示例：术前等待时间与30天死亡率：队列研究

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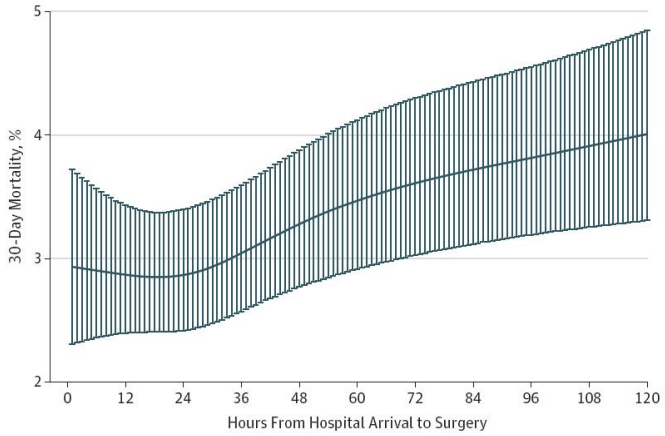
从实例看临床研究的重要性

Figure 1. Probability of the Primary Outcome According to Wait Times for Surgery as a Continuous Variable



Probabilities (95% CIs) models used restricted cubic splines adjusting for age, sex, calendar year, income quintile, rurality, transfer from any health care institution, Deyo-Charlson score, history of frailty, diabetes, heart failure, chronic obstructive pulmonary disease, myocardial infarction, or hypertension, fracture and surgery type, Injury Severity Score, surgeon volume and experience, hospital volume and type, and surgery duration. Analysis conducted among 41 186 of 42 230 patients. C statistic was 0.756. Variance inflation factors were 4 or less for included variable included, indicating an absence of collinearity. Probabilities of the primary outcome according to wait-times for surgery are presented for patients with average fracture, physician, and hospital system characteristics in the cohort.

X：术前等待时间
Y：30天死亡率
人群：成人髋部骨折

Pincus, D., et al. ***JAMA***, 2017. SCI IF=51

提出临床问题开展研究设计

病因

病因混杂

关联分析（X Y）

观察性（队列）

四个表+曲线拟合

X：年龄、BMI、基因等

Y：发生在X之后的

Z：其他可能的影响因素

症状

症状异质

关联分析（X Y）

观察性（队列）

四个表+曲线拟合

X：年龄、BMI、激素等

Y：发生在X之后的

Z：症状等

诊断

诊断争议

诊断/预测模型（Xn Y）

观察性（队列/横断面）

ROC、校准曲线、列线图

Xn：用于诊断的指标

Y：疾病或预后

治疗

治疗多样

关联分析（X Y）

观察性（队列）、RCT

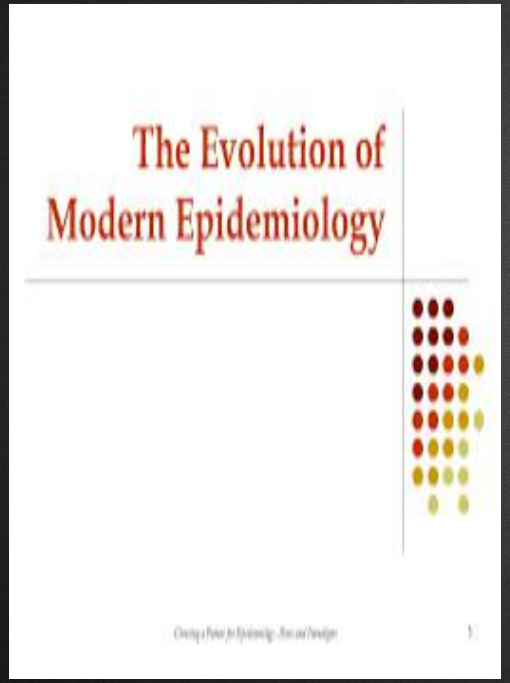
四个表

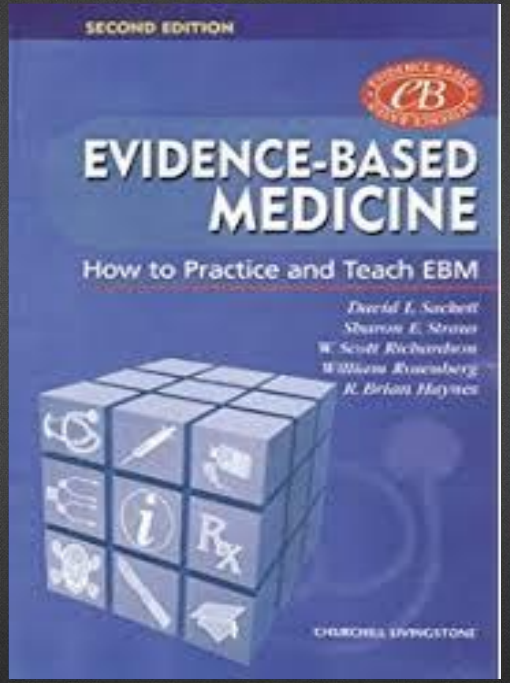
X：治疗方案

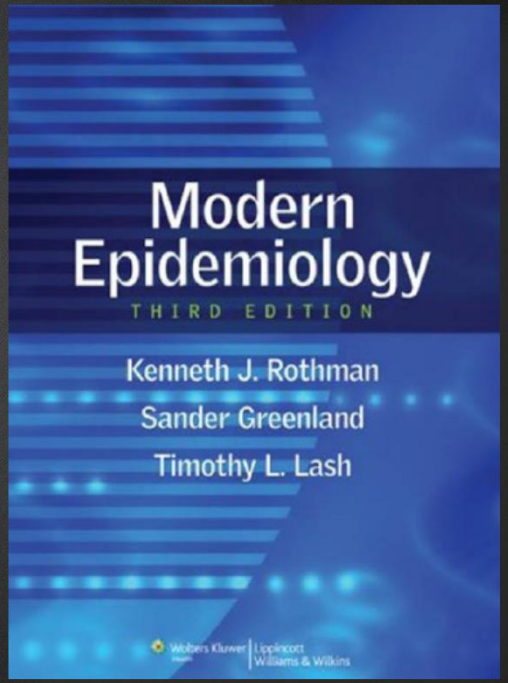
Y：发生在X之后的

Z：年龄、BMI、基因等

我们没有跟上现代临床流行病学的步伐

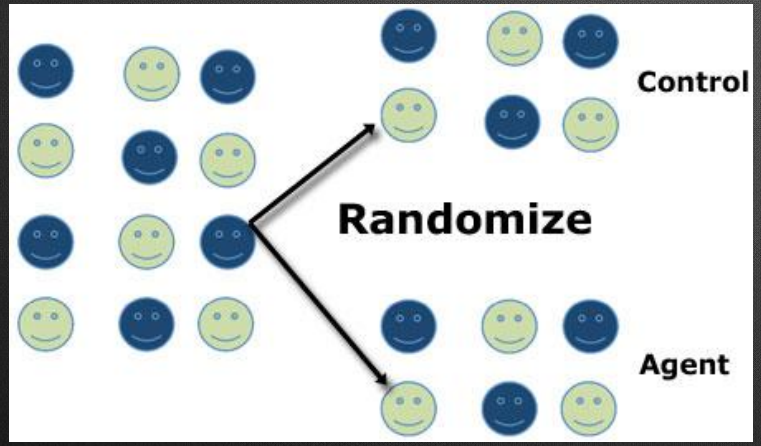






早期的医学科研是以动物实验为主

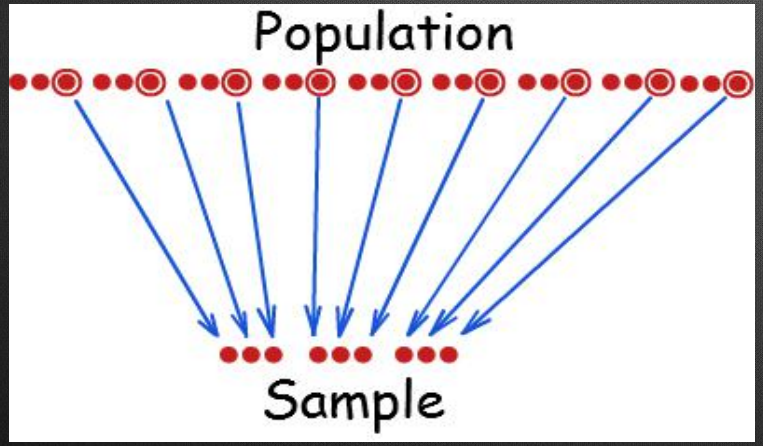
- 控制其它因素的干扰，观察实验因素的作用
- 强调“随机”分组
- 统计方法：t检验、方差分析、卡方检验等组间比较



动物实验

早期的流行病学研究主要以人群抽样调查为主

- 目的是描述疾病在人群中的分布
- 这种人群流调强调“**随机**”，强调样本有“**代表性**”。

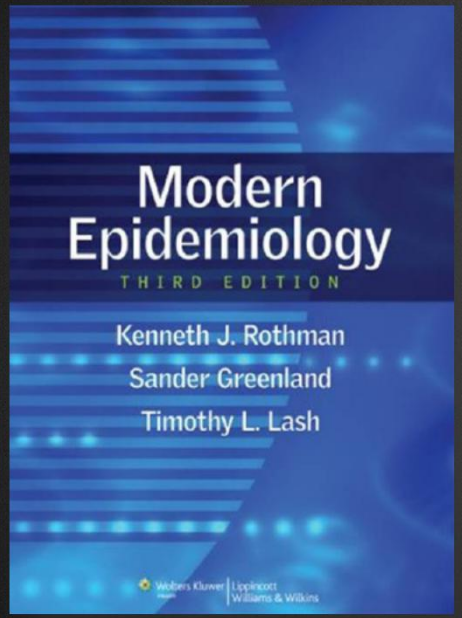


描述性流调

现代流行病学和临床流行病学

- 实际人群
- 观察性研究
- 有众多混杂因素干扰
- 对研究设计、二次资料提取、统计方法，也就是科研分析思路有更高的要求

现代流行病学



- 研究设计：队列、研究人群选择、防止偏性

  ~~“随机抽样”~~ 、~~“随机分组”~~

- 数据分析：多元回归控制混杂、交互作用、曲线关系

  ~~t检验、方差分析、卡方检验~~

跟不上就会被抛弃

- 现代临床流行病学，以在实际人群中开展的观察性研究为主，对研究设计、资料提取、统计分析方法特别是混杂因素的调整与偏性的控制，一句话也就是对科研分析思路有了更高的要求。
- 很多人把随机抽样、随机分组、t检验、方差分析、卡方检验等统计方法学得很透彻，却忽视了现代流行病学科研设计与分析思维的培养，结果仍然看不懂SCI论文，也就是与SCI不接轨。
- 我们缺乏与国际接轨的现代流行病学分析思路培训。

区别

观察性 vs. 试验性

野生的 vs. 圈养的

陈旧的思维模式导致无法进行临床研究课题设计

例：如何验证对某病(D)应用某治疗(T)是否越早越好?

实验性研究思维模式：

随机抽样：从哪个人群中抽?

分组：分成早治疗组与晚治疗组

随机分组：无法随机分配?

组间可比性：早治疗与晚治疗不可比?

双盲法：不可能做到双盲?

统计分析：组间比较T检验与卡方检验

观察性研究思维模式：

选择队列: XX期间在我院治疗的所有符合纳排标准的病人。研究对象之间治疗早晚有差异，不分组。

控制混杂：收集可能与疗效及预后有关的各种混杂因素。

防止偏性：利用既往病历资料分析。

统计分析：用多元回归模型调整混杂，用平滑曲线拟合分析治疗时间与预后的关系，寻找是否有阈值效应或饱和效应，即发现是否有最佳治疗时间段。

明确的研究假设

把题目拆解为 X+Y+研究人群+研究设计

JAMA | Original Investigation

Association Between Wait Time and 30-Day Mortality in Adults Undergoing Hip Fracture Surgery

X → Y

术前等待时间 → 30天死亡率

研究人群：成人髋部骨折

Pincus, D., et al. ***JAMA***, 2017. SCI IF=51

确定研究设计类型

核心

X是否人为分配?
Assigned exposure X?

No → **观察性 Observational**

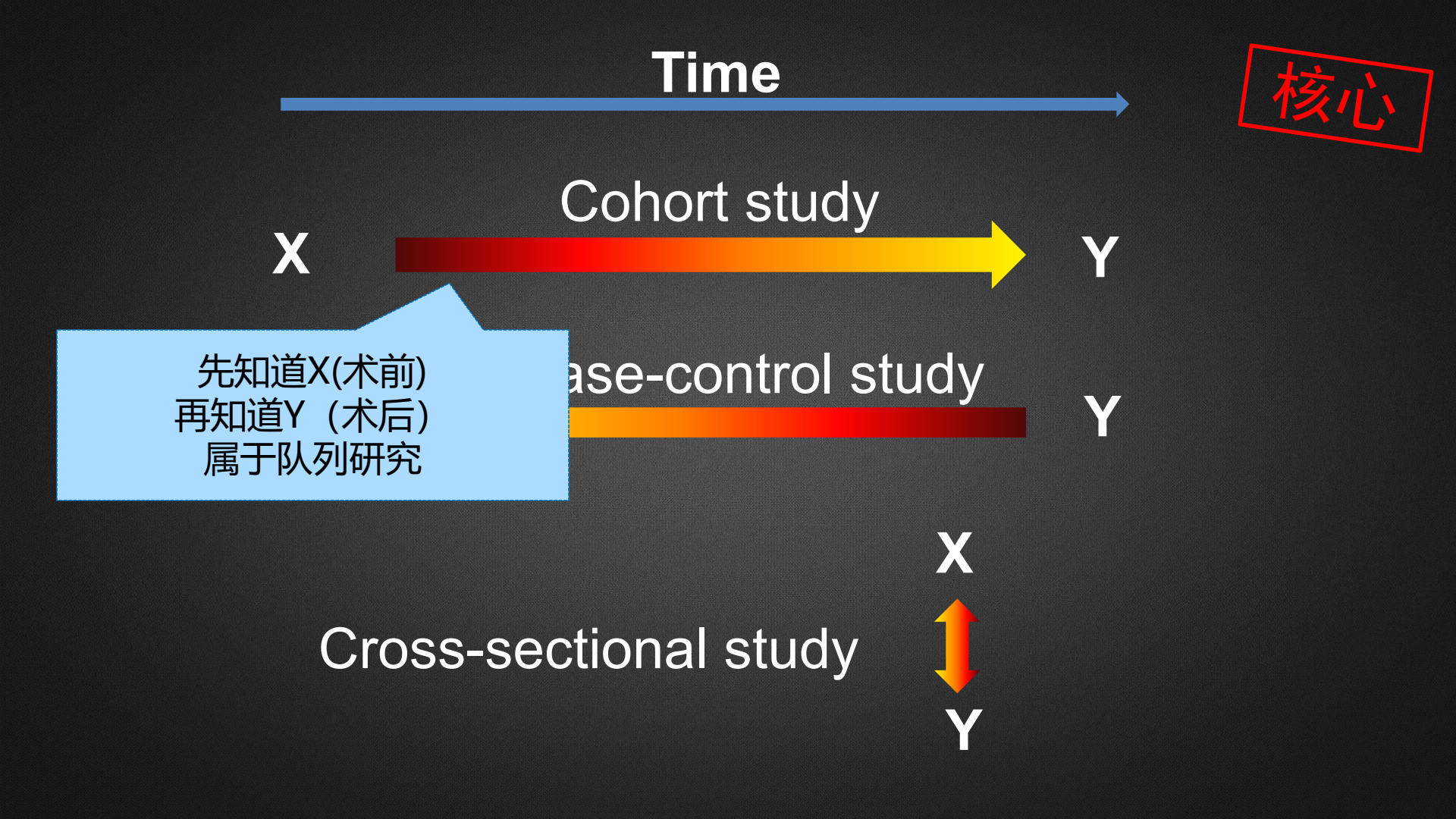
Analytic
- Cross-sectional 横断面
- Case-control 病例对照
- Cohort studies 队列

Yes → **实验性 Experimental**

Randomized controlled trials (RCT)

本研究X是术前等待时间，不是人为分配的，是根据患者病情决定的，是观察性研究。

陈常中 主编《流行病学数据分析与易佾统计软件实现》, 上海科学技术出版社, 2016, 1-2.


Time
核心
Cohort study
X
Y
先知道X(术前)
再知道Y（术后）
属于队列研究
ase-control study
Y
X
Cross-sectional study
Y

选题来源于争议：临床意义和可行性兼备的选题

同X同Y的研究，已经有文章发表
有争议

IMPORTANCE Although wait times for hip fracture surgery have been linked to mortality and are being used as quality-of-care indicators worldwide, controversy exists about the duration of the wait that leads to complications.

OBJECTIVE To use population-based wait-time data to identify the optimal time window in which to conduct hip fracture surgery before the risk of complications increases.

研究对象：不找对照，不分组

队列研究：纳入某段时间在某医院因某原因就诊的所有患者。
术前等待时间是连续指标（小时），不分组。

DESIGN, SETTING, AND PARTICIPANTS Population-based, retrospective cohort study of adults undergoing hip fracture surgery between April 1, 2009, and March 31, 2014, at 72 hospitals in Ontario, Canada. Risk-adjusted restricted cubic splines modeled the probability of each complication according to wait-time. The inflection point (in hours) when complications began to increase was used to define early and delayed surgery. To evaluate the robustness of this definition, outcomes among propensity-score matched early and delayed surgical patients were compared using percent absolute risk differences (RDs, with 95% CIs).

研究假设明确：一个X一个Y

X：定义要清楚（从到达医院到手术，单位：小时）
Y：分主次。主要结局是30天内死亡，次要结局是并发症（包括……）

EXPOSURE Time elapsed from hospital arrival to surgery (in hours).

MAIN OUTCOMES AND MEASURES Mortality within 30 days. Secondary outcomes included a composite of mortality or other medical complications (myocardial infarction, deep vein thrombosis, pulmonary embolism, and pneumonia).

核心结果：回归分析

1. 人口学特征（样本量、年龄、Y）
2. 趋势
3. 作用大小（回归分析效应值和95%CI）

RESULTS Among 42 230 patients with hip fracture (mean [SD] age, 80.1 years [10.7], 70.5% women) who met study entry criteria, overall mortality at 30 days was 7.0%. The risk of complications increased when wait times were greater than 24 hours, irrespective of the complication considered. Compared with 13 731 propensity-score matched patients who received surgery earlier, 13 731 patients who received surgery after 24 hours had a significantly higher risk of 30-day mortality (898 [6.5%] vs 790 [5.8%]; % absolute RD, 0.79; 95% CI, 0.23-1.35) and the composite outcome (1680 [12.2%]) vs 1383 [10.1%]; % absolute RD, 2.16; 95% CI, 1.43-2.89).

核心结果：回归分析

✓人群：患者特征　　不强调样本“代表性”，强调结论的适用范围。

✓写有关联：associated　　不建议写risk factor, independent risk factor等

✓涉及具体数值的结论，委婉严谨留余地：may

CONCLUSIONS AND RELEVANCE Among adults undergoing hip fracture surgery, increased wait time was associated with a greater risk of 30-day mortality and other complications. A wait time of 24 hours may represent a threshold defining higher risk.

研究对象是如何选择的?

- ✓从纳入开始写起
- ✓X或Y缺失的对象可以排除
- ✓其它指标缺失的不需要排除
- ✓最后进入本研究的人数

统计分析部分写缺失数据处理方法:

models.[30] Missing data, which was less than 1% for all variables considered, were excluded from regression models.

Table 1. Assembly of the Study Cohort in Ontario, Canada Between 2009 and 2014

Inclusion and Exclusion Criteria	No.
Inclusion criteria	
Hip fracture surgical procedures in Ontario during study period	48 627
Exclusion criteria	
Non-Ontario resident	31
Dead before or on index date	8
Nonorthopedic surgeon	351
Prior hip fracture	1997
Missing emergency presentation time data	1460
Hip fracture occurring in-hospital	440
Elective hospital admission	1002
Low-volume hospital (<5 hip fracture procedures during study period)	34
Patients aged <45 y	746
Hip fracture surgery delayed >10 d	328
Eligible hip fracture fixation procedures (total study cohort size)	42 230
Eligible treating surgeons	522
Eligible treating hospitals	72

研究设计三要素

核心

随机化	控制混杂	多元回归
盲法	防止偏性	研究设计、数据分析
临床试验 RCT	时相关系	队列研究、病例对照 观察性研究

小结

倒空、放下、守规则

科研宝库：临床病例

努力方向：研究设计

- 明确的研究假设
- 清晰的研究设计
- 结果及临床意义
- 证据力度的思辨