


Scale and effect measure modification/interactions:

Understanding implications of scale for interpreting main effects and interactions

Anna Pearce anna.pearce@glasgow.ac.uk

MRC/CSO Social and Public Health Sciences Unit, University of Glasgow

19th February 2019

Learning objectives

Part 1: Scale

1. Different statistical models / effect measures use different scales
2. These scales matter for interpretation

Part 2: Interaction and effect measure modification:

1. Definitions of interaction and effect measure modification
2. Choice of interaction / effect measure modification may vary depending on your question
3. Scale is especially important

Part 1: Scale

- Relative and absolute effect measures

Odds ratio:

Exposure status	Die	Survive
Drug	5	95
Placebo	10	90

Prevalence ratio?

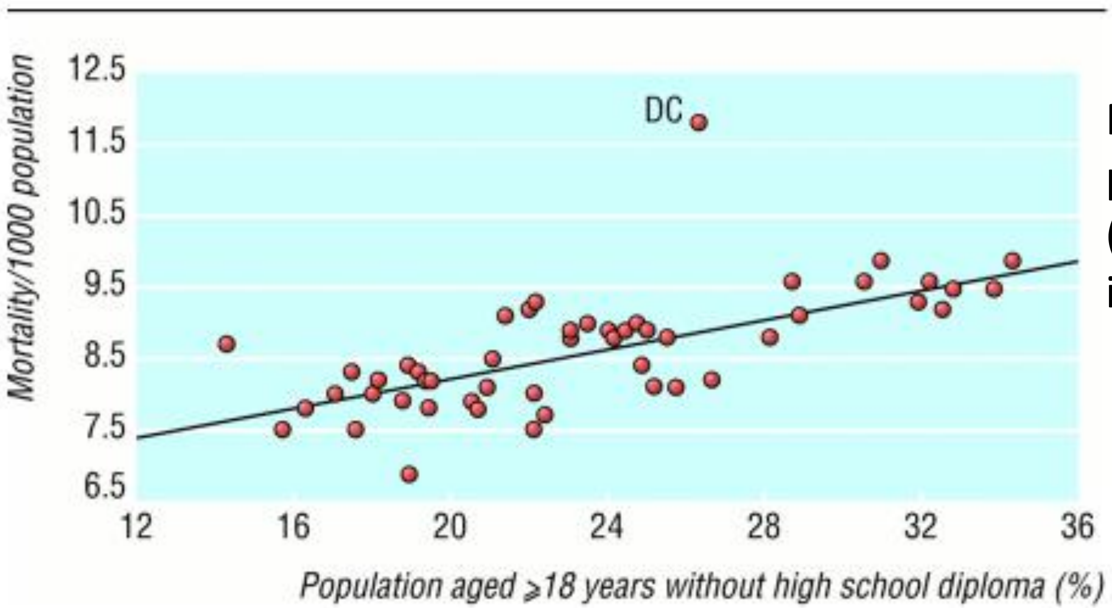
Exposure status	Die	Survive
Drug	5	95
Placebo	10	90

Risk difference…?

Exposure status	Die	Survive
Drug	5	95
Placebo	10	90

Another common measure that gives absolute differences?

Age adjusted death rates by educational attainment for the 50 US states and the District of Columbia (DC), 1989-90 (y=6.16+0.103×x; R2=0.51; weighted regression).



For every unit increase in X (1% population without diploma), Y (deaths/1000 population) increases by 0.103

Andreas Muller BMJ 2002;324:23

thebmj

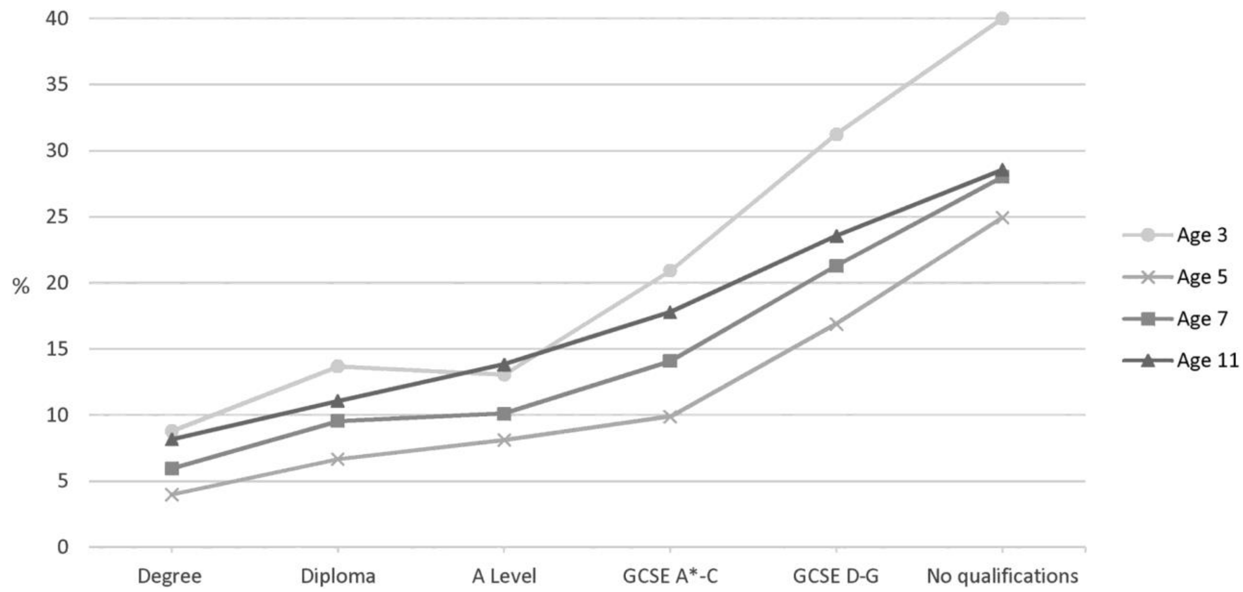
Take home message

- Different models measure effects on different scales
- Relative differences: prevalence ratios, risk ratios, odds ratio, hazard ratios etc.
- Absolute differences: risk differences, mean differences etc.

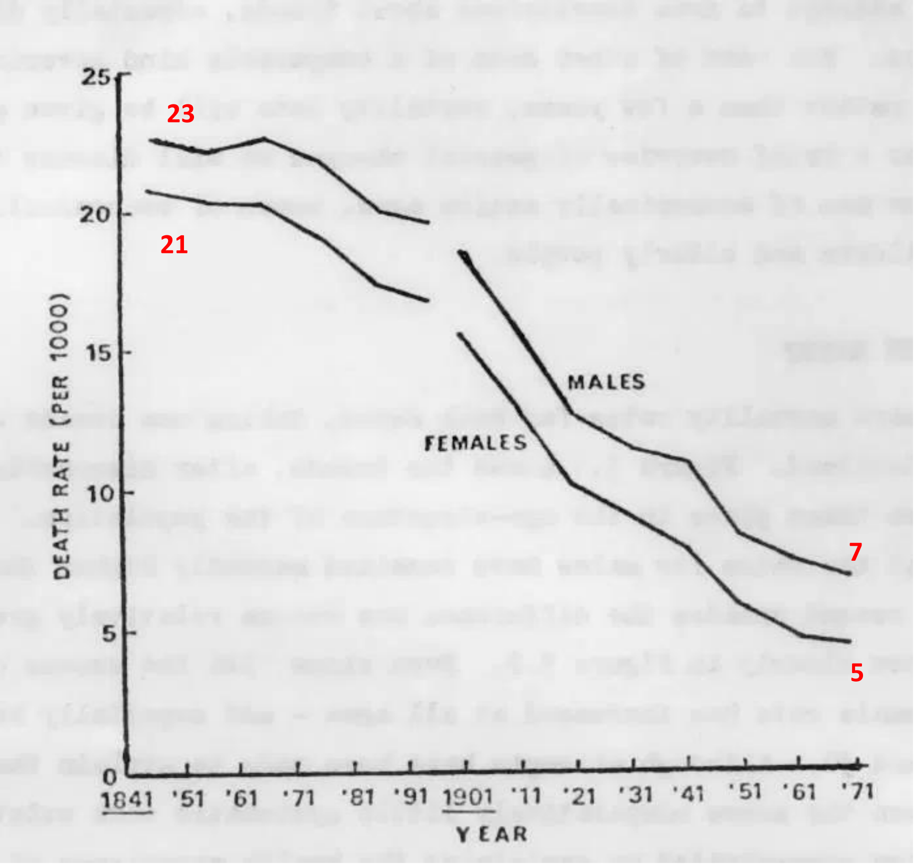
Why scale can matter

Example 1: Absolute vs. relative measures

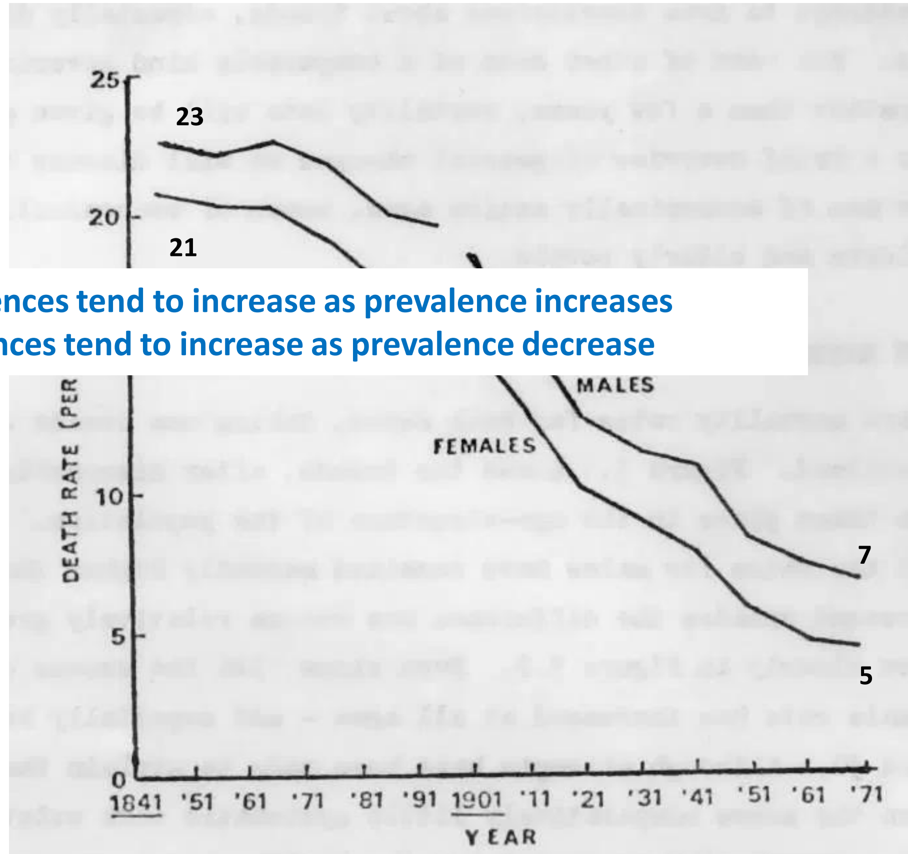
Prevalence of Socio-emotional difficulties in the Millennium Cohort Study in singletons at ages 3 (n=15 381), 5 (n=15 041), 7 (n=13 681) and 11 (n=13 112) by concurrent maternal academic attainment, weighted %.



Emeline Rougeaux et al. BMJ Open 2017;7:e012868



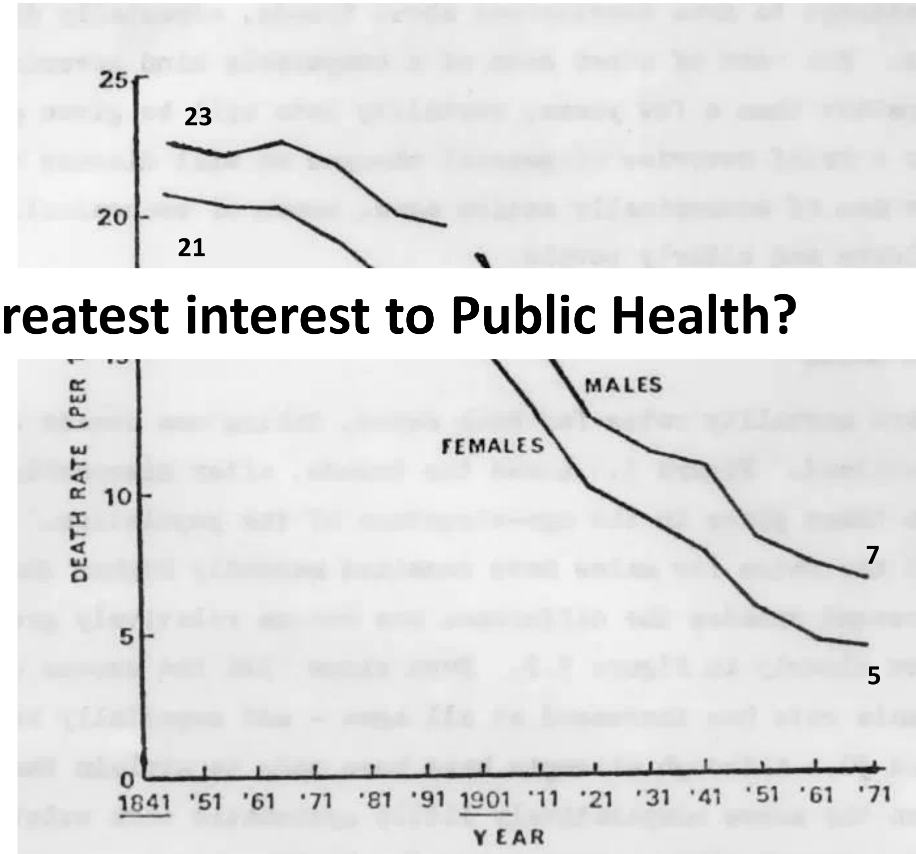
McKeown, T. The Role of Medicine, London, Nuffield Provincial Hospitals Trust 1976 p.30



- **Absolute differences tend to increase as prevalence increases**
- **Relative differences tend to increase as prevalence decrease**

McKeown, T. The Role of Medicine, London, Nuffield Provincial Hospitals Trust 1976 p.30

What's of greatest interest to Public Health?



McKeown, T. The Role of Medicine, London, Nuffield Provincial Hospitals Trust 1976 p.30

Why scale can matter

Example 2: Odds ratios vs. Risk ratios

ORs (vs. RR) with a rarer outcome (8%)

Odds ratio for dying

Risk ratio for dying

Exposure status	Die	Survive
Drug	5	95
Placebo	10	90

ORs (vs. RR) with a common outcome (50%)

Odds ratio for dying

Risk ratio for dying

Exposure status	Die	Survive
Drug	25	75
Placebo	50	50

ORs ~ RRs when prevalence of outcome is rare

- If using ORs when outcome is common, be careful with interpretation….
- There are a couple of advantages of using ORs…

1. ORs are symmetrical

e.g. predicting death vs. survival

Odds ratio for dying

(25/75) / (50/50)
= 0.33 /1 = **0.33**

Risk ratio for dying

(25/(25+75)) / (50/(50+50))
= 0.25 / 0.5 = **0.5**

Exposure status	Die	Survive
Drug	25	75
Placebo	50	50

Odds ratio for surviving

(75/25)/(50/50)
= 3/1 =**3**

Risk ratio for surviving

(75/100)/(50/100)
=0.75 / 0.5 = **1.5**

2. ORs are more portable

- This is because the range of possible values a RR can take on is bound by the risk in the baseline unexposed group
- For example, if the risk in the baseline/unexposed group is 0.5, the RR can never exceed 2

Prob out outcome in Exposed	Prob out outcome in Unexposed	RR	OR
0.6	0.5	0.6/0.5 = 1.2	(0.6/0.4)/1 = 1.5
0.9	0.5	0.9/0.5 = 1.8	(0.9/0.1)/1 = 9
0.99	0.5	0.99/0.5 = 1.98	(0.99/0.01)/1 = 99

However, ORs are not Collapsible….

- This means that an OR may change after adjustment for an additional variable even if that variable is not confounding the relationship
- See here for a relatively simple explanation

https://www.frankpopham.co.uk/2018/04/12/the-odd-odds-ratio/

Scale: Take home messages

- Relative differences tend to ↑ as prevalence of outcome ↑
- Absolute differences tend to ↑ as prevalence of outcome ↓
- Absolute differences may be of greater public health interest
- When outcome is rare, OR ~ RR
- When outcome is common, ORs will exaggerate relationships (if interpreted as RRs)
- ORs are harder to interpret than RRs…..
- And they are not collapsible (RRs are)
- But ORs are symmetrical and more portable than RRs
- They are also more easily calculated (in stats packages)

No right or wrong answer, just know what you're calculating and what's it's limits are…

Present data as complete as possible so others can calculate

Part 2: Interactions & Effect Measure Modification

Definitions

Interaction:

- Interested in the effects of two exposures ('interventions') **A** & **B**
- An interaction is present when:

*the risk in those exposed to **A** and **B** is greater (or smaller) than combined risks of those who are just exposed to **A** and just exposed to **B***

e.g. is being poor and obese worse (for life expectancy) than just being poor plus just being obese

Interaction

e.g. does the impact of poverty on mortality interact with obesity?

	Non-obese	Obese
Not poor	50	72
Poor	80	125

i.e. is the risk of being poor and obese greater than just being poor and just being obese

Definitions

Effect measure modification (EMM):

- Interested in the effects of just one exposure ('intervention') **A**
- And whether its effect varies by a modifier ('targeting' variable) **B**
- EMM is present when:

*the effect of **A** is not the same within subgroups of **B***

e.g. is Drug A more effective for men than women

Effect modification

e.g. is Drug A less effective for men than women?

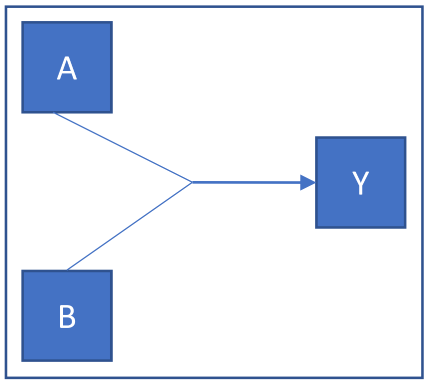
vs

	Males	Females
Placebo	100	125
Drug A	75	50

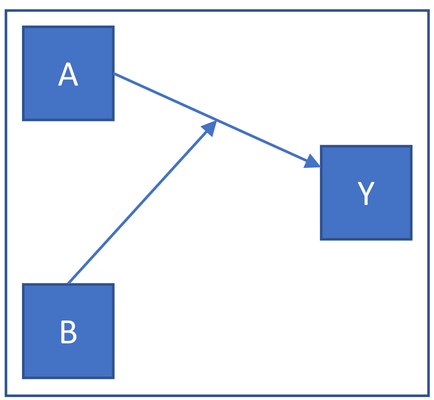
i.e. we are comparing the effect of Drug A in men to women

No consensus, but here's how they might look in a DAG

Interaction



EMM



Weinberg, Epidemiology, 2008

Interaction, using risk differences

- Interventions A and B…

	B=0	**B=1**
A=0	**P(Y)[0,0]**	P(Y)[0,1]
A=1	P(Y)[1,0]	P(Y)[1,1]

- Want to know if the probability associated with having A=1 *and* B=1 (compared to the **baseline**) is different from the probability of just having A *plus* just having B (compared to the **baseline**)

Interaction

- Interventions A and B…

	B=0	**B=1**
A=0	**P(Y)[0,0]**	P(Y)[0,1]
A=1	P(Y)[1,0]	**P(Y)[1,1]**

- Want to know if the probability associated with having A=1 *and* B=1 (compared to the **baseline**) is different from the probability of just having A *plus* just having B (compared to the **baseline**)

(**P(Y)[1,1]** - **P(Y)[0,0]**)

Interaction

- Interventions A and B…

	B=0	B=1
A=0	**P(Y)[0,0]**	P(Y)[0,1]
A=1	**P(Y)[1,0]**	P(Y)[1,1]

- Want to know if the probability associated with having A=1 *and* B=1 (compared to the **baseline**) is different from the probability of just having A *plus* just having B (compared to the **baseline**)

(**P(Y)[1,1]** - **P(Y)[0,0]**) > (**P(Y)[1,0]** - **P(Y)[0,0]**)

Interaction

- Interventions A and B…

	B=0	B=1
A=0	**P(Y)[0,0]**	**P(Y)[0,1]**
A=1	P(Y)[1,0]	P(Y)[1,1]

- Want to know if the probability associated with having A=1 *and* B=1 (compared to the **baseline**) is different from the probability of just having A *plus* just having B (compared to the **baseline**)

(**P(Y)[1,1]** - **P(Y)[0,0]**) > (**P(Y)[1,0]** - **P(Y)[0,0]**) + (**P(Y)[0,1]** - **P(Y)[0,0]**)

Interaction

- Interventions A and B…

	B=0	**B=1**
A=0	**P(Y)[0,0]**	**P(Y)[0,1]**
A=1	**P(Y)[1,0]**	**P(Y)[1,1]**

- Want to know if the probability associated with having A=1 *and* B=1 (compared to the **baseline**) is different from the probability of just having A *plus* just having B (compared to the **baseline**)

(**P(Y)[1,1]** - **P(Y)[0,0]**) = (**P(Y)[1,0]** - **P(Y)[0,0]**) + (**P(Y)[0,1]** - **P(Y)[0,0]**)

➔ RD[1,1] – (RD[1,0] + RD[0,1])

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

(P(Y)[1,1] - P(Y)[0,0]) = (P(Y)[1,0] - P(Y)[0,0]) + (P(Y)[0,1] - P(Y)[0,0])

➔ <u>RD[1,1] – (RD[1,0] + RD[0,1])</u>

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	**B=1**
A=0	**0.2**	0.3
A=1	0.4	**0.8 (RD=0.6)**

(0.8 - **0.2**) = 0.6

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	**B=1**
A=0	**0.2**	0.3
A=1	**0.4 (RD=0.2)**	0.8 (RD=0.6)

(0.8 - 0.2) = 0.6

(0.4 - 0.2) = 0.2

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	**B=1**
A=0	**0.2**	**0.3 (RD=0.1)**
A=1	0.4 (RD=0.2)	0.8 (RD=0.6)

(0.8 - 0.2) = 0.6

(0.4 - 0.2) = 0.2

(0.3 - 0.2) = 0.1

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	B=1
A=0	**0.2**	0.3 (RD=0.1)
A=1	0.4 (RD=0.2)	0.8 (RD=0.6)

(0.8 - 0.2) = 0.6

(0.4 - 0.2) = 0.2

(0.3 - 0.2) = 0.1

=0.6 – 0.2 - 0.1 = 0.3

Conclusion: The effect of A & B is greater than the effect of just A plus the effect of just B ➔ There is an interaction

Hypothetical example. Is there an interaction?

- Interventions A and B…

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

(0.8 - 0.2) = 0.6

(0.4 - 0.2) = 0.2

(0.3 - 0.2) = 0.1

0.6 – 0.2 - 0.1 = 0.3

(P(Y)[1,1] - P(Y)[0,0]) - (P(Y)[1,0] - P(Y)[0,0]) + (P(Y)[0,1] - P(Y)[0,0])
Can be shortened to: P[1,1] – P[1,0] – P[0,1] + P[0,0]
0.8-0.3-0.4+0.2 = 0.3

Effect Measure Modification (EMM), <u>**using risk differences**</u>

- Does effect of A vary by B?

	B=0	**B=1**
A=0	P(Y)[0,0]	P(Y)[0,1]
A=1	P(Y)[1,0]	P(Y)[1,1]

- Want to know if the risk difference for A is different within strata of B

Effect Measure Modification (EMM), **using risk differences**

- Does effect of A vary by B?

	B=0	**B=1**
A=0	**P(Y)[0,0]**	P(Y)[0,1]
A=1	**P(Y)[1,0]**	P(Y)[1,1]

- Want to know if the risk difference for A is different within strata of B

(**P(Y)[1,0]** - **P(Y)[0,0]**) >

Effect Measure Modification (EMM), <u>**using risk differences**</u>

- Does effect of A vary by B?

	B=0	B=1
A=0	P(Y)[0,0]	**P(Y)[0,1]**
A=1	P(Y)[1,0]	P(Y)[1,1]

- Want to know if the risk difference for A is different within strata of B

(P(Y)[1,0] - P(Y)[0,0]) > (**P(Y)[1,1]** - **(P(Y)[0,1]**)

Effect Measure Modification (EMM), <u>**using risk differences**</u>

- Does effect of A vary by B?

	B=0	**B=1**
A=0	P(Y)[0,0]	**P(Y)[0,1]**
A=1	P(Y)[1,0]	P(Y)[1,1]

- Want to know if the risk difference for A is different within strata of B

(P(Y)[1,0] - P(Y)[0,0]) = (**P(Y)[1,1]** - **(P(Y)[0,1]**)

➔ RD(1,0) - RD(1,1) *NB different baseline groups!*

Hypothetical example. Is there EMM?

- Does effect of A vary by B?

	B=0	**B=1**
A=0	0.2	0.3
A=1	0.4	0.8

- Want to know if the probability associated with having A=1 (compared to the baseline) is different when B=0 and B=1

(P(Y)[1,0] - P(Y)[0,0]) - (P(Y)[1,1] - (P(Y)[0,1])

➔ RD(1,0) - RD(1,1) *NB different baseline groups!*

Hypothetical example. Is there an EMM?

- Does effect of A vary by B?

	B=0	**B=1**
A=0	**0.2**	0.3
A=1	0.4 (RD=0.2)	0.8

B=0: (0.4-**0.2**) = **0.2**

Conclusion: The effect of A is bigger when B=1 than B=0 ➔ there is EMM

Hypothetical example. Is there an EMM?

- Does effect of A vary by B?

	B=0	**B=1**
A=0	**0.2**	**0.3**
A=1	0.4 (RD=0.2)	0.8 (RD=0.5)

B=0: (0.4-**0.2**) = **0.2**

B=1: (0.8-**0.3**) = **0.5**

Conclusion: The effect of A is bigger when B=1 than B=0 ➔ there is EMM

Hypothetical example. Is there an EMM?

- Does effect of A vary by B?

	B=0	**B=1**
A=0	**0.2**	**0.3**
A=1	0.4 (RD=0.2)	0.8 (RD=0.5)

B=0: (0.4-**0.2**) = **0.2**

B=1: (0.8-**0.3**) = **0.5**

0.5-0.2 = 0.3

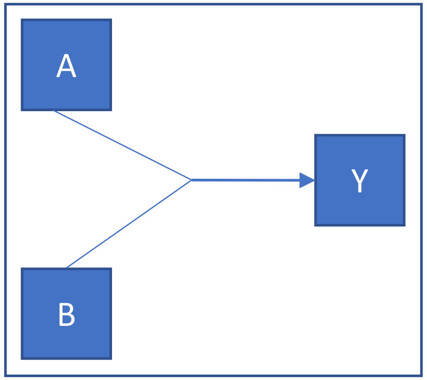
Conclusion: The effect of A is bigger when B=1 than B=0 ➔ there is EMM

Note that….

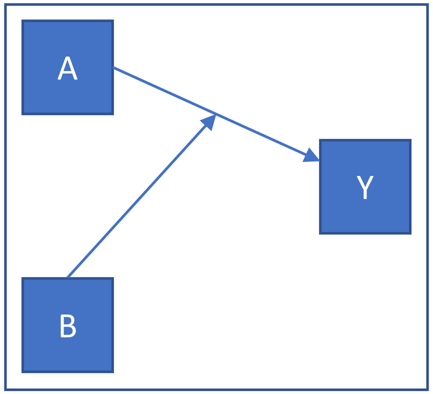
- The results from the Interaction and EMM are the same - They are mathematically equivalent
- But the underlying question and interpretation of the effect is different
- And the confounders you adjust for might be different
  - Interaction: two interventions, two sets of confounders
  - EMM: there might just be one intervention, meaning just one set of confounders….

No consensus, but here's how they might look in a DAG

Interaction



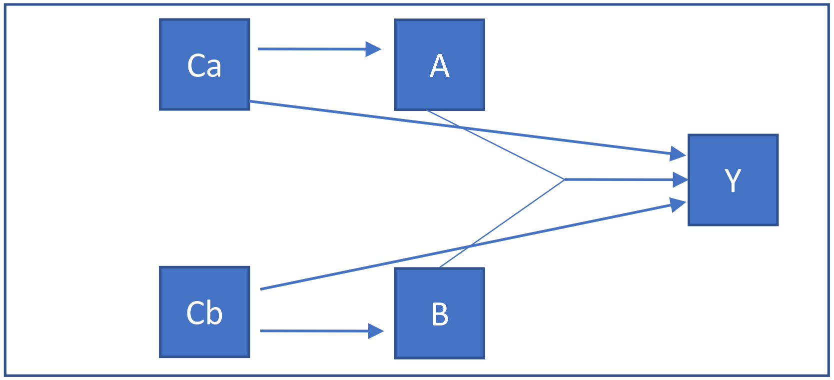
EMM



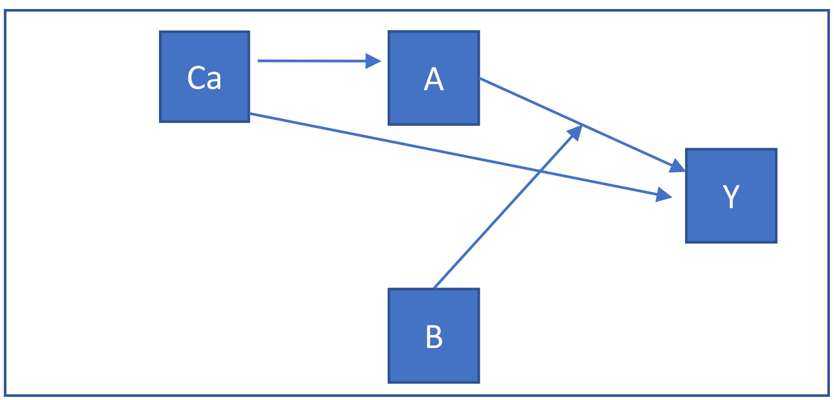
Weinberg, Epidemiology, 2008

With confounding…

Interaction



EMM



What’s of interest? Interaction or EMM?

Scenario	**A**	**B**	***Y***
1	SLC6A4 Gene	Psychosocial support	*Infant attachment*
2	Swine flu vaccine	Gender	*Swine Flu*
3	Smoking	Asbestos	*Lung cancer*
4	Income at birth	Income at 45y	*CVD*

You have two confounders in a model that you think may interact to affect the outcome?

Back to scale!

- So far we’ve been looking at interactions/EMM on the ***Additive Scale***
- i.e. we’ve looked at absolute measures of effect (**RDs**) and focused on **absolute differences in those effects** across levels of the modifier
- ***‘Multiplicative’*** interactions/EMM use relative measures of effect (e.g. **RRs, ORs**) and focus on **relative differences in those effects** across levels of the modifier

Hypothetical example. Interaction on <u>**additive scale**</u>

- Interventions A and B…

	B=0	**B=1**
A=0	**0.2**	0.3
A=1	0.4	0.8

- Want to know if the risk difference when A=1 *and* B=1 is greater than the relative risk of just having A *plus* just having B

(P(Y)[1,1] **-** **P(Y)[0,0]**) = (P(Y)[1,0] **-** **P(Y)[0,0]**) **+** (P(Y)[0,1] **-** **P(Y)[0,0]**)

➔ RD[1,1] **-** (RD[1,0] **+** RD[0,1])

Hypothetical example. Interaction on <u>**multiplicative scale**</u>

- Interventions A and B…

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

- Want to know if the risk difference when A=1 *and* B=1 is greater than the relative risk of just having A *plus* just having B

(P(Y)[1,1] **/** **P(Y)[0,0]**) = (P(Y)[1,0] **/** P(Y)[0,0]) **x** (P(Y)[0,1] **/** P(Y)[0,0])

➔ RR[1,1] **/** (RR[1,0] **x** RR[0,1])

Hypothetical example. Interaction

- Interventions A and B…

	B=0	B=1
A=0	**0.2**	**0.3 (RD=0.1)(RR=1.5)**
A=1	**0.4 (RD=0.2)(RR=2)**	**0.8 (RD=0.6)(RR=4)**

<u>Additive</u>

(0.8 - 0.2) = 0.6

(0.4 - 0.2) = 0.2

(0.3 - 0.2) = 0.1

0.6 – 0.2 - 0.1 = 0.3

<u>Multiplicative</u>

(0.8 / 0.2) = 4

(0.4 / 0.2) = 2

(0.3 / 0.2) = 1.5

4 / (2 x 1.5) = 1.3

Conclusion: ➔ There is an interaction on both scales

Hypothetical example. EMM on **additive scale**?

- Does effect of A vary by B?

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

- Want to know if the probability associated with having A=1 (compared to the baseline) is different when B=0 and B=1

(P(Y)[1,0] - P(Y)[0,0]) - (P(Y)[1,1] - (P(Y)[0,1])

➔ RD(1,0) - RD(1,1) *NB different baseline groups!*

Hypothetical example. EMM on <u>**multiplicative scale**</u>?

- Does effect of A vary by B?

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

- Want to know if the probability associated with having A=1 (compared to the baseline) is different when B=0 and B=1

(P(Y)[1,0] **/** P(Y)[0,0]) **/** (P(Y)[1,1] **x** (P(Y)[0,1])

➔ RR(1,0) **/** RR(1,1) *NB different baseline groups!*

Hypothetical example. EMM

- Does effect of A vary by B?

	B=0	B=1
A=0	0.2	0.3
A=1	0.4 (RD=0.2)(RR=2)	0.8 (RD=0.5)(RR=2.66)

Additive

B=0: (0.4-0.2) = **0.2**

B=1: (0.8-0.3) = **0.5**

0.5-0.2 = 0.3

Multiplicative

B=0: (0.4/0.2) = **2**

B=1: (0.8/0.3) = **2.66**

2.66/2 = 1.33

Conclusion: ➔ there is EMM on additive and multiplicative scales…

Here our conclusions have not changed, but this will not always be the case…

Exercise: Famous example of asbestos, smoking and lung cancer

Death rates from lung cancer (per 100,000). Take from Hammond et al. 1979.

	Asbestos -ve	Asbestos +ve
Non-smoker	11	58
Smoker	123	602

Calculate the following and note down your conclusion for each:

1. Additive interaction for the two exposures asbestos and smoking
RD[1,1] - (RD[1,0] + RD[0,1])
2. Multiplicative interaction for the two exposures asbestos and smoking
RR[1,1] / (RR[1,0] x RR[0,1])
3. Additive effect modification (does smoking modify the effects of asbestos?)
RD(1,1) - RD(1,0) NB different baseline groups!
4. Multiplicative effect modification (does smoking modify the effects of asbestos?)
RR(1,1) / RR(1,0) NB different baseline groups!

Additive vs. Multiplicative

- Some people recommend reporting both
- <u>However</u>, note that:
- If both exposures are associated with the outcome then there will always be an interaction on at least one scale
- If there is no additive and no multiplicative interaction then all shows is that one (or both) of the exposures is not related to the outcome
- Think carefully about which scale is most suitable for your research question
- It is argued that additive interactions are more relevant to public health (identifies the groups/strata with most affected people)

Interactions, terminology, and interpretation

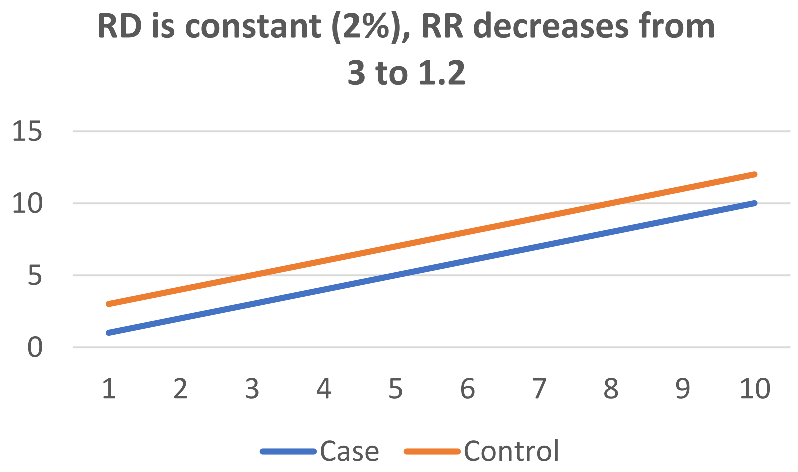
Biological / Mechanistic / Synergistic Interactions

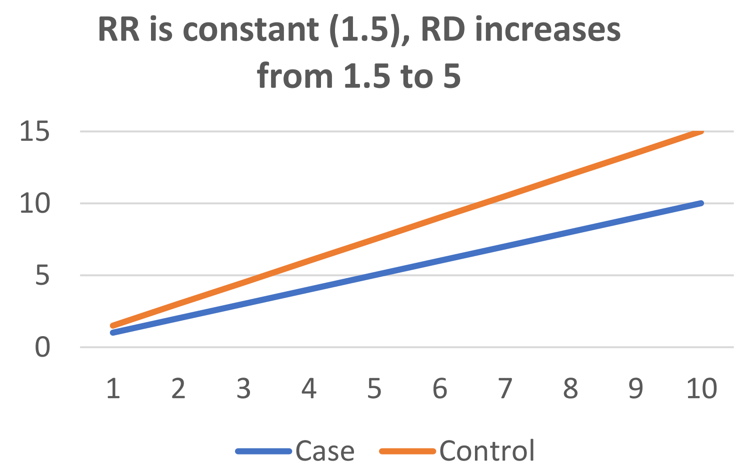
- Interdependent operation / or 'co-participation' of two or more causes to produce (or prevent) an effect
- That is, the outcome only occurs if both exposures are present
- E.g. in order to develop measles you must be exposed to the virus <u>and</u> be susceptible (unvaccinated)
- It has been suggested that a biological interaction can only be demonstrated by an Additive Interaction

Interactions, terminology, and interpretation

Statistical Interactions

- This refers to the interaction term that is produced by a statistical model.
- Logistic regression (or other model that produces relative differences, e.g. Poisson or Cox) reports ***Multiplicative Interactions***
- Linear regression on the other hand produces ***Additive Interactions***
- So the interpretation varies!





Final messages (EMM vs. interaction)

- EMM and interaction are mathematically equivalent (when unadjusted) but can have different interpretations
- EMM: interested if an effect of one variable (intervention) varies across levels of another
- Interaction: interested in the combined effects of two variables (interventions) and whether the sum is greater than the parts
- Present data in a way that both an interaction and EMM can be calculated. Even if you're focus is only on one of these
- NB is considered confounding may change:
  - Interaction: two interventions of interest
  - EMM: just one intervention of interest

Take home messages (Additive vs. Multiplicative)

- Scale matters! Can produce contradictory findings.
- Think about if one approach is more suited to your research question.
- For example do you want to identify a biological interaction? Are you interested in public health impact?

What if you can't calculate RDs to get additive effects?

Relative Excess Risk due to Interaction (RERI)

	B=0	B=1
A=0	**0.2**	0.3
A=1	0.4	0.8

RERI: RR[1,1] – RR[1,0] – RR[0,1] + 1

Remember from earlier how we showed that:

(P(Y)[1,1] - P(Y)[0,0]) - (P(Y)[1,0] - P(Y)[0,0]) + (P(Y)[0,1] - P(Y)[0,0])

Can be shortened to: P[1,1] – P[1,0] – P[0,1] + P[0,0]

An interaction is present if RERI > 0 (or < 0)

What if you can't calculate RDs to get additive effects?

	B=0	B=1
A=0	**0.2**	0.3 (RR=1.5)
A=1	0.4 (RR=2)	0.8 (RR=4)

RERI: RR[1,1] – RR[1,0] – RR[0,1] + 1

Conclusion: There is a relative excess risk due to interaction

What if you can't calculate RDs to get additive effects?

Relative Excess Risk due to Interaction (RERI)

	B=0	B=1
A=0	**0.2**	0.3 (RR=1.5)
A=1	0.4 (RR=2)	0.8 (RR=4)

RERI: RR[1,1] – RR[1,0] – RR[0,1] + 1

= 4 – 2 – 1.5 +1 = 1.5

RERI > 0. Conclusion: There is a relative excess risk due to interaction

Take home messages (Additive vs. Multiplicative)

- Regardless of what scale you decide to use:
- Always refer to them as being interactions/effect measure modification on the ***Additive/Multiplicative scale***
- (or better still, on the ***RR/OR/etc scale***)
- Report sufficient data so that others can estimate multiplicative and /or additive effects
- And so that they can calculate interactions & EMM

Other points to consider

Why is it important to look at interactions / EMM?

If not properly accounted for can:

- produce misleading results (e.g. no association between childcare and injuries until stratified by socio-economic position)
- overlook important between-group differences (e.g. greater dosage required for women for protection against flu vaccine)

Importance of having an *a priori* hypothesis

- E.g. Plausibility; Identified in previous research

Assumptions

- The usual: no selection, measurement, confounding bias
- In the case of EMM: the modifier is not affected by the exposure (i.e. it is not a mediator – in which case the analysis gets a bit more complicated)
- DAGs help!