RESEARCH DESIGNS
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Basic Concepts of Epidemiology (2)
AIMS OF THIS SECTION ARE TO...

1. Understand the basic concepts of epidemiology

2. Know the essential epidemiological study designs and their strengths and weaknesses

3. Apply this knowledge so that is able to give a short presentation on one scientific epidemiological article
BASIC CONCEPTS OF EPIDEMIOLOGY I
18.3. 2014 (Tellervo Korhonen)

BASIC CONCEPTS OF EPIDEMIOLOGY II
21.3. 2014 (Korhonen)
• RESEARCH DESIGNS
• BRIEFING FOR THE SEMINAR

EPIDEMIOLOGY OF CVD
1.4. 2014 (Veikko Salomaa)

GENETIC EPIDEMIOLOGY
2.4. 2014 (Karri Silventoinen)

SEMINAR:
Student presentations on epidemiological papers
4.4. 2014 (Korhonen)
Before going to the topic of today...

...let’s go back a couple of steps...
P-VALUE

- P-value is related to testing the "Zero-hypothesis" (H0) (e.g. Mean of sample 1 = Mean of sample 2)
- p<0.001 (*** → The association is statistically very significant
- p<0.01 (** → The association is statistically moderately significant
- p<0.05 (*) → The association is statistically significant
- The smaller is the P-value the smaller is the probability that the Ho is true!
  → we can accept the "alternative hypothesis" (H1) (e.g. Mean of sample 1 ≠ Mean of sample 2)

NOTE: P-VALUE REFLECTS ONLY STATISTICAL SIGNIFICANCE OF THE ASSOCIATION - NOT CLINICAL SIGNIFICANCE !!
CONFIDENCE INTERVAL

- The 95% Confidence Interval (CI) is an interval where the unknown 'real' parameter is located with 95% certainty.

- If we could repeat the same study \( \infty \) times, there would be a 5% risk that the result would be outside of that interval.

- E.g. OR=1.9 (point estimate)
  
  95%CI = 1.4 (lower limit) – 2.5 (upper limit)

- Calculation:
  
  - Lower = point estimate - 1.96 * SE (standard error)
  - Upper = point estimate + 1.96 * SE (standard error)
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th><strong>INTERVENTION GROUP</strong></th>
<th></th>
<th><strong>CONTROL GROUP</strong></th>
<th></th>
<th><strong>P VALUE†</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=256)</td>
<td>mean ±SD 95% CI</td>
<td>(N=250)</td>
<td>mean ±SD 95% CI</td>
<td></td>
</tr>
<tr>
<td>Change in weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In kilograms</td>
<td>−4.2±5.1</td>
<td>−4.8 to −3.6</td>
<td>−0.8±3.7</td>
<td>−1.3 to −0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent change</td>
<td>−4.7±5.4</td>
<td>−5.0 to −4.4</td>
<td>−0.9±4.2</td>
<td>−1.0 to −0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in waist circumference (cm)</td>
<td>−4.4±5.2</td>
<td>−5.1 to −3.9</td>
<td>−1.3±4.8</td>
<td>−1.9 to −0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in plasma glucose (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>−4±12</td>
<td>−6 to −2</td>
<td>1±12</td>
<td>0 to 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 Hr after oral glucose challenge</td>
<td>−15±34</td>
<td>−19 to −11</td>
<td>−5±40</td>
<td>−8 to −2</td>
<td>0.003</td>
</tr>
<tr>
<td>Change in serum insulin (µg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>−2±9</td>
<td>−3 to −1</td>
<td>−1±7</td>
<td>−2 to 0</td>
<td>0.14</td>
</tr>
<tr>
<td>2 Hr after oral glucose challenge</td>
<td>−29±64</td>
<td>−37 to −21</td>
<td>−11±51</td>
<td>−18 to −4</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in serum lipids (mg/dl)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−5±28</td>
<td>−8 to −2</td>
<td>−4±28</td>
<td>−7 to −1</td>
<td>0.62</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>2±7</td>
<td>1 to 3</td>
<td>1±6</td>
<td>0 to 2</td>
<td>0.06</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−18±51</td>
<td>−24 to −12</td>
<td>−1±60</td>
<td>−8 to 6</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in blood pressure (mm Hg)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−5±14</td>
<td>−7 to −3</td>
<td>−1±15</td>
<td>−3 to 1</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic</td>
<td>−5±9</td>
<td>−6 to −4</td>
<td>−3±9</td>
<td>−4 to −2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* casualised to meet baseline requirements.
Confounding factor ('Confounder') is another risk factor of the disease under investigation. In addition, it is associated also with the risk factor under investigation.
Why is confounding a problem?

- Confounding factors may be harmful, because many risk factors tend to cluster within the same individuals or population subgroups.

- We know, that smoking, heavy alcohol use, and sedentary lifestyle are highly correlated.

- Thus, all these factors can confound the effects of each other when investigating, for example, risk factors of cardiovascular disease incidence.
How can we test confounding?

Compare the risk estimates (e.g. OR) in different models

1) Basic model (sex, age adjusted)
2) Adjusted for most well known confounders
3) Adjusted for all potential confounders

→ If the estimate of the risk factor remains in all models, the association of that factor is independent of the other factors, i.e. robust association

→ If the estimate of the risk factor becomes non-significant, the association is confounded by those factors which were added to the model
SMOKING & DEPRESSION:
Multiple logistic regression models of 1975-1981 smoking status as a predictor of depression in 1990 among Finnish men

<table>
<thead>
<tr>
<th>Smoking 1975-1981</th>
<th>Model 1 (n=4975)</th>
<th>Model 2 (n=4939)</th>
<th>Model 3 (n=4164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Long term former smokers</td>
<td>1.0</td>
<td>0.8 - 1.4</td>
<td>0.7 - 1.3</td>
</tr>
<tr>
<td>Short term former smokers</td>
<td>1.9</td>
<td>1.4 - 2.5</td>
<td>1.2 - 2.3</td>
</tr>
<tr>
<td>Occasional smokers</td>
<td>1.5</td>
<td>1.1 - 2.0</td>
<td>1.0 - 1.9</td>
</tr>
<tr>
<td>Recurrent smokers</td>
<td>1.9</td>
<td>1.2 - 2.9</td>
<td>1.0 - 2.4</td>
</tr>
<tr>
<td>Persistent smokers</td>
<td>1.9</td>
<td>1.5 - 2.3</td>
<td>1.2 - 1.9</td>
</tr>
</tbody>
</table>

Model 1 = Adjusted for age, marital status, social class  
Model 2 = + alcohol use, physical activity  
Model 3 = + somatic health, social network, emotional support, life events, neuroticism and life satisfaction  
(Korhonen et al. 2007)
# Types of Research Designs

<table>
<thead>
<tr>
<th></th>
<th>Cross-Sectional</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Experimental</strong></td>
<td>Correlational Study</td>
<td><strong>Prospective:</strong> Cohort Study <strong>Retrospective:</strong> Case-Control Study</td>
</tr>
<tr>
<td><strong>Experimental</strong></td>
<td>N/A</td>
<td>Randomized Controlled Trial</td>
</tr>
</tbody>
</table>
NON-EXPERIMENTAL (OBSERVATIONAL) CROSS-SECTIONAL DESIGN

- ‘Observational’ design, because the researcher cannot ‘manipulate’ any of the research conditions
- ‘Cross-sectional’ design, because all data are collected at the same time point.
- ‘Correlational’ study because only associations / correlations between variables can be measured
- No assumptions about directions of those associations can be done
- However, good for assessing prevalences of various behaviors, risk factors, symptoms, diseases etc...
- Not very expensive data collection
- For example, population-based surveys via questionnaires, interviews (nowadays via online surveys)
AIM OF THE STUDY

➢ To examine the association of smoking status with weight concerns among adult Finnish ever smokers

EXAMPLE:
Cross-sectional population-based survey

METHODS

- Cross-sectional data collected in conjunction with the National FINRISK2007 Study
  - Random population sample
- Ever smokers (smoked >100 cigarettes) (n=1922)
  - Asked to reply to detailed smoking related questionnaire
  - Response rate 90% (n=1746)
- SMOKING STATUS: (Categorical)
  - Daily smokers
  - Occasional smokers (smoked last time 2-30 days ago)
  - Recent quitters (quit 1 month→<6 months ago)
  - Former smokers (quit 6 or more months ago)
- WEIGHT CONCERNS (Continuous)
  - Sum score (range 0-24) constructed from 6 items (each scored 0-4)
    (Cronbach alpha=0.84)

RESULTS

- **Women** (mean=8.3, SD=6.4) had higher weight concern scores than **men** (mean=6.9, SD=5.4) (p<.001)
- Regression model adjusted for sex, age, BMI, health related behaviors, FTND
- **Daily smokers as reference group:**
  - **Occasional smokers** (β=-2.5, 95%CI -3.4,-1.6, p<.001)
  - **Recent quitters** (β=-3.4, 95%CI -4.7,-2.1, p<.001)
  - **Former smokers** (β=-1.4, 95%CI -2.0,-0.7, p<.001)
  had significantly lower weight concerns

CONCLUSIONS

- Weight concerns may contribute to persistence of daily smoking?
- Longitudinal population-based studies should examine if weight concerns hinder smoking cessation.

“Case-control” or “case referent -study design” is a 'disease- oriented’ research design

Two samples are selected:
1. Those who have the disease under investigation (CASES)
2. Those who do not have that disease (CONTROLS) and often are also 'matched' according to some important background variables (MATCHED CONTROLS)

Afterwards, data on exposure (e.g. to assumed risk factors) are collected retrospectively

Case-Control design is very useful for investigation of rare diseases – WHY?
LONGITUDINAL - PROSPECTIVE DESIGN
Cohort Study

- Exposure data are collected at the baseline phase !!!!

- Follow-up, when the data about incidence of disease are registered

- Temporal order:

  RISK FACTOR \rightarrow OUTCOME
Example on Cohort Study

FinnTwin12

- Data have been collected as Finnish-American collaboration since 1994
- Population based age cohort (born in 1983-1987) from the Finnish Population Register (n=5600)
- Baseline survey at age 11-12
  - 5184 twins participated / 92%
- First follow-up at age 14 (4643 / 82%)
- Second follow-up at age 17 (4168 / 74%) (2000-2005)
- Data were collected by questionnaires and interviews from twins, their parents and teachers
Externalizing Problem Behavior: Risk Factor for Cigarette Smoking & Use of Illicit Drugs?

MEDIATION MODEL

AGE 12
EXTERNALIZING BEHAVIOR EVALUATED BY TEACHER
Here: Hyperactivity-Impulsivity

♂ OR=1.7 ***
♀ OR=2.3 ***

AGE 14
EVER USE OF TOBACCO

AGE 17
EVER USE OF ILLICIT DRUGS

♂ OR=5.9 ***
♀ OR=6.1***

♂ OR=1.2 (ns)
♀ OR=1.2 (ns)

Randomized Controlled Trial (RCT) is a specific type of scientific experiment.

RCT is often used to test the efficacy and/or effectiveness of various types of interventions/treatments within a patient / clinical population.

RCT may also provide an opportunity to gather useful information about adverse effects, such as drug reactions.
EXPERIMENTAL - LONGITUDINAL RANDOMIZED CONTROLLED TRIAL (RCT)

Flowchart of four phases (enrollment, intervention allocation, follow-up, and data analysis) of a parallel randomized trial of two groups, modified from the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement
RCT - ADVANTAGES

- RCTs are considered to be the most reliable form of **scientific evidence** in the **hierarchy of evidence** that influences healthcare policy and practice.

- RCTs reduce spurious causality and bias

- Results of RCTs may be combined in **systematic reviews** which are increasingly being used in the conduct of **evidence-based medicine** (EBM)
APPLICATION OF RCT - NEW DRUG DEVELOPMENT
PHASES OF NEW DRUG DEVELOPMENT
EXAMPLE: CANCER
Phase I

These are the earliest trials in the life of a new drug or treatment.
They are usually small trials, recruiting anything up to about 30 patients, although often a lot less.
The trial may be open to people with any type of cancer.
When laboratory testing shows that a new treatment might help treat cancer, phase I trials are done to find out
  - The safe dose range
  - What the side effects are
  - How the body copes with the drug
  - If the treatment shrinks the cancer
PHASES OF NEW DRUG DEVELOPMENT
EXAMPLE: CANCER
Phase II

- Not all treatments tested in a phase I trial make it to a phase II trial.
- These trials may be for people who all have the same type of cancer, or who have several different types of cancer.
- Phase II trials aim to find out
  - If the new treatment works well enough to test in a larger phase III trial
  - Which types of cancer the treatment works for
  - More about side effects and how to manage them
  - More about the best dose to use
PHASES OF NEW DRUG DEVELOPMENT
EXAMPLE: CANCER
Phase III

- These trials compare new treatments with the best currently available treatment (the standard treatment).
- These trials may compare
  - A completely new treatment with the standard treatment
  - Different doses or ways of giving a standard treatment
- Phase III trials usually involve many more patients than phase I or II.
- Randomisation!!!
- This is because differences in success rates may be small.
- So, the trial needs many patients to be able to show the difference (power calculation done in advance)
Phase IV trials are done after a drug has been shown to work and has been granted a licence.

The main reasons for running phase IV trials are to find out:
- More about the side effects and safety of the drug
- What the long term risks and benefits are
- How well the drug works when it’s used more widely