Air Pollution and Stroke

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Scope of the Problem

•Stroke is the third largest cause of death and a major cause of disability in the United States.

•700,000 new or recurrent cases of stroke occur annually.

•Health care expenditures over $30 billion annually in direct costs, and $21 billion in lost productivity.

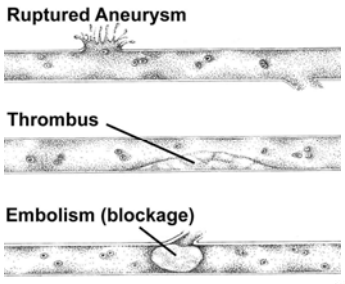
•Because of long term disability, the true cost of stroke due to diminished productivity and reduced quality of life among disabled survivors of stroke and their caregivers is likely even greater.

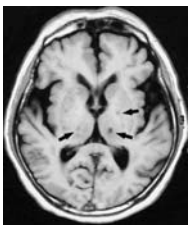
Stroke Pathophysiologic Causes

- Ischemic – A blood vessel gets blocked (80%)
- Hemorrhagic – A blood vessel bursts (15%)
- Subarachnoid hemorrhage and others (5%)

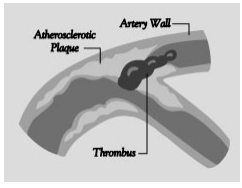
Warlow, Lancet 2003

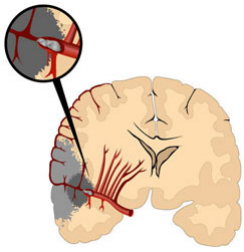
Stroke is Not a Single Entity





Small vessel Infarct





Large vessel Atherothrombotic

Stroke Types and Subtypes

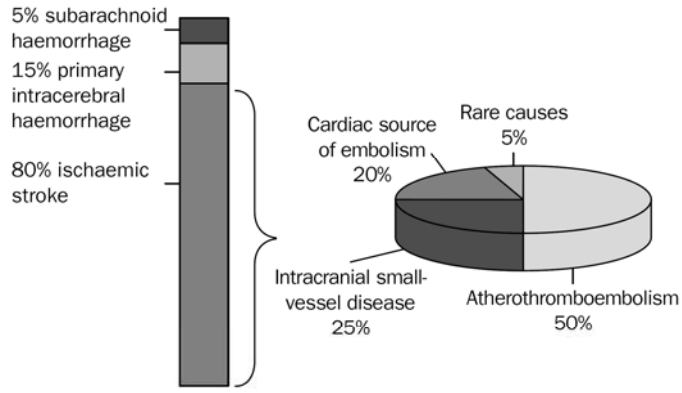


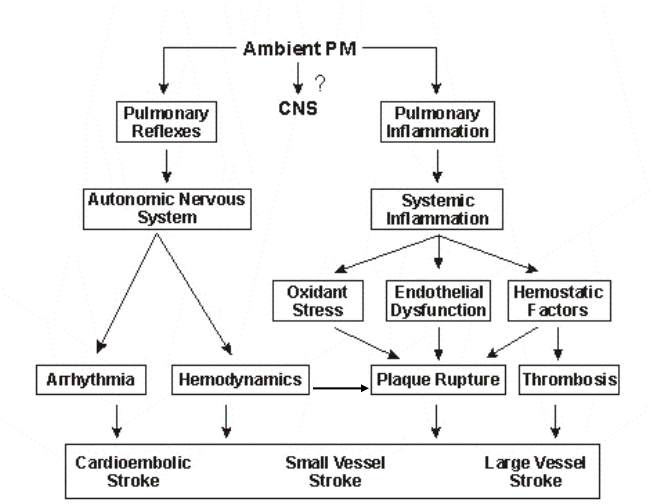
Figure 1: **Approximate frequency of three main pathological types of stroke (in white populations) and of main subtypes of ischaemic stroke as shown by population-based studies**[1]

Warlow, *Lancet* 2003

Triggering of Stroke

- Large-vessel (atherothrombotic), and some small vessel (lacunar) strokes, may result from acute hemodynamic changes that disrupt vulnerable atherosclerotic plaques.
- Transient hemodynamic changes may trigger cardioembolic strokes by dislodging preformed thrombi.

Putative Mechanisms for Cerebrovascular Events



Adapted from: Brook et al. Circulation, 2004

Long-term Exposure: Chronic Effects

Stroke Mortality Associated With Living Near Main Roads in England and Wales

A Geographical Study

Ravi Maheswaran, MD; Paul Elliott, PhD

TABLE 4. Rate Ratios for Stroke Mortality (1990–1992) by Distance to the Nearest Main Road, England and Wales

Distance to Nearest Main Road, m	Men	Women	Both*
	Adjusted for All Confounders‡		
<200	1.07 (1.04–1.09)	1.04 (1.02–1.06)	1.05 (1.04–1.07)
200–<500	1.03 (1.01–1.06)	1.02 (1.00–1.05)	1.03 (1.01–1.05)
500–<1000	1.01 (0.99–1.04)	1.02 (1.00–1.04)	1.02 (1.00–1.03)
≥1000	1	1	1

Stroke 2003

Stroke Mortality and Hospital Admissions: Sheffield, UK

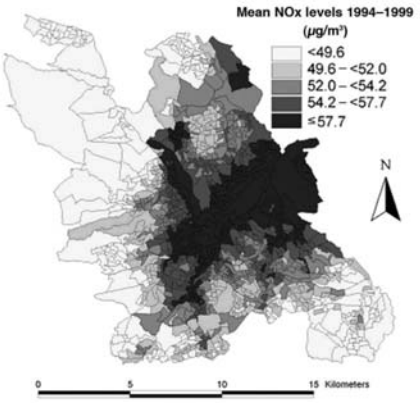


TABLE 2. Rate Ratios for Mortality and Emergency Hospital Admissions Because of Stroke in Relation to Modeled Outdoor Air Pollution (NO_x, PM_{10}, and CO) Categories by Quintile in Sheffield, United Kingdom, 1994 to 1998

Pollution Category	Rate Ratios (95 % CI) Mortality	Hospital Admissions
NO_x		
Adjusted for sex, age, deprivation, and smoking		
5 (highest)	1.37 (1.19–1.57)	1.13 (1.01–1.27)
4	1.20 (1.06–1.36)	1.05 (0.94–1.16)
3	1.04 (0.91–1.18)	0.93 (0.84–1.03)
2	1.09 (0.96–1.24)	1.02 (0.92–1.12)
1 (lowest)	1	1

Maheswaran et al. *Stroke* 2005

Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

Kristin A. Miller, M.S., David S. Siscovick, M.D., M.P.H., Lianne Sheppard, Ph.D., Kristen Shepherd, M.S., Jeffrey H. Sullivan, M.D., M.H.S., Garnet L. Anderson, Ph.D., and Joel D. Kaufman, M.D., M.P.H.

Table 3. Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 μg per Cubic Meter in the Level of Fine Particulate Matter ($PM_{2.5}$).*

Outcome	No. of Events	Hazard Ratio (95% CI)		
		Overall	Between Cities	Within Cities
First cardiovascular event				
Any cardiovascular event†	1816	1.24 (1.09–1.41)	1.15 (0.99–1.32)	1.64 (1.24–2.18)
Coronary heart disease‡	1268	1.21 (1.04–1.42)	1.13 (0.95–1.35)	1.56 (1.11–2.19)
Cerebrovascular disease§	600	1.35 (1.08–1.68)	1.20 (0.94–1.54)	2.08 (1.28–3.40)
Myocardial infarction	584	1.06 (0.85–1.34)	0.97 (0.75–1.25)	1.52 (0.91–2.51)
Coronary revascularization	949	1.20 (1.00–1.43)	1.14 (0.93–1.39)	1.45 (0.98–2.16)
Stroke	554	1.28 (1.02–1.61)	1.12 (0.87–1.45)	2.08 (1.25–3.48)
Death from cardiovascular cause				
Any death from cardiovascular cause	261	1.76 (1.25–2.47)	1.63 (1.10–2.40)	2.28 (1.10–4.75)
Coronary heart disease				
Definite diagnosis	80	2.21 (1.17–4.16)	2.22 (1.06–4.62)	2.17 (0.60–7.89)
Possible diagnosis	59	1.26 (0.62–2.56)	1.20 (0.54–2.63)	1.57 (0.29–8.51)
Cerebrovascular disease	122	1.83 (1.11–3.00)	1.58 (0.90–2.78)	2.93 (1.03–8.38)

NEJM 2007

PM2.5 and the Risk of Stroke: Health Professionals Follow-up Study

	Total CVD (1,661 events)	Ischemic Stroke (230 events)	Hemorrhagic Stroke (70 events)
Basic Model	0.99 (0.90, 1.10)	0.74 (0.56, 0.96)	1.33 (0.86, 2.06)
Full Model	0.99 (0.90, 1.10)	0.76 (0.58, 0.99)	1.35 (0.87, 2.09)

Puett et al. *EHP* 2011

Stroke and Long-term Exposure to NO_2
Danish Diet, Cancer and Health Cohort

	No. of Cases	IR‡	Fully Adjusted† HR (95% CI)
Incident stroke§			
Any stroke	1984	3.9	1.05 (0.99–1.11)
Nonspecified	1010	2.0	1.08 (1.00–1.17)
Ischemic	629	1.2	1.06 (0.96–1.17)
Hemorrhagic	345	0.7	0.93 (0.81–1.07)
Fatal stroke‖			
Any stroke	142	0.28	1.22 (0.99–1.49)
Nonspecified	29	0.06	1.79 (1.19–2.70)
Ischemic	23	0.04	1.47 (0.90–2.38)
Hemorrhagic	90	0.18	1.00 (0.76–1.31)

Andersen et al. *Stroke* 2012

Short-term Exposure: Acute Effects

Association Between Air Pollution and Daily Stroke Admissions in Kaohsiung, Taiwan

TABLE 2. ORs (95% CIs) of Stroke Admissions for Each IQR Increase* in Single-Pollutant Models†

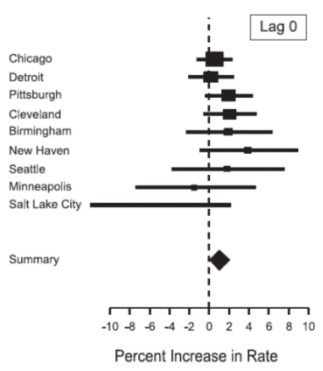
		OR (95% CI)	
Temperature, °C		PIH	IS
≥20		(n=4539)	(n=11528)
	PM_{10}	1.54 (1.31–1.81)‡	1.46 (1.32–1.61)‡
	SO_2	1.06 (0.95–1.18)	1.06 (1.00–1.13)
	NO_2	1.56 (1.32–1.84)‡	1.55 (1.40–1.71)‡
	CO	1.21 (1.09–1.34)‡	1.21 (1.14–1.28)‡
	O_3	1.20 (1.06–1.35)‡	1.15 (1.07–1.23)‡
<20		(n=654)	(n=1230)
	PM_{10}	0.82 (0.48–1.40)	0.97 (0.65–1.44)
	SO_2	0.85 (0.58–1.26)	1.11 (0.83–1.48)
	NO_2	0.81 (0.50–1.31)	1.16 (0.81–1.68)
	CO	1.18 (0.80–1.72)	1.77 (1.31–2.39)‡
	O_3	0.57 (0.24–1.34)	0.88 (0.50–1.53)

*An IQR increase in PM_{10} (66.33 $\mu g/m^3$), SO_2 (6.17 ppb), NO_2 (17.08 ppb), CO (0.29 ppm), and O_3 (21.20 ppb).

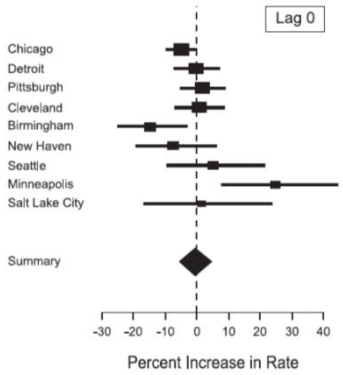
Tsai et al. *Stroke* 2003

Percent change in hospitalization risk for an IQR increase in Same-Day PM_{10} levels

Ischemic Stroke (n=155,503)

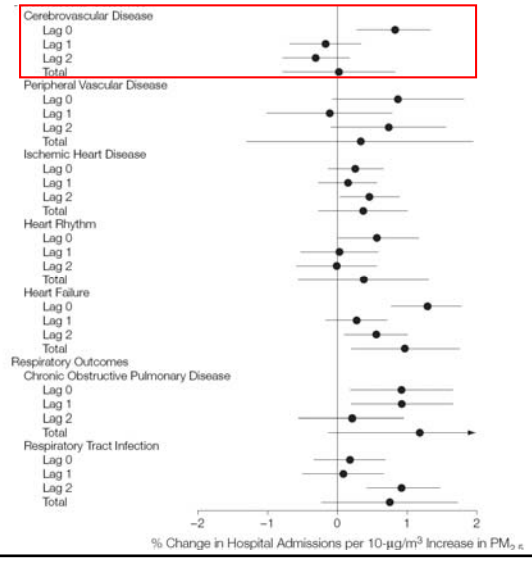


Hemorrhagic Stroke (n=19,314)



Wellenius et al. *Stroke* 2005

Percent change in hospitalization risk for a 10 μg/m^3 increase in $PM_{2.5}$ in 204 US counties.



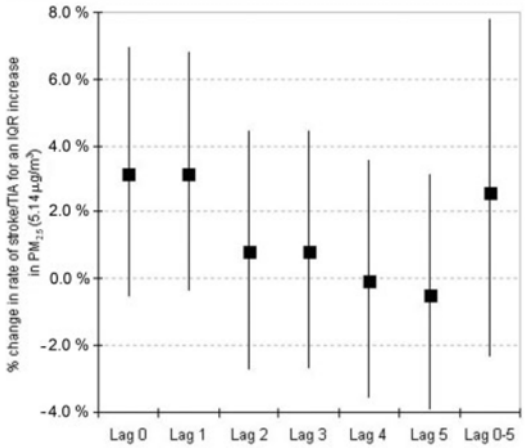
Dominici et al. *JAMA* 2006

Dijon Stroke Register

- Identified 1487 patients hospitalized for ischemic stroke and 220 patients for hemorrhagic stroke
- Found an association between O_3 and ischemic stroke
- Found no association between SO_2, NO_x, CO, or PM_{10} and either ischemic or hemorrhagic stroke

Henrotin et al. *Occup Environ Med* 2007

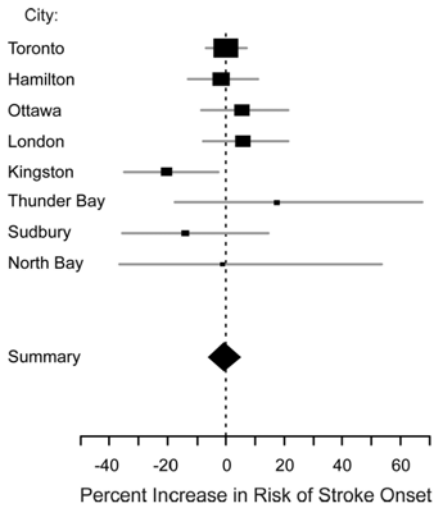
Brain Attack Surveillance in Corpus Christi (BASIC) Project



Lisabeth et al. *Ann Neurol* 2008

Fine Particulate Air Pollution (PM2.5) and Risk of Acute Ischemic Stroke:

Registry of the Canadian Stroke Network, Ontario Canada

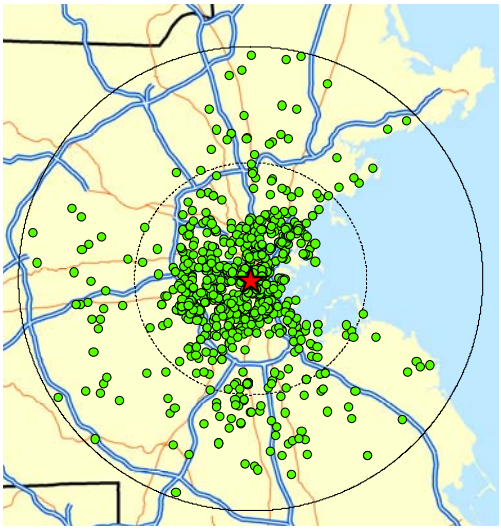


O'Donnell et al. Epidemiology 2011

Common Limitations of Existing Acute Effects Studies

- Outcome Misclassification
  - Low specificity
  - Moderate sensitivity
- Exposure Misclassification
  - Time of event onset
  - Spatial misalignment

Boston APRAISE Study
(Air Pollution and Risk of Acute Ischemic StrokE)



- Subjects hospitalized with confirmed acute ischemic stroke
- N=1705
- 89% lived within 20 km

Table 1. Characteristics of 1705 Patients Hospitalized With Acute Ischemic Stroke and Residing in the Boston Metropolitan Area, 1999-2008

Characteristic	Patients[a]
Age, mean (SD), y	73.1 (14.5)
Female	931 (54.6)
White	1165 (68.3)
Medical history	
Stroke or TIA	482 (28.3)
Atrial fibrillation	424 (24.9)
Hypertension	1216 (71.3)
Coronary artery disease	432 (25.3)
Heart failure	221 (13.0)
Diabetes mellitus	495 (29.0)
Chronic obstructive pulmonary disease	105 (6.2)
Smoking history	
Current	236 (13.8)
Former	457 (26.8)
Presumed stroke cause	
Large-artery atherosclerosis	339 (19.9)
Small-vessel occlusion	450 (26.4)
Cardioembolism	427 (25.0)
Other or undetermined	489 (28.7)

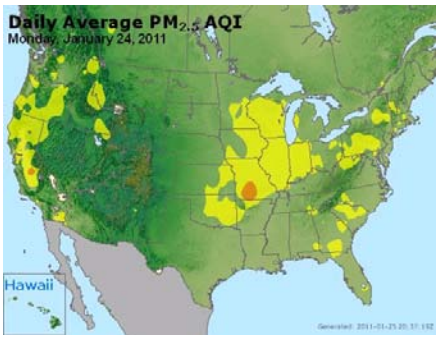
Wellenius et al. *Arch Intern Med* 2012

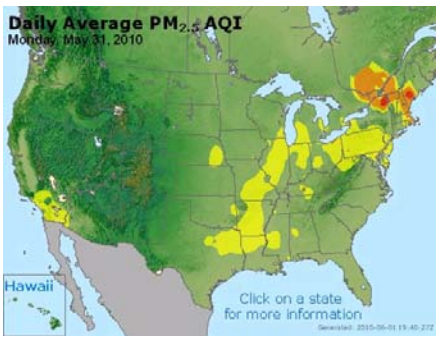
Air Quality Guide for Particle Pollution

Air Quality	Air Quality Index	Health Advisory
Good	0-50	None.
Moderate	51-100	Unusually sensitive people should consider reducing prolonged or heavy exertion.
Unhealthy for Sensitive Groups	101-150	People with heart or lung disease, older adults, and children should reduce prolonged or heavy exertion.
Unhealthy	151-200	People with heart or lung disease, older adults, and children should avoid prolonged or heavy exertion. Everyone else should reduce prolonged or heavy exertion.
Very Unhealthy	201-300	People with heart or lung disease, older adults, and children should avoid all physical activity outdoors. Everyone else should avoid prolonged or heavy exertion.

www.airnow.gov

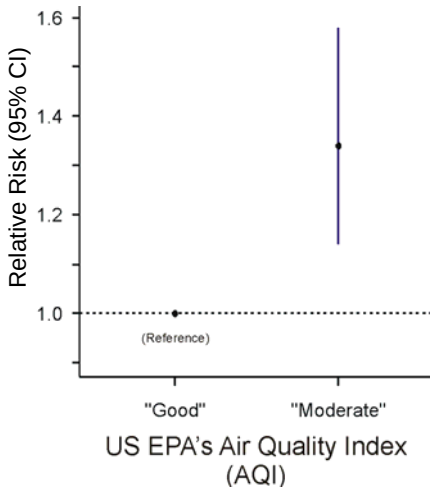
Air Quality Index for $PM_{2.5}$





www.airnow.gov

AQI and Risk of Ischemic Stroke Onset



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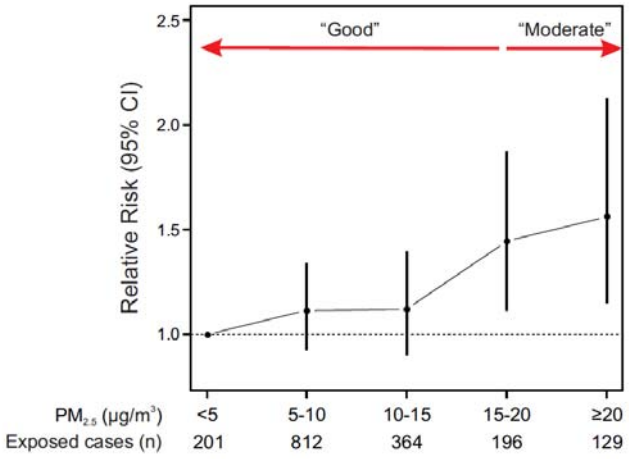
$PM_{2.5}$ and Risk of Ischemic Stroke Onset



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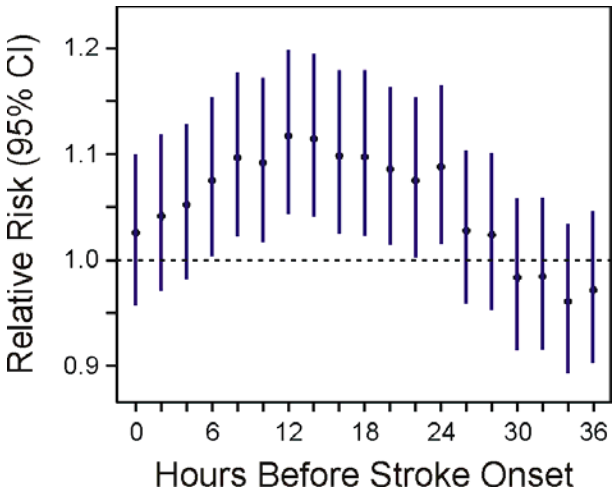
$PM_{2.5}$ and Risk of Ischemic Stroke Onset



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Association with Other Pollutants

Table 2. Odds Ratio of Ischemic Stroke Onset Comparing the 75th to 25th Percentile (Interquartile Range) of Each Pollutant in the 24 Hours Preceding Stroke Onset

Pollutant	IQR	Odds Ratio (95% CI)	*P* Value
$PM_{2.5}$[a]	6.4 μg/m³	1.11 (1.03-1.20)	.006
Black carbon[a]	0.5 μg/m³	1.10 (1.02-1.19)	.02
Estimated residential black carbon[b]	0.6 μg/m³	1.08 (1.01-1.16)	.02
NO_2	8.1 ppb	1.12 (1.03-1.22)	.01
CO	0.3 ppm	1.07 (0.96-1.19)	.24
O_3	15.2 ppb	0.97 (0.87-1.09)	.65
SO_4^{2-}[a]	2.1 μg/m³	1.06 (0.99-1.13)	.12

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Subgroup Analyses

Subgroup		OR (95% CI)	P_h
Presumed Stroke Etiology	**Large Artery**	**1.24 (1.04 ,1.48)**	**0.19**
	Small Vessel	**1.19 (1.02 ,1.37)**	
	Cardioembolic	**1.09 (0.93 ,1.27)**	
	Other/Undetermined	**0.99 (0.85 ,1.15)**	
History of Diabetes	**Yes**	**1.10 (1.00 ,1.21)**	**0.67**
	No	**1.14 (0.99 ,1.32)**	
History of Atrial Fibrillation	**Yes**	**1.11 (1.02 ,1.22)**	**0.92**
	No	**1.13 (0.96 ,1.32)**	
History of Hypertension	**Yes**	**1.10 (0.96 ,1.27)**	**0.86**
	No	**1.12 (1.02 ,1.23)**	
History of Stroke	**Yes**	**1.12 (1.02 ,1.23)**	**0.80**
	No	**1.09 (0.95 ,1.26)**	

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Public Health Impact

- We found an 11% excess relative risk of stroke onset comparing a typical "polluted" day to a typical "clean" day in Boston.
- Public health impact can be high because:
  - The incidence rate of stroke among the elderly is high (184,000 in Northeast in 2007)
  - Nearly everyone is exposed
  - If causal, a 2 $\mu g/m^3$ (~20%) reduction in $PM_{2.5}$ may have averted 6,100 strokes in Northeast in 2007

Public Health Impact

- In Boston, we found a 34% higher risk of stroke onset on the 16% of days where the AQI was above the good category, but still in attainment of the EPA standard.
- Public health impact can be high
  - The incidence of stroke among the elderly is high
  - 148,000 ischemic strokes in the Northeast in 2007
  - If causal, approximately 7,600 excess strokes might have been avoided that year if no days exceeded the AQI good category.

Summary

- Long-term, chronic exposure to air pollution is associated with increased risk of stroke.
  - The association is stronger for fatal than non-fatal stroke
  - New evidence indicates that the association is stronger for ischemic stroke than hemorrhagic stroke
- Short-term, acute exposure to air pollution is associated with a transient increased risk of stroke within less than 1 day.
  - The association is stronger for ischemic than hemorrhagic stroke
  - Accurate data on timing of stroke onset is crucial for estimation of the acute effect of air pollution

It Takes a Village

BIDMC

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