Chulalongkorn University
จุฬาลงกรณ์มหาวิทยาลัย
Pillar of the Kingdom

Chulalongkorn Comprehensive Epilepsy Centre

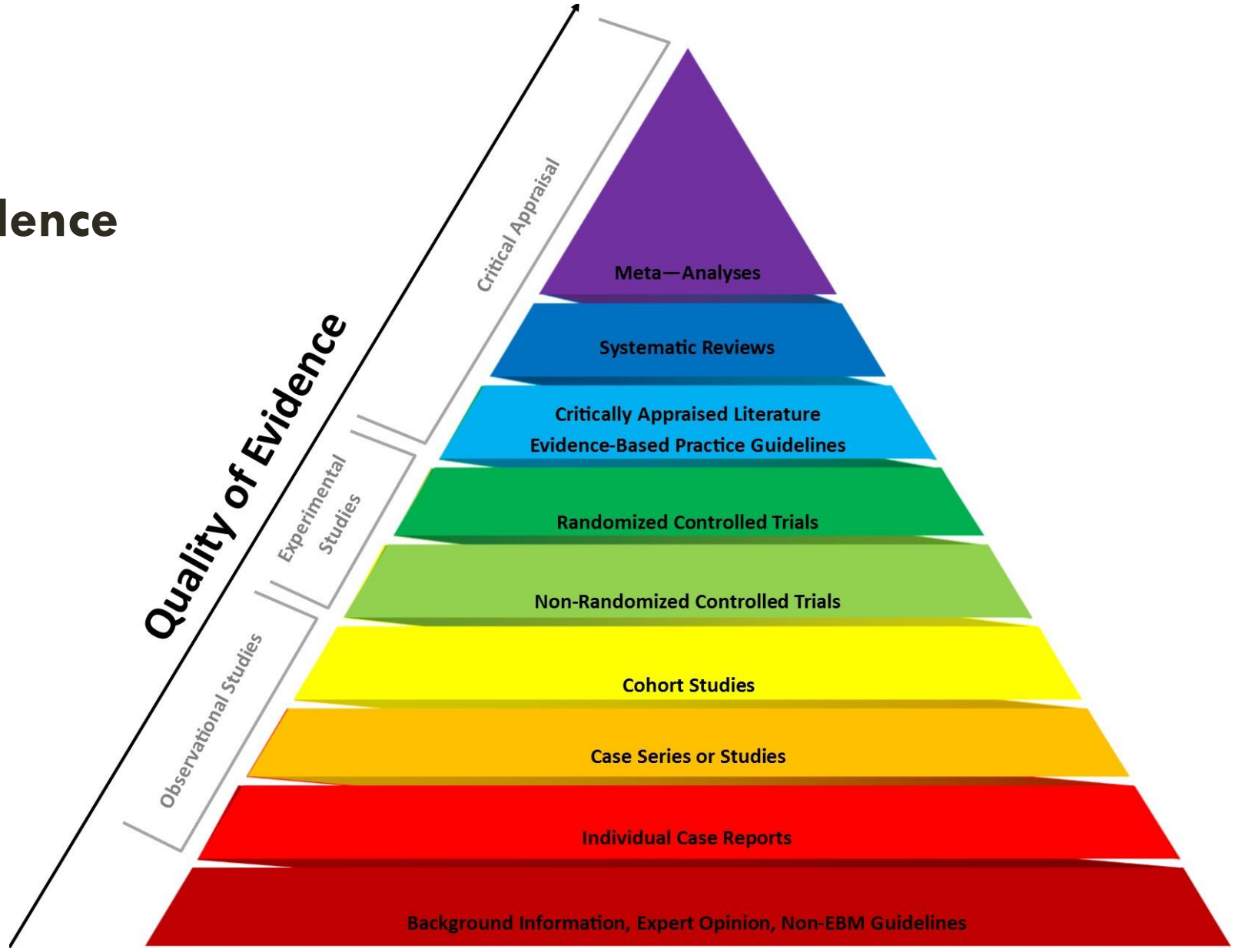
CRITICAL APPRAISAL OF NEUROLOGICAL ARTICLES (1)

Assist. Prof. Chusak Limotai
Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC)

TALK OVERVIEW

- Study design: An overview
- Observational study: Direction of the study
- Experimental design (focusing on RCT)
- Critical Appraisal

Hierarchy of evidence (Validity)



Why EBM?

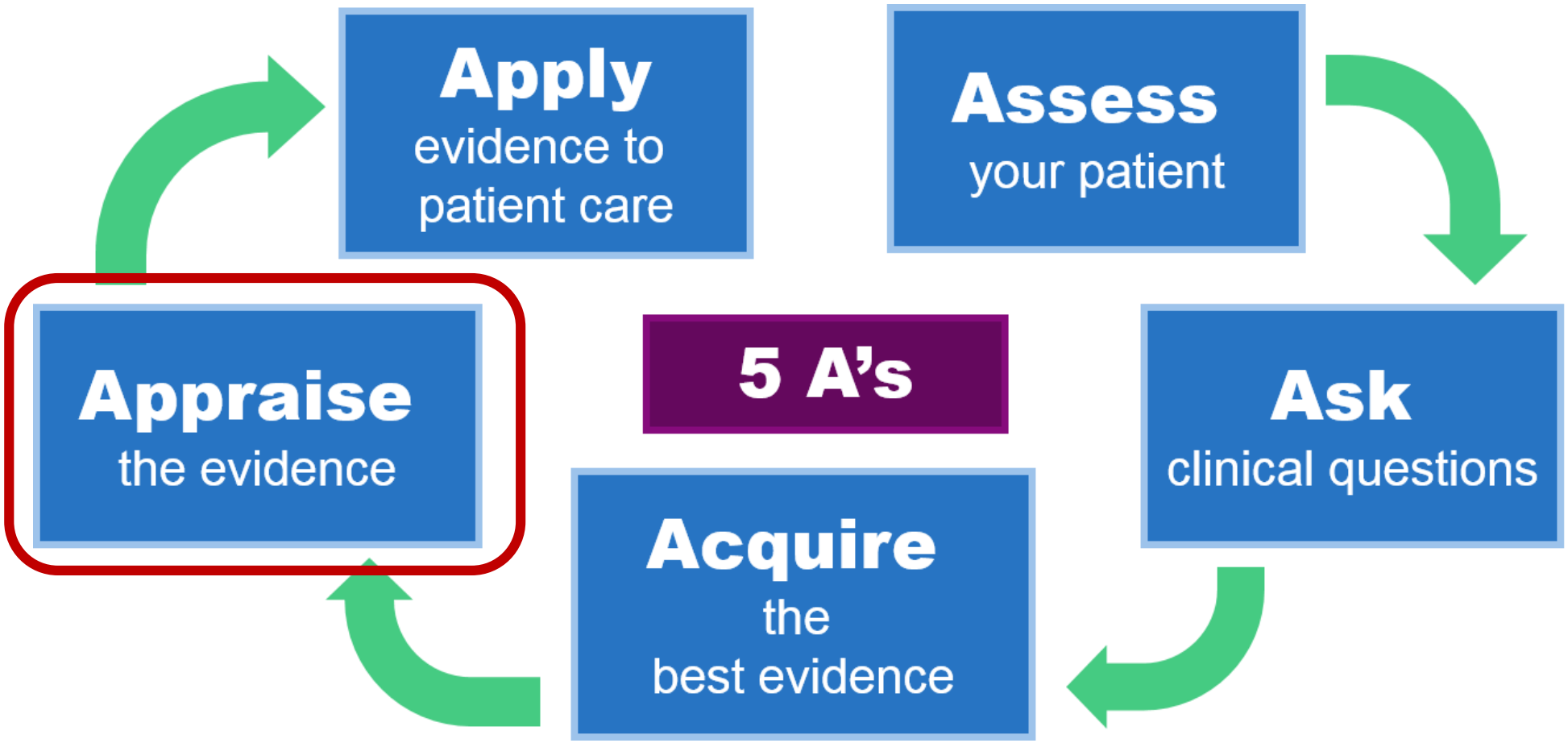
- Too many patients
- Too many problems
- Too many journals
- Information overload
- No time to read
- Read what I am familiar with
- Avoid difficult issues

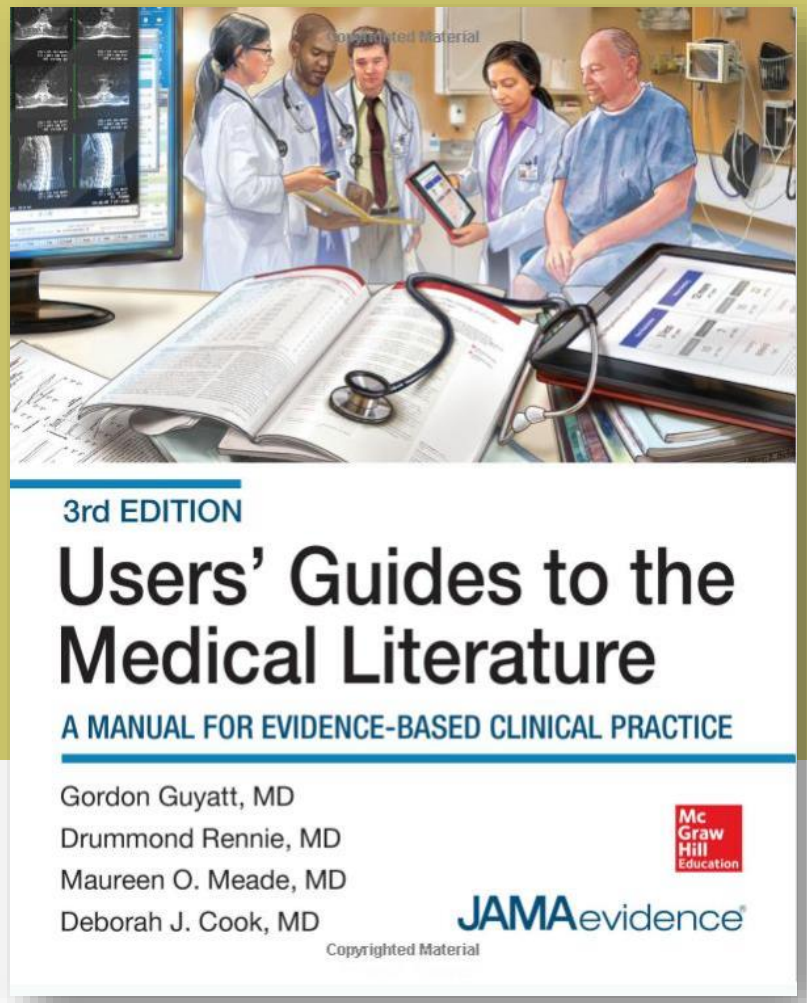
Google

UpToDate®

EBM encourages self directed learning process which should overcome all shortages in practice

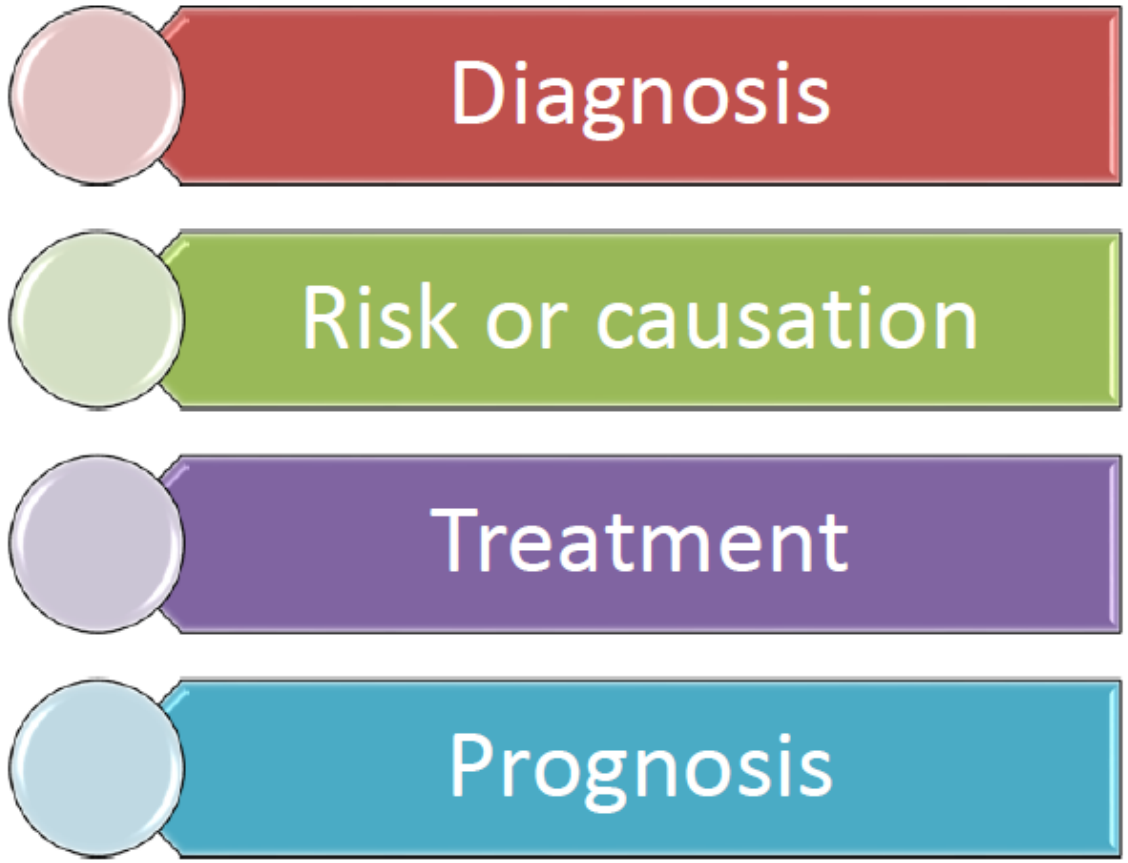
How to apply EBM in our case?





CRITICAL APPRAISAL

Types of clinical question



STUDY DESIGN: AN OVERVIEW

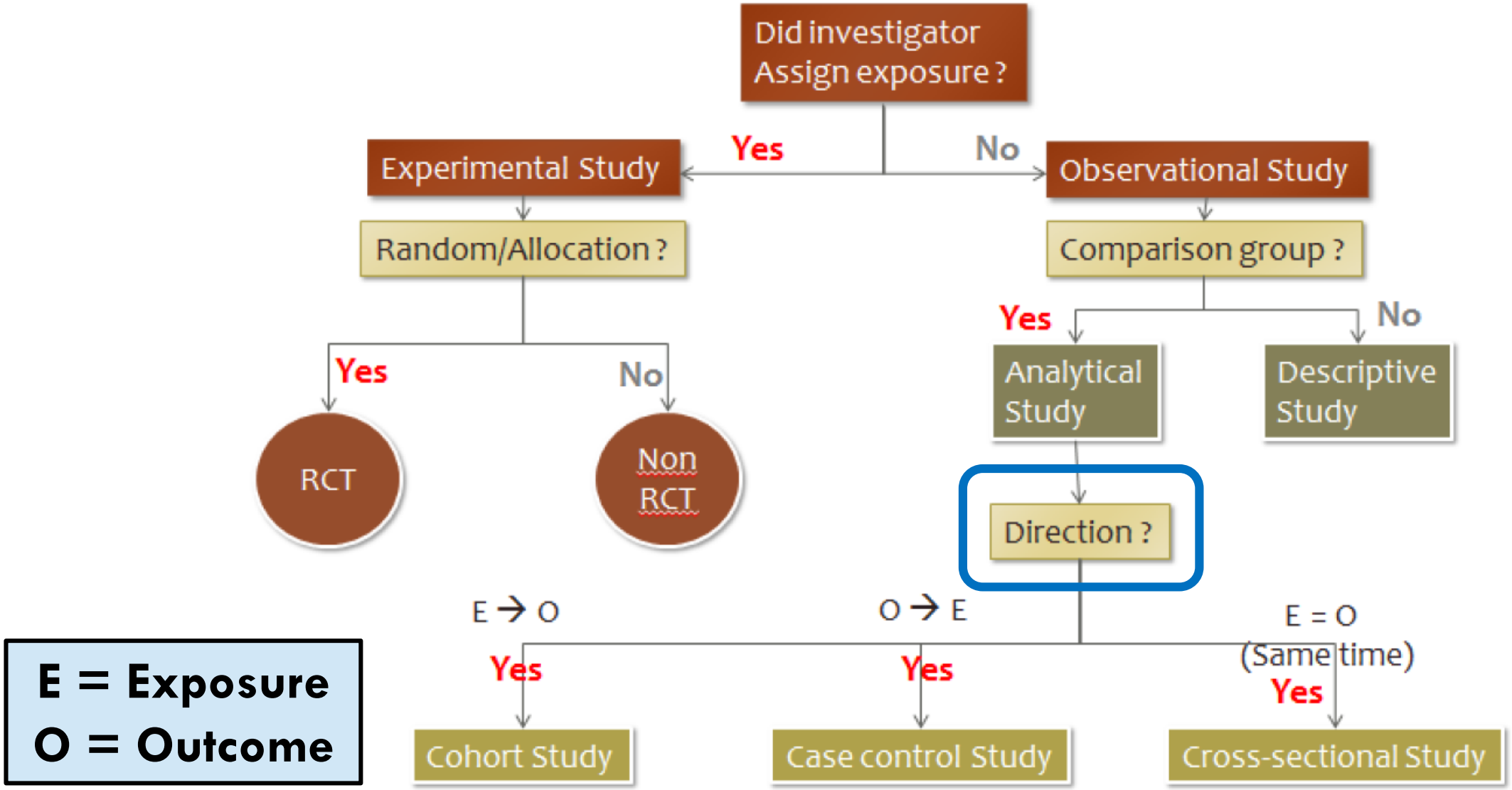


Figure 4. Flow of differentiate of study designs by key elements

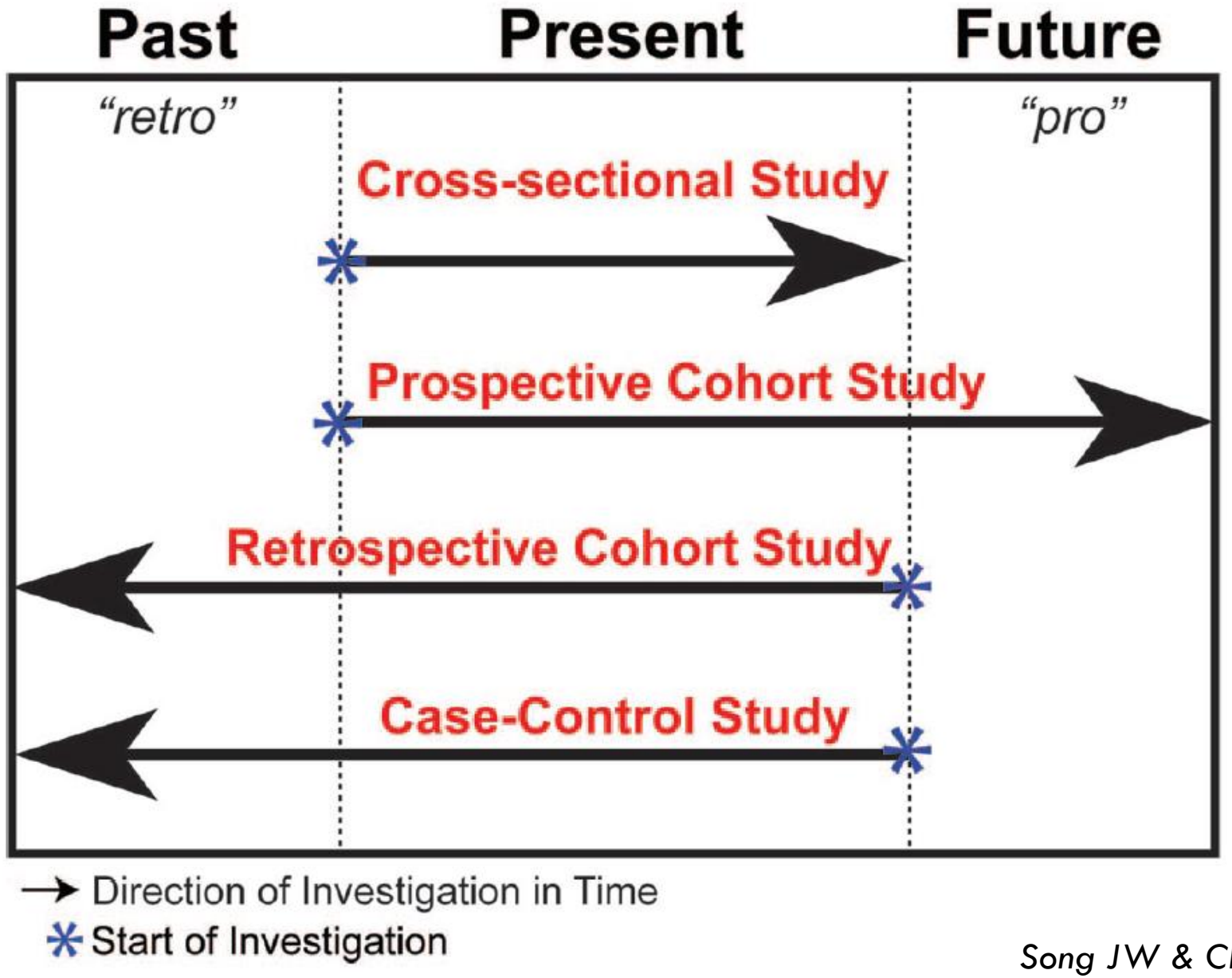
Courtesy of Assoc. Prof. Atiporn Ingsathit, CEB, Mahidol University

Table 1. Notable Differences Between Randomized Clinical Trials and Observational Studies

	Clinical Trials	Observational Studies
Setting	Standardized approach to treating patients may differ from common practice	Usual clinical practice
Ethics	Must meet ethical standards of human experimentation	Researcher does not offer intervention, which limits ethical concerns mainly to privacy issues
Cost of each study subject	High	Low
Subjects	Selection of patients based on strict inclusion and exclusion criteria that depend on ethics and feasibility	Can readily include all patients, a broad range of patients, or can apply specific inclusion or exclusion criteria
Exposure	Usually 1 or 2 interventions	No limit to the number of interventions or comparisons
Compliance	Can often be measured	More difficult to quantify directly
Confounding control	Randomization addresses known and unknown confounding	Known factors, if measured, can be controlled, but very difficult to control adequately for unmeasured factors
Outcome	1. Standardized measure of both surrogate, soft, and hard endpoints defined by the researcher 2. Blinding is possible	1. Based on routine restriction and mean by hard endpoints 2. No blinding
Rare outcome	Cost is too high for rare outcomes	Much more feasible for rare outcomes

Sorensen Lash & Rothman; Hepatology 2006

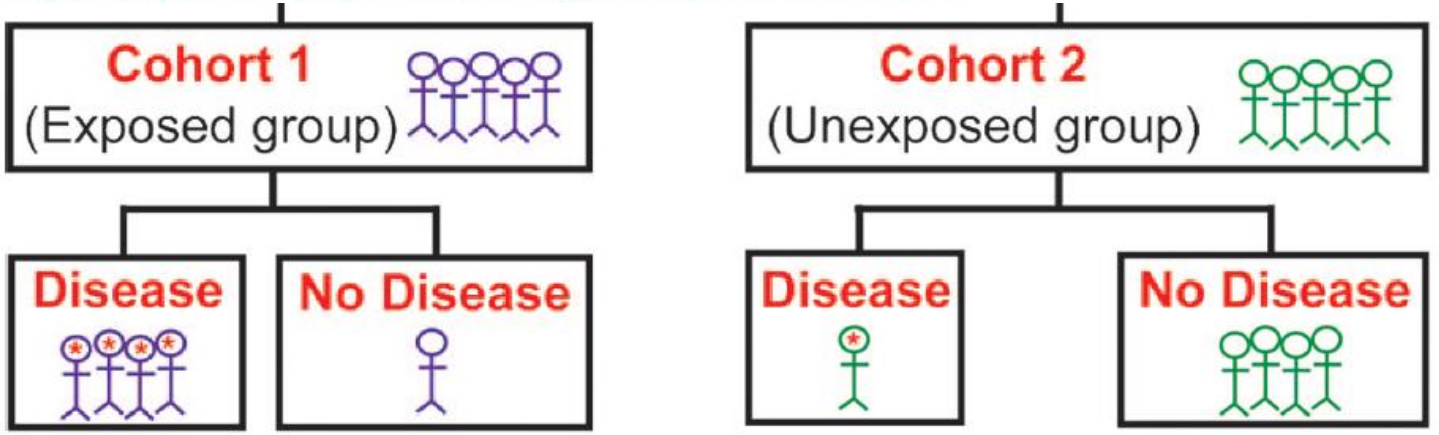
OBSERVATIONAL STUDY:
DIRECTION OF THE STUDY

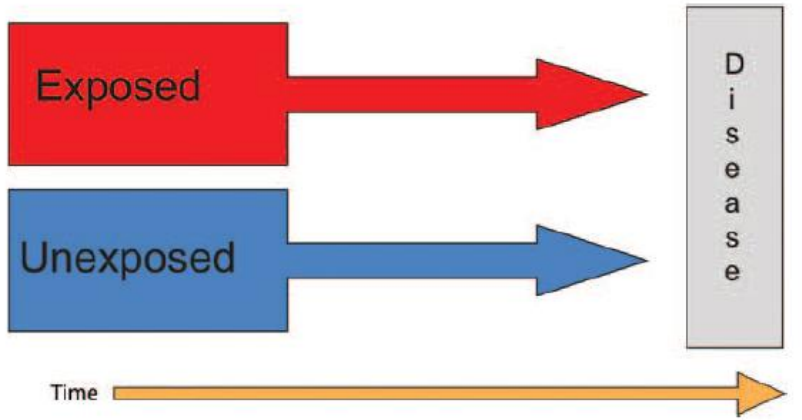


Song JW & Chung KC; PRJS 2010

Cohort is an ancient Roman military unit of 300-600 men

A group of soldiers marching forward in battle





1. Identify exposed and unexposed cohort groups.

Unexposed
Exposed
* Diseased status

2a. PROSPECTIVE STUDY
-During follow-up period, identify diseased subjects (incident cases).

2b. RETROSPECTIVE STUDY
-Identify diseased subjects by interview or written records.

3. Analyze differences (i.e. incidence or relative risk) among those exposed (cohort 1) and those unexposed (cohort 2).

Song JW & Chung KC; PRJS 2010 *Sessler DI & Imrey PB; Anesth Analg 2015;*

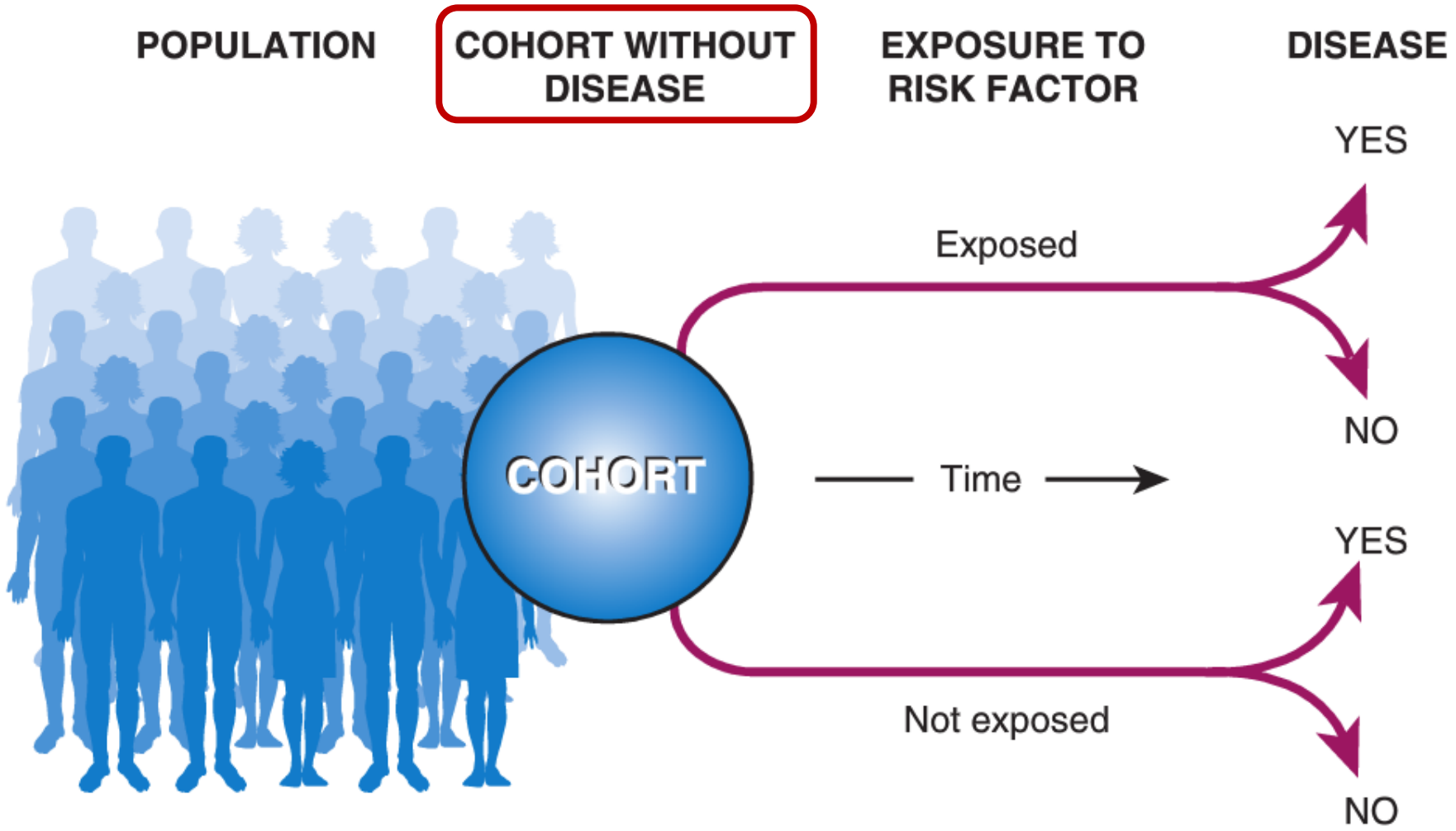


Figure 5.1 ■ Design of a cohort study of risk. Persons without disease are divided into two groups—those exposed to a risk factor and those not exposed. Both groups are followed over time to determine what proportion of each group develops disease.

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition

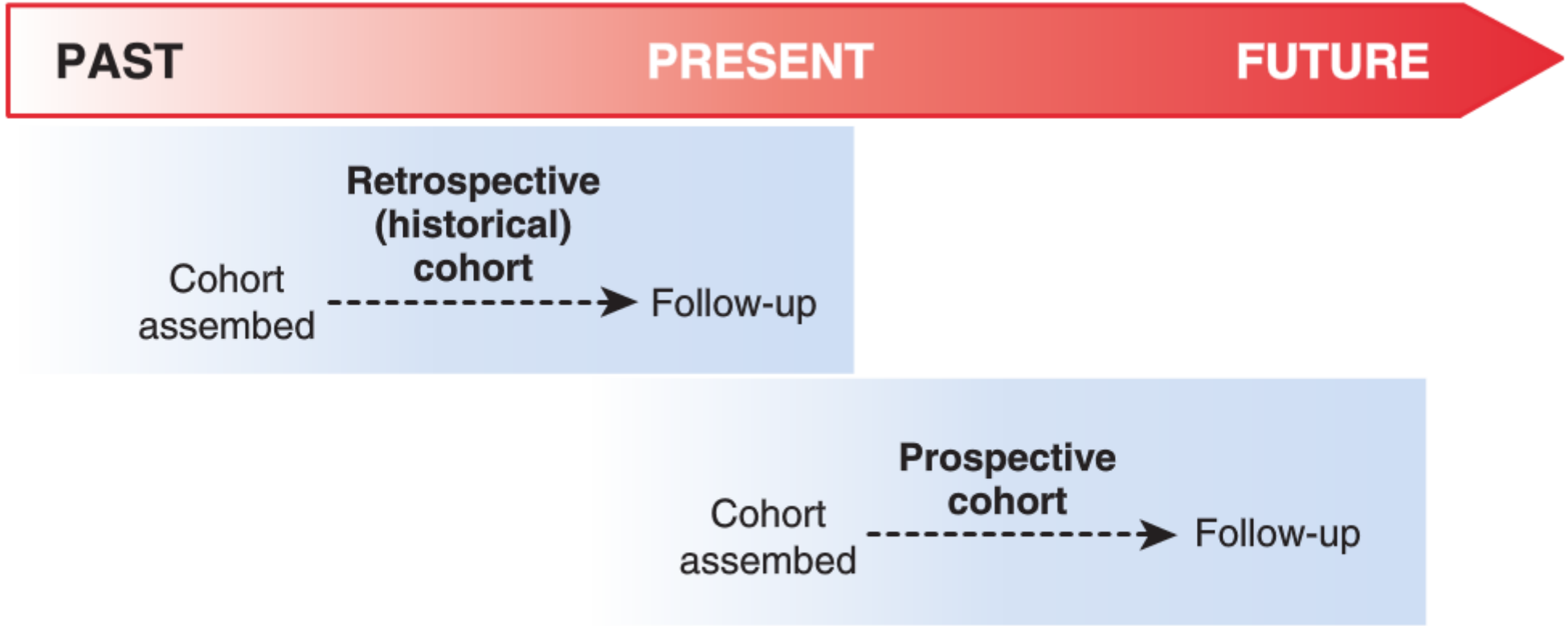
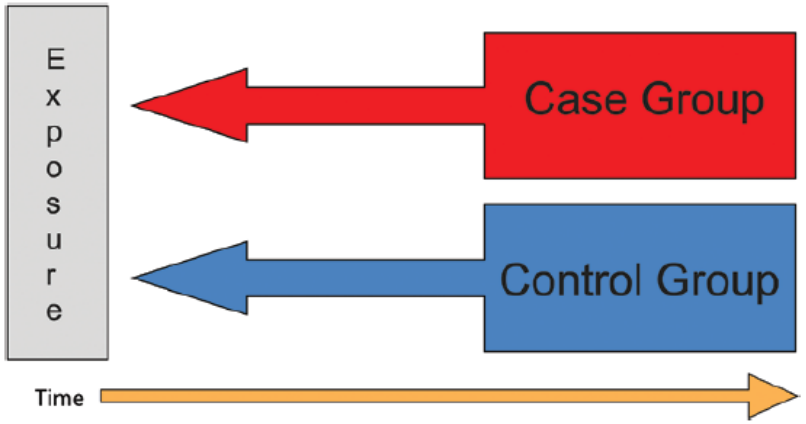
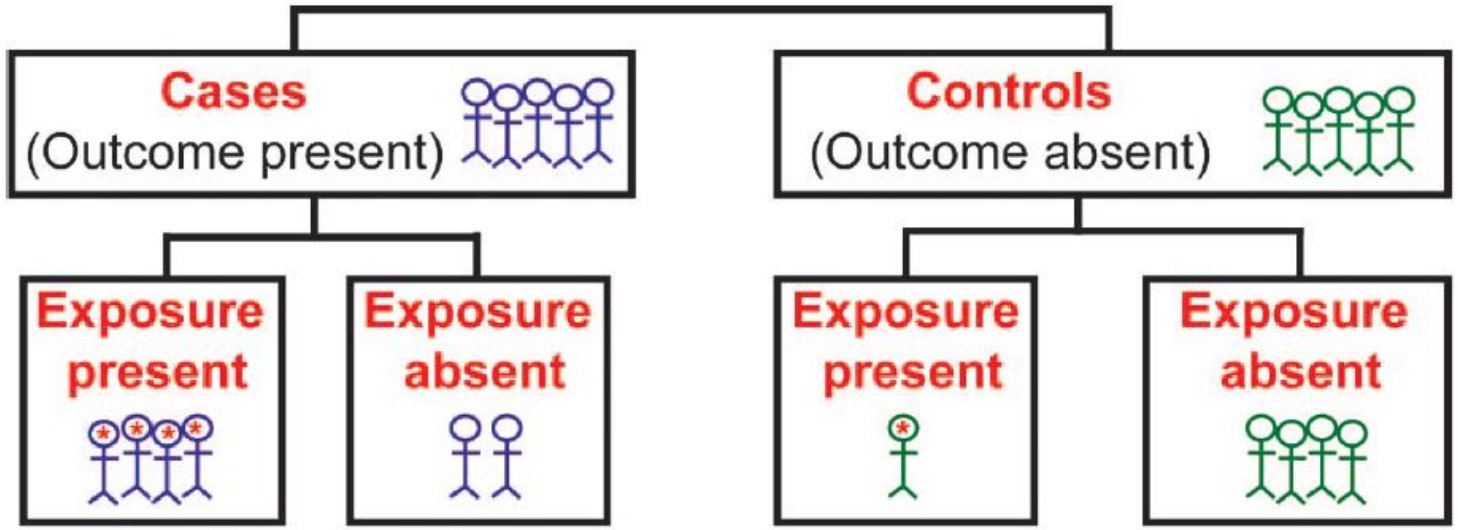


Figure 5.2 ■ Retrospective and prospective cohort studies. Prospective cohorts are assembled in the present and followed forward into the future. In contrast, retrospective cohorts are made by going back into the past and assembling the cohort, for example, from medical records, then following the group forward to the present.

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition



CASE-CONTROL STUDY



1. Identify cases.
2. Select controls, which may be matched to cases.
3. Measure exposure or risk factors of interest.
4. Compare the presence or absence of exposure in cases and controls.

Control
Case
Exposure present

Sessler DI & Imrey PB; Anesth Analg 2015; Song JW & Chung KC; PRJS 2010

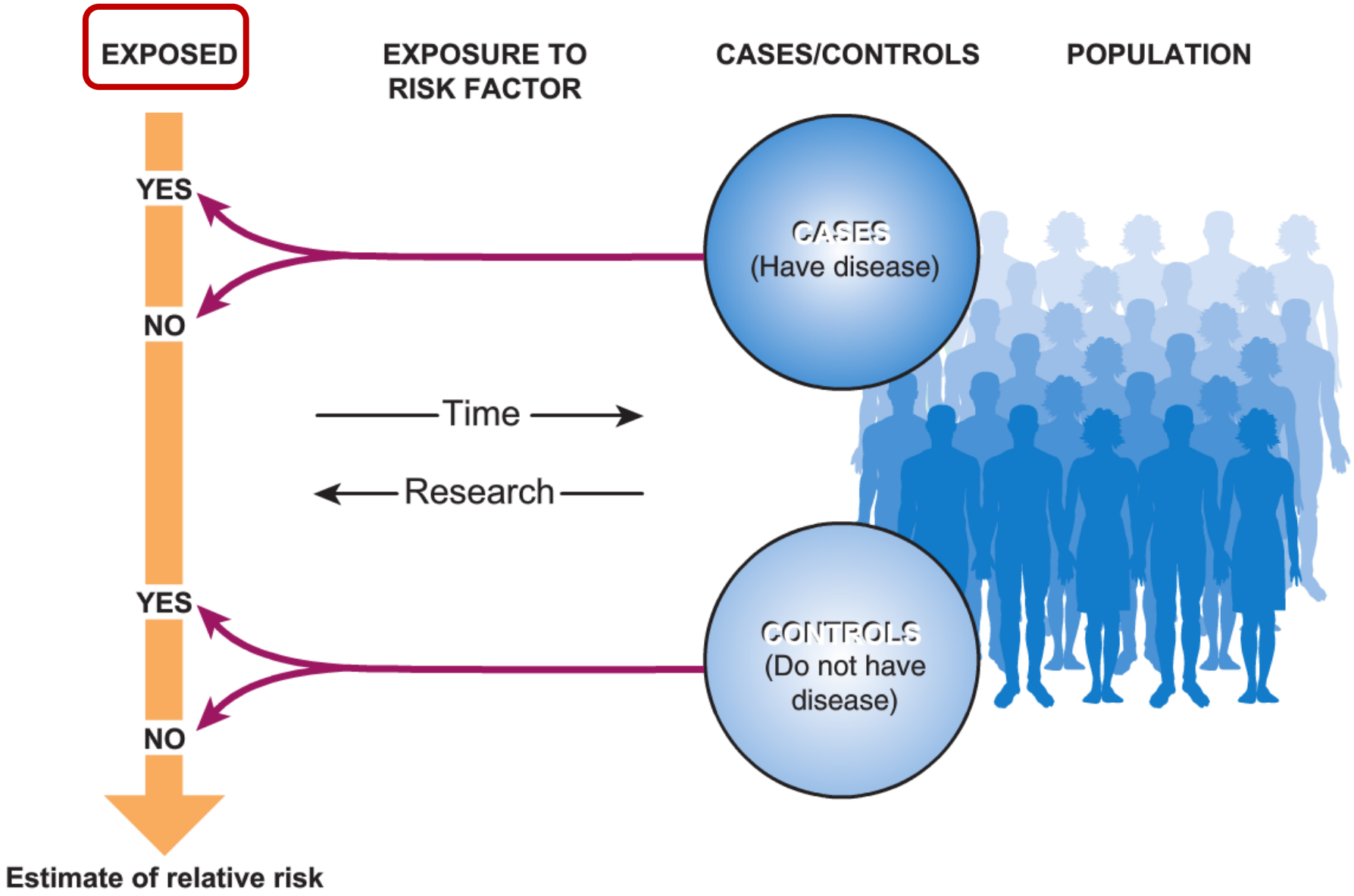


Figure 6.1 ■ Design of case-control studies.

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition

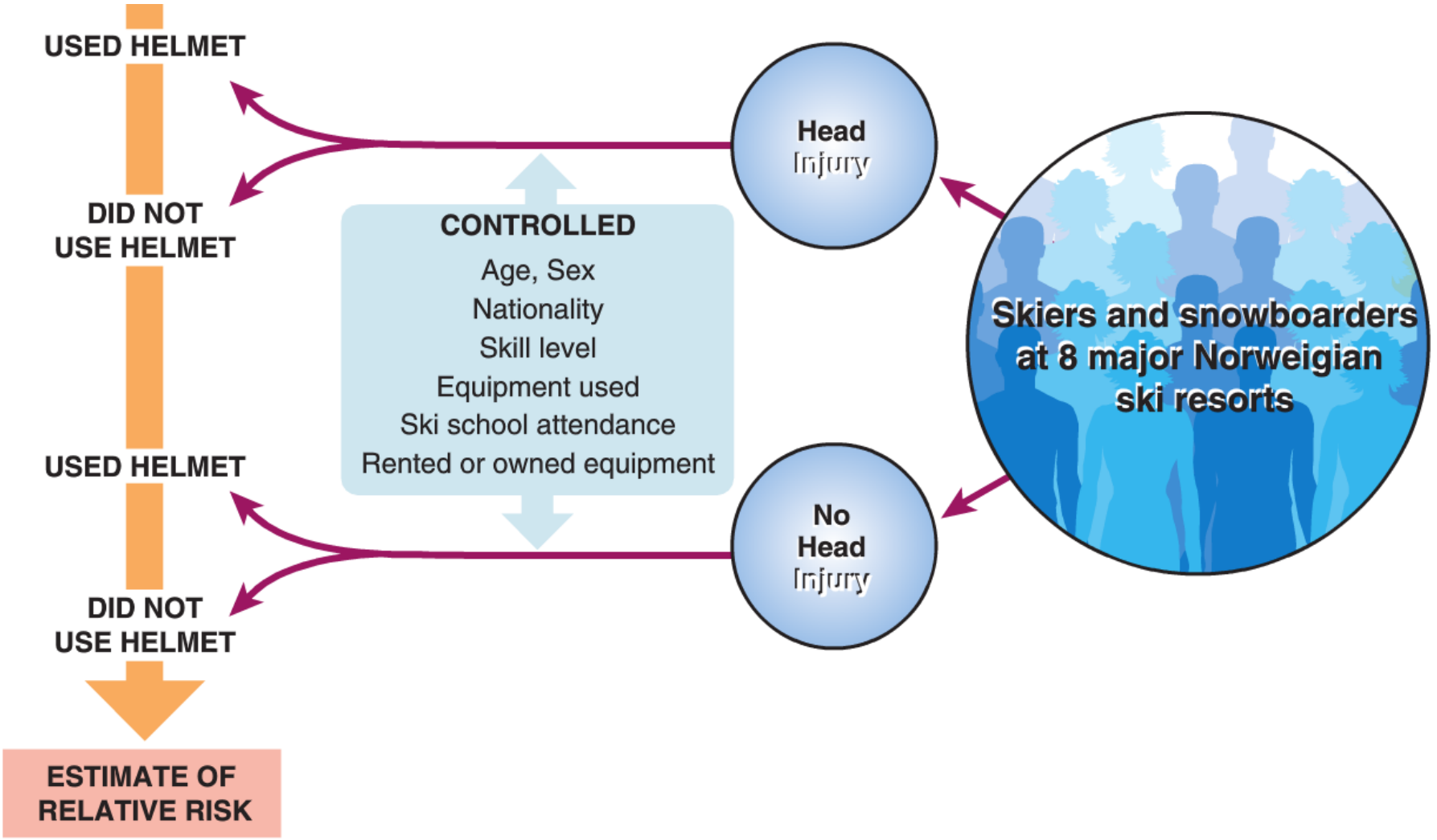


Figure 6.2 ■ A case-control study of helmet use and head injuries among skiers and snowboarders. (Summary of Sulheim S, Holme I, Ekeland A, et al. Helmet use and risk of head injuries in alpine skiers and snowboarders. JAMA 2006;295:919–924.)

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition

ADVANTAGES AND DISADVANTAGES

Table 1. Characteristics, strengths, and weaknesses of study designs used in clinical research

Study design	Characteristics	Strengths	Weaknesses
Case report and case series	One or a few subjects Detailed description of (a) case(s) without a control group	First form of publication Fast, inexpensive Hypothesis generating	Very limited potential to establish causal effects Selection bias*
Cross-sectional study	Exposure and outcome measured at same point in time Subjects with and without outcome are compared	Useful to describe the prevalence of disease Fast, inexpensive Hypothesis generating	Very limited potential to establish causal effects Selection bias* Survival bias* × Causality
Case-control study	Cases (those with the outcome of interest) are compared with controls (those without the outcome of interest) with respect to exposure	Efficient Suitable to study rare outcomes and multiple exposures Relatively inexpensive Hypothesis generating	Some potential to establish causal effects Can only study one outcome Choice of control group can be difficult Selection bias* Recall bias* ± Causality
Cohort study	A cohort of subjects free of the outcome is followed and compared based on the exposure	Suitable to study multiple exposures, rare exposures, and multiple outcomes Hypothesis generating High generalizability	Some potential to establish causal effects Can take a long period Can be expensive Selection bias* ✓ Causality
RCT	Randomization: allocation of subjects to experimental or control group by chance	Gold standard in establishing causal effects in studies on therapy Suitable to study more than one intervention	Very expensive Can take a long period Not suitable to study rare events Can be unethical Often low generalizability due to strict selection criteria

Noordzij M et al.; Nephron Clin Pract 2009

CRITICAL APPRAISAL

CRITICAL APPRAISAL

- **Are the results of the study valid ?**
- **What are the results ?**
- **How can we apply the results to patient care ?**

CRITICAL APPRAISAL

- **Are the results of the study valid ?**
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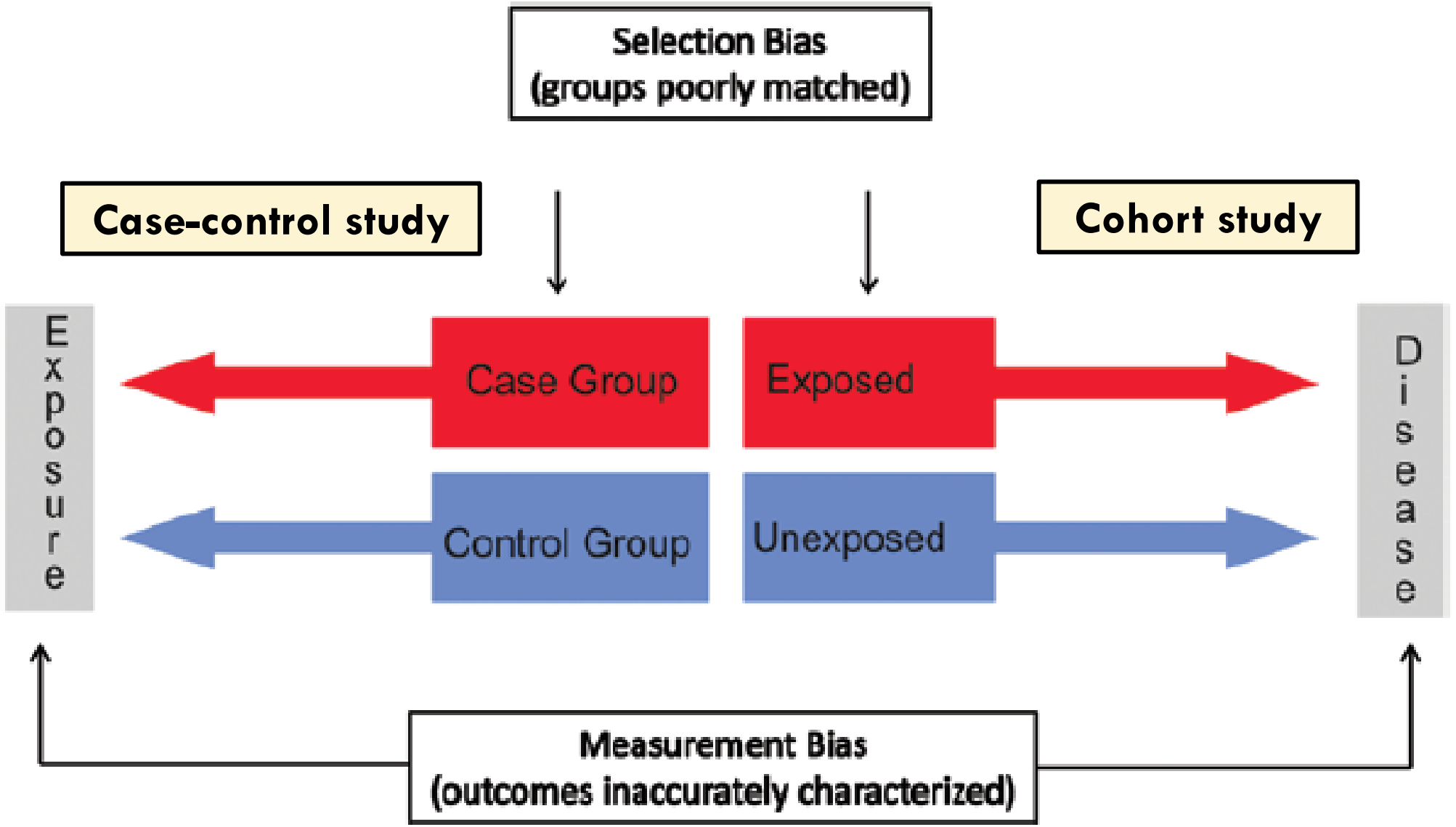
Table 1.4

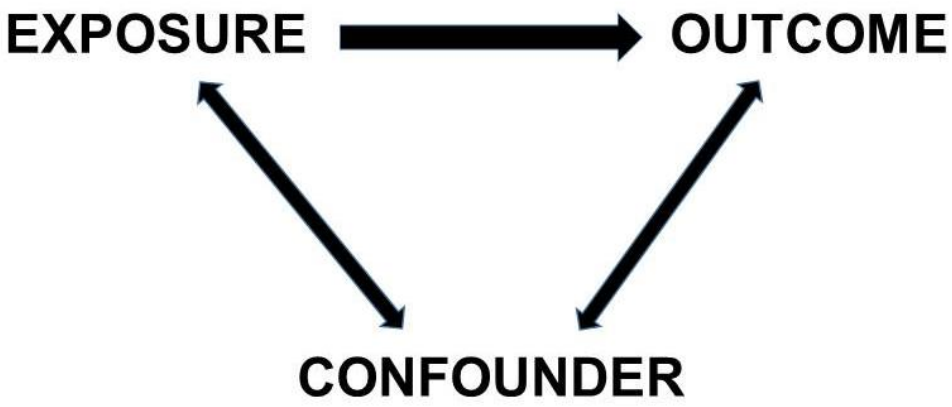
Bias in Clinical Observation

Selection bias	Occurs when comparisons are made between groups of patients that differ in determinates of outcome other than the one under study.
Measurement bias	Occurs when the methods of measurement are dissimilar among groups of patients
Confounding	Occurs when two factors are associated (travel together) and the effect of one is confused with or distorted by the effect of the other



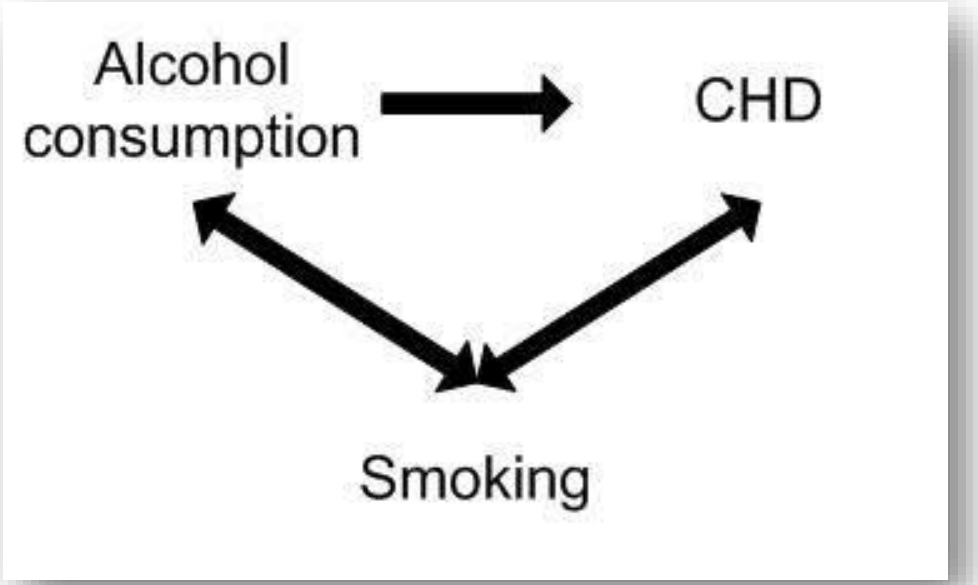
Sessler DI & Imrey PB; Anesth Analg 2015;

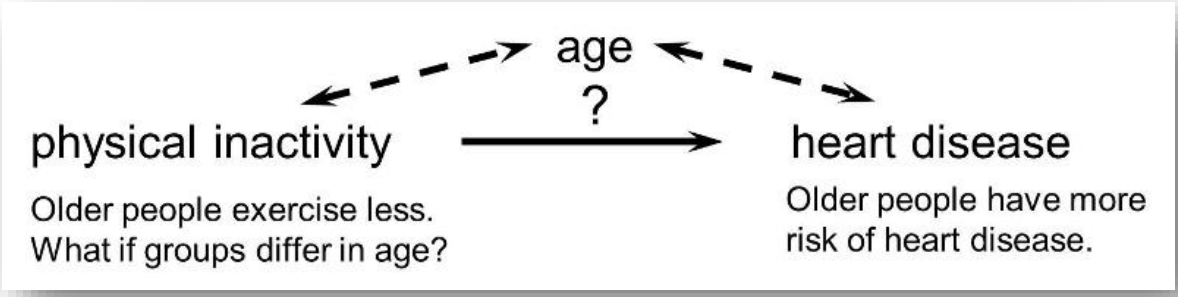
Confounding



A variable that **influences both the dependent variable and independent variable**, causing a **spurious** association

A confounding factor **may mask an actual association or falsely demonstrate an apparent association between the study variables where no real association between them exists**. If confounding factors are not measured and considered, bias may result in the conclusion of the study





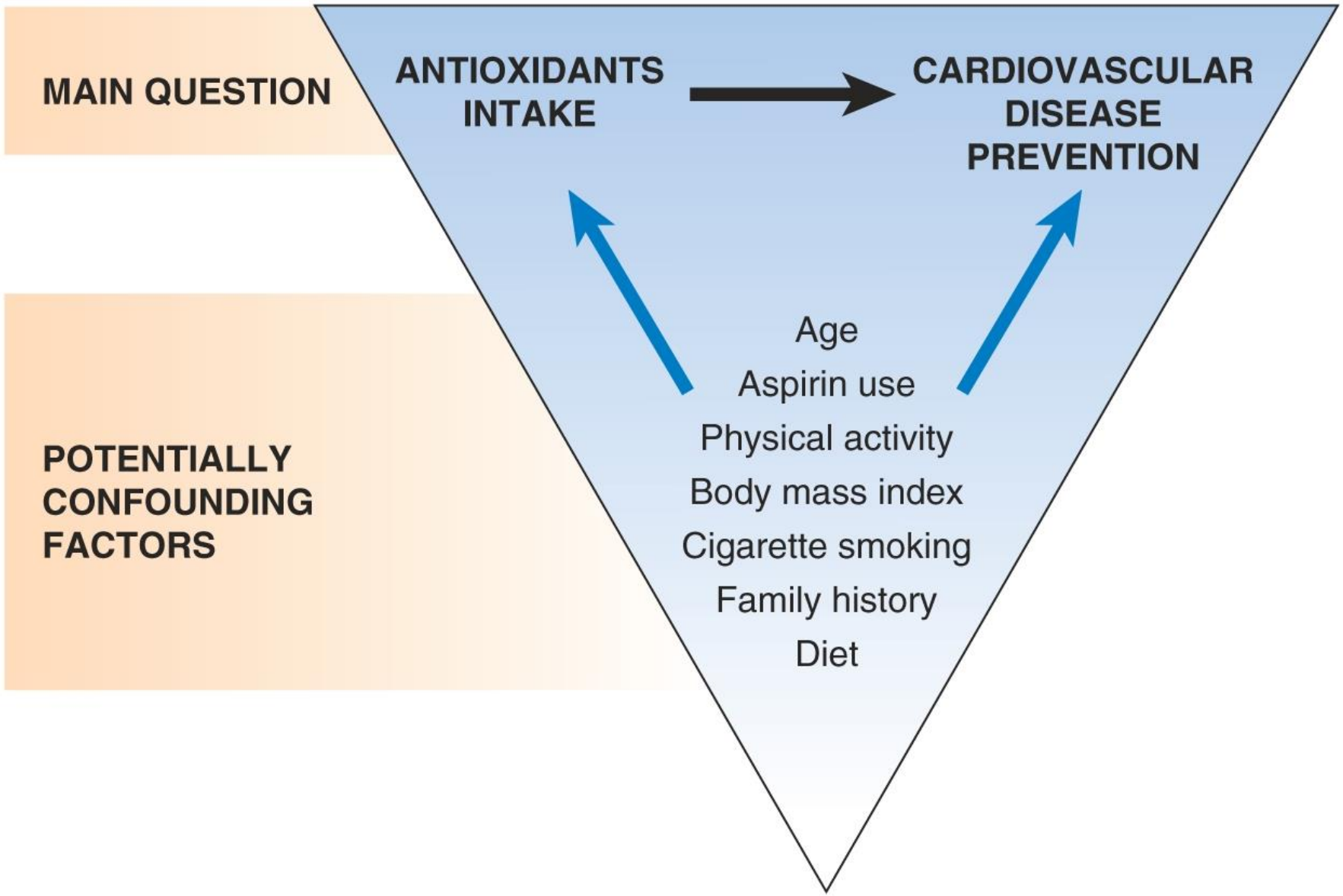


Table 5.6

Methods for Controlling Confounding

Method	Description	Phase of Study	
		Design	Analysis
Randomization	Assign patients to groups in a way that gives each patient an equal chance of falling into one or the other group.	+	
Restriction	Limit the range of characteristics of patients in the study	+	
Matching	For each patient in one group, select one or more patients with the same characteristics (except for the one under study) for a comparison group.	+	+
Stratification	Compare rates within subgroups (strata) with otherwise similar probability of the outcome.		+
Simple adjustment	Mathematically adjust crude rates for one or a few characteristics so that equal weight is given to strata of similar risk.		+
Multivariable adjustment	Adjust for differences in a large number of factors related to outcome, using mathematical modeling techniques.		+
Best-case/Worst-case analysis	Describe how different the results could be under the most extreme (or simply very unlikely) assumption about selection bias.		+

Sorensen Lash & Rothman; Hepatology 2006

Table 2. Factors to Consider When Planning or Interpreting the Results of Observational Studies

1. Does the database fit the research question?
2. Does the study population fit to the research hypothesis and clinical decision making?
3. Is the size of the study population adequate to answer the research question?
4. Does the study design fit to the research question and clinical question? Only cohort studies provide direct risk or rate estimates and allow estimation of differences in risk or rates (most relevant for clinical decision making), while both cohort and case-control studies provide relative risk or rate estimates (more relevant for biological disease mechanism).
5. Is the exposure determined accurately? Was the exposure assessed before the outcome occurred? Can duration of exposure be quantified and a dose-response relation explained?
6. Is the outcome measured accurately and is it relevant for clinical practice.
7. Are confounding factors measured accurately to make it possible to control for confounding? Are there any potentially known unmeasured confounding?
8. Are the patients followed for a long enough time period to let the outcome occur? Length should correspond with the study hypothesis. Is there any loss to follow-up?
9. Are the statistical methods and their assumptions suitable for the research question?

Critical appraisal focused items

Population
- Representativeness
- Fit to the research hypothesis
- Adequate sample size

Study design
- Cross-sectional: prevalence
- Cohort: incidence and causality
- Case-control: rare outcome

Exposure determination (esp. case-control)

Outcome determination (esp. cohort)

Confounding factors

Sufficient follow-up period to let the outcome occur (cohort)

Appropriate statistical method

CROSS-SECTIONAL (PREVALENCE STUDY)

Cross-sectional study (Prevalence study)

= A study in which conduction is **a single point in time**, or over a short period of time

Exposure and outcome measured <u>at same point in time</u>

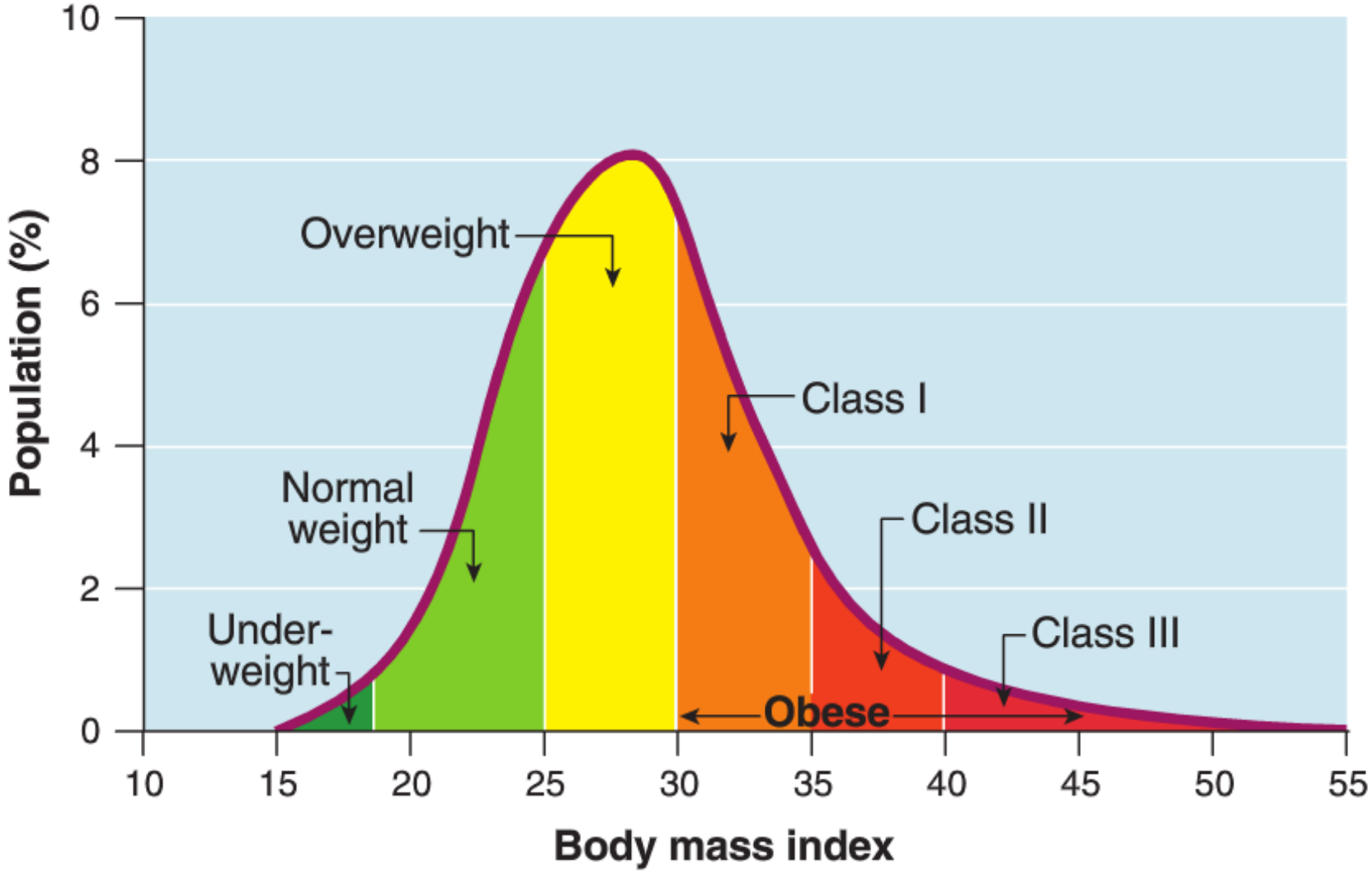


Figure 2.4 ■ The prevalence of overweight and obesity in men, 2007 to 2008. (Data from Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2008. JAMA 2010;303(3):235–241.)

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition

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DOI: 10.1111/ane.12805

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

A survey of epilepsy knowledge, attitudes and practice in school-aged children in Bangkok, Thailand

C. Limotai[1,2] | T. Manmen[2] | K. Urai[2] | C. Limarun[2]

[1]Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[2]Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC), The Thai Red Cross Society, Bangkok, Thailand

Correspondence
C. Limotai, Division of Neurology, King Chulalongkorn Memorial Hospital, Pathumwan, Bangkok, Thailand.
Email: chuneuro@yahoo.com

Objectives: To estimate the level of knowledge about epilepsy, attitude to
and practice in school-aged children in Bangkok, Thailand. Significant fi
this study will be employed to develop a relevant and effective tool
children.

Materials and Methods: This cross-sectional survey study was conducted
Thailand, from August 2014 to December 2015. Study population inclu
aged children between 9 and 14 years (4th to 8th grade). A structured age-a
Thai culture-adjusted and simple 20-item questionnaire was used for this
questionnaire comprised three domains which were eight items for kno

FIGURE 1 Location of Bangkok in relation with the entire country

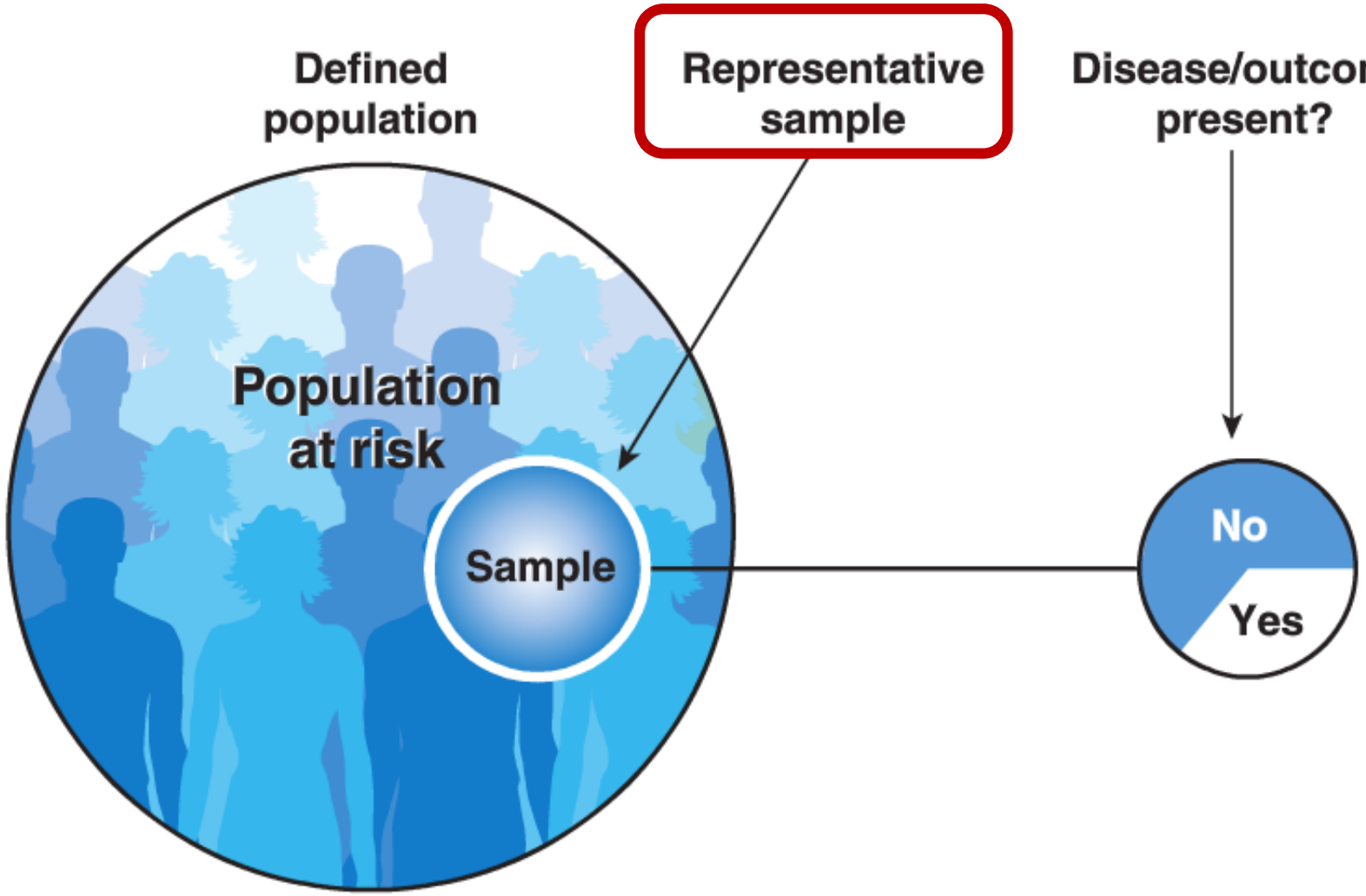


Figure 2.2 ■ The design of a prevalence study.

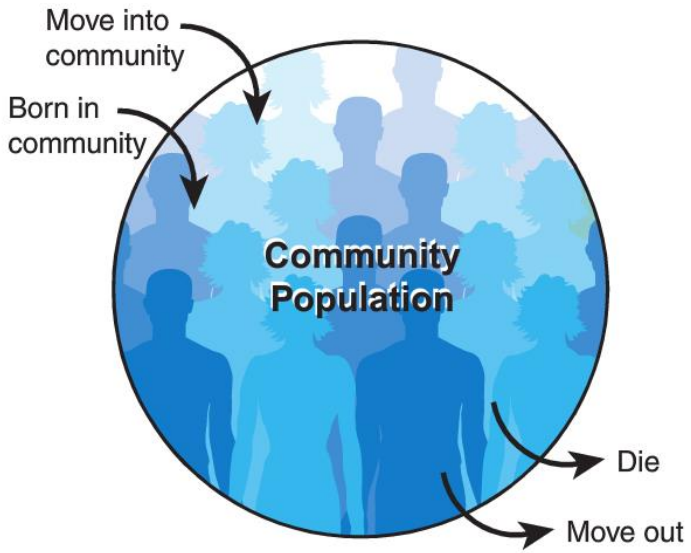
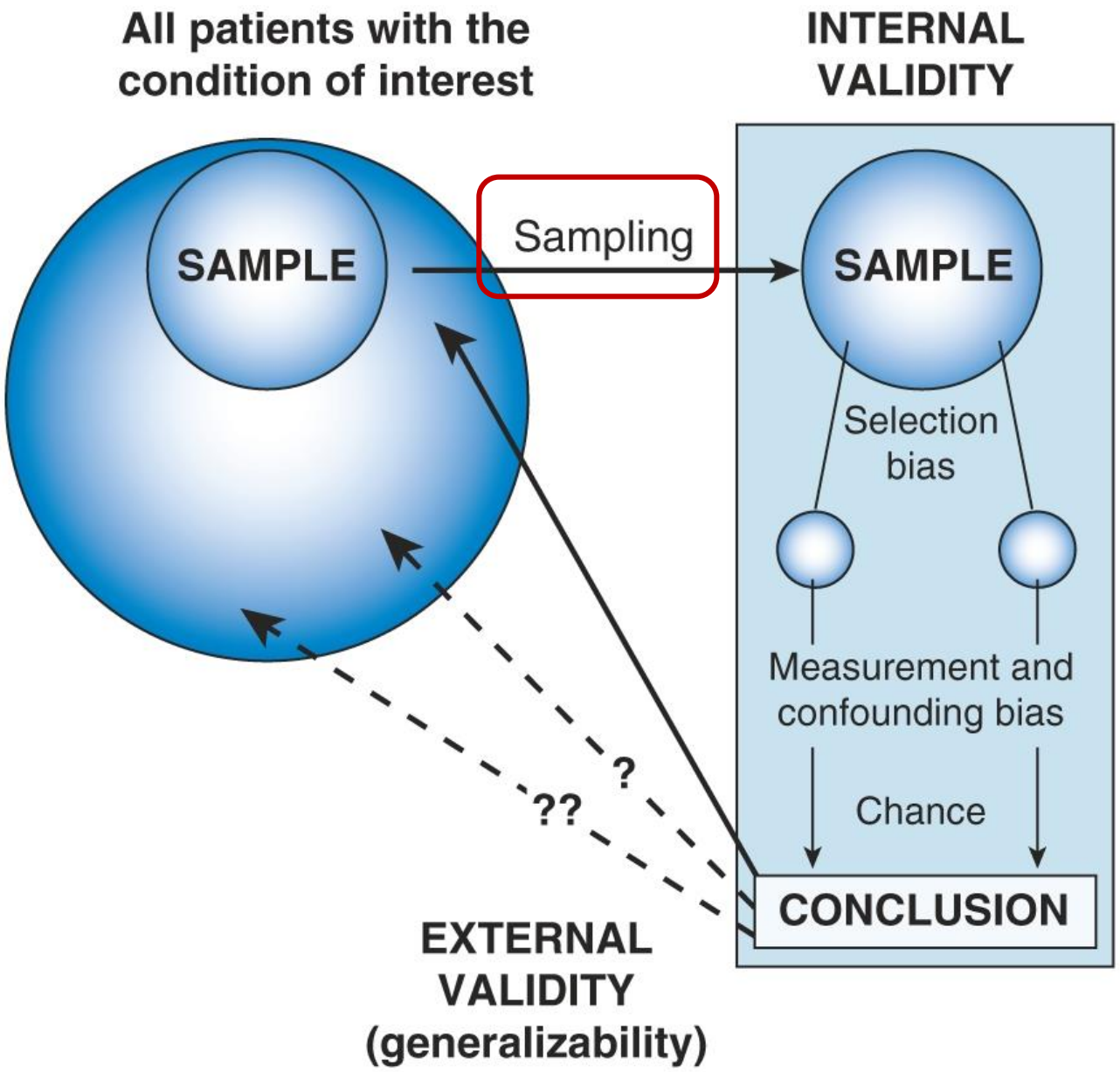


Figure 2.3 ■ A dynamic population.

Fletcher RH, Fletcher SW, Fletcher GS; Clinical Epidemiology; The Essentials; Fifth Edition



Sampling methods

1. **Probability sampling**
   - ✓ Simple random sampling
   - ✓ Stratified random sampling
   - ✓ Cluster sampling
   - ✓ Multistage sampling
   - ✓ Systematic sampling

2. **Non-probability sampling**
   - ✓ Convenience sampling
   - ✓ Consecutive sampling
   - ✓ Quota sampling

2 | MATERIALS AND METHODS

Phase I is a cross-sectional survey study. This study was conducted in Bangkok, Thailand. Bangkok is the capital of Thailand, as shown in Figure 1. The estimated population of Thailand is 64 million, of which approximately 9.3 million live in Bangkok and its vicinities (http://www.un.or.th/services/population/). Among 50 districts of Bangkok, there are 1458 schools in total. These are under jurisdiction of three educational services. One is the Department of Education of Bangkok Metropolitan Administration (BMA), the other two services are Office of the Basic Education Commission (OBEC) and Office of the Higher Education Commission (OHEC), respectively. This survey study began in August 2014 and concluded in December 2015. For every participant school, a survey about epilepsy education was given prior to recreational activities arranged by medical personnel and volunteers.

2.1 | Study subjects

Target population was school-aged children aged between 9 and 14 years (4th to 8th grade) in Bangkok, Thailand. At school level, only schools within BMA jurisdiction were selected. Sample size estimation for one proportion was calculated using overall prevalence (level) of knowledge was 55.35% (0.55) from previous study.[12] Estimated sample size was 1057. Invitation letters from researchers were mailed to all 435 BMA schools. Schools were finally chosen based upon willingness to participate from principals and teachers. At student level, coordinating teachers were informed of the required quota of 80-100 students from each school. The teachers then randomly recruited students aged between 9 and 14 years from 4th to 8th grade until reaching the assigned quota.

CASE-CONTROL STUDY

Case-control study

Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies

OPEN

Neurology, Vol 86 May 2016

Helen Dolk, DrPH
Hao Wang, PhD
Maria Loane, PhD
Joan Morris, PhD
Ester Garne, MD
Marie-Claude Addor, MD
Larraitz Arriola, MD
Marian Bakker, PhD
Ingeborg Barisic, MD
Berenice Doray, PhD, MD
Miriam Gatt, MSc
Karin Kallen
Babak Khoshnood, MD,

ABSTRACT

Objective: To test previous signals of a risk of orofacial cleft (OC) and clubfoot with exposure to the antiepileptic lamotrigine, and to investigate risk of other congenital anomalies (CA).

Methods: This was a population-based case-malformed control study based on 21 EUROCAT CA registries covering 10.1 million births (1995–2011), including births to 2005 in which the clubfoot signal was generated and a subsequent independent study population of 6.3 million births. A total of 226,806 babies with CA included livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. First-trimester lamotrigine monotherapy exposure in OC cases and clubfoot cases was compared to other nonchromosomal CA (controls). Odds ratios (OR) were adjusted for registry. An exploratory analysis compared the proportion of each standard EUROCAT CA subgroup among all babies with nonchromosomal CA exposed to lamotrigine monotherapy with non-AED exposed pregnancies.

Results: There were 147 lamotrigine monotherapy-exposed babies with nonchromosomal CA. For all OC, OR_{adj} was 1.31 (95% confidence interval [CI] 0.73–2.33), isolated OC 1.45 (95% CI 0.80–2.63), isolated cleft palate 1.69 (95% CI 0.69–4.15). Overall OR_{adj} for clubfoot was 1.83

RATIONALES AND OBJECTIVES

- A warning about the specific risk of orofacial clefts (OC) is given in patient information (Medicines and Healthcare Products Regulatory Agency 2015), due to a signal from the **North American AED registry** of **a 6-fold risk of OC, specifically cleft palate**

Holmes LB et.al; Neurology 2008

- However, none of the subsequent studies did find a large excess of OC or cleft palate

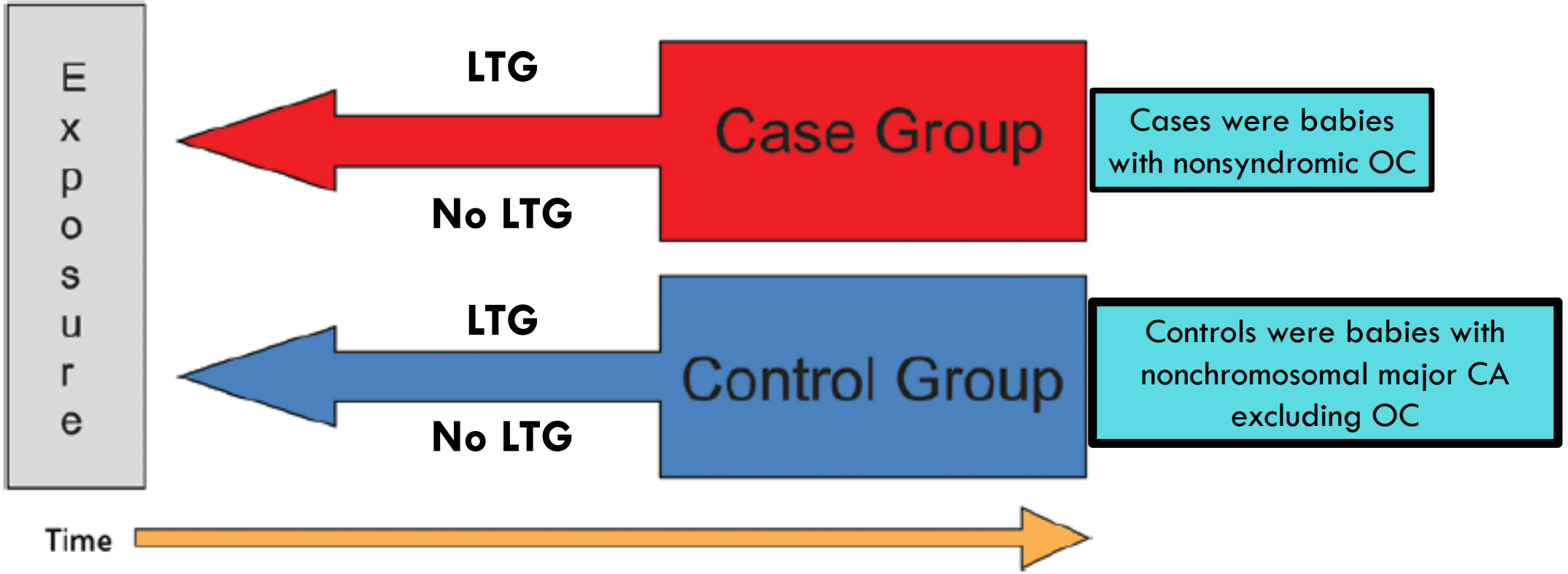
Molgaard-Nielsen D and Hviid A; JAMA 2011
Cunnington MC et.al; Neurology 2011
Tomson T et.al; Lancet Neurol 2011
Hunt SJ et.al; Neurology 2009

RATIONALES AND OBJECTIVES

- In **2008**, the authors tested the signal of an increased risk of OC with lamotrigine monotherapy by analyzing data from 19 registries for the period 1995–2005. In an **exploratory analysis**, we found evidence of an **excess risk of clubfoot**, which could have been a chance finding and constituted a signal requiring confirmation in independent data

- Our objective in **this new study was**

1) **to enlarge the study population in order to estimate more precisely the relative risk of OC**,
2) **to follow-up the clubfoot signal**, and
3) **to explore evidence of risk of other CA subgroups**


Exposure
LTG
No LTG
Case Group
Cases were babies with nonsyndromic OC
LTG
No LTG
Control Group
Controls were babies with nonchromosomal major CA excluding OC
Time

CRITICAL APPRAISAL

- **Are the results of the study valid ?**
- **What are the results ?**
- **How can we apply the results to patient care ?**

ARE THE RESULTS OF THE STUDY VALID ?

1. Case-control study, did the case and control group have the same risk (chance) for being exposed in the past ?

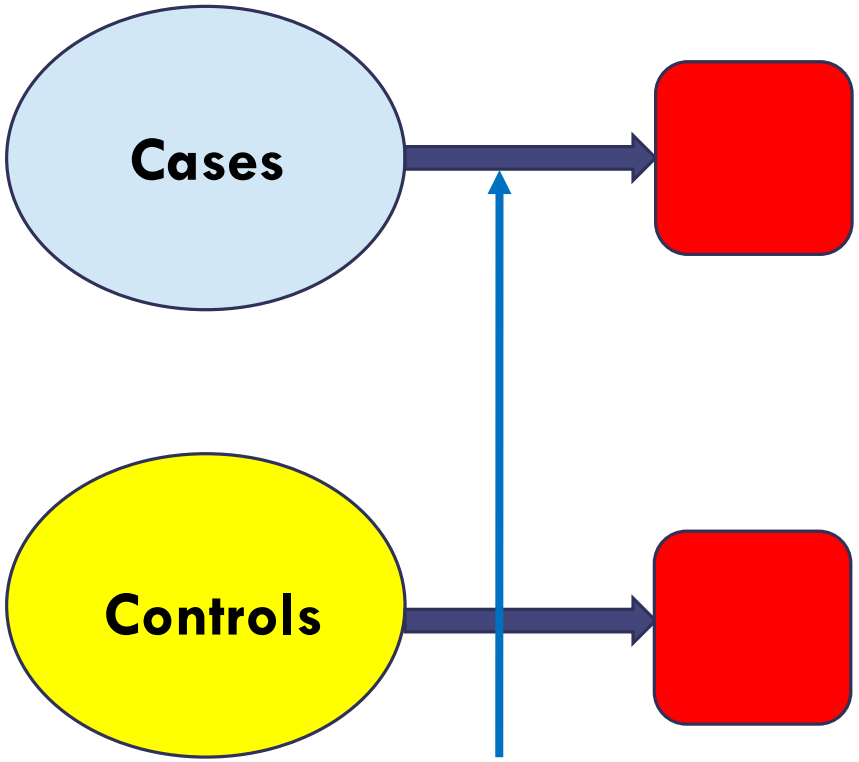
Study population and registry data. The EUROCAT central database contains anonymized, individual CA registrations, including livebirths, fetal deaths from 20 weeks' gestation, and terminations of pregnancy for fetal anomaly (TOPFA)

Exposure definition. Registrations with maternal epilepsy or AED exposure were verified with registries

Answer: Likely yes, since treating physicians independently prescribed the AED/AEDs according to the patient's diagnosis either epilepsy (79%) or other indications in both case and control groups

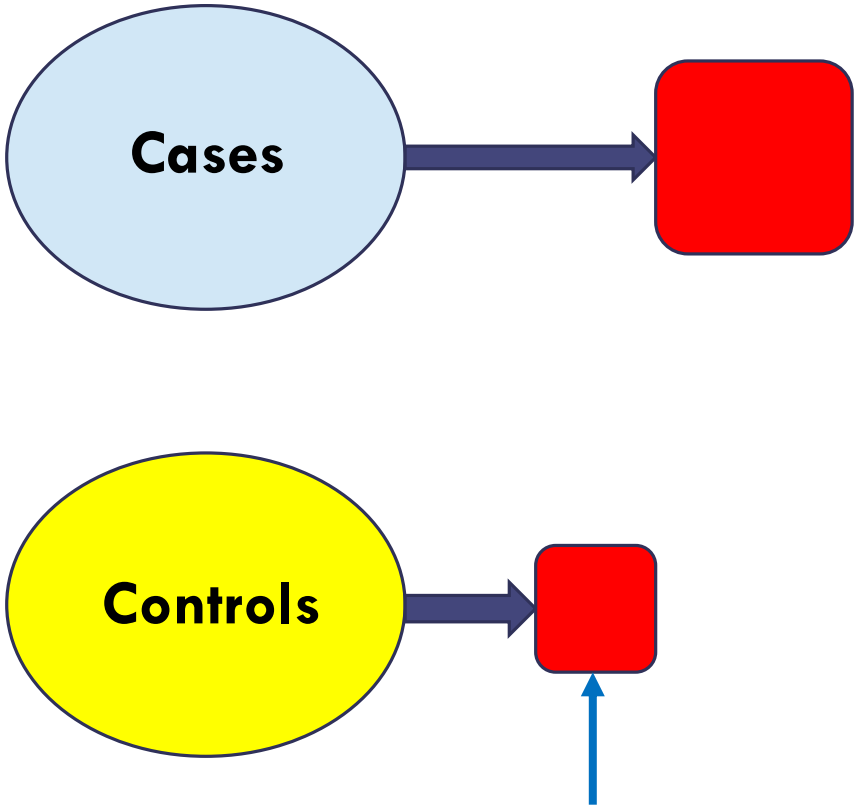
Given the AED had been prescribed prior to the occurrence of CA, likely there was no allocation bias

Real risk/exposure



Similar accessibility to risk (exposure)

Not Real risk/exposure



Lower risk (exposure) due to inaccessibility to risk (exposure)

CASE AND CONTROL

Case

Cases were babies with **nonsyndromic OC**. Cases were excluded where OC was part of a chromosomal, monogenic, or teratogenic syndrome or secondary to another primary anomaly

Versus

Controls

Controls were babies with **nonchromosomal major CA excluding OC**

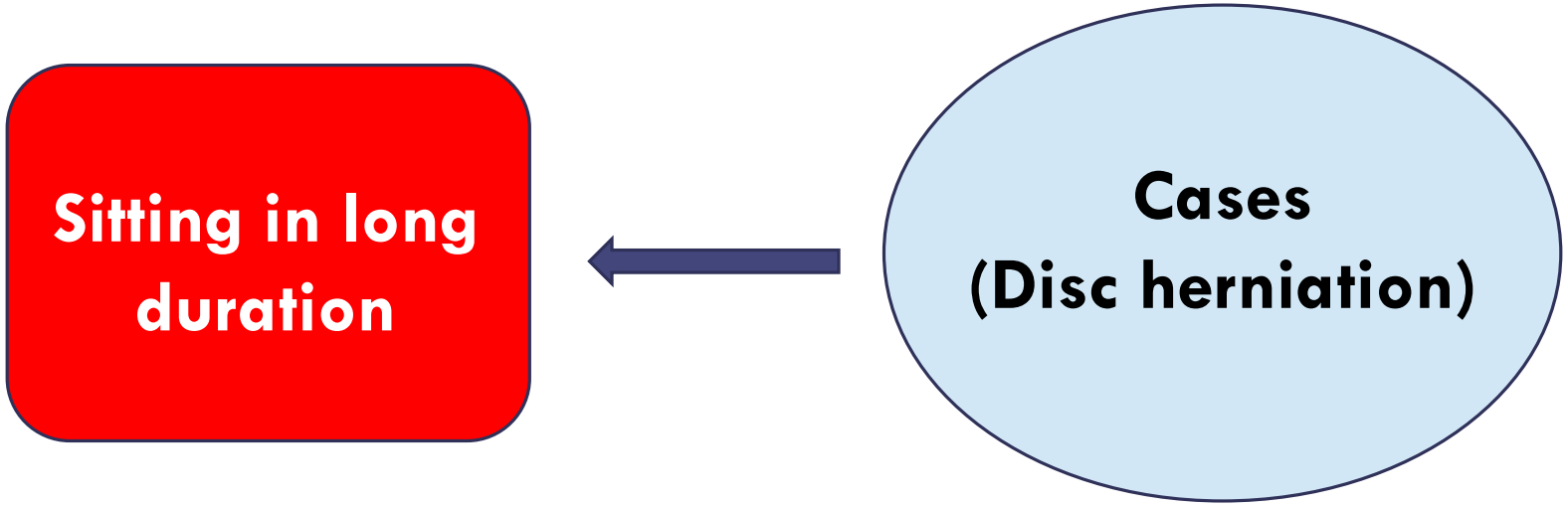
malformed control

The study population comprised 10.1 million births from 1995 to 2011, of which 6.3 million were an independent study population

There were 226,806 CA registrations in the study population, divided into nonchromosomal (n 5,199,515, 88%) and chromosomal CA (n 527,291, 12%)

CASES

- However, they should be **incident cases** and avoid the prevalence cases due to exposure distortion.



Prevalent case (old case) –
may recall not real exposure

CONTROLS

- For the **hospital-based case-control study**, the recommendation for control selection are

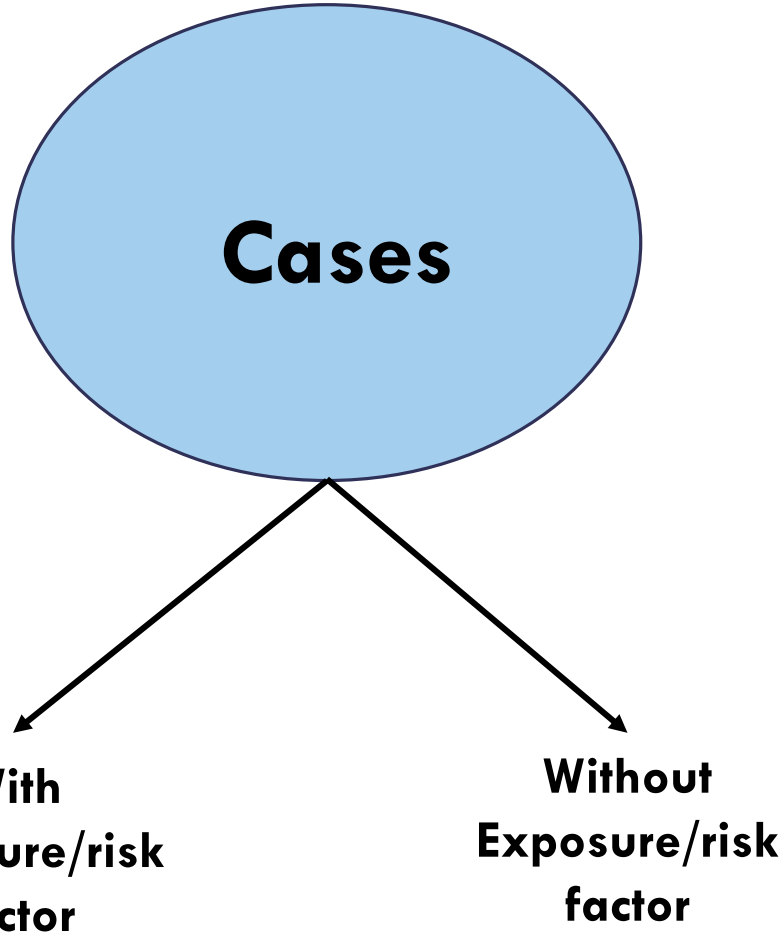
1. **New patients only**
2. Low number of underlying disease
3. Unspecified disease (reflects the real exposure)
4. Avoid disease that is correlated with the interesting exposure

GI clinic – large amount of dyspepsia patients with high rate of NSAIDs use
Outcome of our study – CA colon
"NSAIDs might be protective factor for CA colon (not real)"

CONTROLS (COMMUNITY STUDY)

- Should be similar to the cases in all respects other than the disease in question
- Should be representative of all persons without the disease in the population from which the cases are selected
- **Should have the potential to become cases**

Less vaccinated
High risk of being case



More vaccinated
Low or No risk of being case

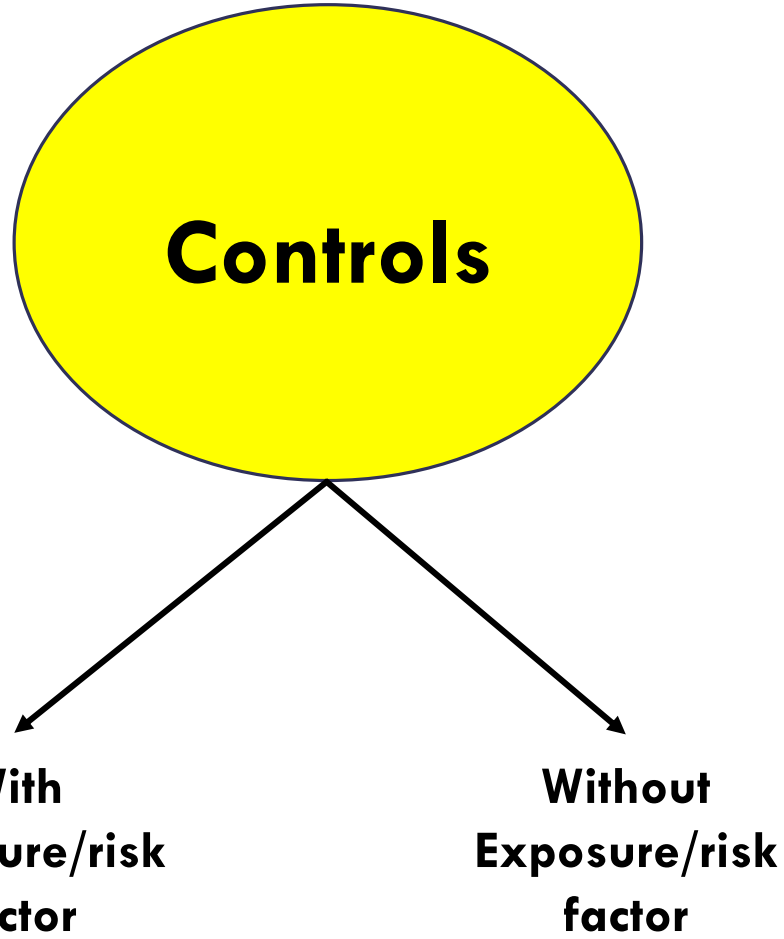


Table 1 Overview of participating registries: Region/country, source of medication exposure information, study years, total birth population covered, total major congenital malformation (MCM) registrations

Registry	EAM[a]	Birth years (independent study population)[b]	Total births	MCM no.	MCM %
Belgium, Antwerp	M	1997-2011 (2006-2011)	286,751	7,107	2.48
Belgium, Hainaut	M, P	1997-2005 (none)	110,557	2,971	2.69
Croatia, Zagreb	M	1995-2010 (2005-2010)	105,353	1,813	1.72
Denmark, Odense	M	1995-2011 (2005-2011)	92,211	2,542	2.76
Finland	P	1996-2008 (all)	753,000	22,839	3.03
France, Paris	M	1997-2011 (2006-2011)	508,721	17,430	3.43
France, Strasbourg	M	1997-2004 (2003-2004)	102,495	3,351	3.27
Germany, Mainz	M, O	1996-2011 (2005-2011)	52,190	2,485	4.76
Germany, Saxony-Anhalt	M, I	1996-2011 (2006-2011)	250,210	8,045	3.22
Ireland, Cork & Kerry	M	1996-2010 (2004-2010)	131,119	3,400	2.59
Italy, Emilia Romagna	M, I	2000-2011 (2005-2011)	426,954	8,455	1.98
Italy, Tuscany	M, I	2002-2011 (2006-2011)	296,483	6,254	2.11
Malta	M	1996-2010 (2005-2010)	63,051	2,020	3.20
Netherlands, North	M, I, P	1995-2011 (2006-2011)	323,728	8,620	2.66
Norway	M	1999-2011 (2006-2011)	713,503	23,423	3.28[c]
Poland	M, I	1999-2010 (2005-2010)	3,228,380	47,851	1.48
Poland, Wielkopolska	M, I	1999-2010 (2005-2010)	440,096	11,269	2.56
Spain, Basque Country	M, P	1995-2010 (2006-2010)	297,531	5,999	2.02
Sweden	M	1999-2011 (all)	1,300,269	18,718	1.44[c]
Switzerland, Vaud	M, O	1997-2011 (2006-2011)	112,156	4,378	3.90
UK, Wales	M	1998-2011 (2006-2011)	466,301	17,836	3.82
Total			10,061,059	226,806	2.25

ARE THE RESULTS OF THE STUDY VALID ?

2. Were the circumstances and methods for determining exposure similar for case and control ?

Information about maternal medication exposure is mainly obtained from medical records of pregnancy, and some registries also use maternal interviews after birth or prescription databases

Answer: Yes, since in both case and control groups were treated in the same way regarding the exposure ascertainment method (EAM)

The researchers tried to avoid misclassification by excluding mothers with epilepsy without recorded AED exposure

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COHORT STUDY

Epilepsy & Behavior,
Epub ahead of print October 17, 2016

Selected article

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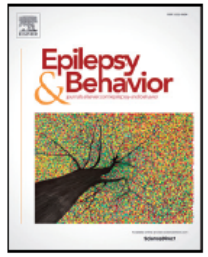

Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy

Ru-Qian He [a,b], Qing-Yi Zeng [a], Pan Zhu [a], Yi-Xin Bao [a], Rong-Yuan Zheng [a,*], Hui-Qin Xu [a,*]

[a] *Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Nanbaixiang Street, Ouhai District, Wenzhou City, Zhejiang Province 325015, PR China*
[b] *Department of Neurology, The Third Affiliated Hospital of Wenzhou Medical University (Ruian People's Hospital), Wansong Street, Ruian District, Wenzhou City, Zhejiang Province 325200, PR China*

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ABSTRACT

Objective: The objective of this study was to estimate the risk of a seizure relapse and the high-risk period of recurrence after antiepileptic drug (AED) withdrawal and to determine the predictive factors for a seizure relapse in adult patients with focal epilepsy who were seizure-free for more than 2 years.
Methods: Using the Wenzhou Epilepsy Follow-Up Registry Database, 200 adult patients with focal epilepsy were recruited, who were undergoing follow-up, met the inclusion criteria of this study, were seizure-free for more than 2 years, began withdrawing between June 2003 and June 2014, and were followed up prospectively for at least 1 year or until a seizure relapse. The risk of recurrence and the time to seizure relapse were analyzed by

RATIONALES

- For patients who attain long-term remission under AED treatment, the most important concern is "**when is it suitable to discontinue AEDs and does it relapse after withdrawal?** "

- In the past decades, numerous studies on AED withdrawal have estimated the relapse risk. The **relapse risk** after withdrawal in patients who were seizure-free for at least 2 years fluctuated from **12% to 67%**

Berg AT and Shinnar S; Neurology 1994
Specchio LM and Beghi E; CNS Drugs 2004
Schmidt D and Loscher W; Acta Neurol Scand 2005

RATIONALES

- The **risk factors** associated with a seizure relapse are yet to be fully identified and still **remain controversial**

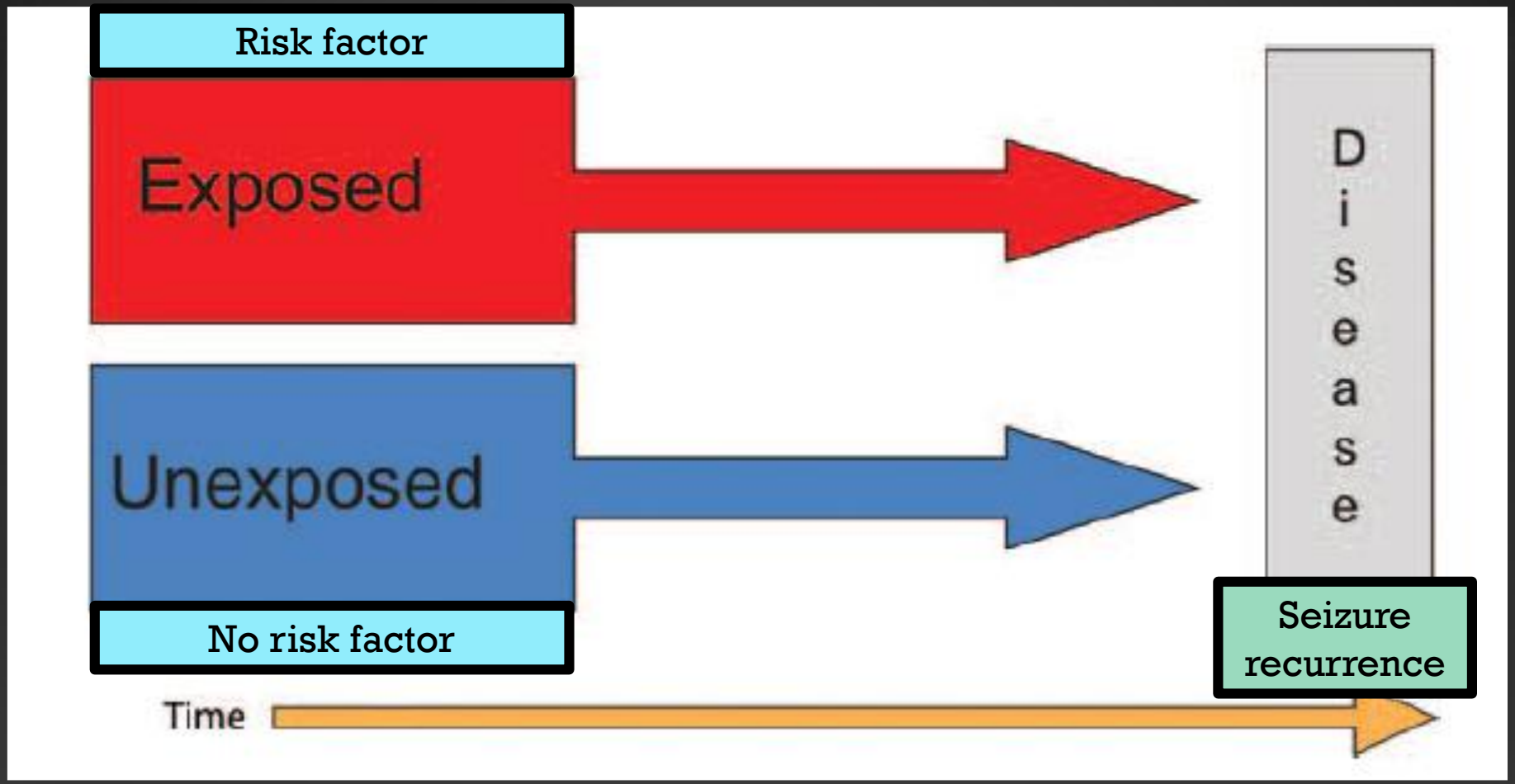
- As the published research on AED withdrawal have relied mainly on the **heterogeneous study population**, the conclusions of these heterogeneous outcomes are challenging to translate to specific types of patients in clinical practice

OBJECTIVES

- To estimate the followings in **adult patients** with **focal epilepsy** who were **seizure-free for at least 2 years**

- ✓ The relapse risk
- ✓ The high-risk period of recurrence after withdrawal
- ✓ To determine the predictive factors for seizure relapse

Cohort entry at date of AED withdrawal



CRITICAL APPRAISAL

- How serious is the risk of bias ?
- What are the results ?
- How can we apply the results to patient care ?

HOW SERIOUS IS THE RISK OF BIAS ?

- **Was the sample of patients representative ?**

❖ How close to “ideal” does the study come in terms of how the disease was defined ?

Answer: The included participants were representative of true disease state since the researchers used a standard definition (ILAE 1989) to define the disease.

“The diagnosis of epilepsy was defined as the occurrence of two or more unprovoked seizures at least 24 h apart. The diagnosis of focal epilepsy was based on a patient's ictal clinical focal semiology (witnessed by doctors, description by patients or their family, or by video records)”

HOW SERIOUS IS THE RISK OF BIAS ?

- **Was the sample of patients representative ?**
  - How the participants were assembled (“full spectrum of illness”) ?

Answer:

Table 1
Demographic and baseline clinical characteristics of enrolled patients.

Sex (m/f)	103 (51.5%)/97 (48.5%)
Age (median, range)	34 (22–77) years
Age at seizure onset (median, quartile range)	21 (17, 29) years
Age at withdrawal (median, range)	30 (19–74) years
Period of follow-up after the beginning of withdrawal (median, range)	3.4 (1–9) years
Duration of active epilepsy (median, quartile range)	33 (9, 85) months
Seizure-free period before withdrawal (median, range)	3.5 (2–15) years
Type of seizures (partial/secondarily generalized)	22 (11.0%)/178 (89.0%)
Seizure frequency before seizure control (≤1/>1 seizure monthly)	131 (65.5%)/69 (34.5%)
Symptomatic/cryptogenic epilepsy	97 (48.5%)/103 (51.5%)
Drug status at the end of study (complete/partial withdrawal)	144 (72.0%)/56 (28.0%)
EEG/VEEG epileptiform at diagnosis (yes/no)	46 (23.0%)/154 (77.0%)
AED at withdrawal (monotherapy/polytherapy)	166 (83.0%)/34 (17.0%)
Tapering period (rapid/gradual withdrawal)	54 (27.0%)/146 (73.0%)

The researchers recruited the participants with varied characteristics. This should be well representative of general patients in clinical practice with potential generalizability

HOW SERIOUS IS THE RISK OF BIAS ?

- **Was the sample of patients representative ?**

However, the target population was recruited from the specialized epilepsy outpatient clinic of the First Affiliated Hospital of Wenzhou Medical University (FAHWMU)

Likely there is a **referral bias** since FAHWMU is a tertiary center. This might compromise the representativeness of participants in terms of disease severity

Wenzhou Epilepsy Follow-Up Registry Database (WEFURD) was established in 2003. Covering a total population of nearly 10 million from Wenzhou and surrounding areas, WEFURD is the largest epilepsy database in Zhejiang Province, China. By March 2014, WEFURD has enrolled 3305 epilepsy patients

HOW SERIOUS IS THE RISK OF BIAS ?

- **Were the patient classified into prognostically similar groups ?**

Answer: Not present

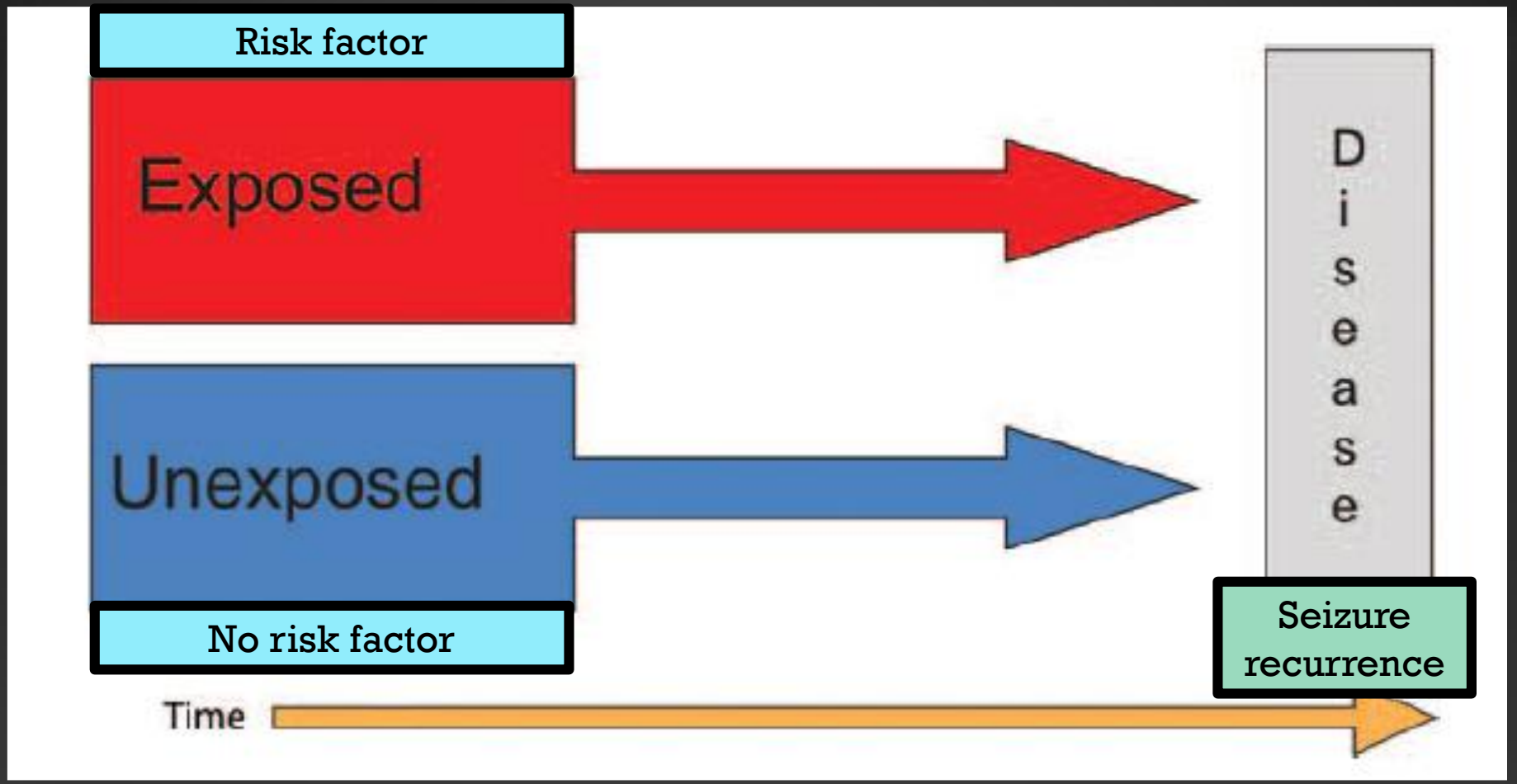

Risk factor
Exposed
Unexposed
No risk factor
Disease
Seizure recurrence
Time

Table 2. Baseline characteristics of study patients

	No withdrawal (n = 78)	Withdrawal (n = 72)	p-values
Mean age (range)	37 (18–66)	40 (19–65)	0.057
Female (percent)	39 (50)	41 (57)	0.39
Epilepsy onset; no. of patients (percent)			
0–11 years	10 (13)	4 (6)	0.31
11–18 years	22 (28)	22 (31)	
18–60 years	46 (59)	46 (64)	
Seizure-free; no. of patients (percent)			
2–3 years	3 (4)	6 (8)	0.41
3–5 years	20 (26)	21 (29)	
>5 years	55 (71)	45 (63)	
Epilepsy type; no. of patients (percent)			
Localization related	59 (76)	55 (76)	0.39
Generalized	17 (22)	17 (24)	
Unclassified	2 (3)	0	
Seizure type; no. of patients (percent)			
Partial epilepsy			
Secondarily generalized tonic–clonic seizures	52 (68)	44 (61)	0.49
Complex partial seizures	19 (25)	26 (36)	0.15
Simple partial seizures	19 (25)	17 (24)	1.00
Unclassified seizures	0	1 (1)	0.48
Generalized epilepsy			
Primarily generalized tonic–clonic seizures	14 (18)	16 (22)	0.55
Absences	1 (1)	1 (1)	1.00
Other	1(1)	1 (1)	1.00
No. of patients (percent)			
Normal neurological status	72 (92)	68 (94)	0.60
MRI pathology	21 (28)	16 (23)	0.45
Known etiology	23 (30)	20 (28)	0.82
Epileptic activity on the EEG	35 (45)	25 (34)	0.13
Serum concentration in therapeutic range	63 (81)	55 (76)	0.51
Medication; no. of patients (percent)			
Carbamazepine	52 (67)	41 (57)	0.22
Valproate	18 (23)	15 (21)	0.74
Phenytoin	5 (6)	8 (11)	0.30
Phenobarbital	2 (3)	3 (4)	NA
Lamotrigine	1 (1)	5 (7)	NA

NA = not applicable.

Akershus Study 2008

Lossius MI; Epilepsia 2008

HOW SERIOUS IS THE RISK OF BIAS ?

- **Was follow-up sufficiency complete ?**

Answer: A total of 200 patients eligible for the present study were derived from WEFURD. Among the 200 patients analyzed, 19 who followed up after withdrawal for more than 1 year **did not return for follow-up** through the end of the study, accounting for **9.5% of the total number**

The rate of relapse was **49.5%** in this study.
The Kaplan–Meier survival curve showed that the
Recurrence probability at

12 mo → **24.0%**	48 mo → **2.7%**	84 mo → **0.98%**
24 mo → **20.4%**	60 mo → **4.6%**	
36 mo → **8.3%**	72 mo → **0.97%**	

after AED withdrawal

The proportion of patients who are lost to follow-up (9%) might not affect the rate of relapse at 12 and 24 months since the proportion of patients who have had seizure relapse at these time points are relatively high

HOW SERIOUS IS THE RISK OF BIAS ?

- **Were outcome criteria objective and unbiased ?**

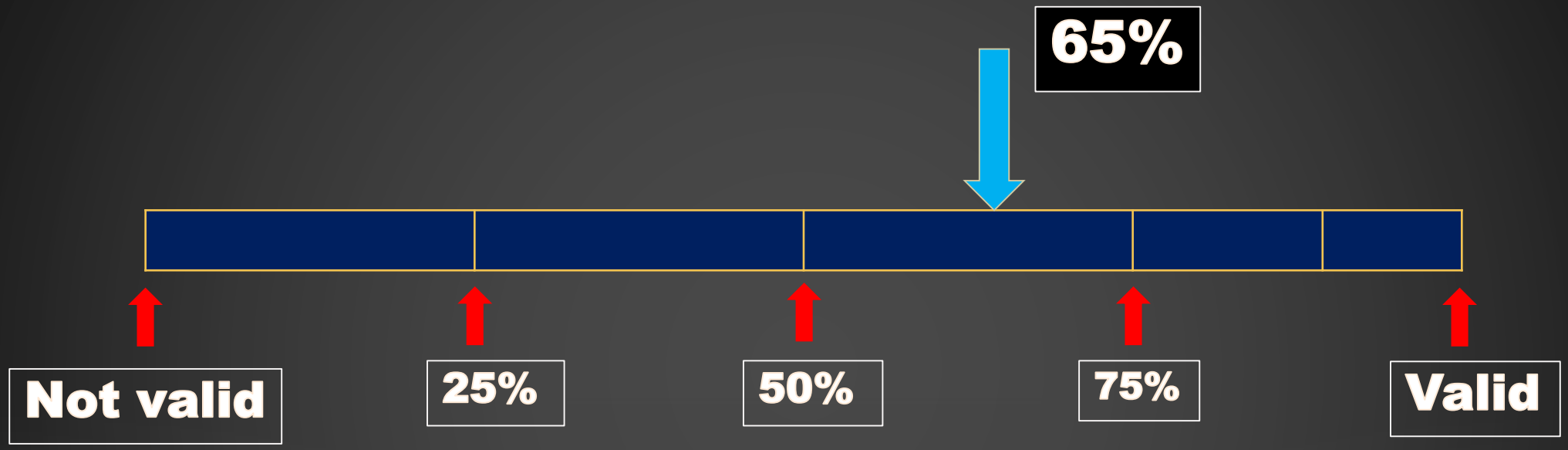
Answer: Yes. There is no measurement bias since all outcomes are objectively measured

The main outcome end points were as follows:

- ***Seizure relapse after withdrawal***: defined as the recurrence of seizures without any provocations after withdrawal (The definition of nonseizure was according to the patients or family report that there had not been any type of epileptic seizure)
- ***Time to the first seizure relapse after withdrawal***

The potential outcome risk factors were as follows: gender, age at epilepsy onset, family history of epilepsy, history of febrile convulsion, perinatal history, history of status epilepticus, types of seizures (partial and/or secondarily generalized seizures) and number, seizure frequency before seizure control, results of MRI or CT examination, etiology, neurological and psychiatric findings, duration of active epilepsy, seizure-free period before withdrawal, initial treatment response, AED at withdrawal (monotherapy or polytherapy), previous unsuccessful withdrawal attempt, number of ineffective drugs used, tapering period, and EEG/VEEG findings at first diagnosis and before AED withdrawal.

RANGE OF VALIDITY



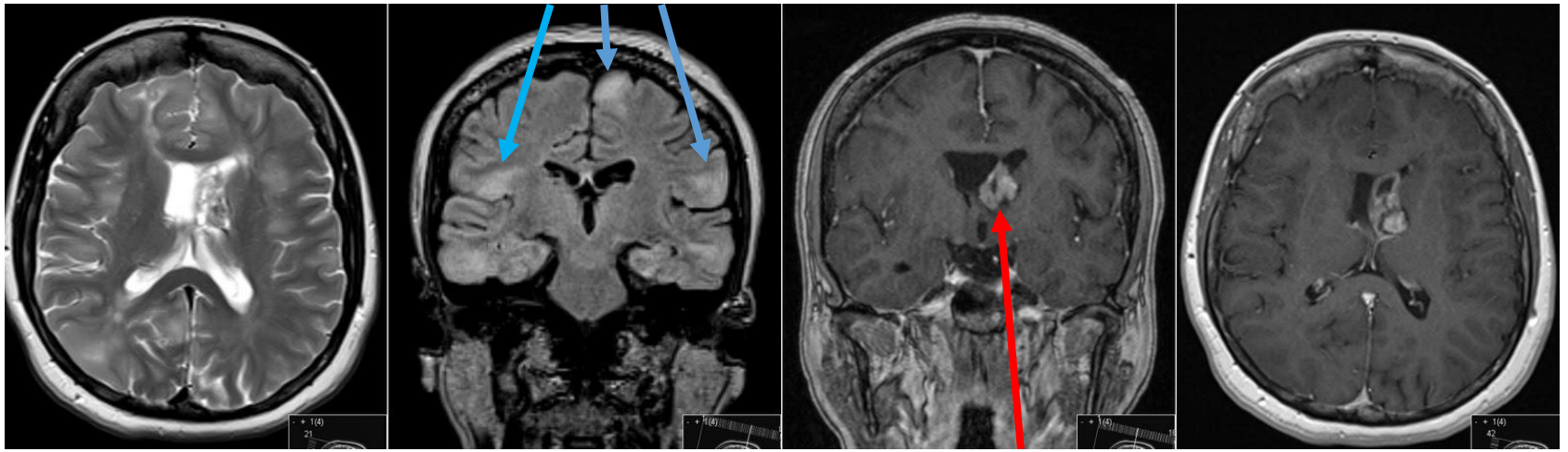
- ✓ Was the sample of patients representative ? (10% from 30%)
- ✓ Were the patient classified into prognostically similar groups ? (not applicable)
- ✓ Was follow-up sufficiency complete ? (25% from 35%)
- ✓ Were outcome criteria objective and unbiased ? (30% from 35%)

RCT

Clinical Scenario

- 25-year-old woman with **medically intractable epilepsy** secondary to tuberous sclerosis. She has been tried on several anti-epileptic drugs (AEDs) including **PB, PHT, CBZ, VPA, LVT, and TPM**, but her seizures have remained frequent on average of 5 seizures in a week. Her current AEDs are PHT, LTG, and ZNM. After a thorough evaluation, she is **not a good candidate for epilepsy surgery**

Tumor-like lesions (hamartoma)



Subependymal giant cell astrocytoma (SGCA)

Selected article

Lancet, Published Online
September 6, 2016

Articles

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz

Summary

Background Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been used for various benign tumours associated with tuberous sclerosis complex. We assessed the efficacy and safety of two trough exposure concentrations of everolimus, 3–7 ng/mL (low exposure) and 9–15 ng/mL (high exposure), compared with placebo as adjunctive therapy for treatment-resistant focal-onset seizures in tuberous sclerosis complex.

Methods In this phase 3, randomised, double-blind, placebo-controlled study, eligible patients aged 2–65 years with tuberous sclerosis complex and treatment-resistant seizures (≥16 in an 8-week baseline phase) receiving one to three concomitant antiepileptic drugs were recruited from 99 centres across 25 countries. Participants were randomly

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(16)31576-8

NYU Comprehensive Epilepsy Center, New York, NY, USA

Rationales and objectives

- **Everolimus** is an **mTOR inhibitor** that has been approved for the treatment of subependymal giant-cell astrocytoma and renal angiomyolipoma in patients with tuberous sclerosis complex

- A Study of Tuberous Sclerosis Complex (**EXIST-3**) evaluated **the efficacy and safety of two dosing regimens of adjunctive everolimus compared with placebo** in patients with tuberous sclerosis complex and treatment-resistant focal epilepsy

Critical appraisal

- Are the results of the study valid ?
- What are the results ?
- How can we apply the results to patient care ?

Study designs and participants

AEDs plus placebo (control)

AEDs plus everolimus 3-7 ng/ml (low-exposure)

AEDs plus everolimus 9-15 ng/ml (high-exposure)

EXIST-3 is a **three-arm**, prospective, randomised, multicentre, double-blind, placebo-controlled, phase 3 study

8-week baseline phase

TS aged 2- 65 yrs,
≥ 16 seizures/8 wks
receiving stable dose of 1-3 AEDs for 12 wks before randomization

18-week core phase

- At the beginning: randomization
- Dose adjustments to attain the target C_{min} were done during the first 6 weeks of the core phase, and as needed during the subsequent 12-week maintenance period

Are the results of the study valid ?

1. Were patients randomized ?

At the end of the baseline phase, eligible patients entered the core phase and were randomly assigned (1:1:1), via permuted-block randomisation (block size of six) implemented by Interactive Response Technology (IRT) software, to receive

- **placebo**
- **low exposure everolimus, C_{min} 3–7 ng/mL**
- **high-exposure everolimus, C_{min} 9–15 ng/mL**

Randomisation was stratified by age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years)

Are the results of the study valid ?

2. Was randomized concealed ?

Yes, using central randomization

Are the results of the study valid ?

3. Were patients in the study groups similar with respect to known prognostic factors ?

All patients: 366
Placebo: 119
Low-exposure: 117
High-exposure: 130

Age, sex, race, body-surface area, AEDs failed before study start, seizure frequency, AEDs during baseline phase, seizure types during baseline phase are comparable between placebo, low-exposure, and high-exposure everolimus groups

	Placebo (n=119)	Everolimus 3–7 ng/mL (n=117)	Everolimus 9–15 ng/mL (n=130)	All patients (n=366)
Age, years				
Median (range)	10·3 (2·2–52·0)	9·7 (2·2–56·3)	10·1 (2·3–50·5)	10·1 (2·2–56·3)
<6	34 (29%)	33 (28%)	37 (28%)	104 (28%)
6 to <12	37 (31%)	37 (32%)	39 (30%)	113 (31%)
12 to <18	25 (21%)	26 (22%)	31 (24%)	82 (22%)
≥18	23 (19%)	21 (18%)	23 (18%)	67 (18%)
Sex				
Female	58 (49%)	53 (45%)	65 (50%)	176 (48%)
Male	61 (51%)	64 (55%)	65 (50%)	190 (52%)
Race				
White	77 (65%)	76 (65%)	84 (65%)	237 (65%)
Black	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Asian	27 (23%)	29 (25%)	31 (24%)	87 (24%)
Native American	0	0	1 (1%)	1 (<1%)
Pacific Islander	0	1 (1%)	0	1 (<1%)
Other	14 (12%)	9 (8%)	13 (10%)	36 (10%)
Body-surface area, m²				
Median (range)	1·10 (0·5–2·2)	1·09 (0·5–2·4)	1·09 (0·5–2·6)	1·10 (0·5–2·6)
Antiepileptic drugs failed before study start				
2	5 (4%)	4 (3%)	8 (6%)	17 (5%)
3	13 (11%)	15 (13%)	9 (7%)	37 (10%)
4	16 (13%)	22 (19%)	27 (21%)	65 (18%)
5	22 (18%)	22 (19%)	25 (19%)	69 (19%)
6	10 (8%)	10 (9%)	17 (13%)	37 (10%)
>6	53 (45%)	44 (38%)	44 (34%)	141 (39%)

Data are n (%), unless otherwise specified.

Table 1: Demographic characteristics and medical history by treatment group

	Placebo (n=119)	Everolimus 3–7 ng/mL (n=117)	Everolimus 9–15 ng/mL (n=130)	All patients (n=366)
Seizure frequency	42·0 (5·3–926·7)	34·5 (5·5–771·5)	37·8 (1·0–873·5)	..
Antiepileptic therapy during baseline phase				
Number of AEDs in the regimen				
1	15 (13%)	7 (6%)	18 (14%)	40 (11%)
2	41 (34%)	55 (47%)	55 (42%)	151 (41%)
3	62 (52%)	55 (47%)	56 (43%)	173 (47%)
>3	1 (1%)	0	1 (1%)	2 (1%)
Vagal nerve stimulation	10 (8%)	13 (11%)	11 (8%)	34 (9%)
Ketogenic diet	4 (3%)	1 (1%)	2 (2%)	7 (2%)
Seizure types during baseline phase				
Focal motor with retained awareness	26 (22%)	20 (17%)	25 (19%)	71 (19%)
Focal non-motor with impaired awareness	47 (39%)	58 (50%)	60 (46%)	165 (45%)
Focal motor with impaired awareness	31 (26%)	32 (27%)	32 (25%)	95 (26%)
Other focal motor seizures	47 (39%)	51 (44%)	51 (39%)	149 (41%)
Focal to bilateral tonic-clonic	26 (22%)	20 (17%)	22 (17%)	68 (19%)
Generalised onset seizure (EEG confirmed)	2 (2%)	2 (2%)	2 (2%)	6 (2%)

Data are median (range) or n (%), unless otherwise specified. AEDs=antiepileptic drugs. EEG=electroencephalogram.

Table 2: **Antiepileptic therapy and seizure frequency during the baseline phase by treatment group**

Are the results of the study valid ?

4. To what extent was the study blinded ?

Blinded to : Patients, investigators, site personnel, and the sponsor's study team

Not blinded to: personnel in charge of drug supply, implementation of the randomisation list, pharmacokinetic bioanalysis

The Data Safety Monitoring Board (DSMB) independent statistician and programmer were semi-blind to treatment allocation at the time of DSMB meetings

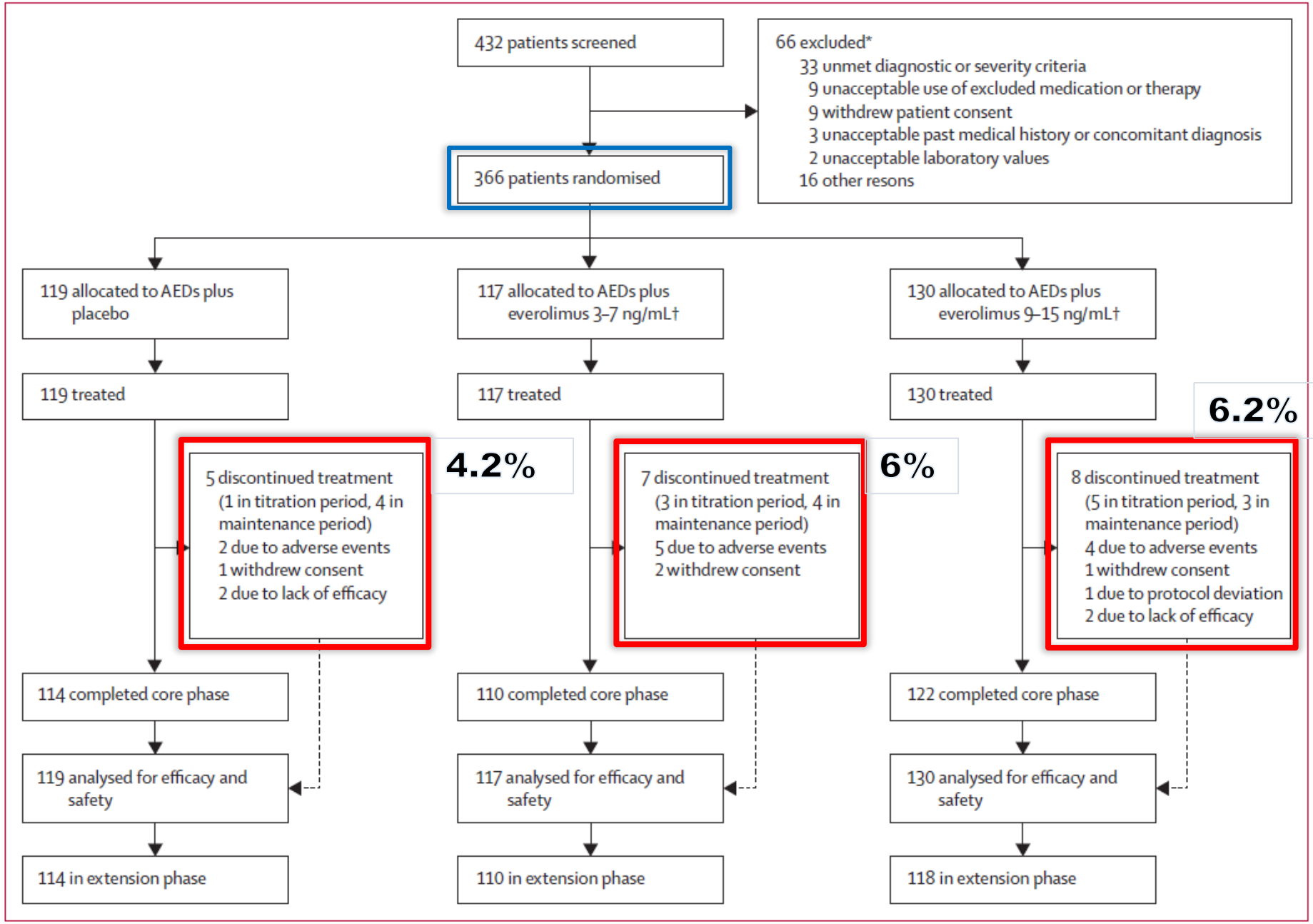
Potential benefits of blinding

Individuals	Potential benefits
Patients	-Less likely to have biased psychological or physical responses to intervention -More likely to comply with trial regimens -Less likely to seek additional adjunct interventions
Clinicians	-Less likely to differentially administer co-interventions -Less likely to differentially adjust dose -Less likely to differentially withdraw participants -Less likely to differentially encourage or discourage participants to continue trial
Assessors	-Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Are the results of the study valid ?

5. Was follow-up complete ?

Yes, no patients loss to follow-up
Discontinuation
Placebo:
5/119 = 4.2%
Low-exposure:
7/117 = 6 %
High-exposure:
8/130 = 6.2%

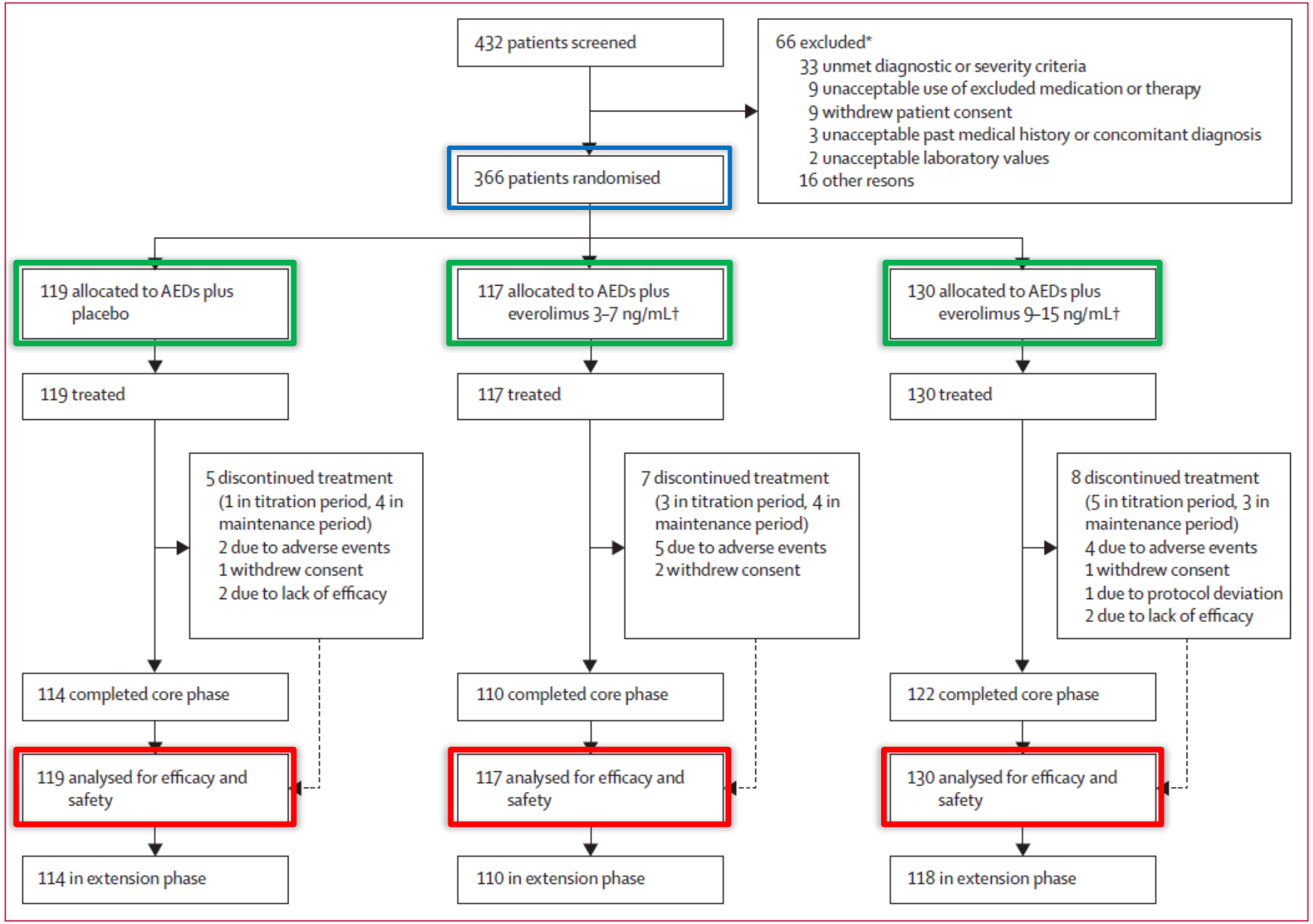


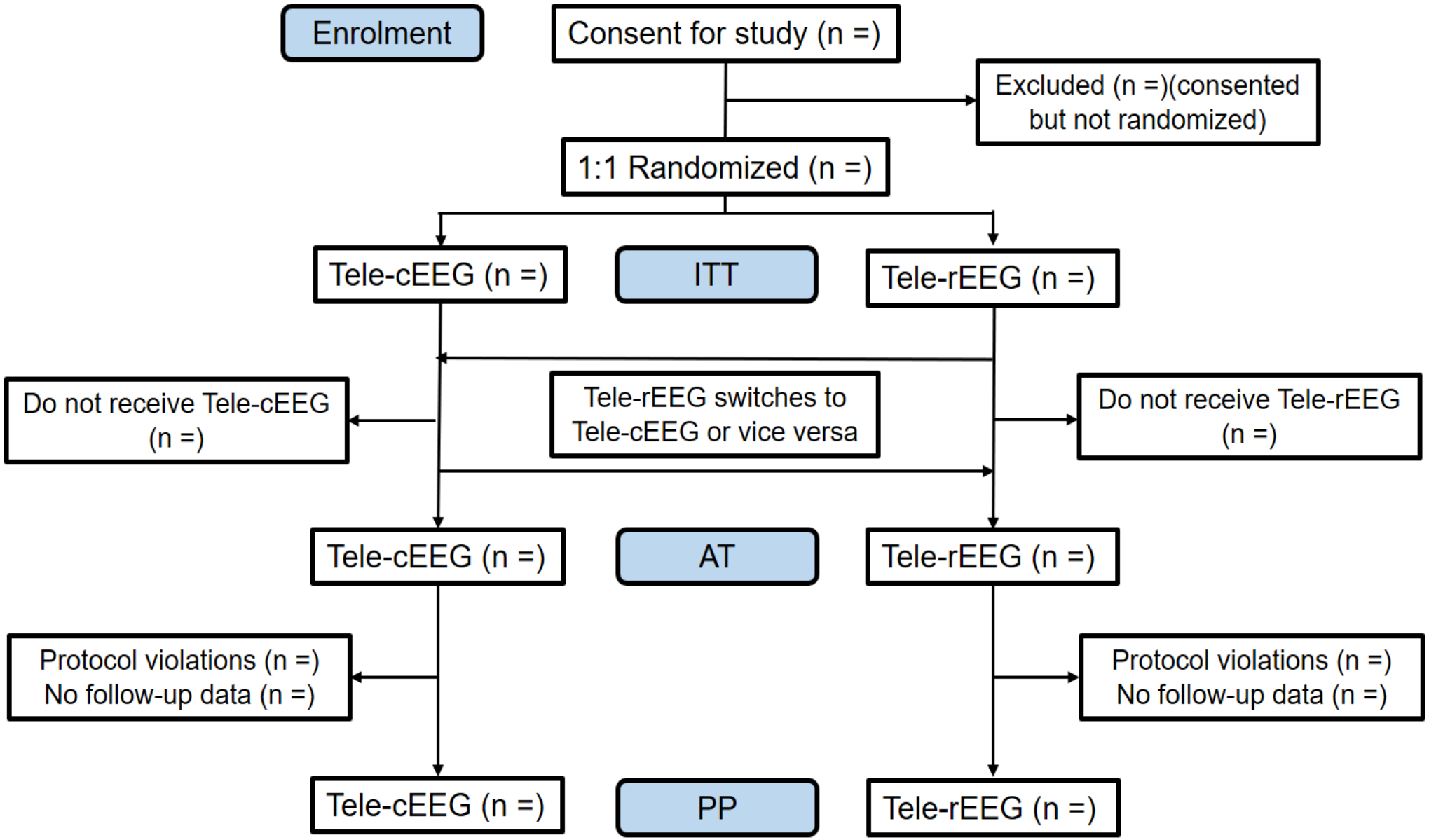
	Trial A		Trial B	
	Rx.	Con	Rx.	Con
No. of pt.	1000	1000	1000	1000
No. of loss F/U	30(3%)	30(3%)	30(3%)	30(3%)
No. of death	200	400	30	60
RRR	(0.4-0.2)/0.4 = 0.50		(0.06-0.03)/0.06 =0.50	
Worst case	0.17/0.4 = 0.43		0.00/0.06 = 0	

Are the results of the study valid ?

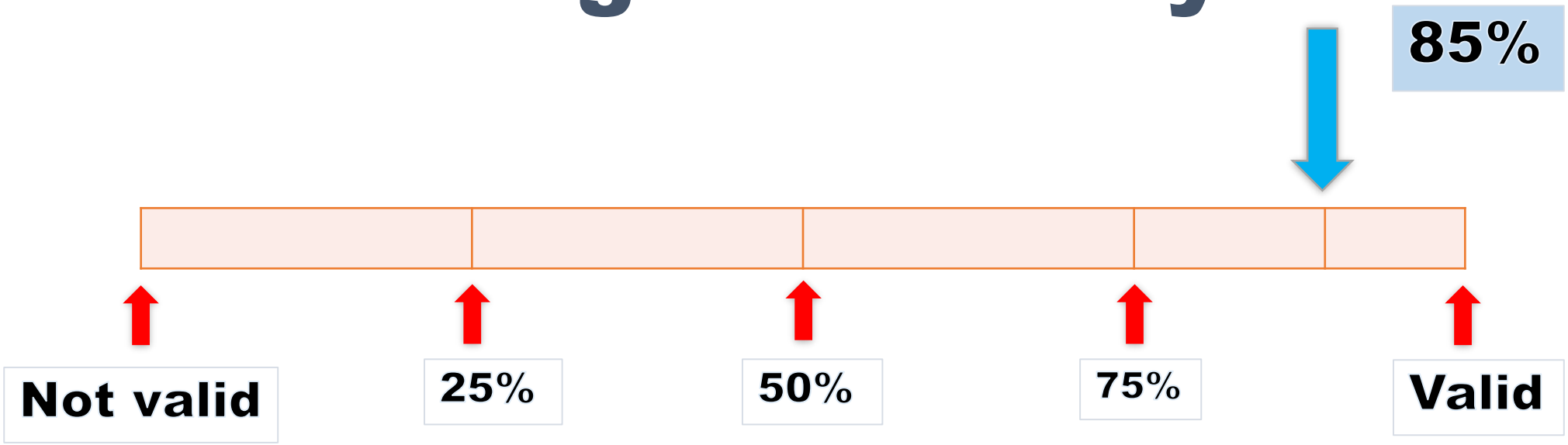
6. Were patients analyzed in the group to which they were analyzed ?

Yes, intention-to-treat was used to analyze the primary efficacy of everolimus




Enrolment
Consent for study (n =)
Excluded (n =)(consented but not randomized)
1:1 Randomized (n =)
Tele-cEEG (n =)
ITT
Tele-rEEG (n =)
Do not receive Tele-cEEG (n =)
Tele-rEEG switches to Tele-cEEG or vice versa
Do not receive Tele-rEEG (n =)
Tele-cEEG (n =)
AT
Tele-rEEG (n =)
Protocol violations (n =)
No follow-up data (n =)
Protocol violations (n =)
No follow-up data (n =)
Tele-cEEG (n =)
PP
Tele-rEEG (n =)

Range of validity



- ✓ Were patients randomized ? = 20%
- ✓ Was randomization concealed ? = 5% (personnel in charge of drug supply, implementation of the randomization list, pharmacokinetic bioanalysis were not blinded)
- ✓ Were patients in the study groups similar ? = 20%
- ✓ To what extent was the study blinded ?
- ✓ Was follow-up complete ? = 20%
- ✓ Were patients analyzed in the group to which they were randomized ? = 20%

“THANK YOU FOR YOUR ATTENTION”