REVIEW ARTICLE

From Observational Studies and Adjustment to Clinical Decision. Part 1

Del estudio observacional y el ajuste a la decisión clínica. Parte 1

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ABSTRACT

In the context of observational studies, the definition of the strength of the association between an exposure variable and an outcome variable, event or endpoint, may be affected by the unequal distribution of covariates among those with and without the specified exposure. In this paper we will review different statistical approaches to the subject matter, from multivariate analysis to adjustment which considers the inverse probability of treatment weighting, and we will apply them to examples taken from the medical literature.

Keywords: Observational studies - Multivariate analysis - Adjustment

RESUMEN

En el contexto de los estudios observacionales, la definición de la fuerza de asociación entre una variable exposición y un resultado, evento o punto final, puede verse alterada por la desigual distribución de covariables entre aquellos que presentan o no la exposición citada. Revisaremos en este escrito diferentes aproximaciones estadísticas al problema en cuestión, desde el análisis multivariado hasta el ajuste que toma en cuenta la inversa de la probabilidad ponderada de tratamiento, y las aplicaremos a ejemplos extraídos de la literatura.

Palabras claves: Estudios observacionales - Análisis multivariado - Ajuste

In recent bibliographic reports the statistical methodology is not the usual one, with terms, tables, and charts that may sometimes be hard to understand, particularly when it comes to making clinical decisions.

Here are some examples.

Trial 1

The aim of this observational study was to compare medical treatment (MT) and percutaneous coronary intervention (PCI) in patients with chronic angina. (1) A total of 9586 patients were included and 1866 were matched in 933 pairs (MT/PCI). The balance between baseline patient characteristics in the paired groups was appropriate. Unadjusted and adjusted hazard ratios (HR) calculated by the Cox model of MT/PCI for the primary endpoint of mortality were 1.50 and 1.49, respectively. (Table 1). The authors conclude that mortality is 49% higher with MT than with PCI.

Table 1. Trial 1. Event rate with medical treatment (MT) and with percutaneous coronary intervention (PCI), and adjusted and unadjusted HR in 933 matched pairs in a model with 20 covariates (modified from reference 1).

n= 9586. Matched pairs (n=933) by propensity score (933 MT/933 PCI).

MT / PCI Result (4 years)	MT % / 4 y	PCI % / 4 y	MT / PCI Adjusted HR	p value	MT / PCI Unadjusted HR	p value
Mortality / infarction	21.6	16.5	1.49	0.002	1.50	0.002

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Trial 2

The aim of this study was to investigate whether prior statin therapy translates into a lower incidence of heart failure in patients hospitalized for acute coronary syndrome. (2) This was a non-randomized observational trial comparing two groups, one with statins and another without statins prior to the acute event. The inverse probability of treatment weighting (IPTW, see explanation below) was used to balance different baseline characteristics and the *standardized difference* to estimate the level of adjustment. Table 2 summarizes the study in terms of the adjustment achieved and the trial outcome expressed as relative risk. The authors conclude that patients with acute coronary syndrome previously treated with statins have a better clinical outcome.

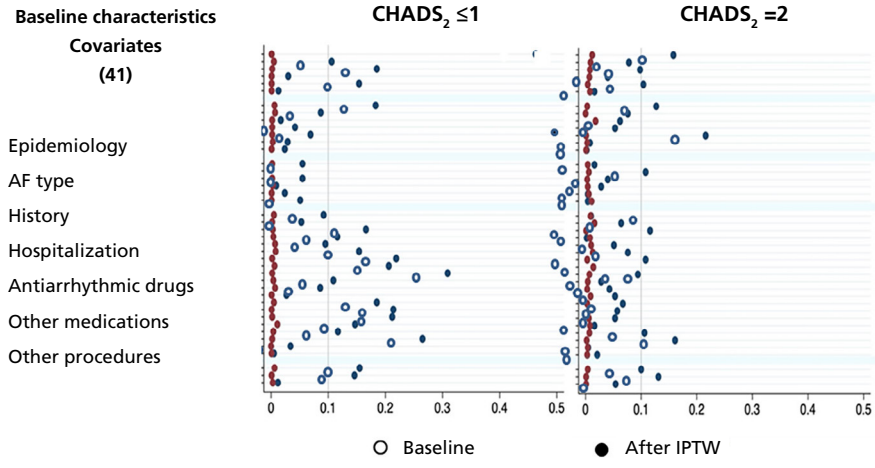
Trial 3

The aim of this observational study was to evaluate the role of oral anticoagulation after atrial fibrillation catheter ablation to prevent systemic thromboembolism and bleeding complications in subgroups according to the $CHADS_2$ score. (3) The authors used different statistical strategies, including IPTW.

	Prior statins Yes n= 1824	Prior statins No n= 12 718	Standardized difference	p
Age (years)	63.2 ± 11.2	61.8 ± 12.2	0.12	
Women	31.2	20.8	0.03	
Cardiovascular risk				
Diabetes	23.2	21.1	0.05	
Hypertension	67.5	61.4	0.13	
Hypercholesterolemia	40.6	36.9	0.08	
Current smoker	42.9	43.5	- 0.01	
Former smoker	13.5	13.5	0.07	
Medical history				
COPD	5.4	5.6	- 0.009	
Kydney disease	5.3	4.3	0.05	
Medication on admission				
Aspirin	19.2	16.6	0.07	
ACEI	35.8	32.6	0.07	
Beta-blockers	23.7	20.1	20.1	
Coronary angiography				
Multiple-vessel disease	43.1	43.8	0.09	
HF on admission	13.4	17.7		<0.0001
RR (95% CI)	0.72 (0.62-0.83)			<0.0001

ACEI: angiotensin-converting enzyme inhibitor; COPD: obstructive pulmonary disease; HF: heart failure; RR: relative risk.

Table 2. Trial 2. The covariates adjusted for IPTW (inverse probability treatment weighting) with the standardized difference after adjustment are shown above. Below, heart failure rates with and without prior statins, and the HR between both groups after IPTW. (Modified from reference 2) Quantitative variables are presented as mean and standard deviation, and qualitative variables as percentages



AF: atrial fibrillation; IPTW: inverse probability treatment weighting

Fig. 1. Trial 3. Standardized difference of more than 40 covariates between groups with and without anticoagulation, before and after adjustment for IPTW in $CHADS_2$ score ≤ 1 and $CHADS_2$ score = 2. The limit was set at 0.10. Confounders were well-balanced after adjustment. The difference was significantly higher in $CHADS_2$ score≤1 before adjustment, indicating that this group was more heterogeneous in terms of confounding variables. (Modified from reference 3)

Figure 1 shows the *standardized difference* in baseline characteristics *before and after adjusting* for IPTW. The acceptance level is <0.10. For the example, the effect of anticoagulation was only considered in the $CHADS_2$ score ≤ 1. The result was expressed as HR by IPTW (primary endpoint), by propensity score matching (PS), and by the Cox proportional hazards model (secondary endpoints).

Table 3 shows the effect of anticoagulation on thromboembolism and major bleeding in $CHADS_2$ score ≤ 1. (The subgroups with $CHADS_2$ score = 2 and $CHADS_2$ score ≥ 3, which were not considered for this methodological analysis, were also analyzed). Figure 2 shows the *incidence* of thromboembolism and major bleeding with and without anticoagulation in the $CHADS_2$ score ≤ 1 subgroup after adjusting for IPTW.

The authors conclude that in $CHADS_2$ score ≤ 1 anticoagulation does not provide any benefit for the prevention of thromboembolism and is associated with higher bleeding rate.

Trial 4

The aim of the investigation was to determine the *risk (prognostic criterion)* of type 2 myocardial infarction compared to type 1. (4) Figure 3 illustrates the *standardized difference before and after adjustment* of several baseline characteristics. The authors highlight that the prognosis for both types of myocardial infarction was similar. However, the detailed analysis in Figure 3 shows differences compared to Figure 1 that could call into question any conclusion about the prognostic value, independent of the type of infarction.

Trial 5

The focus of this investigation differed from the one of the trials mentioned before. (5) The authors wanted to evaluate the natural history of aortic stenosis according to its severity. Although a significant percentage of the sample underwent valve implantation or aortic valve replacement, the aim of the investigators was not to compare the groups with and without intervention, but rather to analyze the spontaneous disease progression. The IPTW methodology was used to adjust for the informative censoring caused by the intervention. Based on the findings presented in Table 4 (adjusted and unadjusted mortality), the authors conclude that the population not intervened represents the natural history of aortic stenosis.

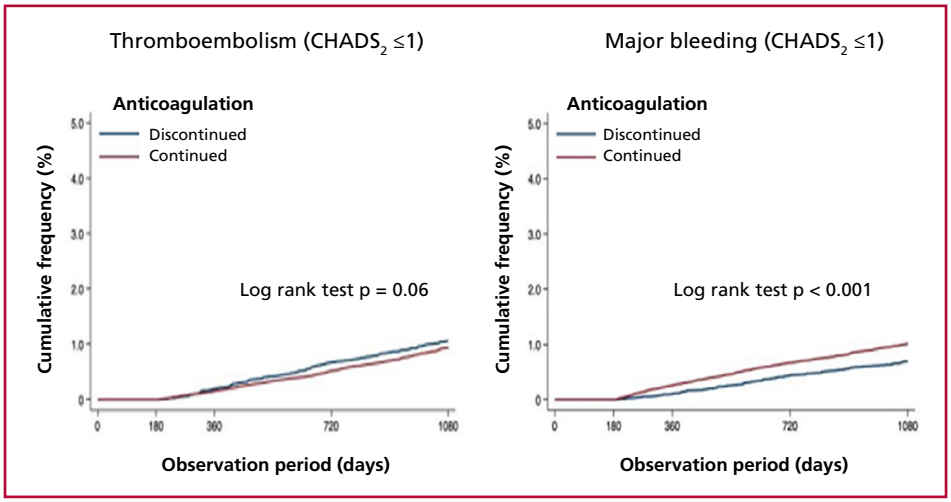


Fig. 2. Trial 3. Incidence of events with and without anticoagulation after atrial fibrillation catheter ablation for the IPTW-adjusted population in the $CHADS_2$ subgroup ≤ 1. There were no differences in the incidence of embolism, but major bleeding was significantly higher (log rank test) in subjects who continued with anticoagulation. (Modified from reference 3)

Table 3. Trial 3. Effect of anticoagulation after atrial fibrillation catheter ablation on thromboembolism and major bleeding in the subgroup with $CHADS_2$ score ≤ 1. The result, expressed in HR and its confidence interval is presented according to three statistical methods. (Modified from reference 3)

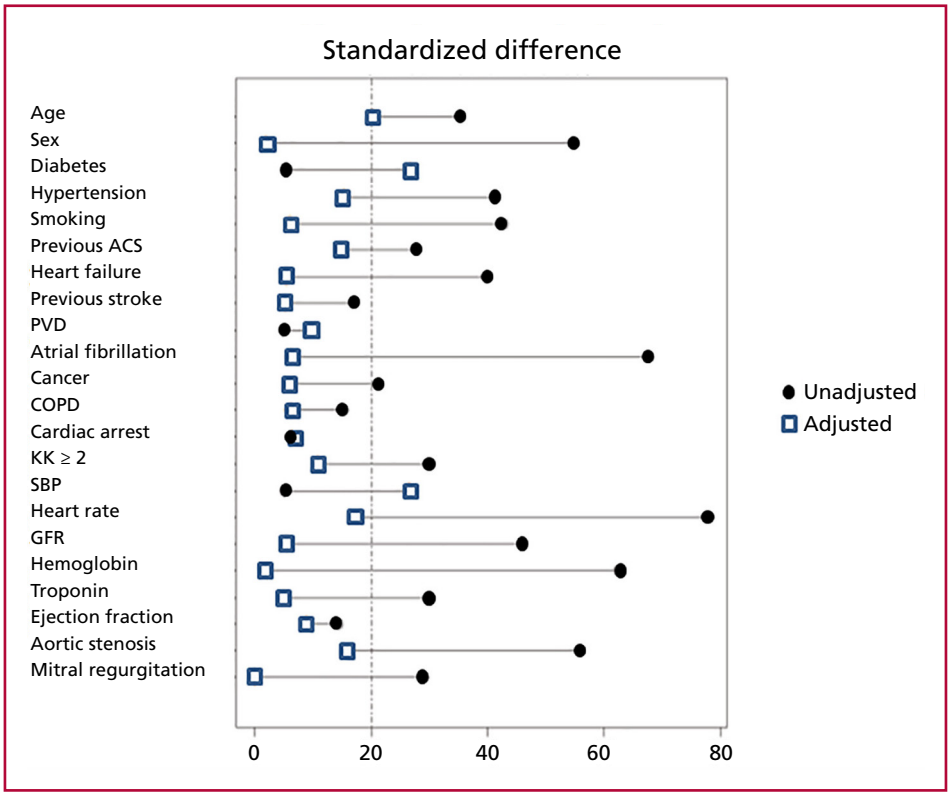
$CHADS_2$ score ≤ 1	HR (95% CI)	p
Thromboembolism		
IPTW	0.86 (0.74-1.01	0.06
Multivariate Cox	0.97 (0.85-1.11)	0.67
PS matching	0.84 (0.71-0.98)	0.03
Major bleeding		
IPTW	1.51 (1.27-1.89)	<0.001
Multivariate Cox	1.57 (1.36-1.82)	<0.001
PS matching	1.50 (1.27-1.78)	<0.001

IPTW: inverse probability treatment weighting; PS: propensity score

Observational studies

The common denominator of the bibliography mentioned can be summarized in the following points:

- design: ***observational study***
- objective: to evaluate the effect of an ***exposure variable*** (intervention or prognostic criterion) on



ACS: acute coronary syndrome; COPD: chronic obstructive pulmonary disease; KK: Killip and Kimball; PVD: peripheral vascular disease; SBP: systolic blood pressure.

Fig. 3. Trial 4. The chart is qualitatively similar to that of Fig. 3. In this case, the adjustment limit was set at 0.20. The differences after adjustment are close to 0.10, which is significantly higher than in the previous example. (Modified from reference 4).

Table 4. Trial 5. Mortality rate in a sample of patients with different grades of severity of aortic stenosis with medical treatment and after adjustment for IPTW. The aim was to adjust for the informative censoring caused by the intervention (valve implantation or replacement). The absence of differences indicates that the medical treatment group is not a selected (biased) population by the intervention. See the explanation in the text. (Modified from reference 5).

Aortic stenosis	Mortality (%/4 years)	
	Unadjusted	Adjusted
No	13.5	13.5
Mild	25.0	25.0
Mild to moderate	29.7	29.7
Moderate	33.5	33.3
Moderate to severe	45.7	42.2
Severe	44.9	42.0

an ***outcome variable*** and estimate the possible association between both variables.

- difficulty: the baseline characteristics of the sample may influence the relationship mentioned above; for this reason, they are often referred to as ***confounding variables*** or simply confounders.
- to affect the association of interest, confounders must be associated with the exposure variable and with the outcome variable.

Perhaps an example will illustrate this point (Figure 4): the outcome variable or study endpoint can be associated with the exposure variable (research objective) but also with a certain number of confounding factors that can influence this association. For example, if an intervention, which can favorably modify the end point, is preferentially indicated for younger patients, this benefit could be attributed to the treatment itself or to the fact that the procedure "selected" young individuals at lower risk. (The example can be extended to a trial investigating the value of a new prognostic criterion). In other words, any imbalance in the prevalence of confounding factors may affect the association that was the research objective.

In randomized (experimental) trials, the indication for intervention is not based on a medical decision but on random allocation. This distributes potential confounding factors uniformly across both groups with and without intervention, so that the exposure/outcome association is "independent" of its effects. However, randomization can sometimes fail, especially if the sample size is small.

The usual procedure to solve the problem is ***multivariate analysis, logistic regression or time-to-event analysis in the Cox proportional hazards model*** (hereafter "Cox model").

This methodology entails the simultaneous analysis of the exposure variable and the selected confounders, which are identified as having either an isolated statistical association or a prior bibliographic contribution (***independent variables***). (Figure 4). This

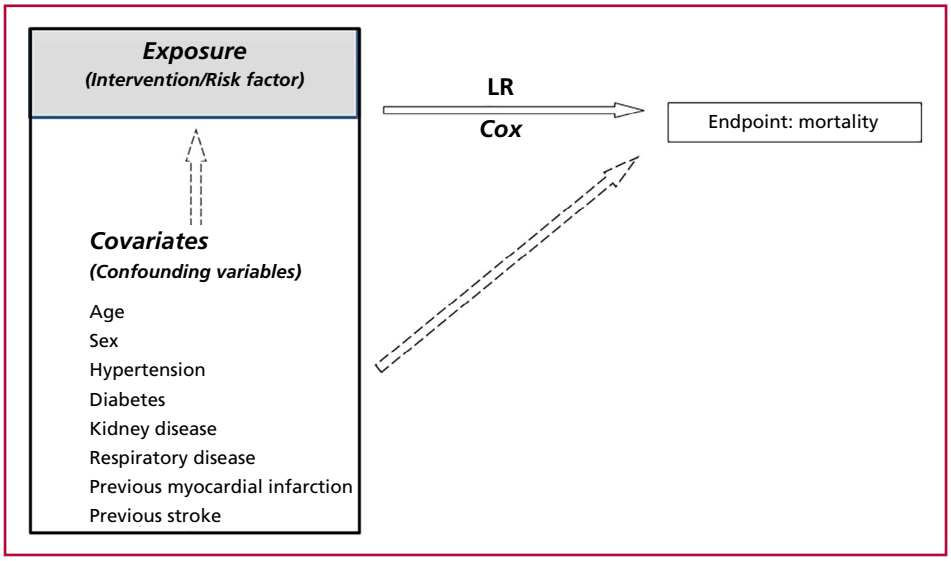


Fig. 4. Multivariate study. Exposure variable (intervention or risk factor, depending on the research objective), and its possible association with the outcome variables (solid arrow). If confounding variables are also associated with the exposure and the outcome variable (dashed arrows), they could attenuate or dilute the exposure/outcome association. The multivariate analysis of the set (box) estimates the "adjusted" association between the exposure and the outcome variable, independently of the confounding variables

Cox: Cox proportional hazards model; LR: logistic regression

procedure is usually referred to as adjustment. If the multivariate analysis determines that the exposure reaches statistical significance, we can conclude that it affects the outcome variable (***dependent variable***) since this association is not conditioned by the confounders.

Multivariate analysis requires a certain proportion between the number of independent variables and the prevalence/incidence of the outcome variable, which in certain circumstances may restrict the applicability of the methodology.

In the second part of this review, we will examine more recent statistical methods used in the statistical analysis of observational studies.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material).

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