Epidemiological evidence and causation: The first thing to do is to find out what you want to know

(Medical student, 1^{st} year exam answer.)

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Association versus causation: epidemiology versus the law?
11 July 2019

Example A: letter dated 19 June 2019

POSSIBLE CLAIMS –V- NORTH LANARKSHIRE COUNCIL

We act on behalf of our above named clients who are employed as teachers by the above il. They both teach at Buchanan High School in Coatbridge. In December 2015 Mrs was diagnosed with bladder cancer and in August 2017 Mr with colon cancer. Four other teachers working within the same have been diagnosed with bladder cancer in the past 2/3 years.

Our clients are concerned that they have developed what they regard as occupational cancer as a result of working within the school. The school was built in around 2012 on a former landfill site used by Gartsherry Ironworks in Coatbridge for the dumping of industrial waste. This included chemicals and hazardous substances such as arsenic nickel and lead.

Staff and pupils have been complaining for a number of years that the mains water supply has been affected because the water consistently is blue in colour. This is believed to have been caused by high levels of copper in corroded pipework.

We are instructed by our clients to investigate the possibility of claims being made against the Council as their employers in view of them both having been diagnosed with cancer. We would appreciate if you would advise whether this is a matter within your area of expertise and if so what your likely fee would be for an epidemiologist to provide a report

Observational epidemiological studies

- Case report
- Case series
- Routine data: ONS, NHSIC
- Survey: cross-sectional (usually)
- Case-control study: disease first, then exposure
- Cohort study: exposure first, then disease
  - Retrospective: exposure first from medical or occupational records
  - Prospective: exposure after selection into cohort, from medical or occupational records

Experimental epidemiological studies

Clinical studies

Phase 1 'first in man', usually given to small group (8-12) healthy volunteers, to assess safety

Phase 2 larger group, usually patients, to assess effectiveness in treating, appropriate dosing levels

Phase 3 typical patients, to demonstrate the safety and effectiveness, confirm dosage, identify side effects

Phase 4 Monitoring medicines, or running trials, after licencing . . . to assess the long term risks and benefits

Laboratory studies

- In vivo: animal experiments
- In vitro: macro-cellular
- In vitro: micro-cellular

Documents reporting animal studies and Phases 1-3 are required to get a licence to advertise.

Bias and confounding

Bias: An estimator is biased if it does not give the correct result on average.

- Selection bias
- Recall bias
- Prevalence-incidence bias
- Missing clinical data bias
- Exposure bias: diagnosis, and exposure
- Unmasking (detection signal) bias - confounding

Confounding: If a risk factor (alcohol) is associated with both the risk factor (smoking) and the disease (heart attack), an estimate of the effect of smoking on heart attach rates ignoring alcohol will probably be misleading.

Bradford Hill, US Surgeon General: aspects of association

The guidelines are

- Strength
- Consistency
- Specificity
- Temporality
- Dose-response curve, or iological gradient
- Coherence
- Plausibility *" What is biologically plausible depends upon the biological knowledge of the day."*
- Experiment
- Analogy *"In some circumstances it would be fair to judge by analogy."*

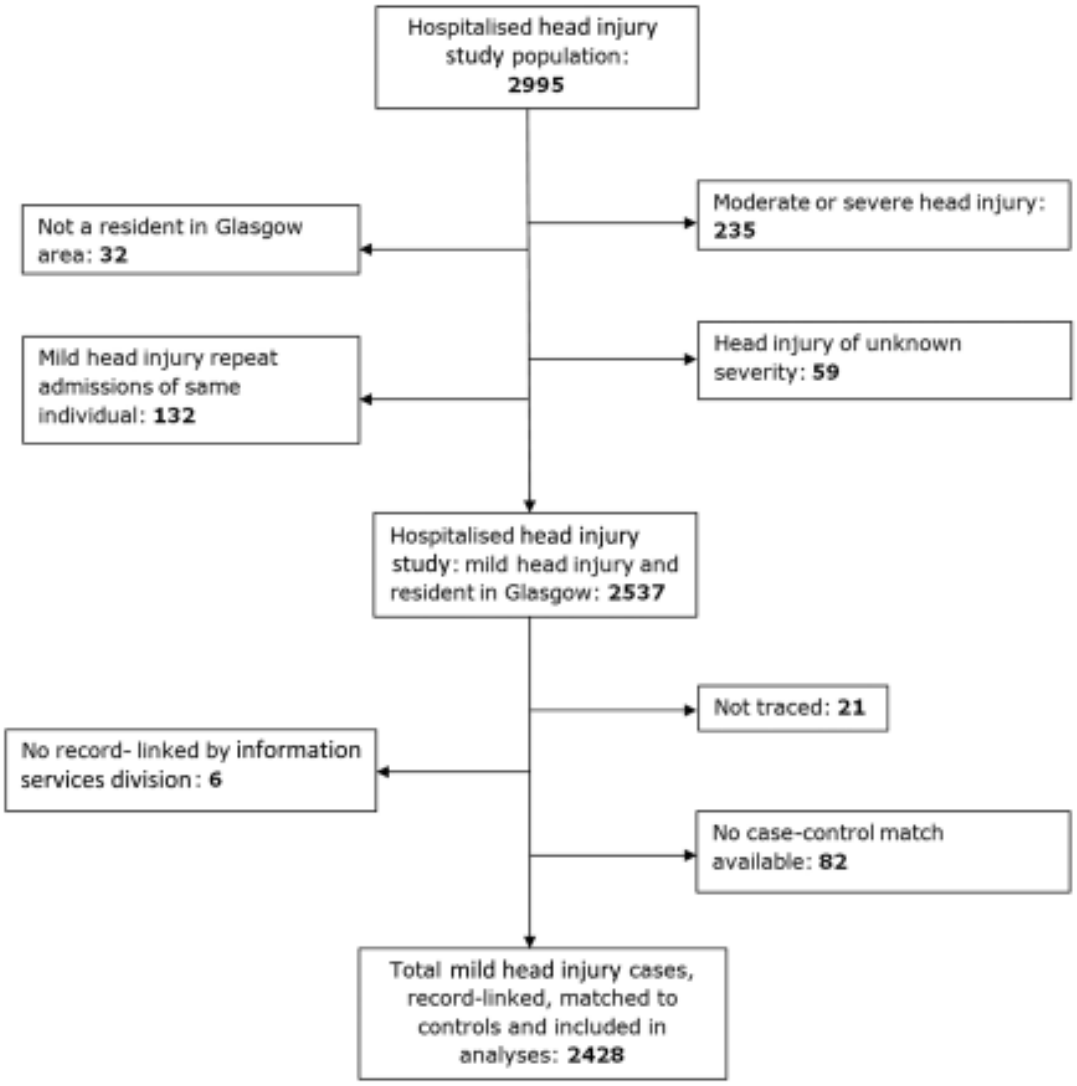
Is the article of reasonable quality? Questions to ask

There are guidelines on information which should be included in research articles which report on data from a range of study designs. The guidelines also facilitate assessment and interpretation.
http://www.equator-network.org/reporting-guidelines/
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
CONSORT, PRISMA
Checklist of 22 items:

- 18 items common to cohort studies, case-control studies and cross-sectional studies
- 4 items specific to each of the designs

The over-riding consideration is clarity and precision.

Study quality: who is in?



McMillan TM, *et al. J Neurol Neurosurg Psychiatry* 2014;**0**:1–7. doi:10.1136/jnnp-2013-307279

Contrast Shavelle 2015:
50 661 patients
reduced to 31 531
Of 49 241 people,
excluded (36%) 17 683;
only 3/5 reasons
explained,
no numbers by reason.
Total number of people
'represented' in Table 1:
66 940

Study quality: what is missing?

Missing data - an example (Shavelle 2001)

Attempted suicide in the past 5 yr[d]				
Yes	1	2	4	3
No	70	73	71	72
Unknown	29	25	25	25
Recent history of drug or alcohol abuse[d]				
Yes	2	5	8	6
No	70	71	68	69
Unknown	28	24	24	25
Assaultive behavior[d,e]				
Yes	4	10	16	12
No	76	71	65	69
Unknown	20	19	19	19
Medication for maladaptive behavior[d,f]				
Yes	10	17	17	16
Not within past 6 months	14	17	18	17
Never/unknown	77	66	65	67

Greater percent unknown than in smaller category.

What are the implications?

Study quality: which relative risk?

Table IV. Independent predictors of revision following entire series of 35 386 Corail/Pinnacle cementless total hip replacements: simple and multi-variable Cox regressions (body mass index excluded, England and Wales, 2003-2010) (HR, hazard ratio; CI, confidence interval)

	Simple analysis		Multi-variable analysis	
Variable*	**HR (99% CI)**	**p-value**	**HR (99% CI)**	**p-value**
Bearing category		< 0.001		< 0.001
Bearing group				
Metal-on-PE	Reference	-	Reference	-
Ceramic-on-PE	1.32 (0.82 to 2.11)	0.135	1.33 (0.83 to 2.12)	0.123
Ceramic-on-ceramic	1.54 (1.06 to 2.25)	0.003	1.55 (1.07 to 2.26)	0.003
Ceramic-on-metal	1.47 (0.64 to 3.37)	0.237	1.45 (0.63 to 3.33)	0.253
Metal-on-metal	1.92 (1.36 to 2.72)	< 0.001	1.93 (1.36 to 2.73)	< 0.001

Study quality: which relative risk?

Table V. Independent predictors of revision following entire series of 35 386 Corail/Pinnacle cementless total hip replacements based on 17 166 patients with valid body mass data using simple and multi-variable Cox regressions (England and Wales, 2003-2010) (HR, hazard ratio; CI, confidence interval)

	Simple analysis		Multi-variable analysis	
Variable*	**HR (99% CI)**	**p-value**	**HR (99% CI)**	**p-value**
Bearing category		< 0.001		0.001
Bearing group				
Metal-on-PE	Reference	-	Reference	-
Ceramic-on-PE	1.32 (0.82 to 2.11)	0.135	1.36 (0.69 to 2.68)	0.242
Ceramic-on-ceramic	1.54 (1.06 to 2.25)	0.003	2.09 (1.21 to 3.63)	0.001
Ceramic-on-metal	1.47 (0.64 to 3.37)	0.237	1.31 (0.45 to 3.83)	0.514
Metal-on-metal	1.92 (1.36 to 2.72)	< 0.001	2.19 (1.29 to 3.72)	< 0.001

Which is relevant: 35 386 hips or 17 166 patients?

Vioxx- Scotland

"The weight of scientific evidence supported, and continues to support, that in VIGOR, naproxen provided a cardioprotective effect."

- No direct numerical assessment of cardioprotective effect of naproxen: only verbal: "no thrombotic cardiovascular risk associated with Vioxx" was observed in osteoarthritis trials; "similar rates of thrombotic cardiovascular events [were found] among those taking Vioxx, placebo and comparator NSAIDS"
- "Subsequent studies provided further evidence of a cardio-protective effect of naproxen. A 2^{nd} clinical pharmacology study found that naproxen at 500mg twice daily demonstrated a sustained anti-platelet effect indistinguishable from that of aspirin": study on 9 healthy volunteers for 6 days - power!
- "A large clinical trial . . . provided further evidence of a cardioprotective effect of naproxen": rates of myocardial infarction (clinical and silent) on naproxen $>$ on the comparison drug, lumiracoxib.

Blockbuster painkiller Vioxx

Stroke rates for RCTs of 25 mg vioxx versus placebo

Study	Dose	Strokes		Strokes + TIA		Person
		No.	Mean	No.	Mean	Years
APPROVe 2005	0	6	1.8	7	2.1	3327
APPROVe 2005	25	12	3.9	15	4.9	3059
Kerr 2007	0	2	2.1	2	2.1	946
Kerr 2007	25	3	3.4	5	5.6	889
VIP 2007	0	3	2.7	3	2.7	1102
VIP 2007	25	2	1.8	2	1.8	1099
APPROVe 2008	0	9	1.6	9	1.6	5711
APPROVe 2008	25	19	3.4	19	3.4	5658

Rates per 1000 person-years; TIA - transient ischemic attack

Blockbuster painkiller Vioxx

Summary for cancer RCTs of 25 mg vioxx versus placebo

Study	Stroke rate			Stroke+TIA rate		
	Mean	V - P	RR	Mean	V - P	RR
APPROVe 2005	2.9	2.1	2.2	3.5	2.8	2.3
Kerr 2007	2.7	1.3	1.6	3.9	3.5	2.7
VIP 2007	2.3	-0.9	0.7	2.3	-0.9	0.7
APPROVe 2008	2.5	1.8	2.1	2.5	1.8	2.1

Rates per 1000 person-years

Stroke rates seem likely to be higher on vioxx than placebo.
However, there is variation between randomised controlled trials.

Which is the right relative risk?

Conclusions

Questions

- What are the questions?
- What are the precise questions?
- Which are the relevant questions?
- What data is available?
- What publications are available?
- What quality are data and publications?
- What are the alternative explanations?
- How should alternatives be compared?

Claims

- Approximate answer to right question is better than the right answer to the wrong question.
- Decide whether false certainty or true uncertainty is required.

I prefer to work cooperatively with experts of other disciplines.