从顶层设计看临床研究的整体流程

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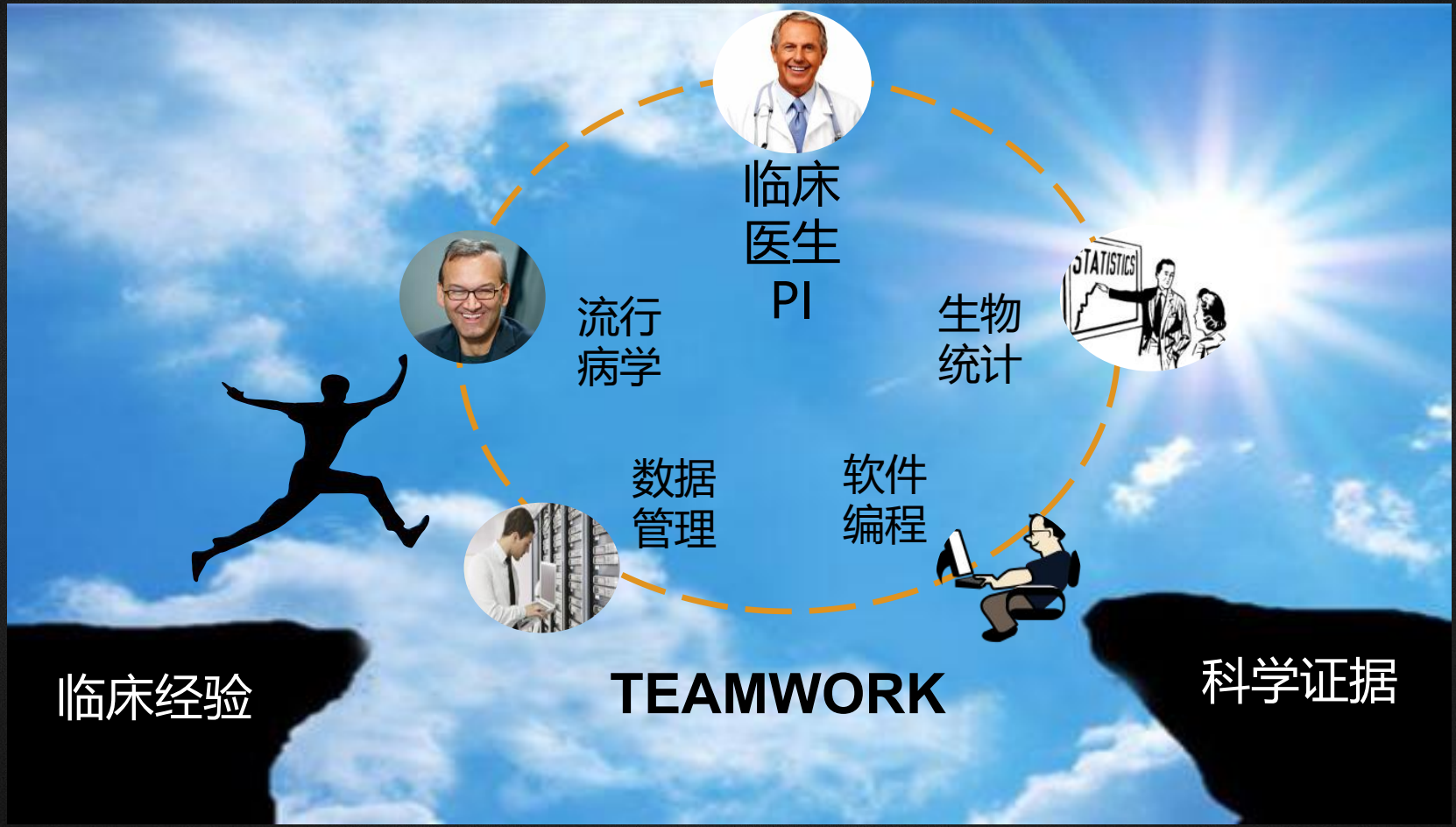
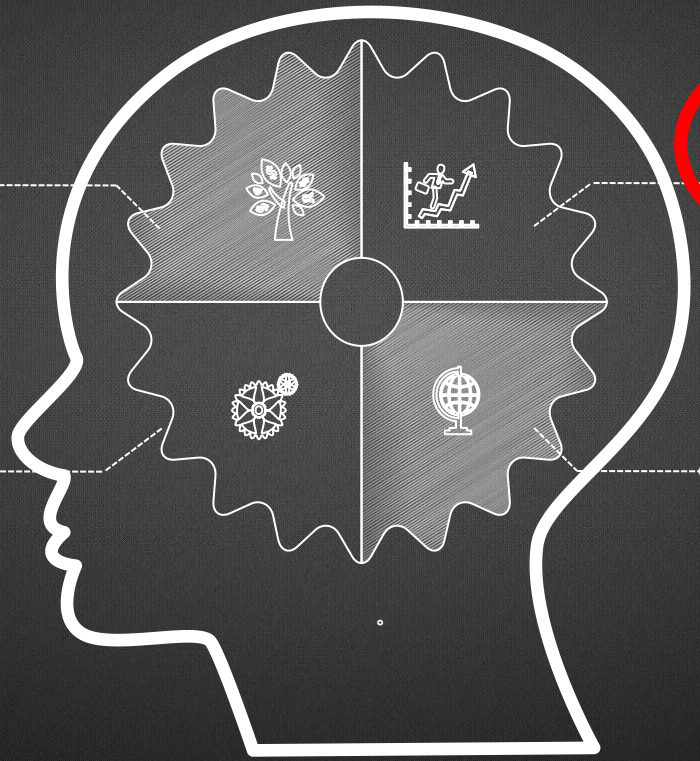
顶层设计：临床问题转化为科研问题



规则是什么?

前言要极其拉风

方法



结果

讨论，要语不惊人死不休

STROBE指南：临床观察性研究规则

前言仅占2项、讨论仅占4项

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

STROBE Statement — checklist of items that should be included in reports of observational studies

STROBE指南：临床观察性研究规则

方法和结果占14项

Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

STROBE Statement — checklist of items that should be included in reports of observational studies

方向错误，停止就是进步

SCI写作技巧
统计方法
软件操作

常见问题：SCI论文投稿选刊

从期刊编辑角度看常见的直接拒稿（不送外审）原因：

1. 选题缺乏临床意义
2. 选题缺乏创新性，未能弥补现有研究的不足之处
3. 选题内容不明确或本期刊不涉及
4. 研究设计类型有明显错误
5. 其他：查重、注册、伦理等

临床研究顶层设计

给期刊量身定制临床研究整体方案：选题、设计、统计图表、论文撰写策略

临床研究顶层设计

论文选刊投稿前，如何兼顾可行性和创新性？

临床科研第一步：明确的研究假设

把题目拆解为 X+Y+研究人群+研究设计

Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age

X

卵巢储备生物标志物
（雌二醇、FSH、AMH等）连续变量

Y

活产
二分类变量

研究人群：医院过去1年IVF的人群（扩展）

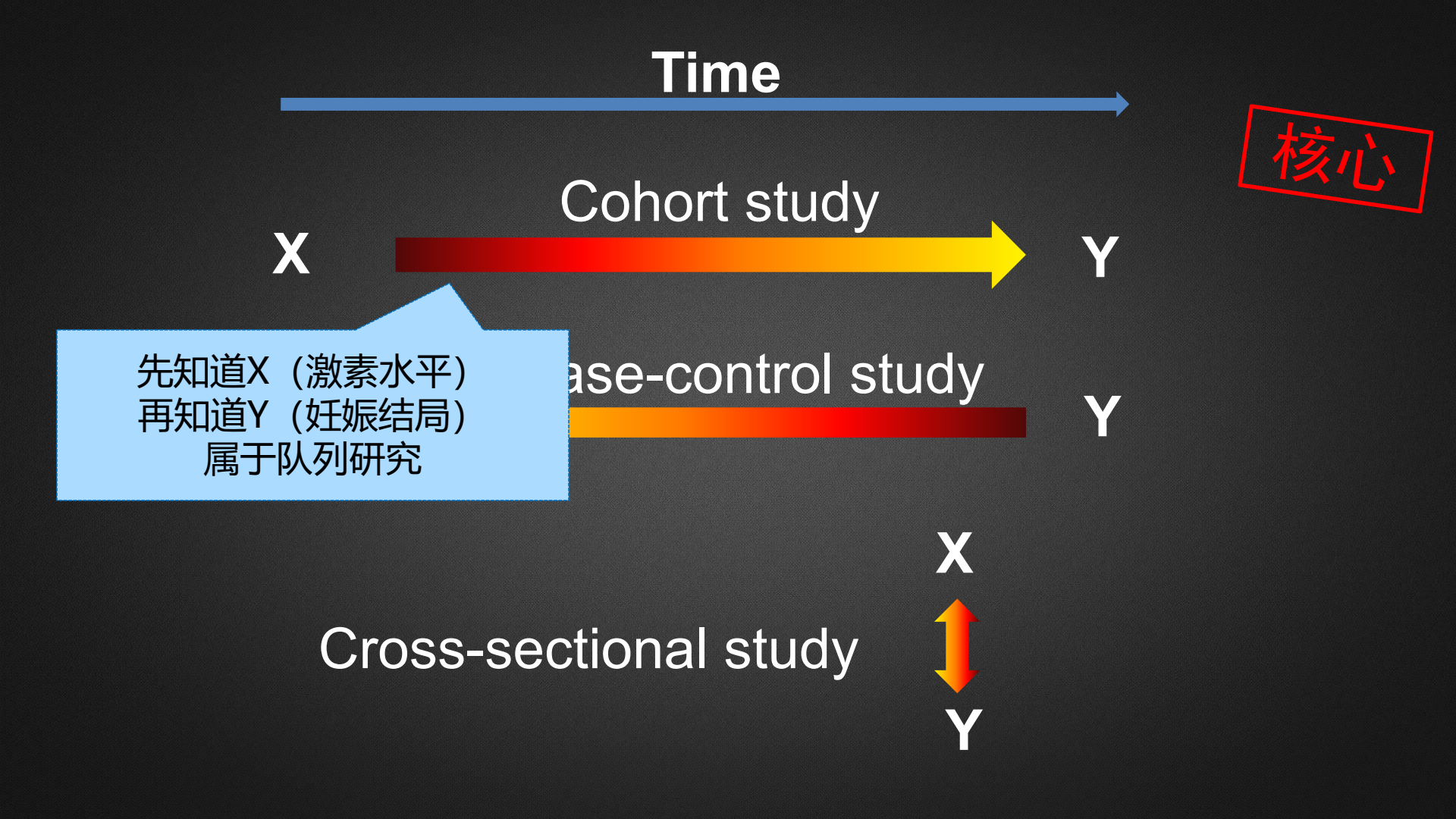
Steiner, A.Z., et al., Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. JAMA, 2017. 318(14): p. 1367-1376. SCI IF=51

确定研究设计类型

核心

本研究X是激素水平，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（激素水平）
再知道Y（妊娠结局）
属于队列研究
ase-control study
Y
X
Cross-sectional study
Y

第二步 制定完善策略：评估文献数据分析

浏览文献图表找关键词：

1. OR、HR、β等归回分析效应值
2. Model1，Model2，Model3：adjust
3. 分层分析：不同人群或森林图
4. 如果X是连续变量，找曲线拟合图

第二步 制定完善策略： 只需要完善一点，足矣

时间	期刊	影响因子	研究类型	样本量	作者单位	XY的主要关系	调整混杂	曲线拟合	交互作用
2017	JAMA	47.6	cohort study	750	Department of Obstetrics and Gynecology, University of North Carolina,	biomarkers indicating diminished ovarian reserve compared with normal ovarian reserve were not associated with reduced fertility.	是	否	否

本研究完善方案

- ✓做曲线拟合
- ✓调整更多混杂
- ✓做分层做交互
- ✓样本量比之前研究大

- ✓换研究人群（之前是30 to 44 years **， 我们是**人群）
- ✓有争议（危险/保护因素），提出本人群的证据
- ✓其他：（了解）
  - •基线的X（测量一次）
  - •X的变化（测量两次，计算变化量和变化率）
  - •X随时间的变量（重复测量三次或以上，GAMM模型）

第三步 规范的数据库： 谋定而后动

易佾DataWeb数据采集管理系统

免费版（2千例，100个变量）

1. 收集_____患者
2. 2018.1.1至12.31收集___例
3. 包括_____个指标
4. 包括_____个表单

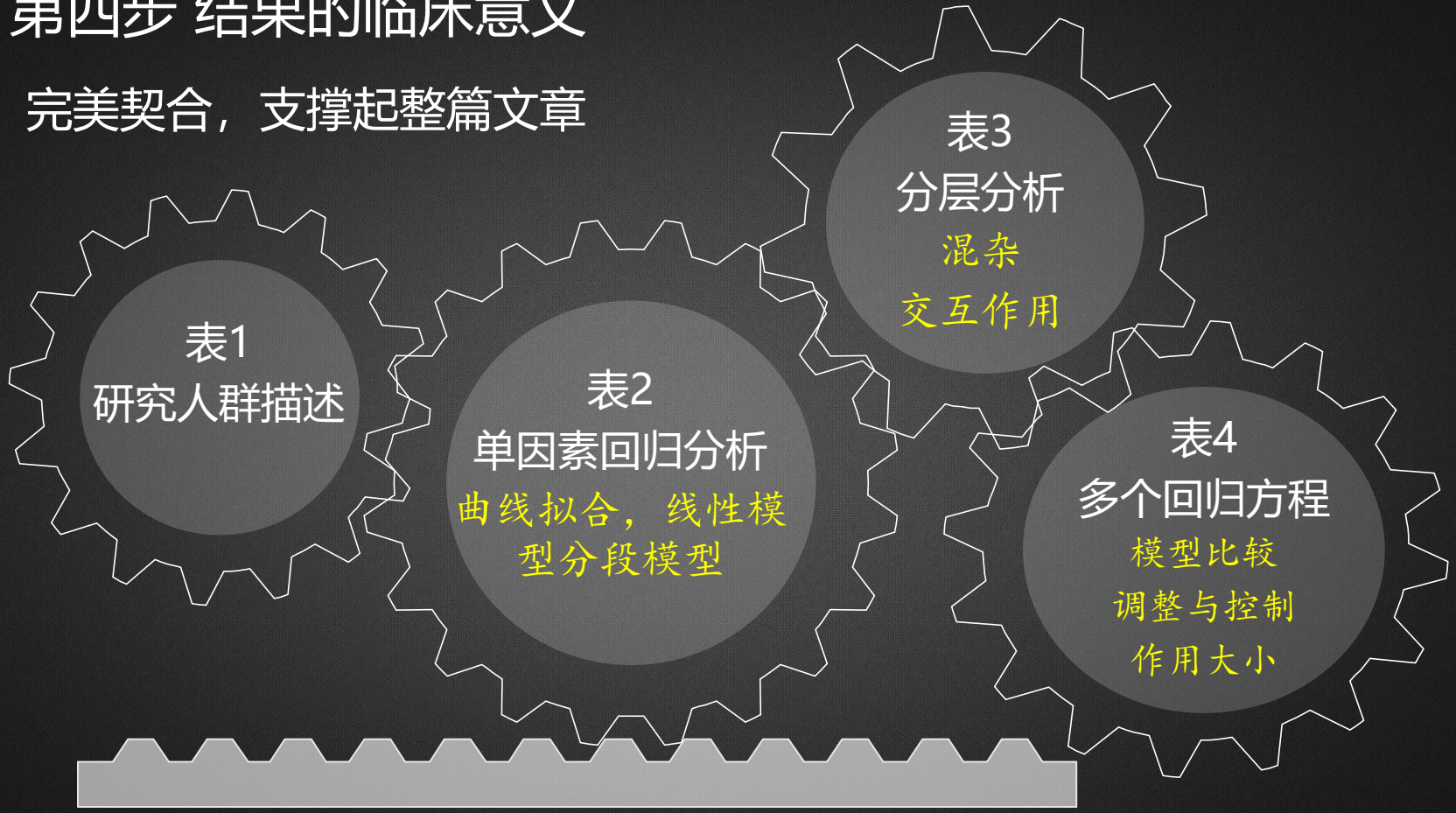
数据结构

✓数据包括三类指标：X、Y、Z（影响因素）
✓一个指标一列，一个研究对象一行（人、周期、卵）

ID	GEN	AGE	ABO	GRA	ETIO	ACU	ANH	WAR	COL	OPTI	CRY	WHO	RED	FRES	PLAT
1	1	53	1	1	2	1	60	3	420	450	20	0	8	10	0
2	1	40	0	1	2	1	60	2	360	540	8	0	12	0	0
3	1	45	1	1	2	1	55	3	480	425	0	0	12	0	0
4	1	41	1	1	2	1	45	5	600	420	0	0	20	3	1
5	1	45	1	1	2	1	60	4	600	420	5	0	0	0	1
6	2	30	1	1	4	1	65	2	540	450	16	0	14	0	0
7	1	38	1	1	2	0	55	5	540	420	0	0	22	10	2
8	1	32	1	1	2	0	60	4	420	420	0	0	6	0	2
9	1	42	1	1	2	0	55	3	540	390	0	6	0	0	2
10	1	40	1	1	2	0	60	4	600	450	0	0	12	0	0
11	1	44	1	1	2	0	60	4	600	480	5	0	10	12	1
12	1	49	1	1	2	0	50	4	600	420	0	0	6	0	0
13	1	47	1	1	2	0	50	4	540	405	0	0	0	3	0
14	1	55	0	1	2	0	60	4	480	415	0	4	12	0	2
15	1	38	1	1	2	0	70	4	720	600	8	10	20	20	2
16	1	41	1	1	2	0	120	3	540	470	0	0	6	2	1
17	2	56	0	1	2	0	85	3	420	470	0	0	14	2	1
18	1	62	1	1	2	0	120	5	720	420	4	7	0	0	1
19	1	59	1	1	2	0	50	4	600	410	0	0	12	0	1
20	1	62	1	1	2	0	60	5	480	480	6	4	0	0	0

第四步 结果的临床意义

完美契合，支撑起整篇文章



常识：从各角度呈现证据

X参与了一个银行抢窃案，你作为律师如何呈现证据为X量罪呢?

表1：哪些人有可能卷入这起抢窃?

表2：哪些人实际参与了这起抢窃？各人抢窃了多少?

表3：哪些人在X的犯罪过程中起到推动作用或制止作用?

也就是说，有没有教唆犯？X是主犯还是从犯?

表4：考虑其他人的犯罪事实后，对X的量刑应该是多少?

表1 研究人群描述

Table I Demographics of the ART cycles.

Mode of fertilization	IVF	ICSI	*P*-value
(*N*, cycles)	(3956)	(3189)	
Year of treatment (%)			
2004–2006	60.3	39.7	<0.0001
2007–2009	54.4	45.6	
2010–2012	50.0	50.0	
Female age, mean yrs, SD	35.3 (4.0)	35.9 (4.0)	<0.0001
(%) 18–29	10.4	7.6	<0.0001
30–34	34.9	32.5	
35–37	26.8	26.8	
38–40	20.4	22.7	
41–43	6.5	8.7	
44–59	1.0	1.6	

1. 人群基本特征（性别、年龄等）
2. 与Y有关的指标
3. 与X有关的指标

（部分截图）

Grimstad, F.W., et al., Use of ICSI in IVF cycles in women with tubal ligation does not improve pregnancy or live birth rates. Hum Reprod, 2016. 31(12): p. 2750-2755.

表2：变量与Y的单因素分析

Models	Group	Number	Low birthweight		Preterm birth	
			OR/AOR	95 % CI	OR/AOR	95 % CI
First birth group status						
Unadjusted	Fertile	57,384	1.00	Reference	1.00	Reference
	Subfertile	892	1.25	0.96, 1.62	1.20	0.94, 1.54
	ART	1488	1.40	1.15, 1.70	1.60	1.34, 1.90
Adjusted 1A	Fertile	57,384	1.00	Reference	1.00	Reference
	Subfertile	892	1.39	1.07, 1.81	1.23	0.96, 1.58
	ART	1488	1.58	1.29, 1.93	1.63	1.36, 1.95

(部分截图)

Luke, B., et al., Perinatal outcomes of singleton siblings: the effects of changing maternal fertility status. J Assist Reprod Genet, 2016. 33(9): p. 1203-13.

表3：分层分析

TABLE 2

Models of live birth by day of transfer and number of embryos transferred.

	Cycle 1						Over five cycles					
	One embryo			Two embryos			One embryo			Two embryos		
	AOR	95% CI	*P* value	AOR	95% CI	*P* value	AOR	95% CI	*P* value	AOR	95% CI	*P* value
Day3												
Grade												
Good	1.00	Reference	.02	1.00	Reference	.006	1.00	Reference	.009	1.00	Reference	.0001
Fair	1.06	0.88, 1.27		0.88	0.80, 0.97		1.17	1.02, 1.34		0.92	0.86, 0.97	
Poor	0.45	0.25, 0.82		0.72	0.55, 0.95		0.78	0.55, 1.11		0.72	0.61, 0.85	
Stage (i.e., cell number)												
4	0.22	0.15, 0.33	<.0001	0.18	0.12, 0.26	<.0001	0.21	0.17, 0.28	<.0001	0.18	0.14, 0.23	<.0001
5	0.23	0.14, 0.36		0.30	0.23, 0.39		0.20	0.15, 0.27		0.29	0.24, 0.34	
6	0.45	0.34, 0.58		0.45	0.39, 0.52		0.40	0.33, 0.47		0.39	0.35, 0.43	
7	0.54	0.42, 0.69		0.70	0.63, 0.79		0.60	0.51, 0.70		0.71	0.66, 0.77	
8	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
>8	0.64	0.48, 0.85		0.95	0.87, 1.03		0.64	0.53, 0.77		0.98	0.92, 1.04	

(部分截图)

Luke, B., et al., Using the Society for Assisted Reproductive Technology Clinic Outcome System morphological measures to predict live birth after assisted reproductive technology. Fertil Steril, 2014. 102(5): p. 1338-44.

表4：多个回归方程—核心结果得出独立作用

Table IV Adjusted fertilization/pregnancy/LB rates.

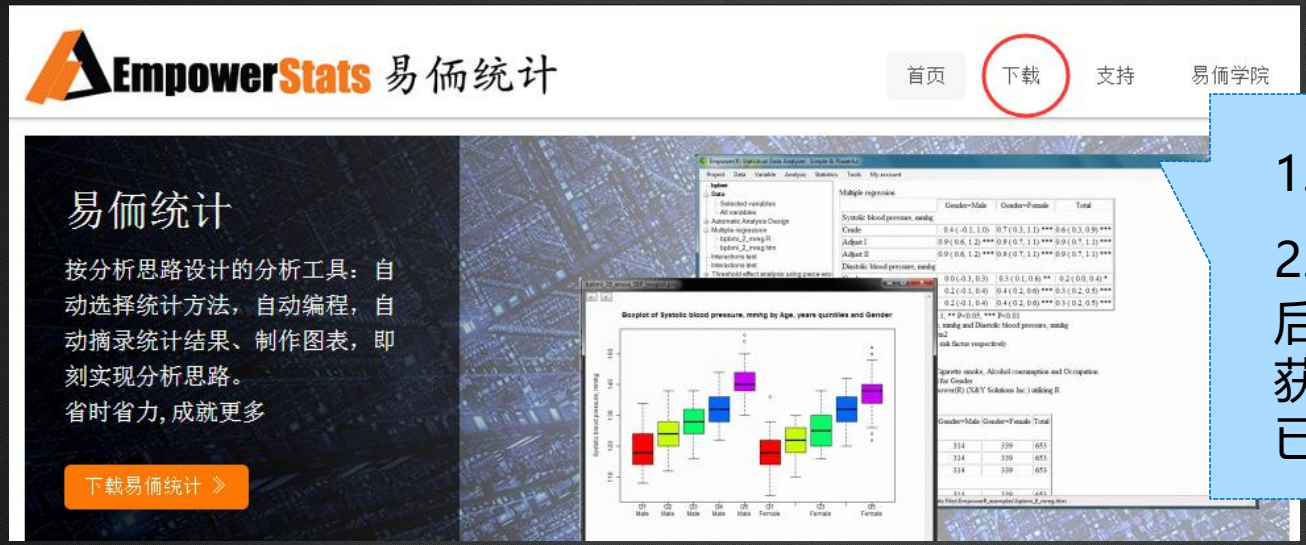
Type of fertilization	Fertilization			CIG			LB		
	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
IVF	49.1	1.00	Reference	48.4	1.00	Reference	39.6	1.00	Reference
ICSI	57.5	1.14	0.97, 1.35	41.6	0.78	0.70, 0.86	33.0	0.77	0.69, 0.85

Model adjusted for year of treatment, maternal age, race and ethnicity, number of oocytes retrieved, day of transfer, and number of embryos transferred. AOR; adjusted odds ratio; CIG, clinical intrauterine gestation; LB, live birth.

视频1

Grimstad, F.W., et al., Use of ICSI in IVF cycles in women with tubal ligation does not improve pregnancy or live birth rates. Hum Reprod, 2016. 31(12): p. 2750-2755.

工欲善其事，必先利其器！



1. 百度“易侕软件”
2. 免费下载安装
后台是R语言程序
获得国际认可
已有多篇SCI论文发表

http://www.empowerstats.com/empowerU/#

第五步 让撰写论文变成填空题：守规则

“照抄”论文模板

- ✓ 方法学部分：纳排标准、X和Y的测量方法
- ✓ 前言、讨论、参考文献等

“替换”数据分析模板

- ✓ 统计分析方法
- ✓ 结果部分
- ✓ 图表设计：四个表、曲线拟合阈值效应、交互作用等内容

资源：可以参考用易佰软件发表的文献库
https://mp.weixin.qq.com/s/MCs7wwZQnJpQQR0T5FiZOQ

流程

一 **明确的研究假设**：X+Y+研究人群+研究设计

二 **制定完善策略**：评估文献数据分析

三 **规范的数据库**：易佾Dataweb与Dataclean系统

四 **结果的临床意义**：数据分析思路指导下的统计

五 **撰写论文的要点**：让SCI变成填空题

六 **与审稿人的沟通**：回修策略

解决方案：从顶层设计角度进行全局规划

拟投稿期刊发表论文情况

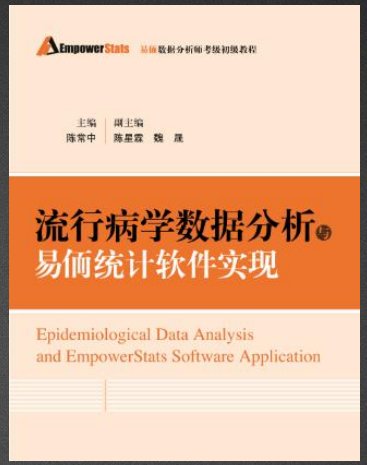
- 查不到同类文献：创新？临床意义低？
- 论文的结论：ABCD均是Y的影响因素
- 统计学意义：组间比较得出*p* 值、相关分析
- 没有考虑混杂的影响
- 当X是连续变量时，分组分析
- 粗略地看整体
- 随机抽样、随机分组、组间配平？

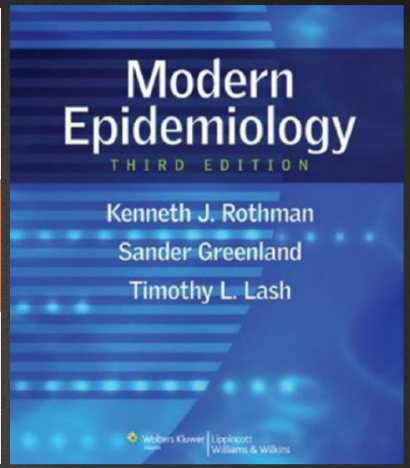
完善策略

- 近年高质量参考文献：有争议是热点
- 明确的研究假设：一个X对应Y
- 临床意义：效应值体现作用大小
- 调整混杂
- 曲线拟合精准量化
- 找到特殊人群：分层分析
- 观察性研究、队列设计、偏性

从“独木桥”到“高速公路”


生物医学信息基础课系列教材
医学统计方法
及SPSS实现


EmpowerStats
主编
陈常中
流行病学数据分析与
易侃统计软件实现
Epidemiological Data Analysis
and EmpowerStats Software Application


Modern
Epidemiology
THIRD EDITION
Kenneth J. Rothman
Sander Greenland
Timothy L. Lash