دانشگاه علوم پزشکی و خدمات
بهداشتی درمانی شهید بهشتی

Must Know Concepts in Research Articles for Clinicians

منوچهر کرمی
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به اهتمام جناب آقای دکتر پاشاپور و سرکار خانم دین پژوه

با تشکر از معاونت آموزشی و پژوهشی مرکز شهید مدرس و
گروه اپیدمیولوژی دانشگاه علوم پزشکی شهید بهشتی

مقالات مورد بحث ۱

Cazzoletti *et al. Respiratory Research* (2022) 23:83
https://doi.org/10.1186/s12931-022-02003-y

Respiratory Research

RESEARCH Open Access

Six-minute walk distance in healthy subjects: reference standards from a general population

Methods: In the frame of the multi case–control population-based study Gene Environment Interaction in Respiratory Diseases (GEIRD), we studied 530 healthy subjects: 287 females ranging 21–76 and 243 males ranging 21–78 years of age. We measured 6MWD, demographic and anthropometric data and collected the reported physical activity. A multiple linear regression model for the 6MWD included age, age^2, height, weight and physical activity for both sex equations. The two-way interaction age-height and age-weight and the quadratic terms of weight and height were also tested for inclusion separately in each model.

Results: The mean ± SD for 6MWD was 581.4 ± 66.5 m (range 383–800 m) for females and 608.7 ± 80.1 m (range 410–875 m) for males. The reference equations were 6MWD = 8.10*age + 1.61*height$_{cm}$ − 0.99*weight$_{kg}$ + 22.58*active − 0.10*age^2 + 222.55 for females (R squared = 0.238) and 6MWD = 26.80*age + 8.46*height$_{cm}$ − 0.45*weight$_{kg}$ − 2.54*active − 0.06*age^2 − 0.13*age*height$_{cm}$ − 890.18 for males (R squared = 0.159), where "active" is 1 when the subject is physically active, 0 otherwise.

of healthy adults of a wide age range.

Methods: In the frame of the multi case–control population-based study Gene Environment Interaction in Respiratory Diseases (GEIRD), we studied 530 healthy subjects: 287 females ranging 21–76 and 243 males ranging

مقالات مورد بحث ۲

Acinetobacter baumannii is a nosocomial pathogen associated with severe illness and death. Glucocorticoid aerosol is a common inhalation therapy in patients receiving invasive mechanical ventilation. We conducted a prospective cohort study to analyze the association between glucocorticoid aerosol therapy and *A. baumannii* isolation from ventilator patients in China. Of 497 enrolled patients, 262 (52.7%) received glucocorticoid aerosol, and *A. baumannii* was isolated from 159 (32.0%). Glucocorticoid aerosol therapy was an independent risk factor for *A. baumannii* isolation (hazard ratio 1.5, 95% CI 1.02–2.28; p = 0.038). Patients receiving glucocorticoid aerosol had a higher cumulative hazard for *A. baumannii* isolation and analysis showed that glucocorticoid aerosol therapy in-

مقالات مورد بحث ۳

Research

JAMA Internal Medicine | Original Investigation

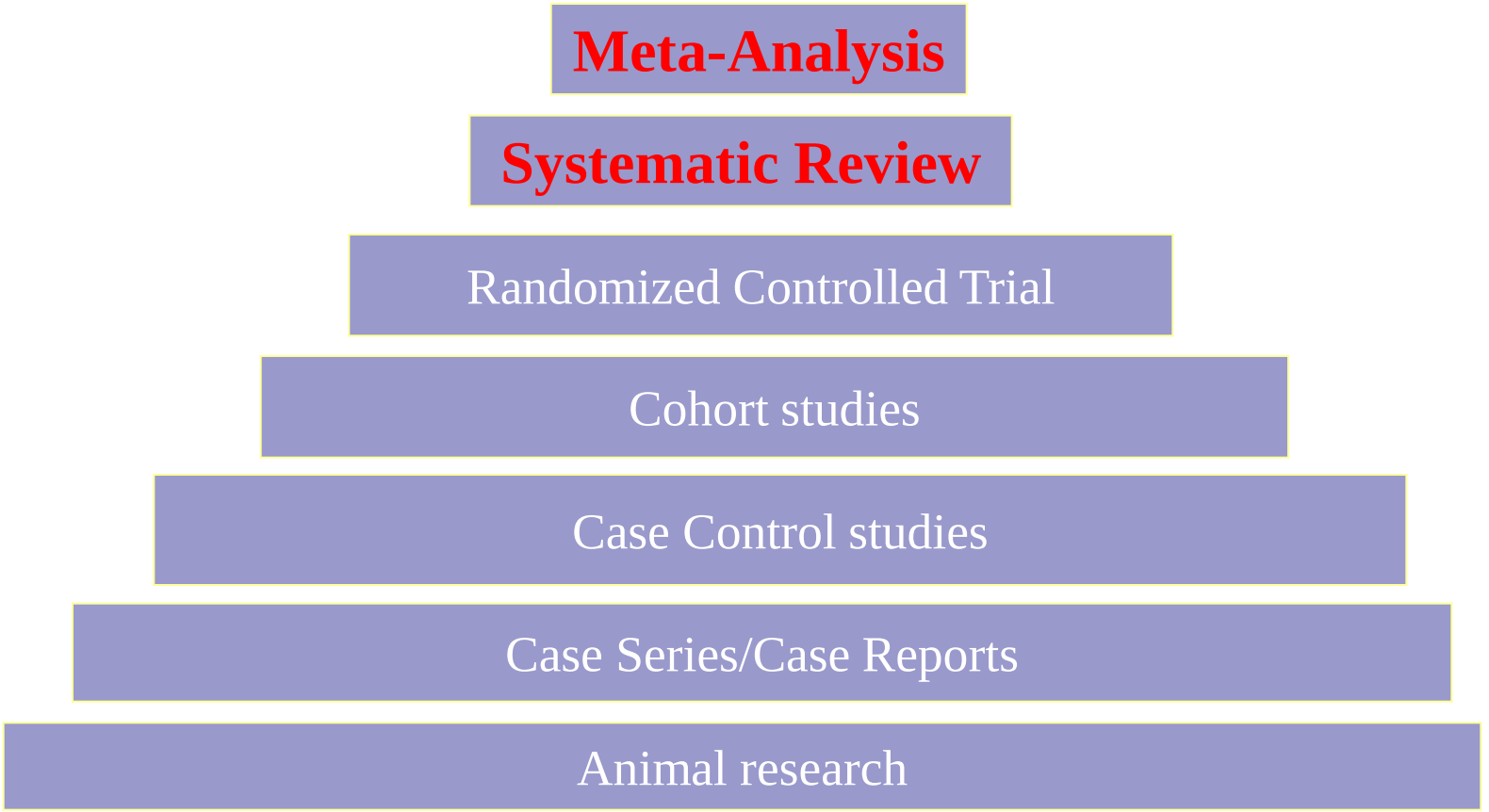
Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities

The I-TECH Randomized Clinical Trial

Table 2. Outcomes in the Primary Analysis Population

Outcomes[a]	No. (%)		Absolute difference (95% CI)	Relative risk (95% CI)	*P* value
	Ivermectin	Control			
No.	241	249	NA	NA	NA
Primary outcome					
Progression to severe disease (WHO scale 5-9)	52 (21.6)	43 (17.3)	4.31 (−2.69 to 11.31)[b]	1.25 (0.87 to 1.80)	.25
Secondary outcomes					
Time of progression to severe disease, mean (SD), d	3.2 (2.4)	2.9 (1.8)	0.3 (−0.6 to 1.2)[c]	NA	.51
Patients who had mechanical ventilation	4 (1.7)	10 (4.0)	−2.36 (−5.28 to 0.57)[b]	0.41 (0.13 to 1.30)	.17

سطح بندی و هرم شواهد



Levels of Evidence

Level of Evidence	Type of Study
1a	Systematic reviews of randomized clinical trials (RCTs)
1b	Individual RCTs
2a	Systematic reviews of cohort studies
2b	Individual cohort studies and low-quality RCTs
3a	Systematic reviews of case-controlled studies
3b	Individual case-controlled studies
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion based on clinical experience

Adapted from: Sackett DL et al. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. Churchill Livingstone; 2000.

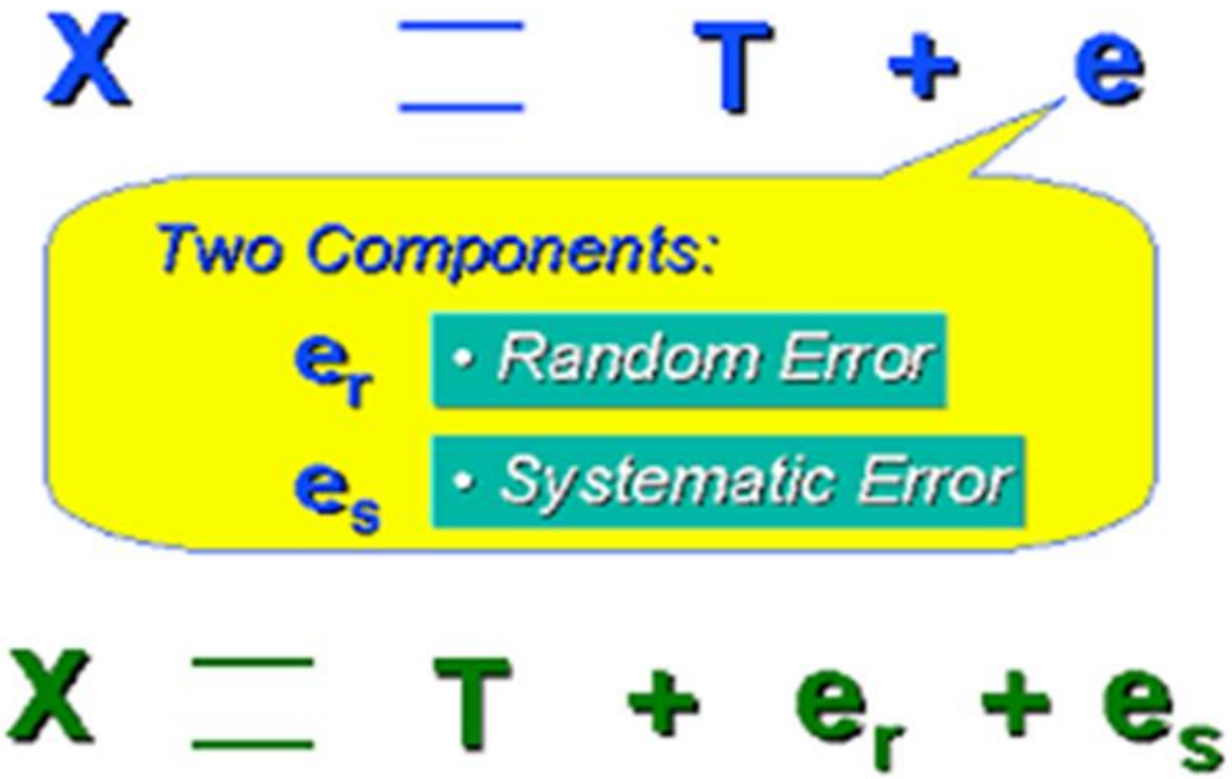
کارگروهی: با کدامیک از مفاهیم زیر کمتر آشنا هستید؟

- SD
- SE
- CI: Confidence Intervals
- Statistical Test
- Null hypothesis
- P Value
- Alpha(α)
- Odds ratio
- Risk ratio
- Hazard ratio
- Univariate analysis
- Multivariate Analysis

کارگروهی: با کدامیک از مفاهیم زیر کمتر آشنا هستید؟.

- Measures of Association
- Measures of Effect
- Bias
- Confounding
- Crude RR/OR
- Adjusted RR/OR

انواع خطاها در پژوهش ها:
خطای تصادفی و خطای منظم (Bias)



اگر می توانستیم همه اعضای یک جامعه را مطالعه کنیم نیازی به حدس و برآوردها نبود!

Question1

- **What is the best way to reduce sampling error in a study?**
- (a) Select people from the population at random.
- (b) Increase the size of the study.
- (c) Calculate a 95% confidence interval for the results.
- (d) Use a more reliable instrument to measure exposure.

Question1

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- (c) Calculate a 95% confidence interval for the results.
- (d) Use a more reliable instrument to measure exposure.

- **The answer is (b). There will always be some random sampling error in a study even when study participants are selected at random and a 95% confidence interval will just give an indication of how much random sampling error is present. Exposure measurement is a completely different issue.**

مقادیر احتمال در آزمون های آماری P Value

- P Value یک آماره کمی با دامنه بین صفر و یک است.
- P Value درجه تطابق بین داده های مشاهده شده با فرض صفر با لحاظ صحیح بودن فرض صفر است.
  - مقادیر کوچک P Value یعنی کمتر از ۰/۰۵ به معنی حداقل درجه توافق کمی با فرض صفر است و تصمیم به تفسیر معنی داری آماری گرفته می شود.

خطای معیار برای میانگین یا نسبت یک برآورد

- 95% confidence limits = estimate±(1.96 ×standard error)
  - **مبنای محاسبه خطای معیار** SE **از روی انحراف معیار** SD **و حجم نمونه** n **در مطالعه است.**
- SE(Mean)= SD/√n
- SE(Proportion)= √p(1-p)/n

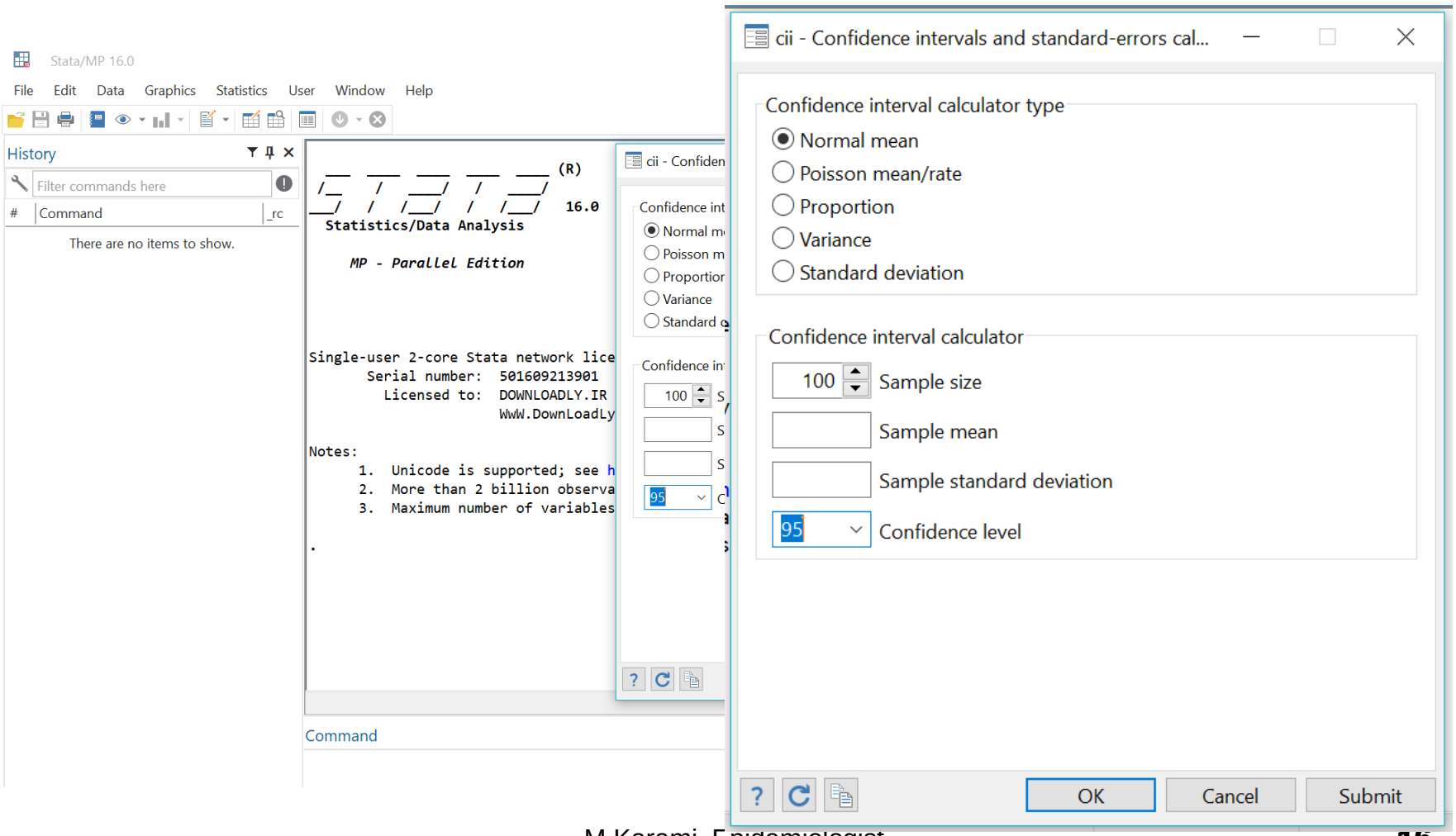
انواع برآوردها برای تخمین مقادیر یک سنجه در جامعه

- برآورد نقطه ای بر مبنای نمونه مورد مطالعه
- برآورد فاصله اطمینان بر مبنای نمونه برای جامعه

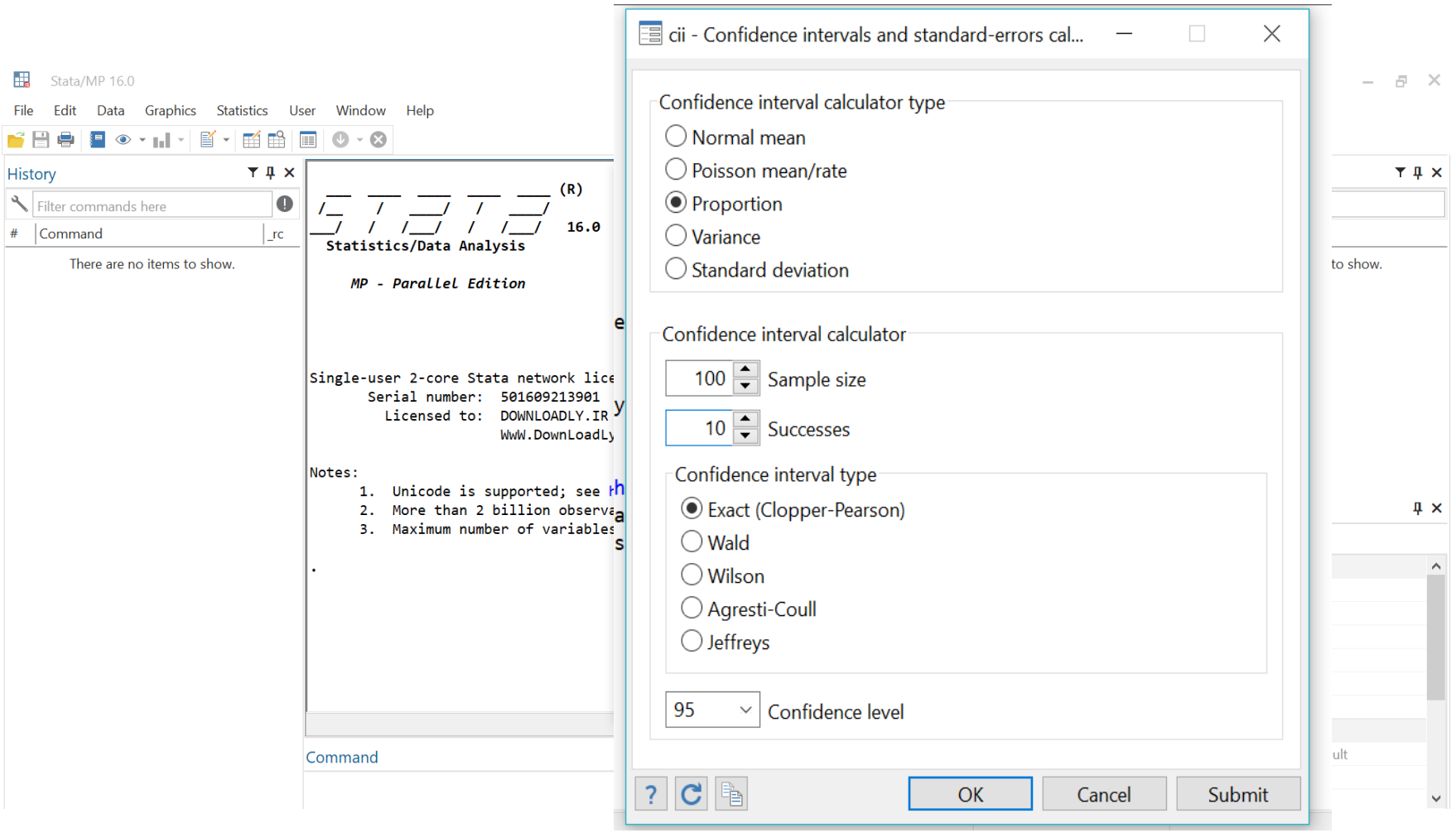
95% confidence limits=

estimate± (1.96× standard error)

مثالی از محاسبه فاصله اطمینان با نرم افزار



مثالی از محاسبه فاصله اطمینان با نرم افزار



Measuring Associations Between Exposures and Outcomes: RR, OR, HR

TABLE 3-1 Types of measures of association used in analytical epidemiologic studies.

Type	Examples	Usual application
Absolute difference	Attributable risk in exposed	Primary prevention impact; search for causes
	Population attributable risk	Primary prevention impact
	Effectiveness, efficacy	Impact of intervention on recurrence, case fatality, etc.
	Mean differences (continuous outcomes)	Search for causes
	Relative risk/rate	Search for causes
Relative difference	Relative odds (odds ratio)	Search for causes

Measuring Effect of Intervention and Outcomes: RR, OR, HR

TABLE 3-1 Types of measures of association used in analytical epidemiologic studies.

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	Relative risk/rate	Search for causes
Relative difference	Relative odds (odds ratio)	Search for causes

Heads or tails: the role of chance

- If the results of a study reveal an interesting association between some exposure and a health outcome, there is a natural tendency to assume that it is real.
- However, before we can even contemplate this possibility we have to try to rule out other possible explanations for the results.
- There are three main 'alternative explanations' that we have to consider whenever we analyse epidemiological data or read the reports of others, no matter what the study design:

chance, bias or error, or confounding?

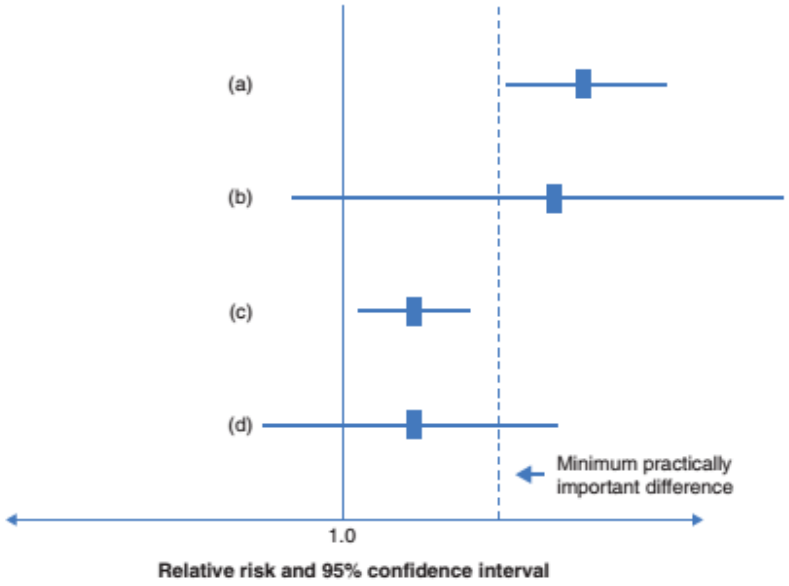
Statistical versus clinical significance

- **Statistically significant means that it is unlikely to have arisen by chance**

- **Clinical significance describes whether or not a result is clinically or practically meaningful.**

Statistical versus clinical significance

- [a] The result is both practically important and statistically significant because the point estimate falls beyond the 'minimum practically important difference' line and the confidence interval does not include the value 1.0.



Question 2

- What is the difference between statistical significance and clinical significance?

Question 2

What is the difference between statistical significance and clinical significance?

- **If a result is statistically significant it means that it is unlikely to have arisen by chance while clinical significance describes whether or not a result is clinically or practically meaningful.**
- **In a large study even quite small differences can be statistically significant, but if the difference is so small that it has no practical effect**

What are dichotomous outcomes?

- when the outcome for every participant is one of two possibilities or events
  - alive or dead
  - healed or not healed
  - pregnant or not pregnant

Risk

- 24 people drank coffee
  6 developed a headache
- risk of a headache

  = 6 headaches / 24 people who could have had one

  = 6/24 = ¼ = 0.25 = 25%

risk = $\frac{\text{no. participants with event of interest}}{\text{total no. participants}}$

Odds

- 24 people drank coffee
  6 developed a headache
- odds of a headache
  = 6 headaches/18 without headaches
  = 6/18 = 1/3 = 0.33 = 1:3 (not usually as %)

odds = $\frac{\text{no. participants with event of interest}}{\text{no. participants without event of interest}}$

Comparing two groups

	Headache	No headache	Total
Caffeine	17	51	**68**
Decaf	9	55	**64**
Total	**26**	**106**	**132**

Comparing two groups

- effect measures
  - risk ratio (RR) (relative risk)
  - odds ratio (OR)
  - risk difference (RD) (absolute risk reduction)
- all estimates are uncertain, and should be presented with a confidence interval

Risk ratio

- risk of event with intervention
  = **17/68**
- risk of event with control
  = **9/64**

$$\text{risk ratio} = \frac{\text{intervention risk}}{\text{control risk}}$$

$$= \frac{17/68}{9/64} = \frac{0.25}{0.14} = 1.79$$

	Headache	No headache	Total
Caffeine	17	51	68
Decaf	9	55	64
Total	26	106	132

Where risk ratio = 1, there is no difference between the groups

Expressing it in words

- Risk ratio 1.79
  - the risk of having a headache with treatment was 179% of the risk in the control group
  - intervention increased the risk of headache by 79%

or for a reduction in risk:

- Risk ratio 0.79
  - the risk of having a headache with treatment was 79% of the risk in the control group
  - intervention reduced the risk of headache by 21%

Odds ratio

- odds of event with intervention = **17/51**
- odds of event with control = **9/55**

$$\text{odds ratio} = \frac{\text{intervention odds}}{\text{control odds}}$$

$$= \frac{17/51}{9/55} = \frac{0.33}{0.16} = 2.06$$

	Headache	No headache	Total
Caffeine	17	51	68
Decaf	9	55	64
Total	**26**	**106**	**132**

Where odds ratio = 1, there, is no difference between the groups

Expressing it in words

- Odds ratio 2.06
  - intervention doubled the odds of headache
  - intervention increased the odds to 206% of the odds in the control group
  - intervention increased the odds of headache by 106%

or for a reduction in odds:

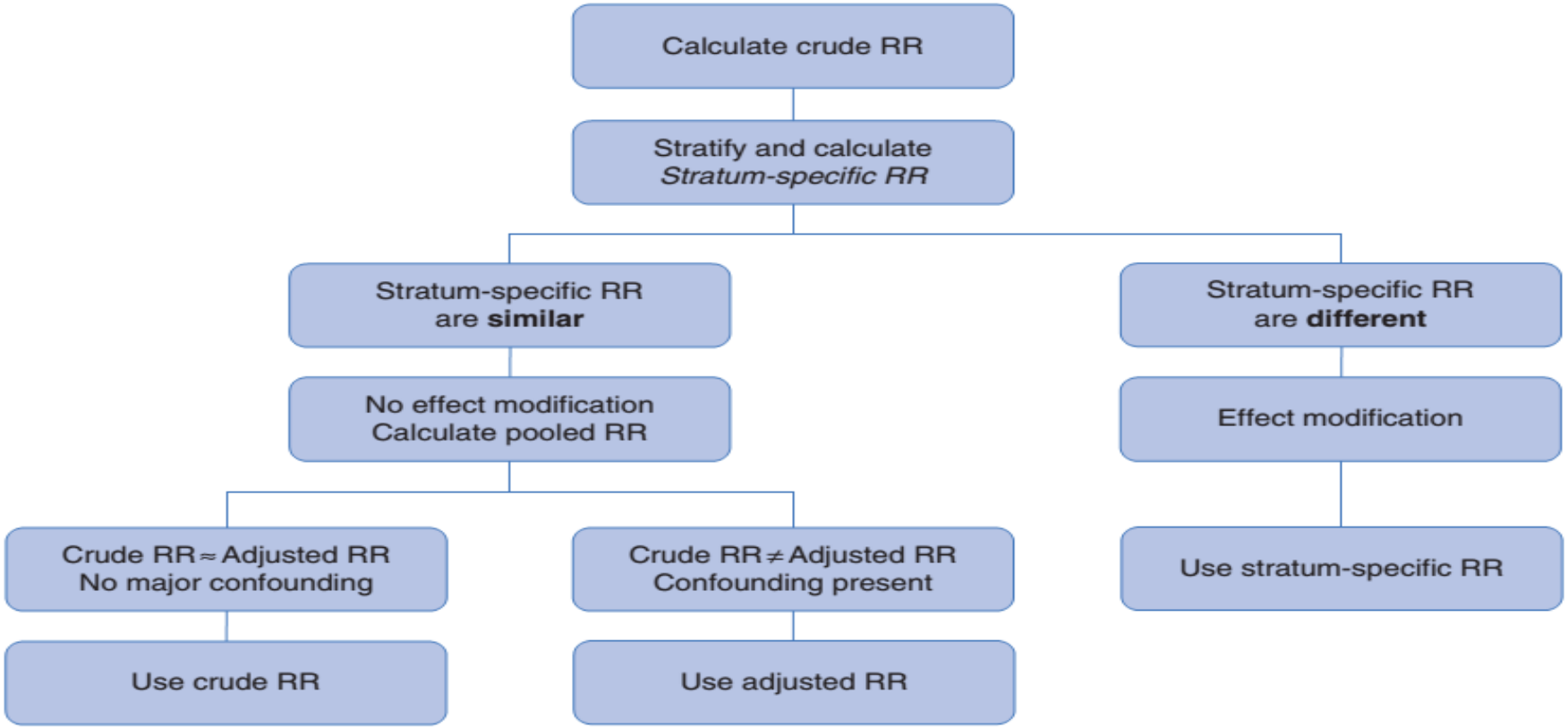
- Odds ratio 0.06
  - intervention reduced the odds of headache to 6% of the odds in the control group
  - intervention reduced the odds of headache by 94%

مدل های رگرسیونی پرکاربرد

TABLE 7-15 Multiple-regression models and interpretation of the regression coefficients = b_1.

	Model	Interpretation of b_1
Linear	$y = b_0 + b_1x_1 + b_2x_2 + \cdots + b_kx_k$	Increase in outcome y mean value (continuous variable) per unit increase in x_1, adjusted for all other variables in the model
Logistic	$\log(\text{odds}) = b_0 + b_1x_1 + b_2x_2 + \cdots + b_kx_k$	Increase in the log odds of the outcome per unit increase in x_1, adjusted for all other variables in the model
Cox	$\log(\text{hazard}) = b_0 + b_1x_1 + b_2x_2 + \cdots + b_kx_k$	Increase in the log hazard of the outcome per unit increase in x_1, adjusted for all other variables in the model
Poisson	$\log(\text{rate}) = b_0 + b_1x_1 + b_2x_2 + \cdots + b_kx_k$	Increase in the log rate of the outcome per unit increase in x_1, adjusted for all other variables in the model

A scheme for identifying and dealing with confounding and effect modification



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