Departamento de Neurociências e Ciências do Comportamento

Faculdade de Medicina de Ribeirão Preto Av. Bandeirantes 3900 - Campus Universitário

ESTUDOS OBSERVACIONAIS
COORTE

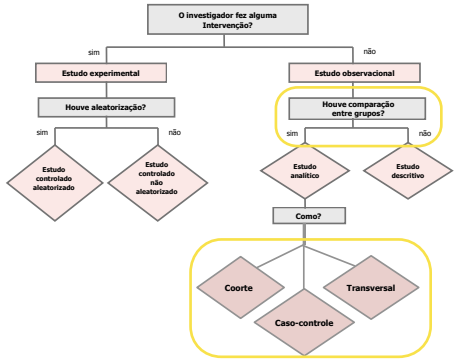
Taiza E. G. Santos-Pontelli

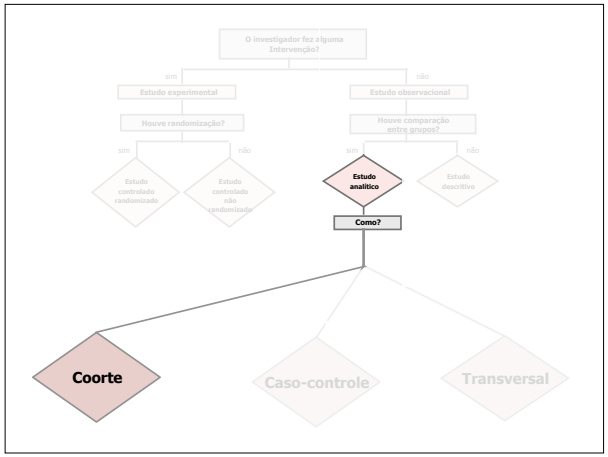
NCC5701 - Metodologia Científica e Estudos Clínicos

Tópicos da Apresentação

1. Estudos coorte: características principais
1. Estudos coorte: medidas
2. Estudos coorte: classificação em relação ao tempo
3. Critérios para desenhar bem um estudo coorte
4. Definição e seleção de controles e casos
5. Estudos caso-control: vantagens e desvantagens
6. Estudos com desenhos mistos*

TIPOS DE ESTUDO CLÍNICO





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	Exp	Não Exp	
Doentes	**a**	**b**	D
Não Doentes	**c**	**d**	nD
	E	**nE**	**N**

E e nE são fixos pelo desenho!

ESTUDOS COORTE

	Exp	Não Exp	
Doentes	**a**	**b**	D
Não Doentes	**c**	**d**	nD
	E	**nE**	**N**

E e nE são fixos pelo desenho!

Podemos estimar: $p_1 = P(D \mid E) = a/E$ $p_0 = P(D \mid nE) = b/nE$

$RR = p_1/p_0$ $OR = \frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ $RD = p_1 - p_0$

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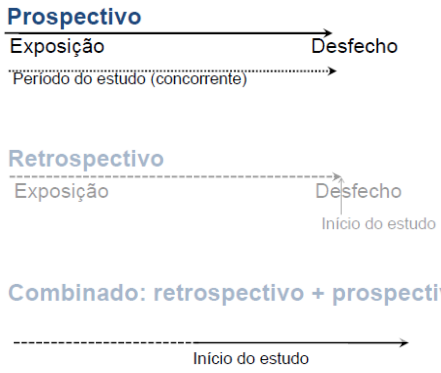
MEDIDAS DE FREQUÊNCIA

- Risco ou proporções (razão de risco; diferença de proporções)
- Rate or Hazard (hazard ratio)
- Tempo de demora para ocorrer o desfecho ou duração do desfecho (diferença ou mudança relativa)
- Médias (diferença das médias)

ESTUDOS COORTE



ESTUDOS COORTE

ESTUDOS COORTE

Prospectivo

Exposição → Desfecho

Período do estudo (concorrente)

Retrospectivo

Exposição → Desfecho

Início do estudo

Combinado: retrospectivo + prospectivo

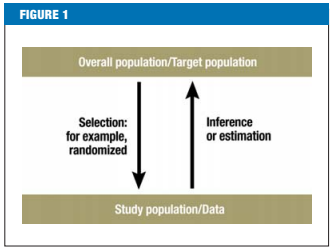
Início do estudo

ESTUDOS COORTE

- Melhores para compreender a história natural da doença
- Sequência natural dos eventos clara
  - Pessoas com dor crônica evoluem com depressão ou pessoas com depressão evoluem com dor crônica?
- Muito útil quando uma exposição pode levar a mais de um tipo de desfecho
  - Ex.: fumo = AVC, Ca de pulmão, etc...
- Melhor que o caso-controle
  - Determinar fator de risco e risco relativo

CRITÉRIOS DESENHAR BEM UM ESTUDO COORTE

- A população do estudo foi representativa?



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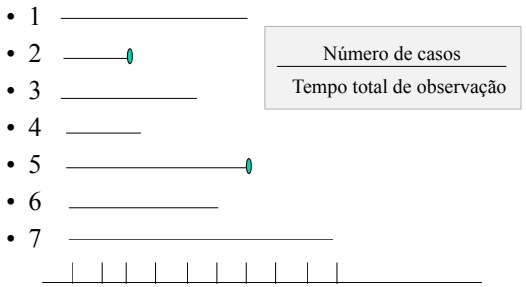
CRITÉRIOS DESENHAR BEM UM ESTUDO COORTE

- A exposição foi a mesma para todos os pacientes ou mensurável?
- Os grupos são similares em todos os aspectos com exceção da exposição?
- O desfecho foi claro e mensurável para ambos os grupos?
- A mensuração do desfecho foi feita por um investigador cego ao tratamento/exposição?
- Fatores antecedentes ou intervenientes foram investigados?

CRITÉRIOS DESENHAR BEM UM ESTUDO COORTE

- Todas as variáveis de confusão serão coletadas?
- Todos os possíveis vieses (*bias*) foram listados e estrategicamente manejados?
  - Quais seriam os possíveis vieses?

ESTUDOS COORTE
CONCEITO PESSOA-TEMPO



$$\frac{\text{Número de casos}}{\text{Tempo total de observação}}$$

CRITÉRIOS DESENHAR BEM UM ESTUDO COORTE

- Todas as variáveis de confusão serão coletadas?
- Todos os possíveis vieses (*bias*) foram listados e estrategicamente manejados?
  - Quais seriam os possíveis vieses?
    - *Confounding bias*
    - *Selection bias: self selection, volunteer bias*
    - *Information bias:*
      - *differential and random misclassification*
      - *recall bias, data collection bias*

TABLE 2

Advantages and disadvantages of observational studies (taken from [16])*

	Ecological study	Cross-sectional study	Case control study	Cohort study
Selection bias	N/A	2	3	1
Recall bias	N/A	3	3	1
Loss to follow-up	N/A	N/A	1	3
Confounding	3	2	2	1
Time required	1	2	2	3
Costs	1	2	2	3

1 = slight; 2 = moderate; 3 = high; N/A, not applicable.
*Individual cases may deviate from this pattern.

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- **<u>Vantagens</u>**
- É possível estudar vários desfechos para a exposição
- Estabelece associação temporal
- Se prospectivo, informação sobre exposição pouco sujeita a vícios
- Pode-se calcular incidência

ESTUDOS COORTE

- **Desvantagens**
- Podem demorar vários anos
- Não são adequados para doenças raras
- Pode-se estudar poucas exposições
- Logisticamente difíceis
- Perda de indivíduos

COORTE x CASO CONTROLE

Critérios de escolha	Coorte	Caso-controle
Freqüência da doença	Doença freqüente	Doença rara
Interesse principal	Exposição	doença
Duração do estudo	Não urgência dos resultados	Urgência dos resultados

TABLE 1

Specially well suited study types for epidemiological investigations (taken from [e8])

Study objective	Study type
Study of rare diseases such as cancers	Case control studies
Study of rare exposure, such as exposure to industrial chemicals	Cohort studies in a population group in which there has been exposure (e.g. industrial workers)
Study of multiple exposures, such as the combined effect of oral contraceptives and smoking on myocardial infarction	Case control studies
Study of multiple end points, such as mortality from different causes	Cohort studies
Estimate of the incidence rate in exposed populations	Exclusively cohort studies
Study of covariables which change over time	Preferably cohort studies
Study of the effect of interventions	Intervention studies

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EXEMPLOS

Neurology. 2015 Jan 27;84(4):382-90. doi: 10.1212/WNL.0000000000001182. Epub 2014 Dec 24.

IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study.

Baker GA[1], Bromley RL[2], Briggs M[1], Cheyne CP[1], Cohen MJ[1], García-Fiñana M[1], Gummery A[1], Kneen R[1], Loring DW[1], Mawer G[1], Meador KJ[1], Shallcross R[1], Clayton-Smith J[1]; Liverpool and Manchester Neurodevelopment Group.

Abstract

OBJECTIVE: To delineate the risk to child IQ associated with frequently prescribed antiepileptic drugs.

METHODS: Children born to women with epilepsy (n = 243) and women without epilepsy (n = 287) were recruited during pregnancy and followed prospectively. Of these, 408 were blindly assessed at 6 years of age. Maternal and child demographics were collected and entered into statistical models.

RESULTS: The adjusted mean IQ was 9.7 points lower (95% confidence interval [CI] -4.9 to -14.6; p < 0.001) for children exposed to high-dose (>800 mg daily) valproate, with a similar significant effect observed for the verbal, nonverbal, and spatial subscales. Children exposed to high-dose valproate had an 8-fold increased need of educational intervention relative to control children (adjusted relative risk, 95% CI 8.0, 2.5-19.7; p < 0.001). Valproate at doses <800 mg daily was not associated with reduced IQ, but was associated with impaired verbal abilities (-5.6, 95% CI -11.1 to -0.1; p = 0.04) and a 6-fold increase in educational intervention (95% CI 1.4-18.0; p = 0.01). In utero exposure to carbamazepine or lamotrigine did not have a significant effect on IQ, but carbamazepine was associated with reduced verbal abilities (-4.2, 95% CI -0.6 to -7.8; p = 0.02) and increased frequency of IQ <85.

CONCLUSIONS: Consistent with data from younger cohorts, school-aged children exposed to valproate at maternal doses more than 800 mg daily continue to experience significantly poorer cognitive development than control children or children exposed to lamotrigine and carbamazepine.

Neurology. 2014 Sep 16;83(12):1075-9. doi: 10.1212/WNL.0000000000000804. Epub 2014 Aug 13.

Increased risk of osteoporosis in patients with myasthenia gravis: a population-based cohort study.

Yeh JH[1], Chen HJ[1], Chen YK[1], Chiu HC[1], Kao CH[2].

Abstract

OBJECTIVE: To determine the risk of osteoporosis in patients with myasthenia gravis (MG) in a large cohort representing 99% of the population of Taiwan.

METHODS: Data from the Taiwan National Health Insurance Research Database were used to conduct retrospective cohort analyses. The study cohort consisted of 2,073 patients with MG who were 3-fold frequency-matched by age and sex and assigned the same index year as a comparison cohort without MG. Cox proportional hazard regression analysis was conducted to estimate the risk of osteoporosis.

RESULTS: The MG cohort had a 1.96-fold increased risk of developing osteoporosis compared with the comparison cohort (hazard ratio [HR] = 1.96, 95% confidence interval [CI] = 1.57-2.44). Patients with MG older than 30 years developed an increased risk of osteoporosis, with the highest risk in the age group from 30 to 44 years, compared with the control cohort. Corticosteroid-naive patients with MG had a 1.52-fold increased risk of developing osteoporosis (HR = 1.52, 95% CI = 1.11-2.08), and the corticosteroid-treated cohort had a 2.37-fold increased risk of developing osteoporosis (HR = 2.37, 95% CI = 1.82-3.07).

CONCLUSION: This population-based retrospective cohort study provides evidence that MG is associated with a high risk of osteoporosis regardless of corticosteroid use.

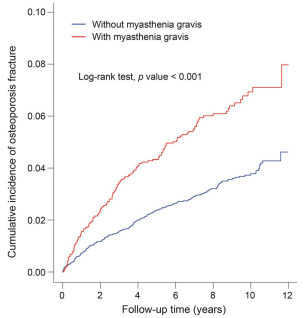
Qual a fator de exposição e o fator "doença" neste caso?

Neurology. 2014 Sep 16;83(12):1075-9. doi: 10.1212/WNL.0000000000000804. Epub 2014 Aug 13.

Increased risk of osteoporosis in patients with myasthenia gravis: a population-based cohort study.

Yeh JH[1], Chen HJ[1], Chen YK[1], Chiu HC[1], Kao CH[2].

Figure Cumulative incidence curves of osteoporosis fracture for myasthenia gravis and control groups



Neurology. 2014 Sep 30;83(14):1253-60. doi: 10.1212/WNL.0000000000000842. Epub 2014 Aug 29.

Predictors of dementia in Parkinson disease: a prospective cohort study.

Anang JB[1], Gagnon JF[2], Bertrand JA[1], Romenets SR[1], Latreille V[1], Panisset M[1], Montplaisir J[1], Postuma RB[2].

Abstract

OBJECTIVE: We investigated an array of possible markers of early dementia in Parkinson disease.

METHODS: We performed a comprehensive assessment of autonomic, sleep, psychiatric, visual, olfactory, and motor manifestations in 80 patients with Parkinson disease who were dementia-free at baseline. After 4.4 years' follow-up, patients were evaluated for dementia. Predictive variables were assessed using logistic regression adjusting for disease duration, follow-up duration, age, and sex.

RESULTS: Of 80 patients, 27 (34%) developed dementia. Patients destined to develop dementia were older and more often male (odds ratio [OR] = 3.64, p = 0.023). Those with baseline mild cognitive impairment had increased dementia risk (OR = 22.5, p < 0.001). REM sleep behavior disorder at baseline dramatically increased dementia risk (OR = 49.7, p = 0.001); however, neither daytime sleepiness nor insomnia predicted dementia. Higher baseline blood pressure increased dementia risk (OR = 1.37 per 10 mm Hg, p = 0.032). Orthostatic blood pressure drop was strongly associated with dementia risk (OR = 1.84 per 10 mm Hg, p < 0.001); having a systolic drop of >10 mm Hg increased dementia odds 7-fold (OR = 7.3, p = 0.002). Abnormal color vision increased dementia risk (OR = 3.3, p = 0.014), but olfactory dysfunction did not. Among baseline motor variables, proportion of gait involvement (OR = 1.12, p = 0.023), falls (OR = 3.02, p = 0.042), and freezing (OR = 2.63, p = 0.013), as well as the Purdue Pegboard Test (OR = 0.67, p = 0.049) and alternate tap test (OR = 0.97, p = 0.033) predicted dementia.

CONCLUSION: Cardiovascular autonomic dysfunction, REM sleep behavior disorder, color discrimination ability, and gait dysfunction strongly predict development of dementia in Parkinson disease.

OR: regressão logística / RR: log binomial ou Poisson

Fraquezas deste estudo?

Neurology. 2015 Apr 15. pii: 10.1212/WNL.0000000000001580. [Epub ahead of print]

Longitudinal relationships among posturography and gait measures in multiple sclerosis.

Fritz NE[1], Newsome SD[2], Eloyan A[2], Marasigan RE[2], Calabresi PA[2], Zackowski KM[2].

Objective: Gait and balance dysfunction frequently occurs early in the multiple sclerosis (MS) disease course. Hence, we sought to determine the longitudinal relationships among quantitative measures of gait and balance in individuals with MS.

Methods: Fifty-seven ambulatory individuals with MS (28 relapsing-remitting, 29 progressive) were evaluated using posturography, quantitative sensorimotor and gait measures, and overall MS disability with the Expanded Disability Status Scale at each session.

Results: Our cohort's age was 45.8 ± 10.4 years (mean ± SD), follow-up time 32.8 ± 15.4 months, median Expanded Disability Status Scale score 3.5, and 56% were women. Poorer performance on balance measures was related to slower walking velocity. Two posturography measures, the anterior-posterior sway and sway during static eyes open, feet apart conditions, were significant contributors to walk velocity over time (approximate $R^2 = 0.95$), such that poorer performance on the posturography measures was related to slower walking velocity. Similarly, the anterior-posterior sway and sway during static eyes closed, feet together conditions were also significant contributors to the Timed 25-Foot Walk performance over time (approximate $R^2 = 0.83$).

Conclusions: This longitudinal cohort study establishes a strong relationship between clinical gait measures and posturography. The data show that increases in static posturography and reductions in dynamic posturography are associated with a decline in walk velocity and Timed 25-Foot Walk performance over time. Furthermore, longitudinal balance measures predict future walking performance. Quantitative walking and balance measures are important additions to clinical testing to explore longitudinal change and understand fall risk in this progressive disease population. ***Neurology*® 2015;84:1–8**

DÚVIDAS?