Epidemiology in EMF- Research Strength and Limitations

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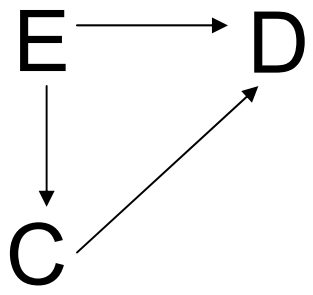
Dr. Jørn Olsen

Department on Epidemiology, UCLA

Professor and Chair

- Are EMF's causing diseases/ill health in human population?
- Addressing this question is epidemiology no matter how you do it-bad or good.
- Epidemiologic studies are experimental or non-experimental.

- Randomize exposure (E) eliminates confounders (back door paths) in the long run



- Standard requirement in drug trials due to ‘confounding by indication’.
- No indication for non-medical EMF exposure – opens up for observational epidemiology.

- The population experience of interest what is the shape of the incidence rate as a function of EMF exposure?

L	t_e	D_e	1.0 ref
M	t_m	D_m	$(D_m/t_m) / (De/te)$
H	t_h	D_h	$(D_h/t_h) / (De/te)$

- Counterfactual reasoning: What is the risk among exposed had they not been exposed?
- We only have design manipulations and statistical adjustments to offer.
- We are interested in causes but we study associations.

- The most economic way to harvest the population experience is by selecting those with the disease of interest (cases) and a sample from the population that gave rise to the cases- the case-control study.

Requires

- Case identification and accurate recording of exposures from the past (and accurate recording of confounders).

- If exposure assessment is based on recall we must have symmetry in recall. Must be recalled with the same sensitivity and specificity.

Exp	Cases	Controls	OR
+	a	b	$\frac{a/c}{b/d}$
-	c	d	

- These exposure odds must reflect E→D causes and not misclassification. Is this really possible for cell phone use and brain cancer?

Exposure?

Rapidly changing:
1996 and 2000 mobile phone use in the general Swedish population increased from 28% to71%.
Short latency, particularly for high use

measurement error in self-reported mobile phone use is substantial, even for short-term recall

Cases?

Long delay between diagnosis and case recruitment tend to lead to loss of high-grade tumours
Brain tumors might limit cognitive ability
Use of proxies problematic
Recall bias
Acoustic neuroma: disease might reduce phone use
being diagnosed more often among cell phone users as they experience loss of hearing
(detection bias)

Controls?

Low participation
Selection bias
Hospital controls:
included cases constitute a selected group that have survived long enough to be recruited to the study; if survival time is in any way related to the exposure (directly or indirectly), this might introduce bias
Representativness of mobile phone use among hospital controls

… *Hearing loss may be a negative confounder – presence of hearing problems prior to diagnosis may prevent cases from becoming regular users and limit their lifetime calling time*

… Reduced risk for high-grade glioma may reflect selection and/or recall bias – 18% of the glioma cases not interviewed and patients with high-grade glioma had low scores on mental state test

Exposure assessment

- Records of mobile phone use
- Questionnaire
- Combination of both?

Exposure assessment

- Exposed = private mobile phone subscribers - *no differential recall bias*?
  - no information about corporate subscriptions
  - no information about who is the actual user of the phone
  - no information on hands free device

  misclassification of exposure

- Exposed = based on questionaire

  recall bias

Exposure assessment

- Crude exposure assessment (even Interphone)
  - No. of years
  - Different latency periods
  - Average duration/day or month
  - Cumulative time

Difficult to estimate exposure intensity

(power level, phone model, hands free, urban/rural)

Recall (Parslow, et al. 2003)

- 93 volunteers recruited through advertisements over a study period of six months.
- subjects had to recall their phone use during the last six months
- Mobile phone use reported in postal questionnaires was compared with operator records.
- Only out-going calls were analysed as not all operators were able to provide data on in-coming calls
- For number of calls, a reasonable agreement was found (κ=0.39, r=0.48). Slightly better agreement was reported for total duration of calls (κ=0.50, r=0.60)
- However, there was substantial over-reporting of both numbers of calls (by a factor of 1.7) and duration of calls (by a factor of 2.8)

Recall (Samkange-Zeeb, et al. 2004)

- 68 subjects (volunteers and subscribers randomly selected from phone book).
- Interview data were compared with operator records, obtained at the end of the three-month study period (recall period).
- A moderate correlation was found between the two sources of information. The mean number of calls per day was reported as 1.0 vs. 1.3 in the operator records and mean duration of call 2 min vs. 1.4 min ($r=0.62$ for number of calls and 0.34 for duration). The cumulative calling time during the monitoring period was 3.2 hours vs. 3.1 hours ($\kappa=0.34$, $r=0.56$).

Recall (Berg, et al. 2005)

- 45 volunteers
- interview data (on a three-month period) vs. software-modified phones (used for one month)
- For number of calls, the ratio of reported to recorded was 0.71 with a moderate correlation (r=0.48). For total duration of calls, the ratio of reported to recorded was 1.14 with a correlation (r=0.48)

Recall bias

- Cases try harder to remember their mobile phone use, perhaps overestimate it
  - Lead to overestimated risk
- Cases have impaired memory, may forget their use
  - Lead to underestimated risk
- Some evidence of recall bias:
  - No overall increased risk, but increased risk for ipsilateral and reduced risk for contralateral tumors

Recall bias

- What can we do?
  1. Obtain information about phone use from operators
     - Some evidence that information about outgoing calls is sufficient
     - Combine information from operators and questionnaires
  2. Use strictly standardized interviews and well trained interviewers
     - Impossible to hide case/control status from interviewer unless only ”healthy” cases are included

Avoiding recall bias

- Use a cohort design
  - Obtain information about number and duration of calls from operators
  - Information about other important parameters from questionnaires
    - Who is the phone user
    - Hands-free device and laterality
    - Use in urban or rural area

Selection (participation) bias

- Controls who are mobile phone users are more likely to participate
  - Lead to underestimated risk
- Some evidence of selection bias:
  - Substantially reduced risk in some studies
  - Validation studies

Assessing selection bias (Lahkola, et al. 2005)

- 103 cases and 321 controls, who refused to participate in the full interview, but gave a short telephone interview.
- Among both cases and controls, refusers had used mobile phones less than participants.
- The proportion of regular users was 10% lower among non-participants than participants in both groups (83% vs. 73% among controls and 76% vs. 64% among cases).
- Use of mobile phone was also assessed from a database among subjects who declined even the short interview. Complete refusers had used mobile phones even less than those who gave a short interview.

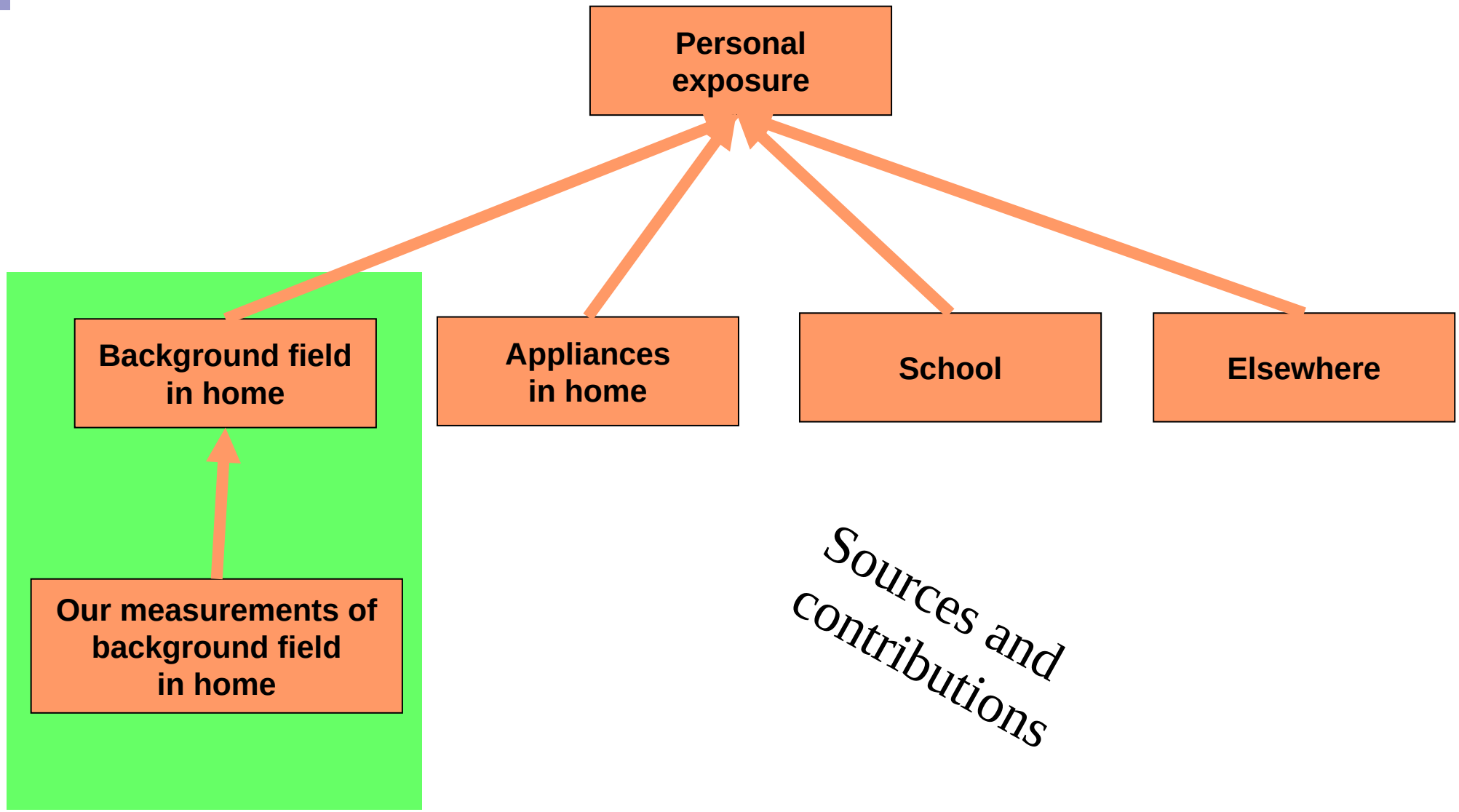
Assessing selection bias (Lönn, et al. 2004)

- 16% of the non-participating controls answered a few questions about their mobile phone use over the phone
- The proportion of regular mobile phone users (at least once per week) among the non-participants was 33% compared to 59% among participating controls
- However, that the questions were answered by only a small proportion of the non-participants, and they were not a random sample from this group; these were persons who could be reached by telephone.
- It is possible that the proportion of mobile phone users is higher among the non-participating controls that could not be reached over the phone, as this might be persons who are seldom at home, and therefore perhaps more likely to have a mobile phone.

EMF and childhood cancers

EMF and childhood leukemia

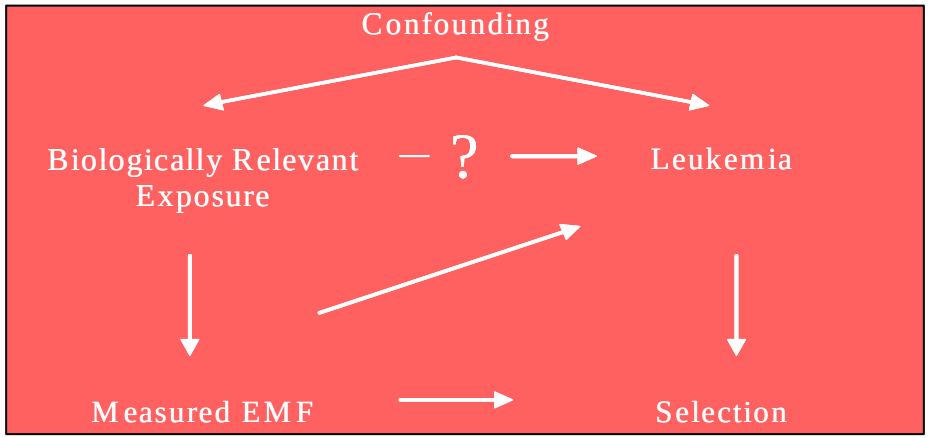
Study	>.3μT		>.4μT	
	RR	95% CI	RR	95% CI
Wertheimer & Leeper*	3.1	1.1-8.5		
Fulton	0.5	0.2-1.4		
Tomenius	1.5	0.4-5.7		
Coghill		1/0		
Savitz	3.5	0.8-15.4		
Coleman	1.5	0.7-3.5		
Myers*	0.8	0.1-9.6		
London	1.6	0.7-3.5		
Feychting	4.5	1.7-12.0	3.7	1.2-11.4
Olsen	2.0	0.4-10.0		2/0
Verkasalo	2.0	0.2-18.0	6.2	0.7-56.9
Tynes		0/0		0/0
Michaelis	2.4	0.8-7.6	2.0	0.3-15.2
Linet	1.5	0.9-2.4	3.4	1.2-9.6
Dockerty		3/0		0/0
McBride	1.4	0.6-3.2	1.6	0.7-3.7
Green*	4.5	1.3-15.9		
UKCCS	1.7	0.4-7.0	1.0	0.3-3.4
Kabuto*	1.7	0.7-3.8		


Personal exposure
Background field in home
Appliances in home
School
Elsewhere
Our measurements of background field in home
Sources and contributions

Causality: Consistent association between childhood leukemia and exposure > 0.3-0.4 μT

Possible explanations:

- Chance????
- Misclassification???
- Confounding??
- Selection bias?
- Other?
- Causal relationship?



Causality and Magnitude of Risk: Multiple-Bias Modeling

- Confounding seems least important concern
- Selection bias present, but unlikely to explain the association by itself
- Misclassification leads to underestimate under most assumptions and vastly increases uncertainty
- Probability that the combination of misclassification, selection bias, confounding and random error explain the association 2-4%

Greenland 2005

Causality other problems:

- Biophysical mechanisms: plausibility becomes shaky below 50 μT
- *In vitro* models: lack of robust and reproducible effect
- Lack of support from animal data

- If present uncertainty is unacceptable invest in:

1. Cohort studies
2. Ecological studies