Confounding and Effect Modification

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Outline

1. Causal inference: comparing “otherwise similar” populations
2. “Confounding” is “confusing”
3. Graphical representation of causation
4. Addressing confounding
5. Effect modification

Counterfactual Data Table

Person	Drug	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	16	-6
2	0	18	17	-1
3	0	20	15	-5
4	1	20	18	-2
5	1	18	16	-2
6	1	22	14	-8
Average		**20**	**16**	**-4**

Actual Data Table

Person	Drug	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	?	?
2	0	18	?	?
3	0	20	?	?
4	1	?	18	?
5	1	?	16	?
6	1	?	14	?
Average		**20**	**16**	**-4**

Goal of Statistical "Causal" Inference

- "Fill-in" missing information in the counterfactual data table
- Use data for persons receiving the other treatment to fill-in a persons missing outcome
- Inherent assumption that the other persons are similar except for the treatment: "otherwise similar"
- *Compare like-to-like*

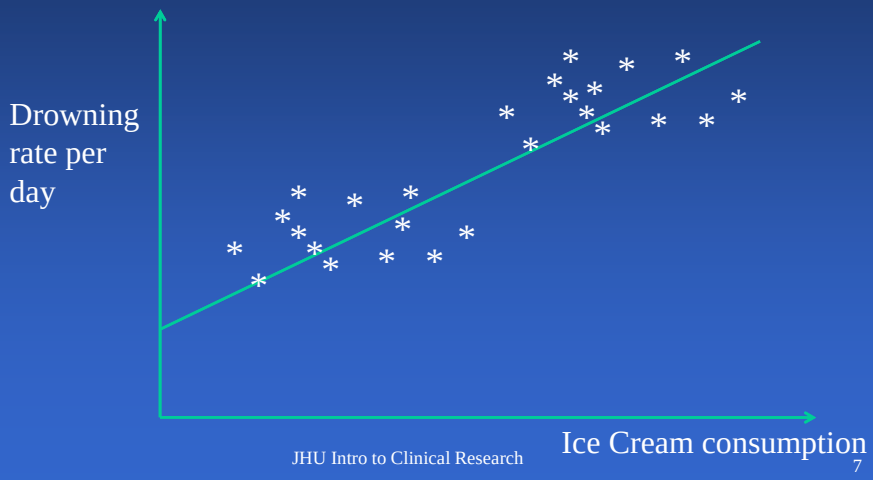
Confounding

Confound means to "confuse"

When the comparison is between groups that are otherwise not similar in ways that affect the outcome

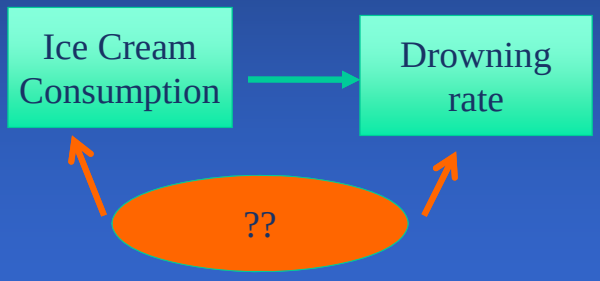
Simpson's paradox; lurking variables,….

Confounding Example:
Drowning and Ice Cream Consumption



Confounding

Epidemiology definition: A characteristic "C" is a confounder if it is associated (related) with both the outcome (Y: drowning) and the risk factor (X: ice cream) and is not causally in between



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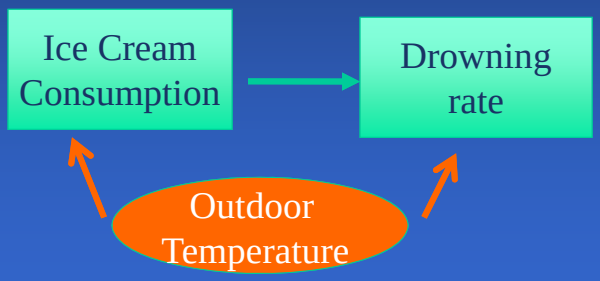
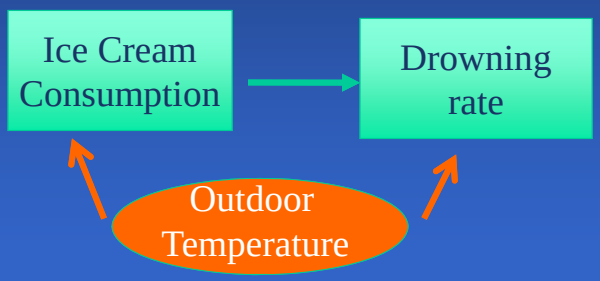
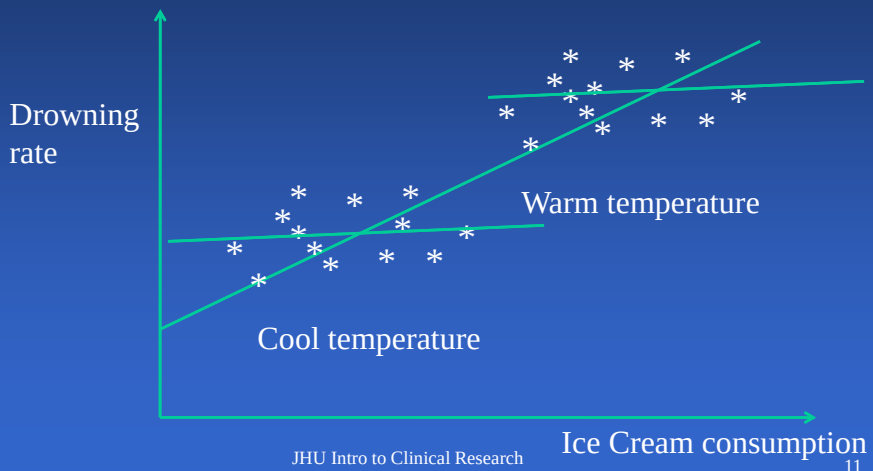


Confounding

Statistical definition: A characteristic "C" is a confounder if the strength of relationship between the outcome (Y: drowning) and the risk factor (X: ice cream) differs overall, versus within values for C

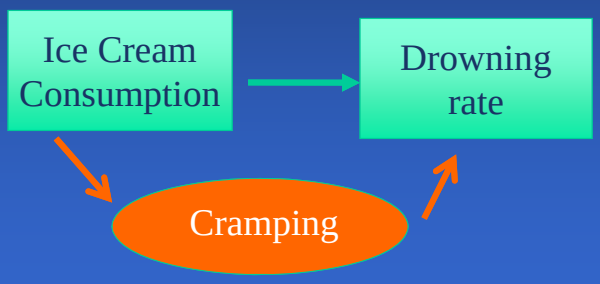


Confounding Example:
Drowning and Ice Cream Consumption



Mediation

A characteristic "M" is a mediator if it is causally in the pathway by which the risk factor (X: ice cream) leads the outcome (Y: drowning)



Confounding

Statistical definition: A characteristic "C" is a confounder if the strength of relationship between the outcome and the risk factor differs with, versus without, comparing like to like on C

Thought example:
Outcome = frailty
Exposure = vitamin D intake
Confounders= SES, "health mindedness," etc.

Example: Graduate School Admissions UC Berkeley

	Number Applied	Percent Accepted
Male	1901	55
Female	1119	36

	Number Males Applied	Number Males Accepted	Male % Accepted	Female % Accepted	Number Females Accepted	Number Females Applied
A	825	512	62	82	89	108
B	560	353	63	68	17	25
C	325	120	37	34	202	593
D	191	53	28	24	94	393
Total	1901	1038	55	36	402	1119

	Percent Admitted	Percent Male Applicants	Percent Female Applicants
A	65	43	10
B	63	30	2
C	35	17	53
D	25	10	35
Total	48	100	100

Sex Bias in Graduate Admissions: Data from Berkeley

Measuring bias is harder than is usually assumed, and the evidence is sometimes contrary to expectation.

P. J. Bickel, E. A. Hammel, J. W. O'Connell

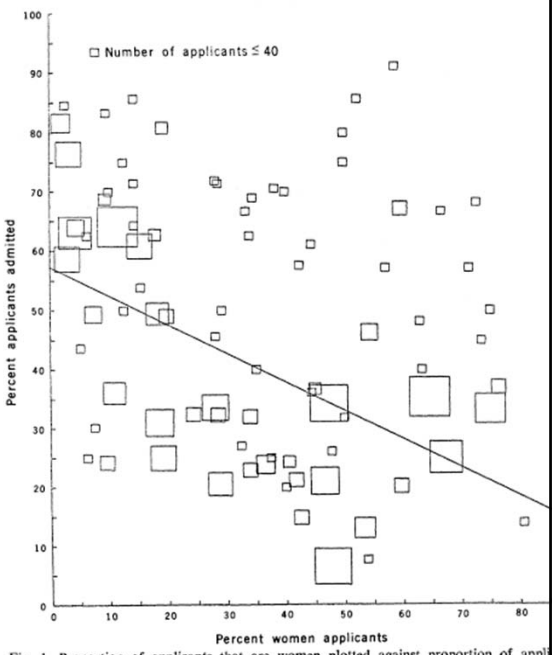
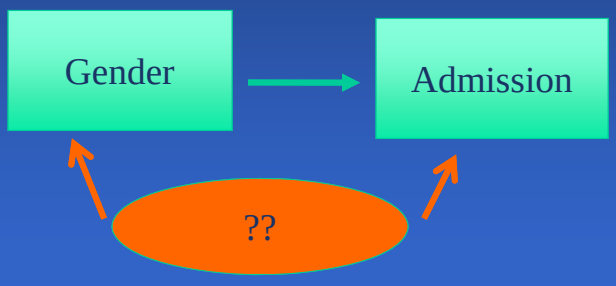
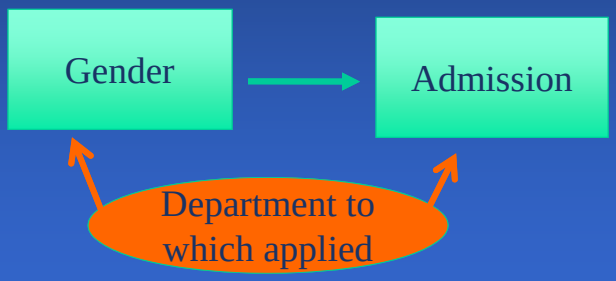


Fig. 1. Proportion of applicants that are women plotted against proportion of appli cants admitted, in 85 departments. Size of box indicates relative number of applicant to the department.

What is the lurking variable causing admissions rates to be lower in departments to which more women apply?



What is the lurking variable causing admissions rates to be lower in departments to which more women apply?



	Number Males Applied	Number Males Accepted	Male % Accepted	Female – Male % Accepted	Female % Accepted	Number Females Accepted	Number Females Applied
A	825	512	62	+20	82	89	108
B	560	353	63	+5	68	17	25
C	325	120	37	-3	34	202	593
D	191	53	28	-4	24	94	393
Total	1901	1038	55	-19	36	402	1119

Controlling for Confounding

Unadjusted (for department) difference in admission rates between women and men: 36-55 = -19%

Adjusted (for department) difference in admission rates between women and men:

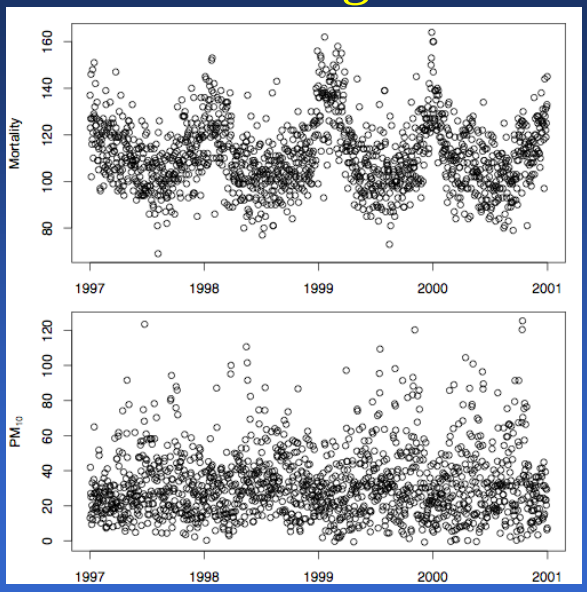
Average(20, 5, -3, -4) = 4.5%

Weighted ave(20, 5,-3, -4) = 3.2%

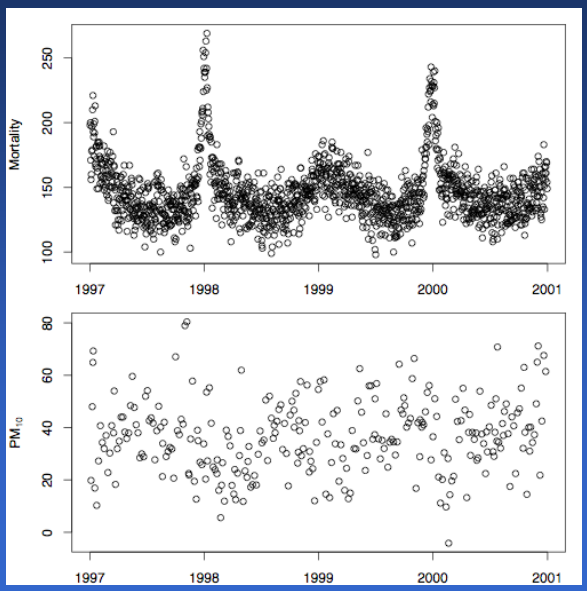
…Now for something entirely different

Particulate air pollution and mortality

Chicago



Los Angeles



July 2010

Correlation: Daily mortality and PM_{10}

- New York -0.031
- Chicago -0.036
- Los Angeles -0.019

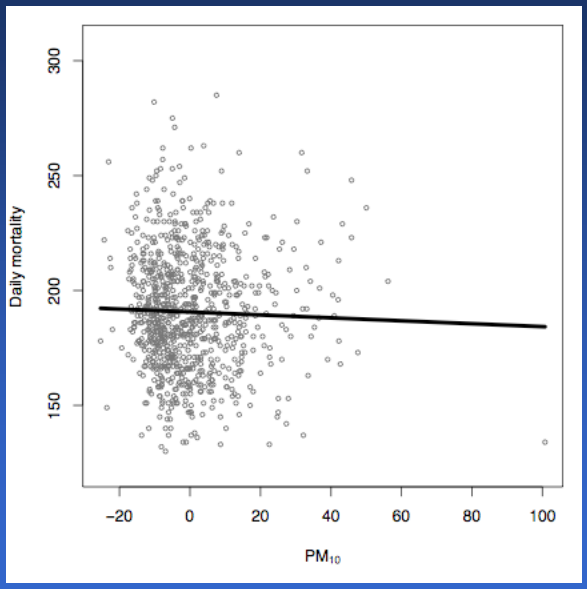
> Season could be confounding the correlation between PM_{10} and mortality.

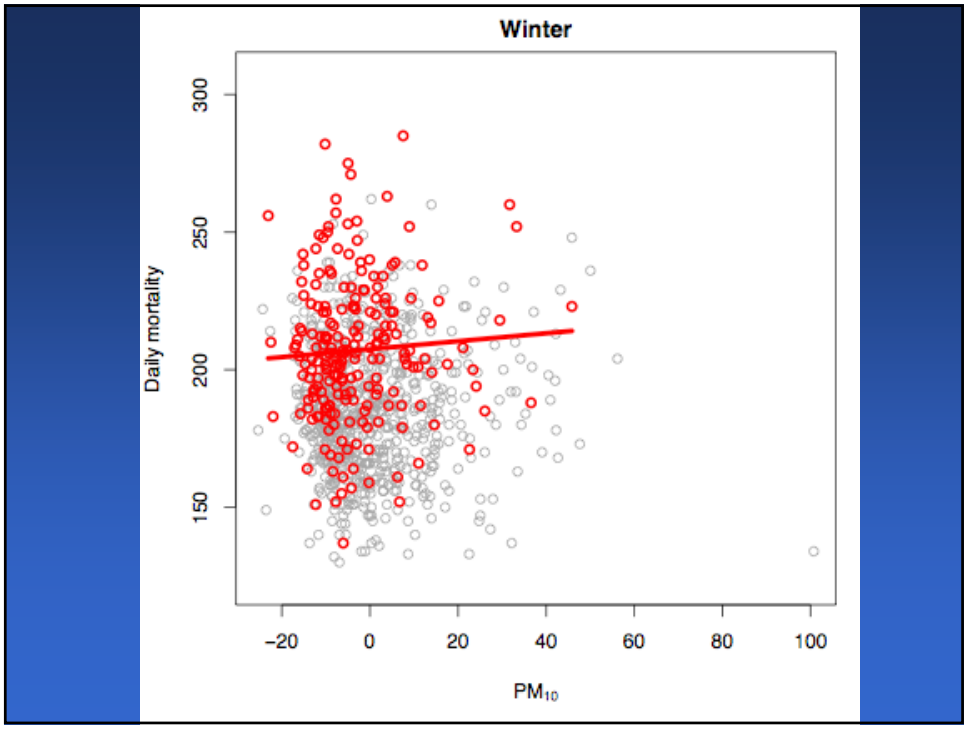
> What would happen if we "removed" season from the analysis?

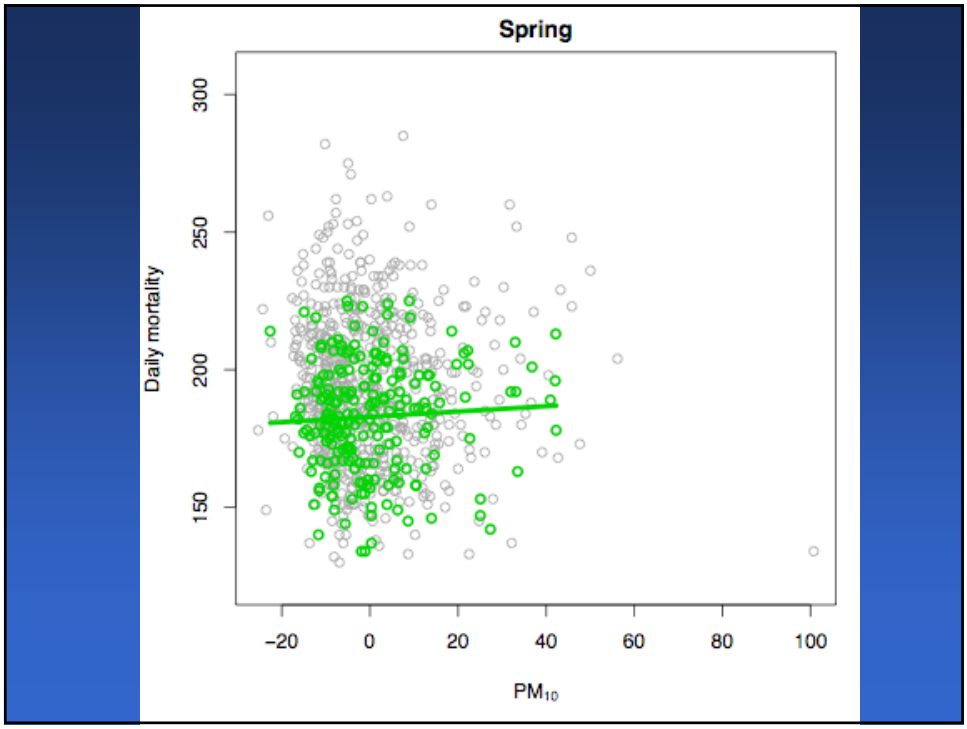
Season-specific correlations

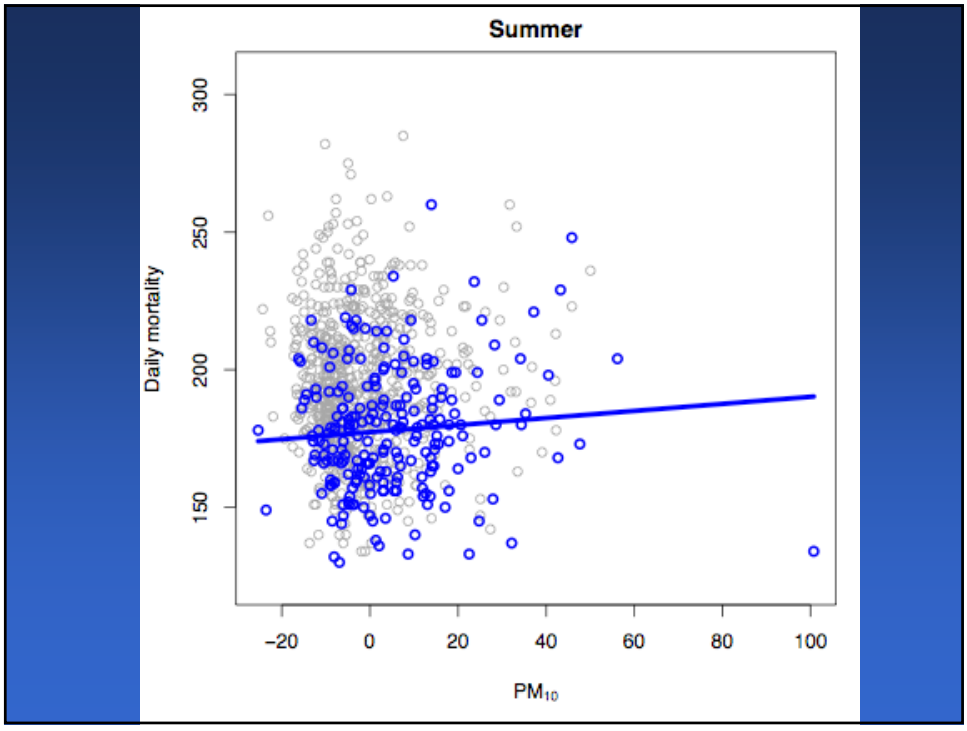
	All Year	Winter	Spring	Summer	Fall
NY	-0.031	0.059	0.059	0.086	0.100
Chicago	-0.036	-0.017	0.054	0.140	-0.030
LA	-0.019	0.157	0.063	0.042	-0.118

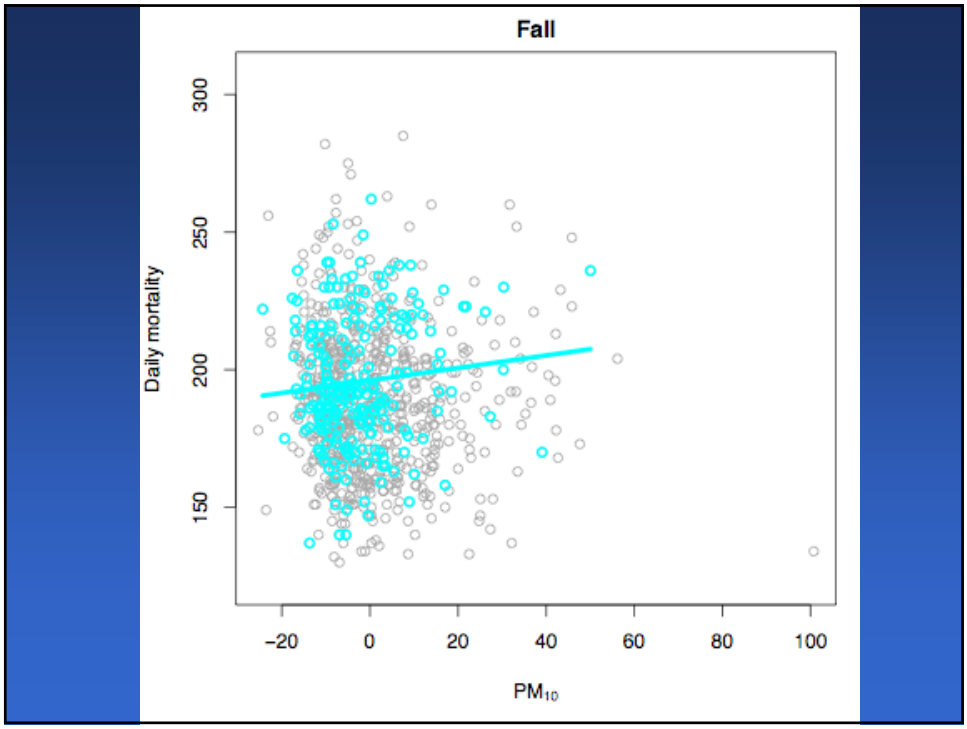
Overall association for New York



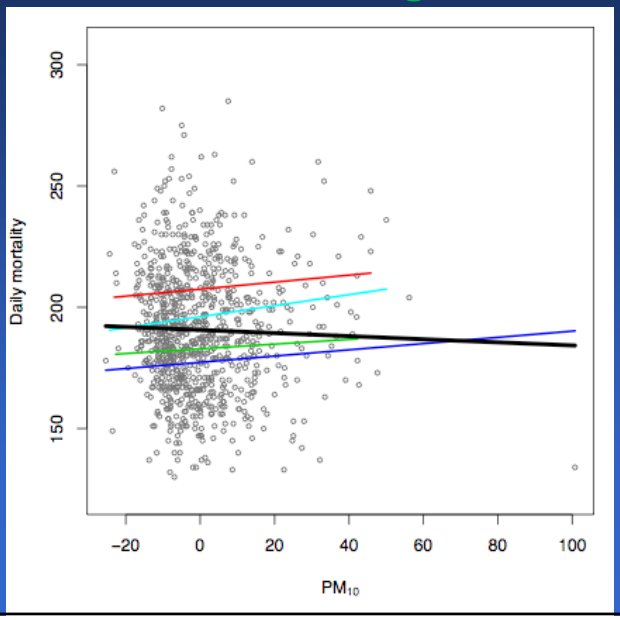



Spring
Daily mortality
300
250
200
150
−20
0
20
40
60
80
100
PM10


Summer
Daily mortality
300
250
200
150
−20
0
20
40
60
80
100
PM10



Season-specific associations are positive, overall association is negative



Overall correlations

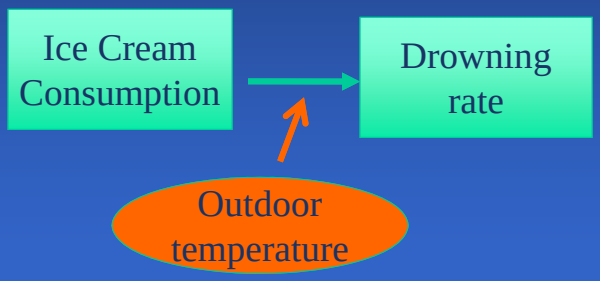
	All Year	Average over Seasons
New York	-0.031	0.076
Chicago	-0.036	0.037
LA	-0.019	0.036

Overall correlations

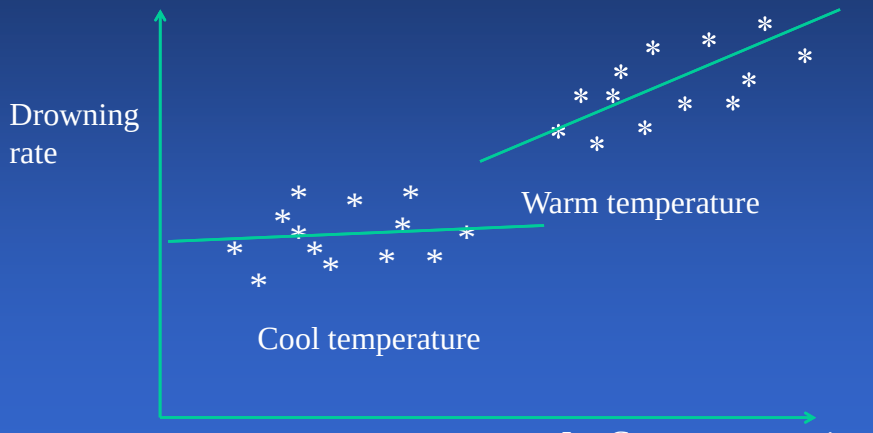
	All Year "Unadjusted"	Average 4 within-season values "Adjusted"	Average 12 within month values "Adjusted"
New York	-0.031	0.076	0.079
Chicago	-0.036	0.037	0.063
LA	-0.019	0.036	0.050

Effect modification

A characteristic "E" is an effect modifier if the strength of relationship between the outcome (Y: drowning) and the risk factor (X: ice cream) differs within levels of E



Effect Modification Example: Drowning and Ice Cream Consumption



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The Effect of Losartan Versus Atenolol on Cardiovascular Morbidity and Mortality in Patients With Hypertension Taking Aspirin

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

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Question: Does aspirin use modify the association between treatment and adverse outcomes?

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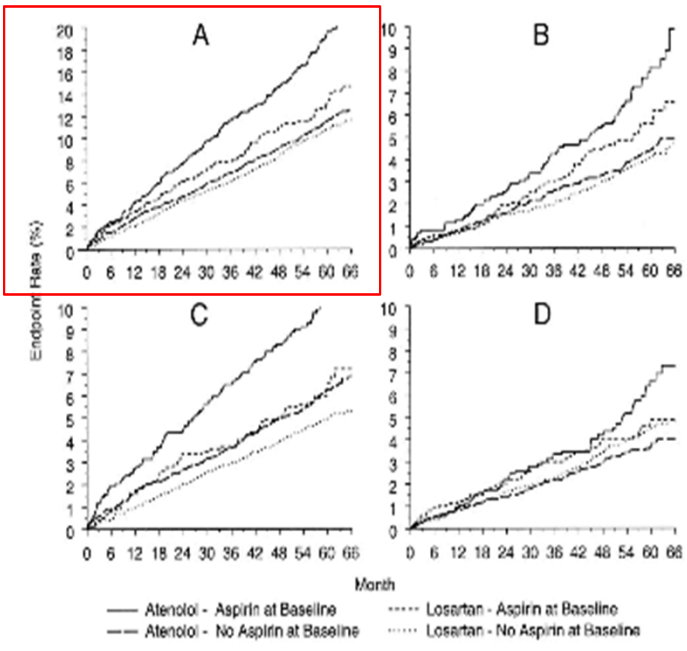


Figure 1. (A) Kaplan-Meier curves for the primary end point; p = 0.016 for aspirin interaction. (B) Kaplan-Meier curves for cardiovascular death. (C) Kaplan-Meier curves for stroke. (D) Kaplan-Meier curves for myocardial infarction; p = 0.037 for aspirin interaction.

Table 4. End Points in Losartan- and Atenolol-Treated Patients Taking Aspirin at Baseline

End Point	Losartan (n = 1,004) n	%	Rate†	Atenolol (n = 966) n	%	Rate†	Adjusted* Hazard Ratio (95% CI)	p Value
Primary composite end point‡	128	12.7	28.3	180	18.6	42.1	0.68 (0.55–0.86)	0.001
Cardiovascular mortality	56	5.6	11.8	76	7.9	16.7	0.73 (0.52–1.03)	0.074
Stroke	61	6.1	13.4	94	9.7	21.8	0.63 (0.45–0.86)	0.004
Myocardial infarction	44	4.4	9.6	58	6.0	13.1	0.75 (0.51–1.11)	0.16
Other prespecified end points								
Total mortality	106	10.6	22.4	121	12.5	26.6	0.86 (0.66–1.12)	0.26
Hospitalization for								
Angina pectoris	53	5.3	11.6	48	5.0	10.9	1.10 (0.74–1.62)	0.64
Heart failure	45	4.5	9.8	53	5.5	12.1	0.84 (0.56–1.25)	0.39
Revascularization	100	10.0	22.5	109	11.3	25.5	0.91 (0.70–1.20)	0.51
New-onset diabetes§	58	6.9	15.3	57	7.1	15.6	0.98 (0.68–1.41)	0.91

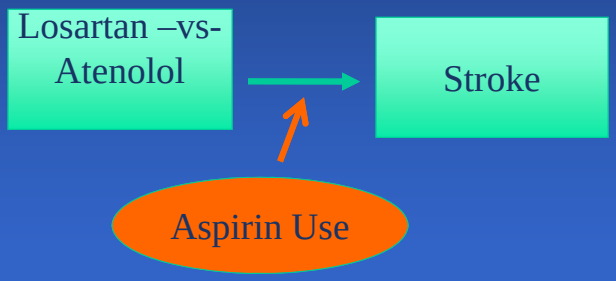
*For degree of left ventricular hypertrophy and Framingham risk score at randomization. †Per 1,000 patient-years of follow-up. ‡Cardiovascular mortality, stroke, and myocardial infarction; patients with a first primary end point. §Among patients without diabetes at randomization (losartan n = 843; atenolol n = 799).
CI = confidence interval.

Table 5. End Points in Losartan- and Atenolol-Treated Patients Not Taking Aspirin at Baseline

End Point	Losartan (n = 3,601) n	%	Rate†	Atenolol (n = 3,622) n	%	Rate†	Adjusted* Hazard Ratio (95% CI)	p Value
Primary composite end point‡	380	10.6	22.6	408	11.3	24.3	0.95 (0.82–1.09)	0.46
Cardiovascular mortality	148	4.1	8.5	158	4.4	9.1	0.96 (0.77–1.20)	0.71
Stroke	171	4.7	10.1	215	5.9	12.7	0.80 (0.66–0.98)	0.034
Myocardial infarction	154	4.3	9.0	130	3.6	7.6	1.21 (0.96–1.53)	0.11
Other prespecified end points								
Total mortality	277	7.7	15.9	310	8.6	17.8	0.91 (0.77–1.07)	0.24
Hospitalization for								
Angina pectoris	107	3.0	6.3	93	2.6	5.4	1.18 (0.89–1.56)	0.25
Heart failure	108	3.0	6.3	108	3.0	6.3	1.02 (0.78–1.34)	0.86
Revascularization	161	4.5	9.5	175	4.8	10.3	0.94 (0.76–1.17)	0.58
New-onset diabetes§	184	5.8	12.4	263	8.3	17.9	0.70 (0.58–0.85)	<0.001

*For degree of left ventricular hypertrophy and Framingham risk score at randomization. †Per 1,000 patient-years of follow-up. ‡Cardiovascular mortality, stroke, and myocardial infarction; patients with a first primary endpoint. §Among patients without diabetes at randomization (losartan n = 843; atenolol n = 799).
CI = confidence interval.

Aspirin use modifies the effect of treatment on the risk of stroke?



Confounding vs. Effect Modification

Confounding

- Bias (overall) because treatment groups differ by a relevant characteristic
- Persons taking vitamin D appear less frail because they have more resources to protect their health
- Addressed by computing effects in comparable people (vit D effect in persons with equal resources)

Effect modification

- Subgroup effects; contextual effects; different mechanisms
- Vitamin D more effectively prevents frailty in younger-old because they better metabolize Vitamin D
- Addressed by comparing effects across groups (Vit D effect in older-old minus Vit D effect in younger-old)

Summary

1. Causal inference: comparing “otherwise similar” populations
2. Confounding means confusing: comparing otherwise dissimilar groups
3. Stratify by confounders and make comparisons within strata, then pool results across strata to avoid the effects of confounding
4. Effect modification when the treatment effect varies by stratum of another variable