multifamily Housing				
Gas stove	**2.27 (1.15, 4.47)**	1.19 (0.66, 2.16)	**2.38 (1.12, 5.06)**	**4.34 (1.76, 10.69)**
Gas dryer	0.78 (0.23, 2.57)	1.19 (0.40, 3.53)	2.39 (0.77, 7.43)	1.09 (0.31, 3.90)
Smoker in the home	1.08 (0.48, 2.39)	1.30 (0.64, 2.62)	0.98 (0.41, 2.33)	1.60 (0.62, 4.12)
Single Family Housing				
Gas stove	0.61 (0.35, 1.05)	0.92 (0.55, 1.51)	0.91 (0.50, 1.64)	0.68 (0.34, 1.32)
Gas dryer	1.02 (0.50, 2.12)	0.98 (0.49, 1.94)	0.93 (0.42, 2.07)	1.41 (0.61, 3.26)
Smoker in the home	1.92 (0.92, 4.04)	0.90 (0.41, 1.96)	1.26 (0.53, 2.97)	0.62 (0.20, 1.90)

Abbreviations: CI confidence interval; OR odds ratio.

Significant ($p < 0.05$) results are in shown in boldface type. Separate models were run for each symptom, and all models were adjusted for age, ethnicity, mold/mildew, water leaks, maintenance medication use, and season of sampling. Analyses were stratified by housing type.

Am J Respir Crit Care Med **2006;173:297-303. (Table 4)**

Results of models relating symptoms in the month before sampling to levels of NO_2 measured **indoors** (Southern New England, 1998-2000)

Model	Wheeze	Persistent cough	Shortness of breath	Chest tightness
Multifamily Housing				
Logistic regression				
predicting any symptom [OR (95% CI)]	**1.52 (1.04, 2.21)**	1.06 (0.75, 1.49)	1.28 (0.85, 1.91)	**1.61 (1.04, 2.49)**
Poisson regression				
predicting days of symptom [RR (95% CI)]	**1.33 (1.05, 1.68)**	1.07 (0.84, 1.35)	1.23 (0.95, 1.59)	**1.51 (1.18, 1.91)**
Single Family Housing				
Logistic regression				
predicting any symptom [OR (95% CI)]	0.99 (0.71, 1.38)	1.07 (0.78, 1.47)	0.83 (0.52, 1.31)	1.10 (0.78, 1.57)
Poisson regression				
predicting days of symptom [RR (95% CI)]	0.98 (0.78, 1.22)	0.91 (0.69, 1.20)	0.86 (0.63, 1.18)	0.92 (0.68, 1.25)

Abbreviations: CI confidence interval; OR odds ratio; RR rate ratio.

Significant ($p < 0.05$) results are in shown in boldface type. Separate models were run for each symptom, and all models were adjusted for age, ethnicity, mold/mildew, water leaks, maintenance medication use, and season of sampling. Analyses were stratified by housing type. Estimates of OR and 95% CI are from logistic regression models predicting any symptom and rate ratios (RRs) from Poisson models predicting number of days of symptoms. ORs and RRs are given for each 20-ppb increase in NO_2.

Am J Respir Crit Care Med **2006;173:297-303. (Table 5.)**

Outdoor NO_2

Asthma severity in children on maintenance medication

Estimates of odds ratios (OR) and 95% confidence intervals (CI) for **co-pollutant** logistic regression models for same- and previous-day levels of NO_2, ozone, and $PM_{2.5}$ related to each respiratory symptom or rescue medication (bronchodilator) use of children who are users of maintenance medication (n = 130). (Southern New England, April 1 – September 30, 2001.)

Pollutant	Wheeze OR (95% CI)	Cough OR (95% CI)	Shortness of breath OR (95% CI)	Chest tightness OR (95% CI)	Bronchodilator use OR (95% CI)
Same day					
NO_2 (15 ppb, 1-h max)	**1.14 (1.03, 1.26)**	1.05 (0.97, 1.13)	**1.14 (1.01, 1.30)**	**1.12 (1.00, 1.27)**	1.02 (0.98, 1.05)
O_3 (50 ppb, 1-h max)	0.99 (0.81, 1.20)	0.97 (0.81, 1.14)	1.03 (0.85, 1.26)	1.03 (0.84, 1.26)	1.03 (0.97, 1.10)
$PM_{2.5}$(10mg/m^3, 24-h ave)	1.00 (0.93, 1.07)	1.02 (0.96, 1.07)	1.07 (0.98, 1.17)	1.06 (0.97, 1.15)	1.01 (0.99, 1.03)
Previous day					
NO_2 (15 ppb, 1-h max)	1.00 (0.92, 1.09)	1.00 (0.94, 1.06)	1.01 (0.91, 1.12)	0.99 (0.89, 1.10)	1.00 (0.98, 1.03)
O_3 (50 ppb, 1-h max)	1.06 (0.91, 1.23)	**1.09 (1.00, 1.21)**	**1.26 (1.07, 1.48)**	**1.22 (1.02, 1.45)**	1.02 (0.97, 1.06)
$PM_{2.5}$(10mg/m^3, 24-h ave)	1.02 (0.96, 1.09)	1.01 (0.96, 1.05)	1.06 (0.98, 1.15)	1.07 (0.98, 1.17)	0.99 (0.97, 1.02)

Significant ($p < 0.05$) ORs are in boldface type.

Separate logistic regression analyses were performed for each outcome measure. All models include same- and previous-day levels of NO_2 (1-hr max), ozone (1-hr max), and $PM_{2.5}$ (24-hr average) adjusted for maximum daily temperature. Logistic regressions were performed using generalized estimating equations and specifying a one-day lagged autoregressive structure (AR1) for the correlation matrix.

Conclusions

Indoor NO_2 exposure associated with:

- respiratory symptoms in infants at risk for asthma
- respiratory symptoms in asthmatic children

Outdoor NO2 exposure associated with:

- increased respiratory symptoms in asthmatic children using maintenance medication

Interpretation of epidemiologic studies of NO_2 and health effects: Cautions

- Contaminants - NO_2 found in complex mixtures and often highly correlated with other pollutants
- Exposure assessment – measurements averaged from central sites may misclassify personal exposure
- Sources - Indoor and outdoor sources of NO_2 rarely considered together
- Other risk factors - NO_2 exposure often confounded by other risk factors associated with low SES

Study of Traffic, Air Quality and Respiratory Health (STAR)

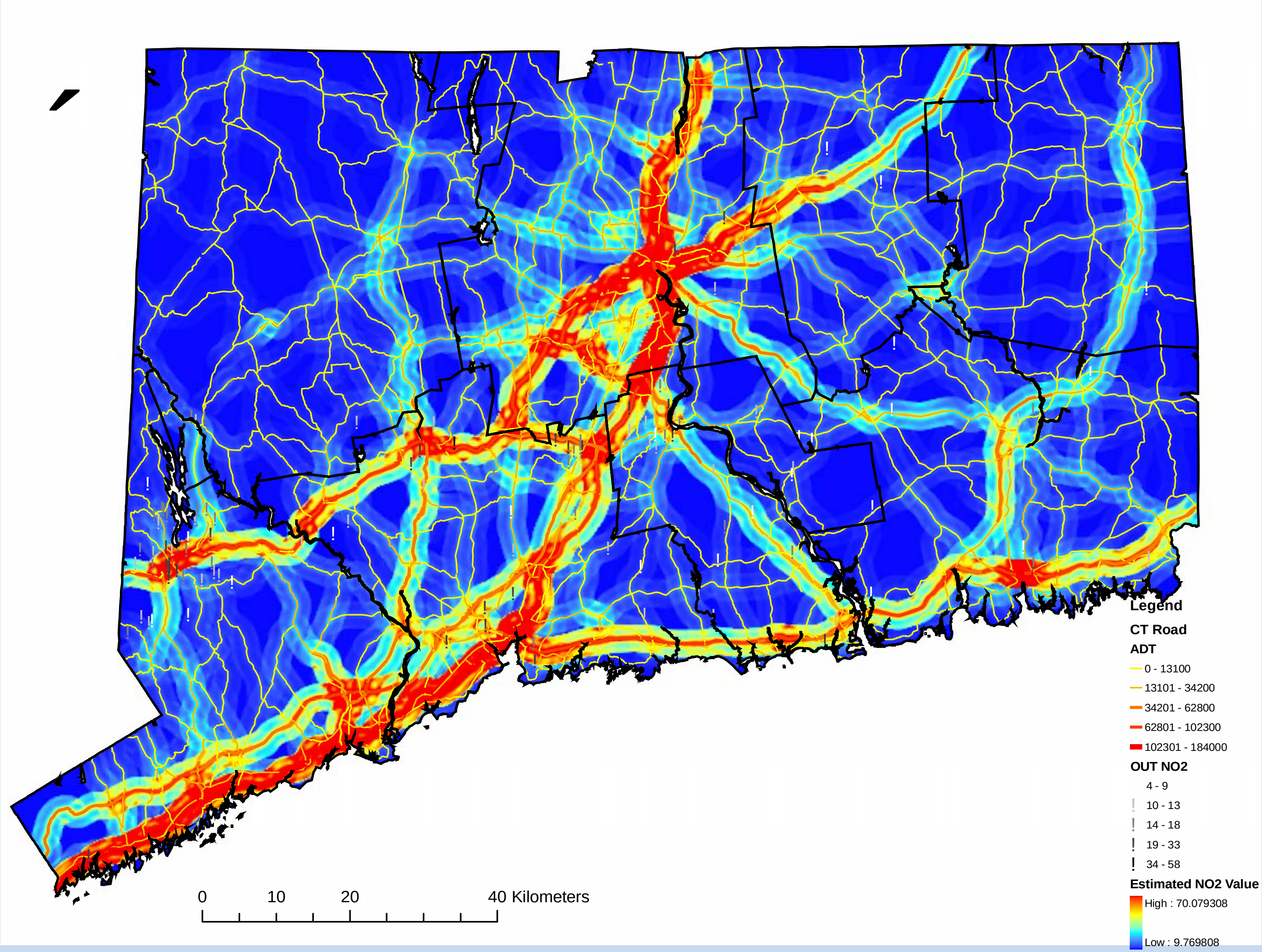
- Asthma severity associated with
  1) Indoor & outdoor NO_2
  2) Traffic emission
  3) Interaction between allergens & NO_2

Yale STAR study

- Recruiting 1500 asthmatic children in Connecticut
- Measuring NO_2 for 1 month in each season
  - indoors in child's bedroom & playroom
  - outdoors outside of child's home
- Estimating traffic exposure within 2 km of child's home

Yale STAR study

- Health outcomes recorded daily
  - respiratory symptoms
  - medication use
  - physician visits



Estimated average daily level of NO_2 along major roadways in Connecticut. Model based on traffic density data from the State Dept. of Transportation and outdoor NO_2 measurements taken at study subjects' homes (1997 – 2000).

Yale Center for Perinatal, Pediatric and Environmental Epidemiology

- Brian Leaderer, Principal Investigator
- Kathleen Belanger
- Michelle Bell
- Michael Bracken
- Janneane Gent
- Theodore Holford
- Elizabeth Triche

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