Cómo optimizar los análisis de los estudios observacionales de IE

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Dos técnicas estadísticas destacan, en este ámbito y, además, compiten:

- Regresión logística múltiple.
- Análisis de propensiones (Propensity score analysis).

THIAZIDES AND ACUTE CHOLECYSTITIS

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Abstract An association between acute cholecystitis and the use of thiazide-containing drugs was observed during routine screening of data from a case-control drug-surveillance program. Evaluation of this relation among 419 patients with acute cholecystitis and 1676 control patients yielded a relative risk estimate of 2.0 for subjects who had used thiazides in the month before admission, as compared with subjects who had never used these drugs (95 per cent confidence interval, 1.4 to 2.7). There was a significant trend of increasing relative risk with increasing duration of use ($P < 0.01$), and the estimate for subjects who had used thiazides for five or more years was 2.9. The association was not explained by confounding due to the indications for thiazide use, such as hypertension, or other factors, such as obesity or the use of other drugs. No single epidemiologic study can eliminate chance or bias as an explanation for an association; the relation found here should be regarded as a hypothesis that requires independent confirmation. (N Engl J Med. 1980; 303:546-8.)

The central role of the propensity score in observational studies for causal effects

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SUMMARY

The propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates. Both large and small sample theory show that adjustment for the scalar propensity score is sufficient to remove bias due to all observed covariates. Applications include: (i) matched sampling on the univariate propensity score, which is a generalization of discriminant matching, (ii) multivariate adjustment by subclassification on the propensity score where the same subclasses are used to estimate treatment effects for all outcome variables and in all subpopulations, and (iii) visual representation of multivariate covariance adjustment by a two-dimensional plot.

Impact of Inadequate Empirical Therapy on the Mortality of Patients with Bloodstream Infections: a Propensity Score-Based Analysis

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The impact of the adequacy of empirical therapy on outcome for patients with bloodstream infections (BSI) is key for determining whether adequate empirical coverage should be prioritized over other, more conservative approaches. Recent systematic reviews outlined the need for new studies in the field, using improved methodologies. We assessed the impact of inadequate empirical treatment on the mortality of patients with BSI in the present-day context, incorporating recent methodological recommendations. A prospective multicenter cohort including all BSI episodes in adult patients was performed in 15 hospitals in Andalucía, Spain, over a 2-month period in 2006 to 2007. The main outcome variables were 14- and 30-day mortality. Adjusted analyses were performed by multivariate analysis and propensity score-based matching. Eight hundred one episodes were included. Inadequate empirical therapy was administered in 199 (24.8%) episodes; mortality at days 14 and 30 was 18.55% and 22.6%, respectively. After controlling for age, Charlson index, Pitt score, neutropenia, source, etiology, and presentation with severe sepsis or shock, inadequate empirical treatment was associated with increased mortality at days 14 and 30 (odds ratios [ORs], 2.12 and 1.56; 95% confidence intervals [95% CI], 1.34 to 3.34 and 1.01 to 2.40, respectively). The adjusted ORs after a propensity score-based matched analysis were 3.03 and 1.70 (95% CI, 1.60 to 5.74 and 0.98 to 2.98, respectively). In conclusion, inadequate empirical therapy is independently associated with increased mortality in patients with BSI. Programs to improve the quality of empirical therapy in patients with suspicion of BSI and optimization of definitive therapy should be implemented.

Use of Azithromycin
and Death from Cardiovascular Causes

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ABSTRACT

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BACKGROUND

Azithromycin use is associated with an increased risk of death from cardiovascular causes among patients at high baseline risk. Whether azithromycin confers a similar risk in the unselected general population is unknown.

METHODS

We conducted a nationwide historical cohort study involving Danish adults (18 to 64 years of age), linking registry data on filled prescriptions, causes of death, and patient characteristics for the period from 1997 through 2010. We estimated rate ratios for death from cardiovascular causes, comparing 1,102,050 episodes of azithromycin use with no use of antibiotic agents (matched in a 1:1 ratio according to propensity score, for a total of 2,204,100 episodes) and comparing 1,102,419 episodes of azithromycin use with 7,364,292 episodes of penicillin V use (an antibiotic with similar indications; analysis was conducted with adjustment for propensity score).

RESULTS

The risk of death from cardiovascular causes was significantly increased with current use of azithromycin (defined as a 5-day treatment episode), as compared with no use of antibiotics (rate ratio, 2.85; 95% confidence interval [CI], 1.13 to 7.24). The analysis relative to an antibiotic comparator included 17 deaths from cardiovascular causes during current azithromycin use (crude rate, 1.1 per 1000 person-years) and 146 during current penicillin V use (crude rate, 1.5 per 1000 person-years). With adjustment for propensity scores, current azithromycin use was not associated with an increased risk of cardiovascular death, as compared with penicillin V (rate ratio, 0.93; 95% CI, 0.56 to 1.55). The adjusted absolute risk difference for current use of azithromycin, as compared with penicillin V, was −1 cardiovascular death (95% CI, −9 to 11) per 1 million treatment episodes.

CONCLUSIONS

Azithromycin use was not associated with an increased risk of death from cardiovascular causes in a general population of young and middle-aged adults. (Funded by the Danish Medical Research Council.)

Impact of a Multidisciplinary Management Strategy on the Outcome of Patients With Native Valve Infective Endocarditis

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Strategies to improve management of patients with native valve endocarditis (NVE) are needed because of persistently high morbidity and mortality. We sought to assess the impact of an operative protocol of multidisciplinary approach on the outcome of patients with NVE. A formal policy for the care of infective endocarditis was introduced at our hospital in 2003 in which patients were referred to and managed by a preexisting team involving a cardiologist, a specialist in infectious diseases, and a cardiac surgeon. The initial multidisciplinary evaluation was performed within 12 hours of admission. Whenever conditions associated with impending hemodynamic impairment, high-risk for systemic embolization, or unsuccessful medical therapy were found, patients were operated on within 48 hours. Stable patients were evaluated weekly by the multidisciplinary team, and on-treatment surgery was performed whenever the above high-risk conditions had developed. Comparing the period 2003 through 2009 with 1996 through 2002 (when a multidisciplinary policy was not followed), patients were more numerous (190 vs 102), older (mean age 59.1 vs 54.2, p = 0.01), and had more co-morbidities (mean Charlson index 3.01 vs 2.31, p = 0.02). The pattern of infection did not change in terms of valve infected or paravalvular complications. In the second period, fewer patients had culture-negative NVE (8% vs 21%, p = 0.01) and worsened renal function (37% vs 58%, p = 0.001). A significant reduction in overall in-hospital mortality (28% to 13%, p = 0.02), mortality for surgery during the active phase (47% to 13%, p ≤0.001), and 3-year mortality (34% vs 16%, p = 0.0007) was observed. In conclusion, formalized, collaborative management led to significant improvement in NVE-related mortality, notwithstanding the less favorable patients' baseline characteristics. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;■:■−■)

The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results?

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Aims	The aim of this study was to evaluate the effect of valve surgery (VS) in infective endocarditis (IE) on 5-year mortality and to evaluate whether conflicting results reported by previous studies could be due to differences in their methodological approaches.
Methods and results	Four hundred and forty-nine patients with a definite left-sided IE were selected from a prospective, population-based study. Association between VS and 5-year mortality was examined with a Cox model. To determine the impact of different methodological approaches, we also analysed the relationship between VS and mortality in our database, according to each method used in the five previous studies. Valve surgery was performed in 240 patients (53%). It was associated with an increase in short-term mortality [within the first 14 post-operative days; adjusted hazard ratio (HR), 3.69; 95% confidence interval (CI), 2.17–6.25; $P < 0.0001$] and a decrease in long-term mortality (adjusted HR, 0.55; 95% CI, 0.35–0.87; $P = 0.01$). At least 188 days of follow-up were required for VS to provide an overall survival advantage. When applying each study's method to our database, we obtained results similar to those reported.
Conclusion	Previous conflicting results appear to be related to differences in statistical methods. When using appropriate models, we found that VS was significantly associated with reduced long-term mortality.
Keywords	Infective endocarditis • Valve surgery • Mortality • Propensity analysis

The Impact of Valve Surgery on 6-Month Mortality in Left-Sided Infective Endocarditis

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Background—The role of valve surgery in left-sided infective endocarditis has not been evaluated in randomized controlled trials. We examined the association between valve surgery and all-cause 6-month mortality among patients with left-sided infective endocarditis.

Methods and Results—A total of 546 consecutive patients with left-sided infective endocarditis were included. To minimize selection bias, propensity score to undergo valve surgery was used to match patients in the surgical and nonsurgical groups. To adjust for survivor bias, we matched the follow-up time so that each patient in the nonsurgical group survived at least as long as the time to surgery in the respective surgically-treated patient. We also used valve surgery as a time-dependent covariate in different Cox models. A total of 129 (23.6%) patients underwent surgery within 30 days of diagnosis. Death occurred in 99 of the 417 patients (23.7%) in the nonsurgical group versus 35 deaths among the 129 patients (27.1%) in the surgical group. Eighteen of 35 (51%) patients in the surgical group died within 7 days of valve surgery. In the subset of 186 cases (93 pairs of surgical versus nonsurgical cases) matched on the logit of their propensity score, diagnosis decade, and follow-up time, no significant association existed between surgery and mortality (adjusted hazard ratio, 1.3; 95% confidence interval, 0.5 to 3.1). With a Cox model that incorporated surgery as a time-dependent covariate, valve surgery was associated with an increase in the 6-month mortality with an adjusted hazard ratio of 1.9 (95% confidence interval, 1.1 to 3.2). Because the proportionality hazard assumption was violated in the time-dependent analysis, we performed a partitioning analysis. After adjustment for early (operative) mortality, surgery was not associated with a survival benefit (adjusted hazard ratio, 0.92; 95% confidence interval, 0.48 to 1.76).

Conclusions—The results of our study suggest that valve surgery in left-sided infective endocarditis is not associated with a survival benefit and could be associated with increased 6-month mortality, even after adjustment for selection and survivor biases as well as confounders. Given the disparity between the results of our study and those of other observational studies, well-designed prospective studies are needed to further evaluate the role of valve surgery in endocarditis management. (***Circulation.*** 2007;115:1721-1728.)

Impact of Valve Surgery on 6-Month Mortality in Adults With Complicated, Left-Sided Native Valve Endocarditis
A Propensity Analysis

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THE ADVENT OF SURGICAL therapy for complicated native valve infective endocarditis has been associated with reduced mortality in published observational experiences.[1-3] Since the initial descriptions of valve replacement for active infective endocarditis,[4,5] valve surgery has been recommended for patients with native valve endocarditis who exhibit complications that adversely affect prognosis: congestive heart failure, new valvular regurgitation, systemic embolization to vital organs, refractory infection (eg, perivalvular abscess, persistent fever and bacteremia, or fungemia), and demonstration of a vegetation on echocardiography.[3,6-10] However, documentation of improved clinical outcome that results from valve surgery has been unproven due to the lack of controlled trials and the inherent biases of observational studies.

Recently, our group derived and externally validated a prognostic classification system in a large cohort of patients with complicated, left-sided native valve

Context Complicated, left-sided native valve endocarditis causes significant morbidity and mortality in adults. The presumed benefits of valve surgery remain unproven due to lack of randomized controlled trials.

Objective To determine whether valve surgery is associated with reduced mortality in adults with complicated, left-sided native valve endocarditis.

Design and Setting Retrospective, observational cohort study conducted from January 1990 to January 2000 at 7 Connecticut hospitals. Propensity analyses were used to control for bias in treatment assignment and prognostic imbalances.

Patients Of the 513 adults with complicated, left-sided native valve endocarditis, 230 (45%) underwent valve surgery and 283 (55%) received medical therapy alone.

Main Outcome Measure All-cause mortality at 6 months after baseline.

Results In the 6-month period after baseline, 131 patients (26%) died. In unadjusted analyses, valve surgery was associated with reduced mortality (16% vs 33%; hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.29-0.63; $P<.001$). After adjustment for baseline variables associated with mortality (including hospital site, comorbidity, congestive heart failure, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection), valve surgery remained associated with reduced mortality (adjusted HR, 0.35; 95% CI, 0.23-0.54; $P<.02$). In further analyses of 218 patients matched by propensity scores, valve surgery remained associated with reduced mortality (15% vs 28%; HR, 0.45; 95% CI, 0.23-0.86; $P=.01$). After additional adjustment for variables that contribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR, 0.40; 95% CI, 0.18-0.91; $P=.03$). In this propensity-matched group, patients with moderate to severe congestive heart failure showed the greatest reduction in mortality with valve surgery (14% vs 51%; HR, 0.22; 95% CI, 0.09-0.53; $P=.001$).

Conclusions Valve surgery for patients with complicated, left-sided native valve endocarditis was independently associated with reduced 6-month mortality after adjustment for both baseline variables associated with the propensity to undergo valve surgery and baseline variables associated with mortality. The reduced mortality was particularly evident among patients with moderate to severe congestive heart failure.

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Use of surgery in patients with native valve infective endocarditis: Results from the International Collaboration on Endocarditis Merged Database

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Background Early surgery has been shown to be beneficial for patients with infective endocarditis (IE), yet surgery is not used in most patients. Evidence of the uncertainty around the use of surgery can be found in the wide variations in the use of cardiac surgery in IE with few precise indications for cardiac surgery yet defined. The aim of the study was to characterize patients with native valve IE relative to surgery and to determine if patients who benefit from an early surgical intervention can be identified.

Methods The International Collaboration on Endocarditis Merged Database was used to quantify the differences between patients with IE receiving medical and surgical intervention in 1516 patients with definite native valve IE. Propensity models were built to identify a group of patients that benefit from early surgery.

Results Patients in the early surgical group were more likely to be male, younger, and with less comorbidities compared with the early medical group ($P < .001$ for all) and were less likely to have infection with *Staphylococcus aureus* or viridans group streptococci ($P < .05$ for all). Intracardiac abscess and heart failure were much more common in the surgical group ($P < .001$ for all). In an unadjusted comparison, there was no statistically significant survival advantage in the surgical group. However, in the propensity analysis, in the subgroup of patients with the most indications for surgery, there was a significant decrease in mortality associated with early surgery (11.2% vs 38.0%, $P < .001$).

Conclusions The benefits of surgery are not seen uniformly in all patients with native valve IE, but are most realized in a targeted population. This observation requires confirmation in other populations of patients with definite IE. (Am Heart J 2005;150:1092-8.)

The use and effect of surgical therapy for prosthetic valve infective endocarditis: A propensity analysis of a multicenter, international cohort

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Background Although surgical intervention is often used in the treatment of prosthetic valve infective endocarditis (PVIE), an understanding of its effect on survival has been limited by the biases of observational studies and lack of controlled trials.

Methods The International Collaboration on Endocarditis Merged Database is a large, multicenter, international registry of patients with definite endocarditis by Duke criteria, including 367 patients with PVIE. Clinical, microbiologic, and echocardiographic variables were analyzed to determine those factors associated with the use of surgery for PVIE. Logistic regression analysis was performed to create a propensity model of predictors of surgery use. Patients who underwent surgery during initial hospitalization were matched by propensity score with patients treated with medical therapy alone. Logistic regression analysis was performed to determine variables independently associated with inhospital mortality in this matched subset.

Results Surgical therapy for PVIE was performed in 148 (42%) of 367 patients. Inhospital mortality was similar for patients treated with surgery compared with those treated with medical therapy alone (25.0% vs 23.4%, P = .729). Surgical therapy was independently associated with patient age, microorganism, intracardiac abscess, and congestive heart failure. After adjustment for these determinants, inhospital mortality was predicted by brain embolization (OR 11.12, 95% CI 4.16-29.73) and *Staphylococcus aureus* infection (OR 3.67, 95% CI 1.29-9.74), with a trend toward benefit for surgery (OR 0.56, 95% CI 0.23-1.36).

Conclusions Despite the frequent use of surgery for the treatment of PVIE, this condition continues to be associated with a high inhospital mortality rate in the contemporary era. After adjustment for factors related to surgical intervention, brain embolism and S aureus infection were independently associated with inhospital mortality and a trend toward a survival benefit of surgery was evident. (Am Heart J 2005;150:1086-91.)

Early Surgery in Patients with Infective Endocarditis: A Propensity Score Analysis

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Background. An accurate assessment of the predictors of long-term mortality in patients with infective endocarditis is not possible using retrospective data because of inherent treatment biases and predictable imbalances in the distribution of prognostic factors. Largely because of these limitations, the role of surgery in long-term survival has not been adequately studied.

Methods. Data were collected prospectively from 426 patients with infective endocarditis. Variables associated with surgery in patients who did not have intracardiac devices who had left-side–associated valvular infections were determined using multivariable analysis. Propensity scores were then assigned to each patient based on the likelihood of undergoing surgery. Using individual propensity scores, 51 patients who received medical and surgical treatment were matched with 51 patients who received medical treatment only.

Results. The following factors were statistically associated with surgical therapy: age, transfer from an outside hospital, evidence of infective endocarditis on physical examination, the presence of infection with staphylococci, congestive heart failure, intracardiac abscess, and undergoing hemodialysis without a chronic catheter. After adjusting for surgical selection bias by propensity score matching, regression analysis of the matched cohorts revealed that surgery was associated with decreased mortality (hazard ratio, 0.27; 95% confidence interval, 0.13–0.55). A history of diabetes mellitus (hazard ratio, 4.81; 95% confidence interval, 2.41–9.62), the presence of chronic intravenous catheters at the beginning of the episode (hazard ratio, 2.65; 95% confidence interval, 1.31–5.33), and paravalvular complications (hazard ratio, 2.16; 95% confidence interval, 1.06–4.44) were independently associated with increased mortality.

Conclusions. Differences between clinical characteristics of patients with infective endocarditis who receive medical therapy versus patients who receive surgical and medical therapy are paramount. After controlling for inherent treatment selection bias and imbalances in prognostic factors using propensity score methodology, risk factors associated with increased long-term mortality included diabetes mellitus, the presence of a chronic catheter at the onset of infection, and paravalvular complications. In contrast, surgical therapy was associated with a significant long-term survival benefit.
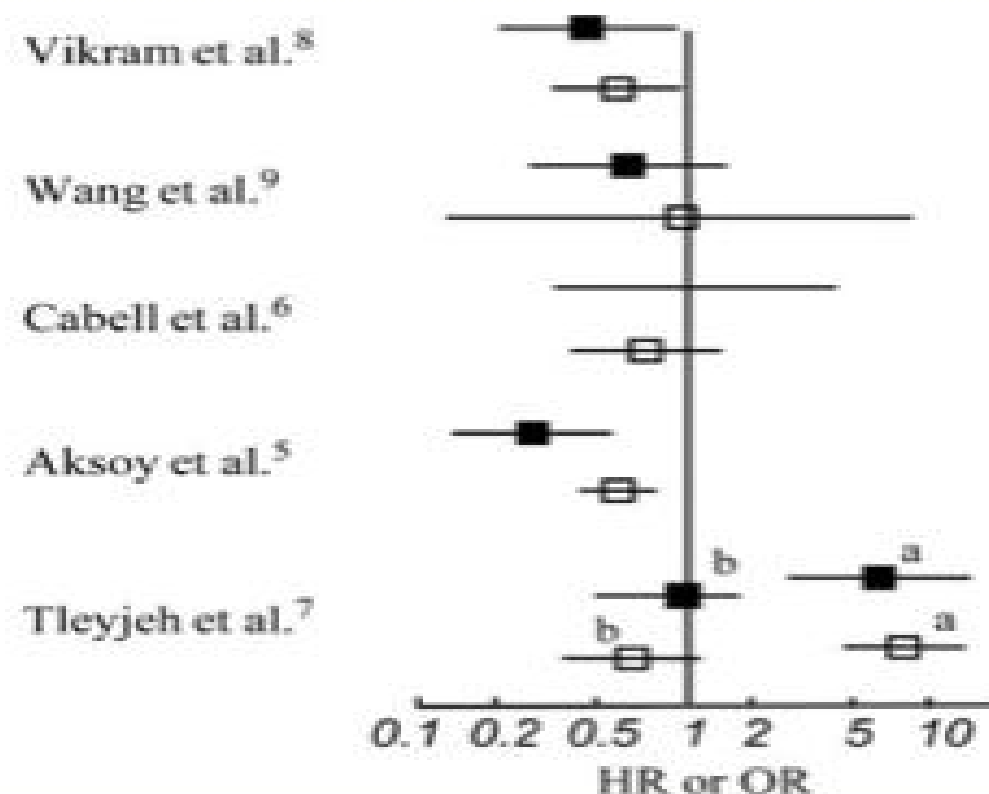
Figure 3 Relationship between valve surgery and death. Comparison between results from previous reports (black squares) and results from re-analysis from our database using the same methods (white squares). The squares and horizontal lines correspond to the study-specific adjusted hazard ratio (odds ratio for Wang and Cabell), and their 95% confidence interval. [a]Short-term mortality, 0–7 days after surgery; [b]mid-term mortality, 8 days to 6 months after surgery.

Análisis de propensiones
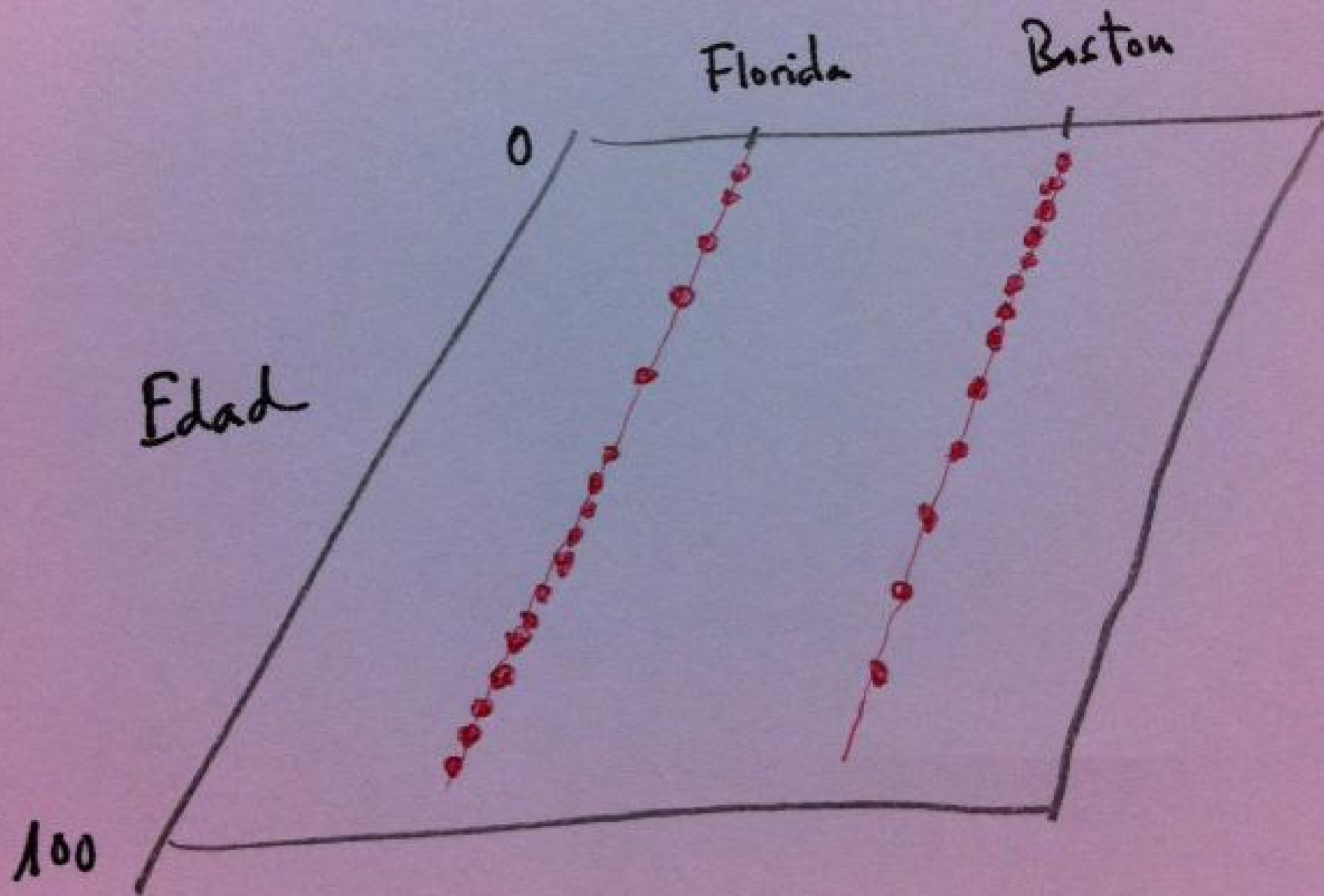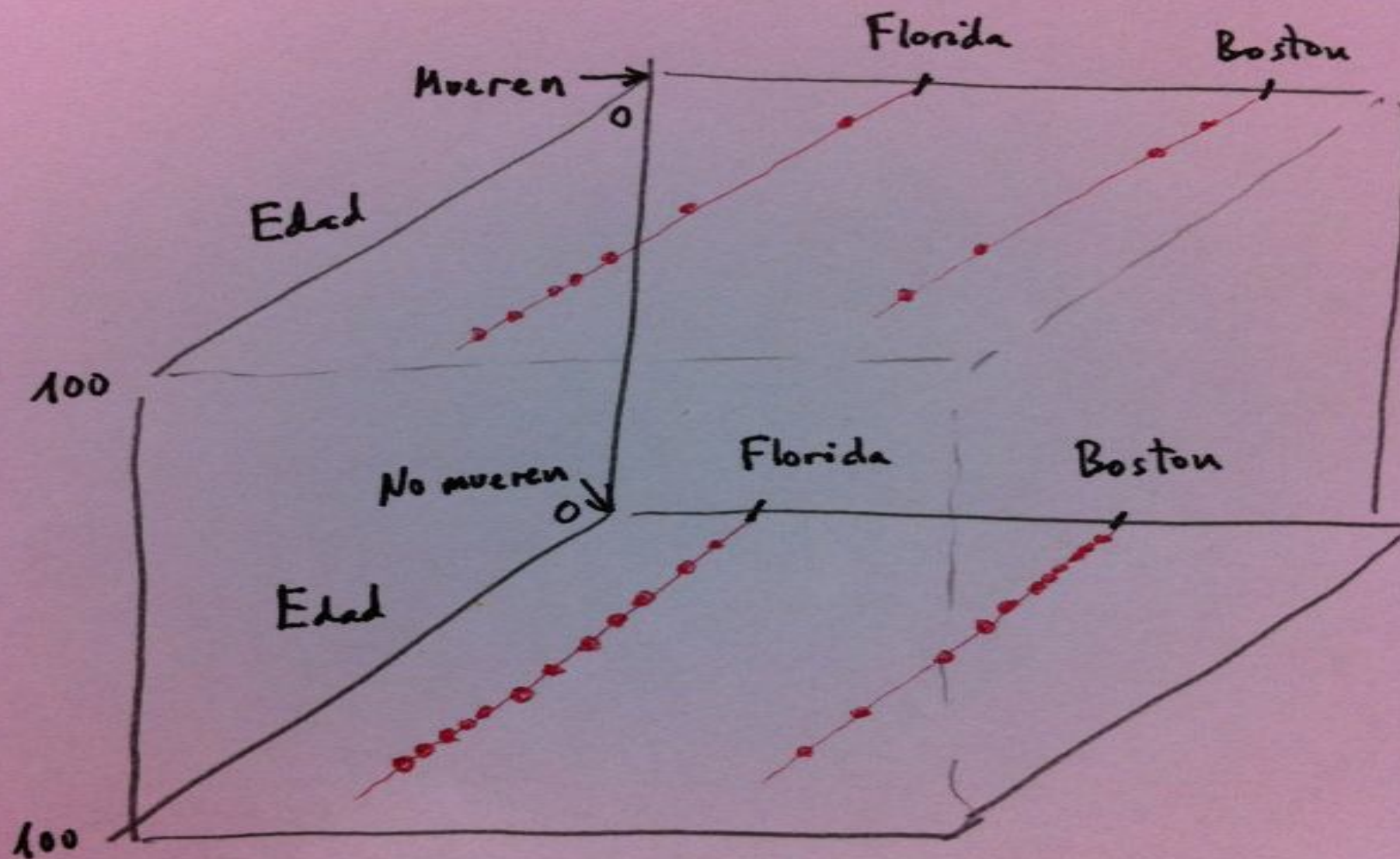# (Propensity score analysis)
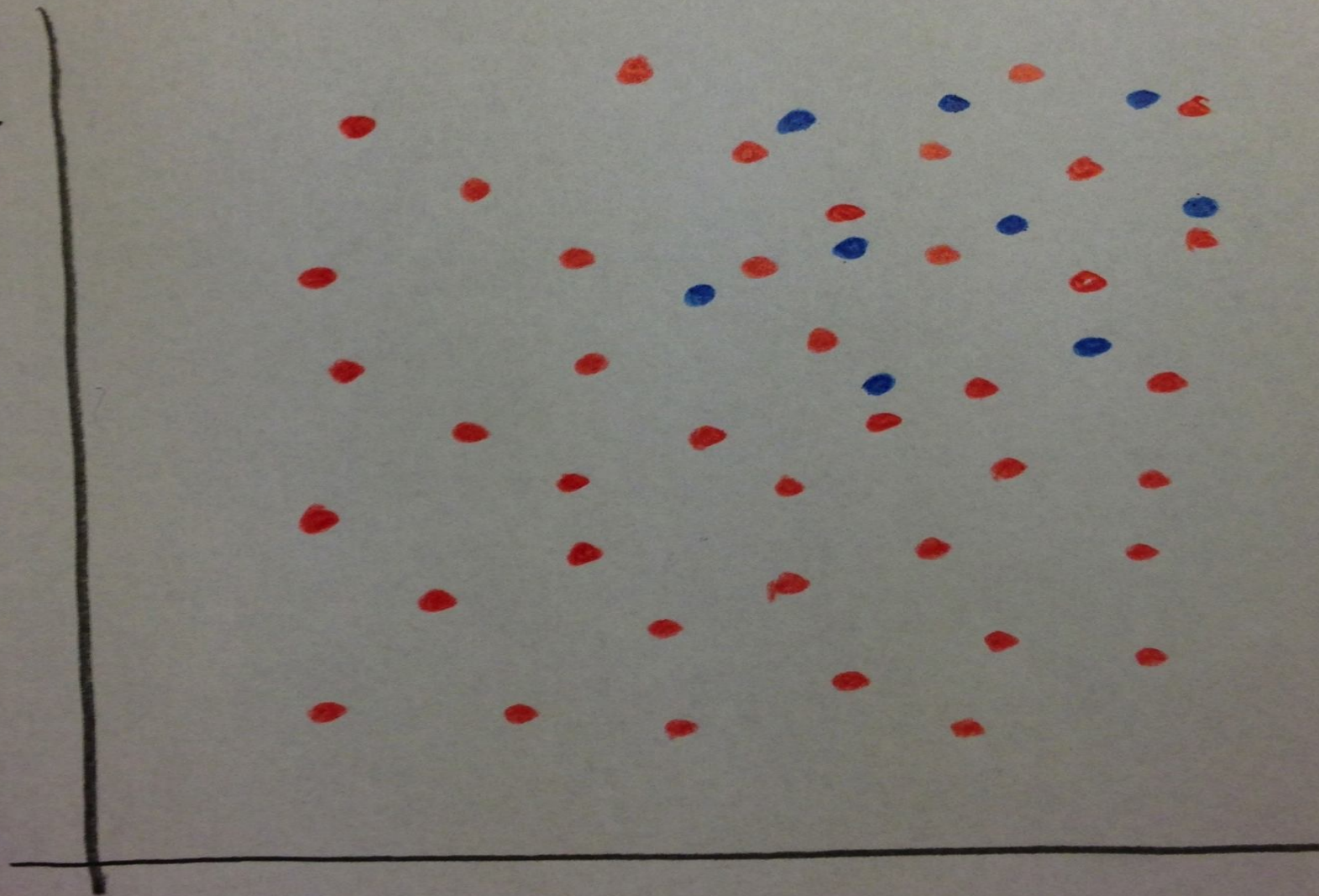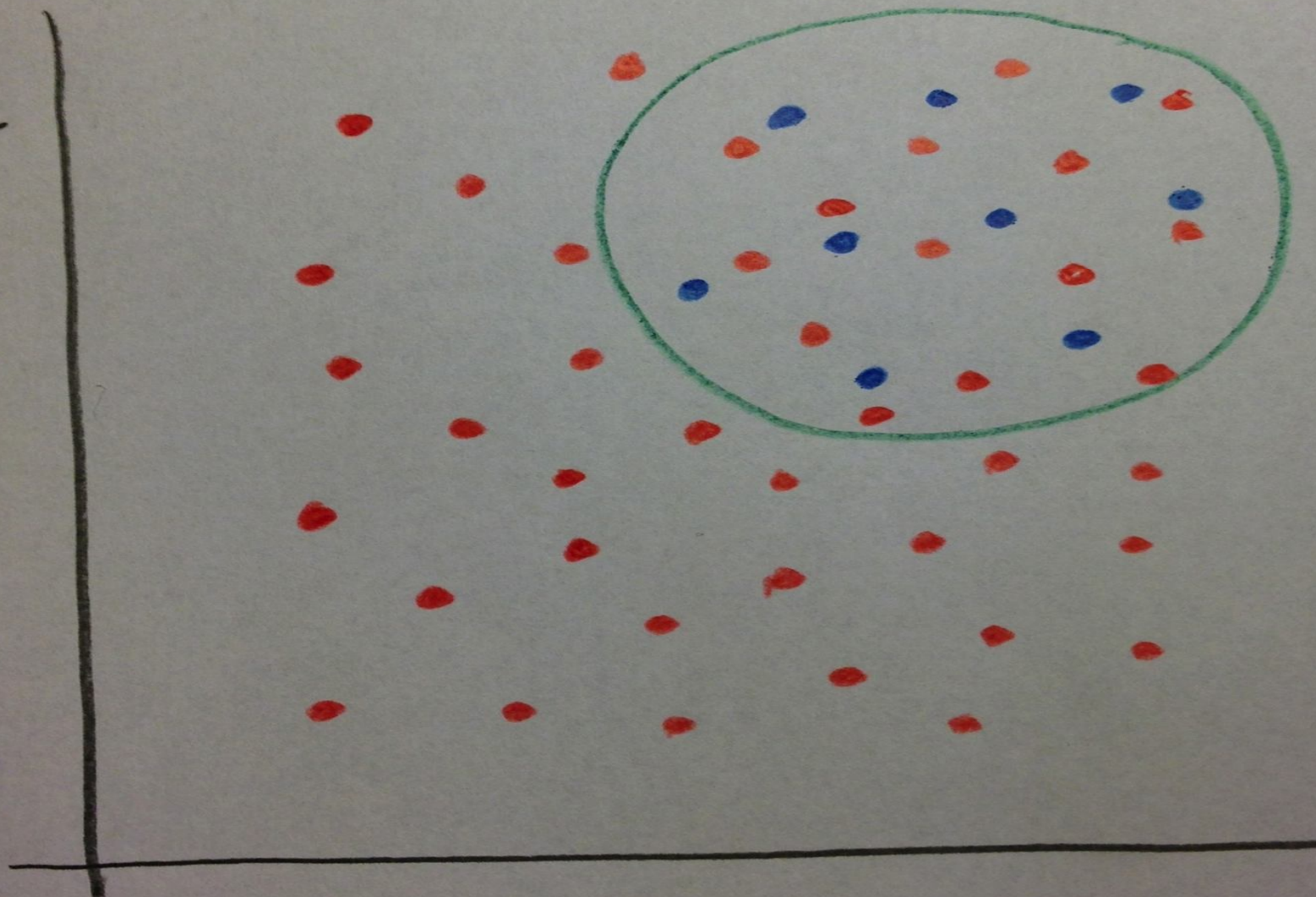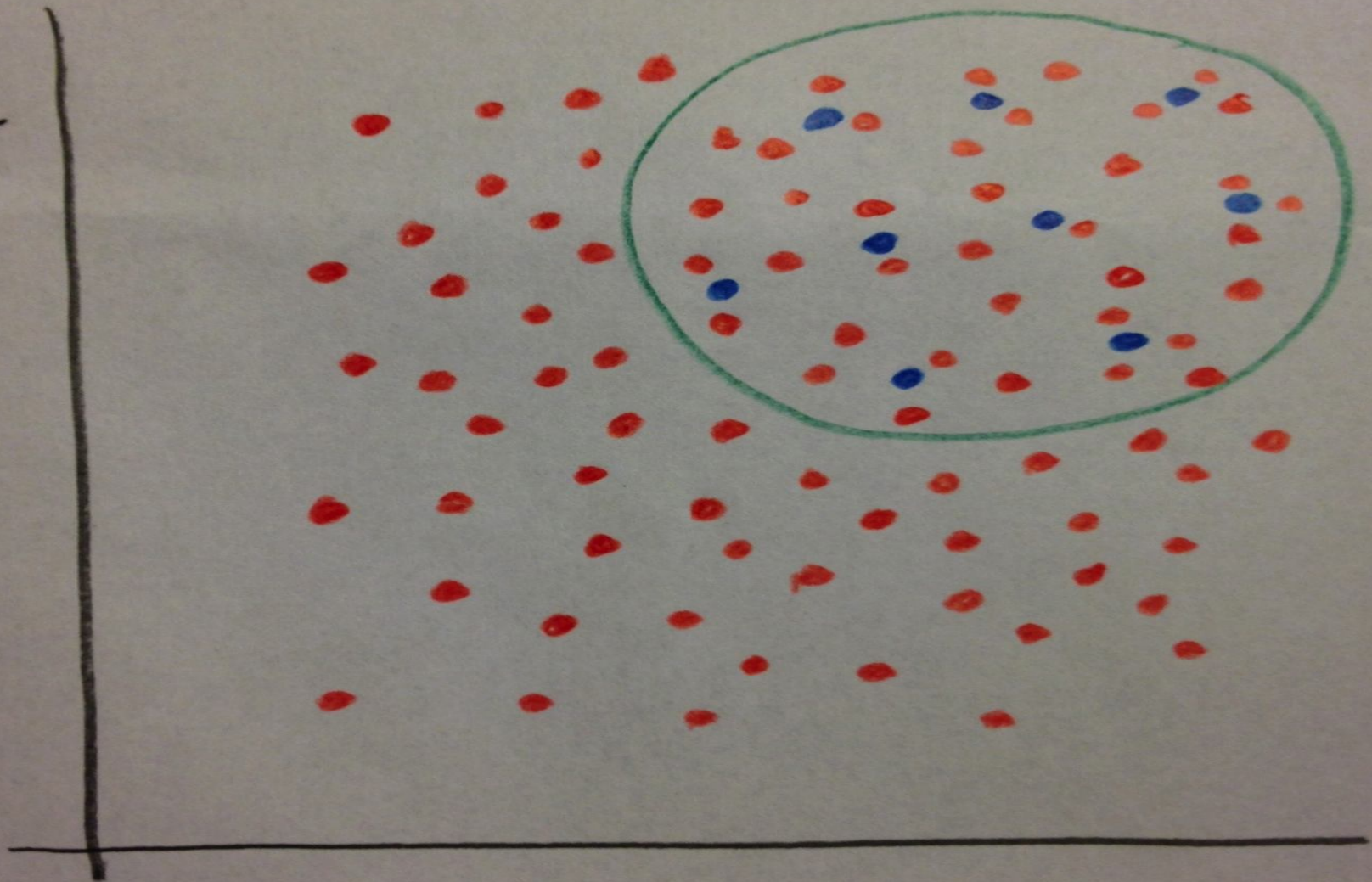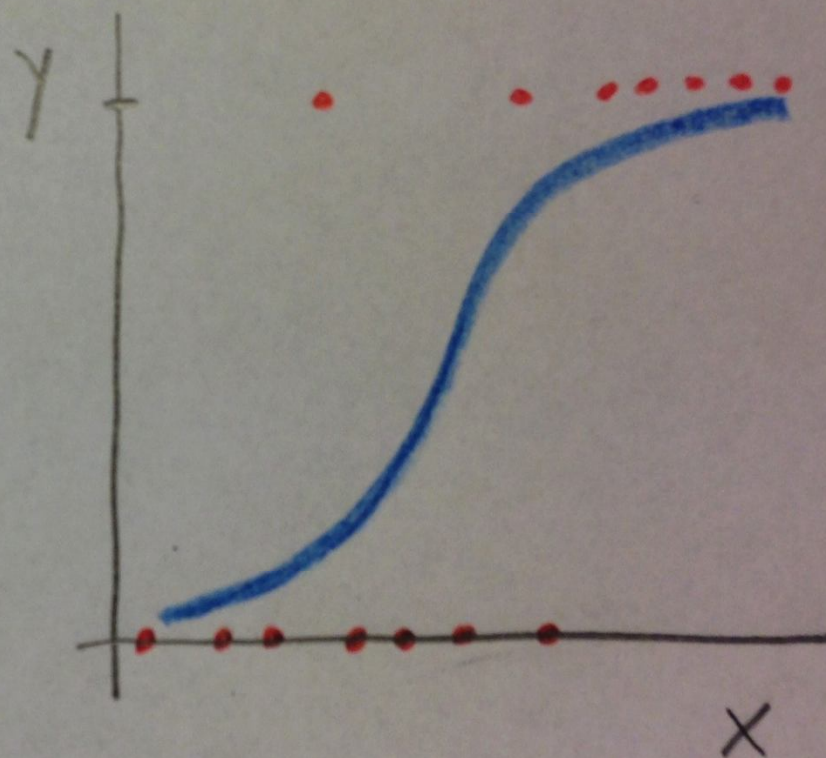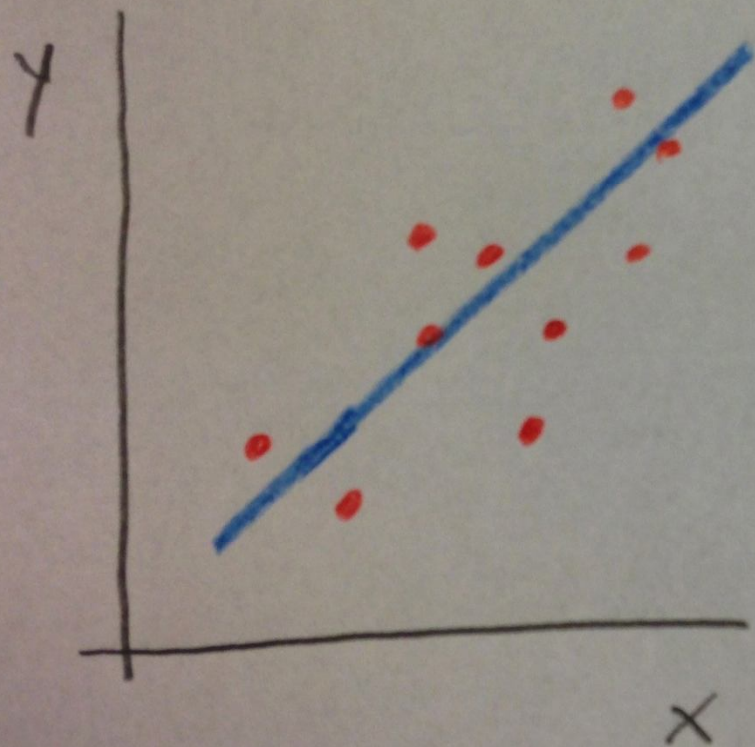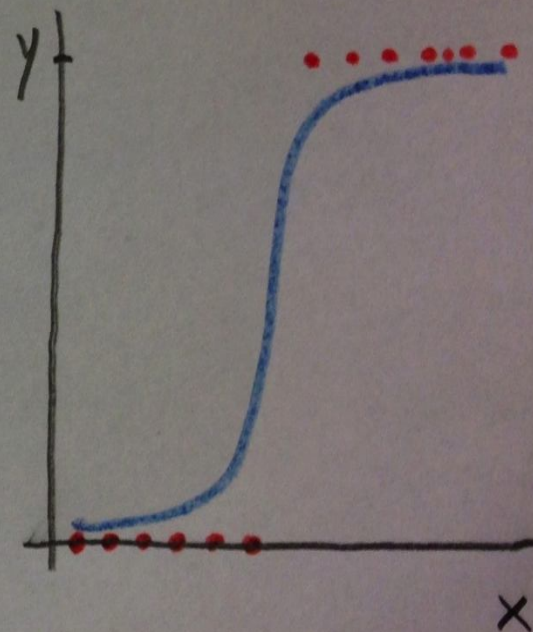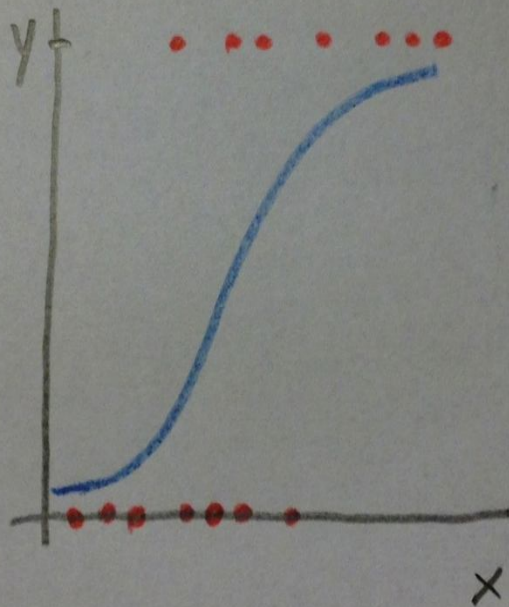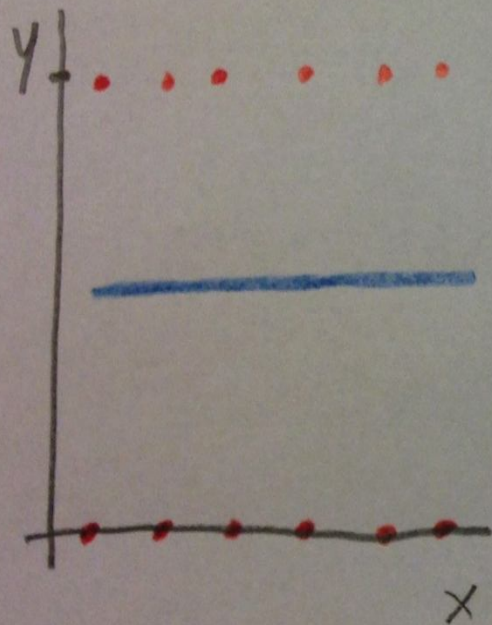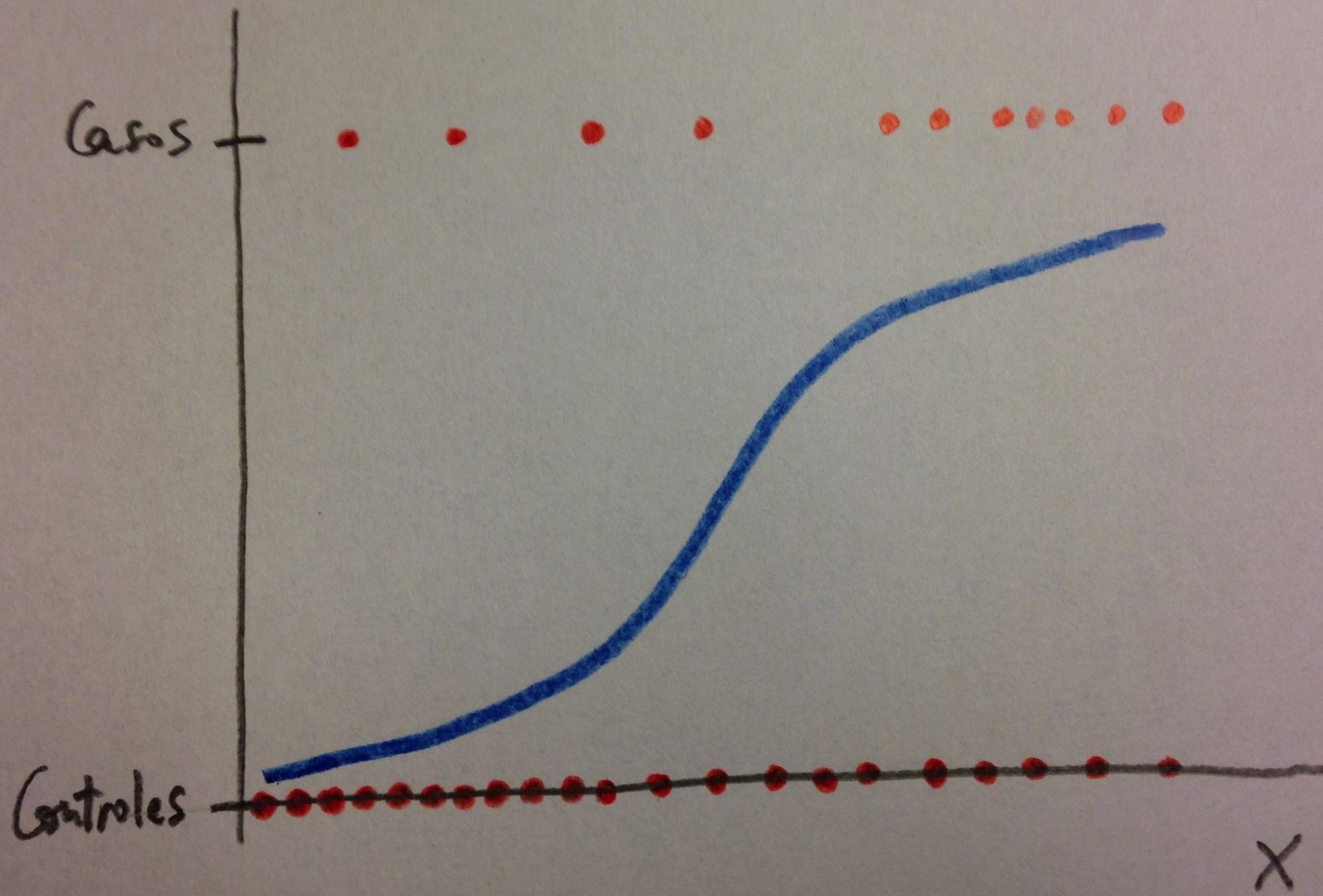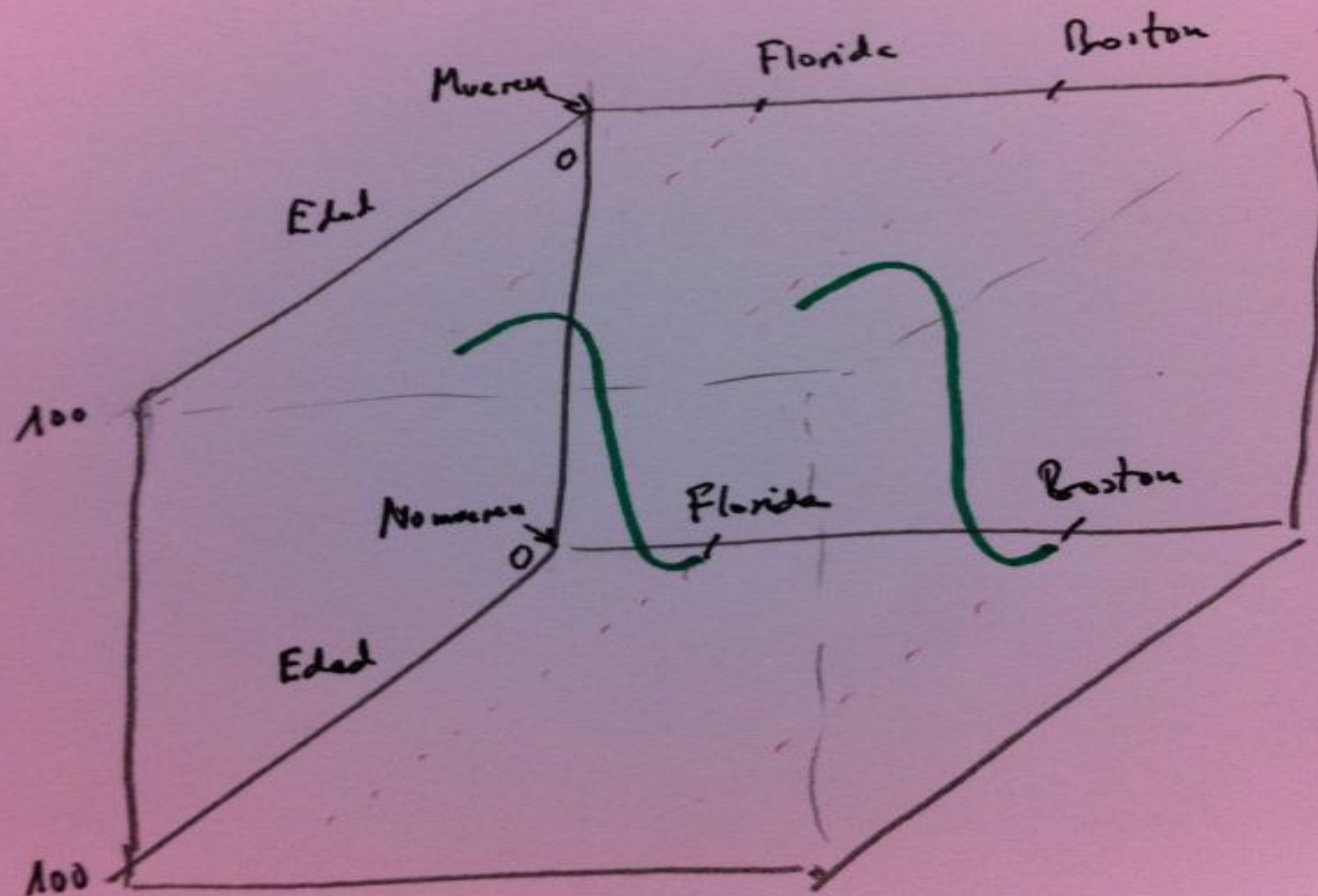
(1) Casos

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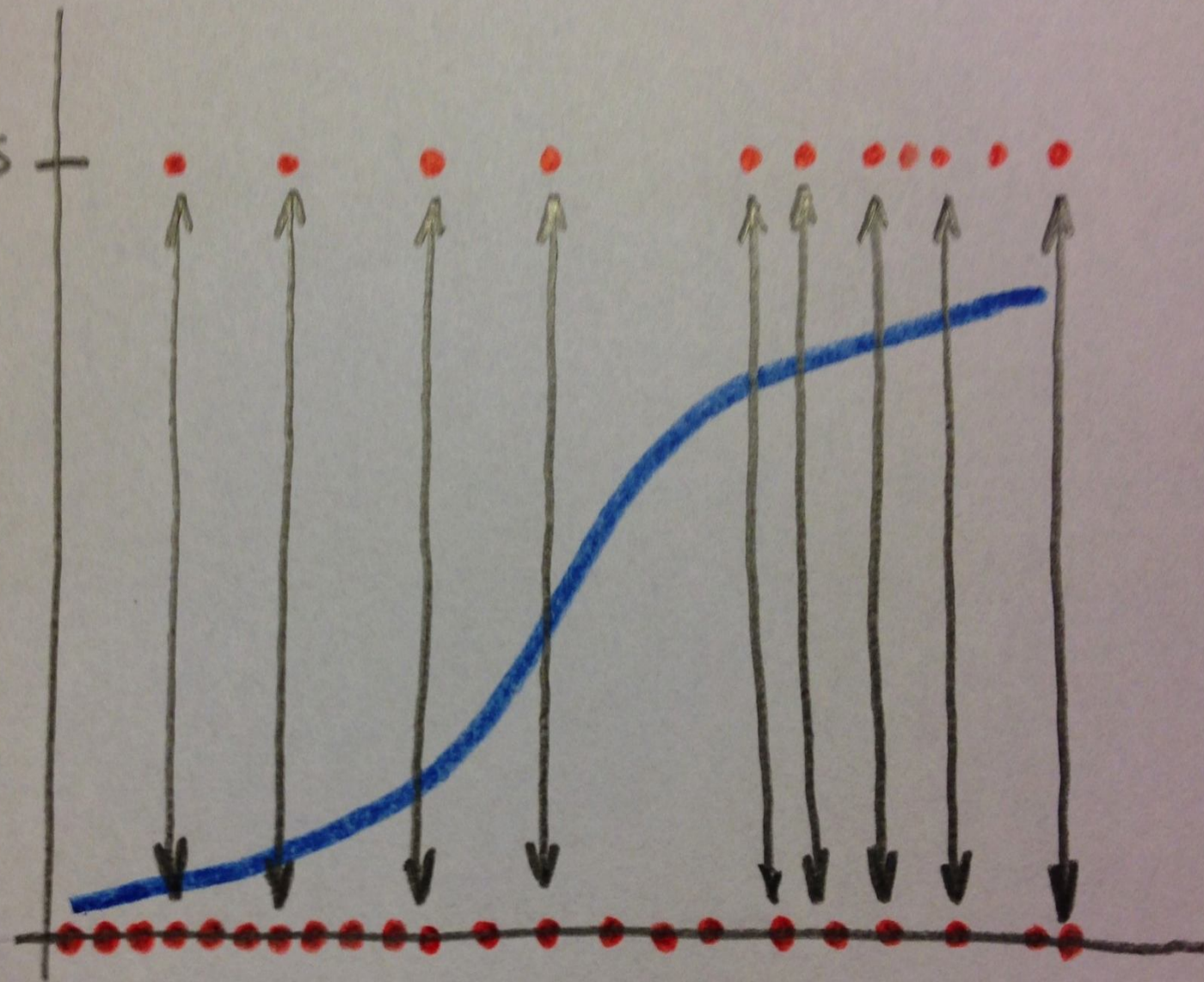
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Regresión logística múltiple

Comparison of Logistic Regression versus Propensity Score When the Number of Events Is Low and There Are Multiple Confounders

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The aim of this study was to use Monte Carlo simulations to compare logistic regression with propensity scores in terms of bias, precision, empirical coverage probability, empirical power, and robustness when the number of events is low relative to the number of confounders. The authors simulated a cohort study and performed 252,480 trials. In the logistic regression, the bias decreased as the number of events per confounder increased. In the propensity score, the bias decreased as the strength of the association of the exposure with the outcome increased. Propensity scores produced estimates that were less biased, more robust, and more precise than the logistic regression estimates when there were seven or fewer events per confounder. The logistic regression empirical coverage probability increased as the number of events per confounder increased. The propensity score empirical coverage probability decreased after eight or more events per confounder. Overall, the propensity score exhibited more empirical power than logistic regression. Propensity scores are a good alternative to control for imbalances when there are seven or fewer events per confounder; however, empirical power could range from 35% to 60%. Logistic regression is the technique of choice when there are at least eight events per confounder.
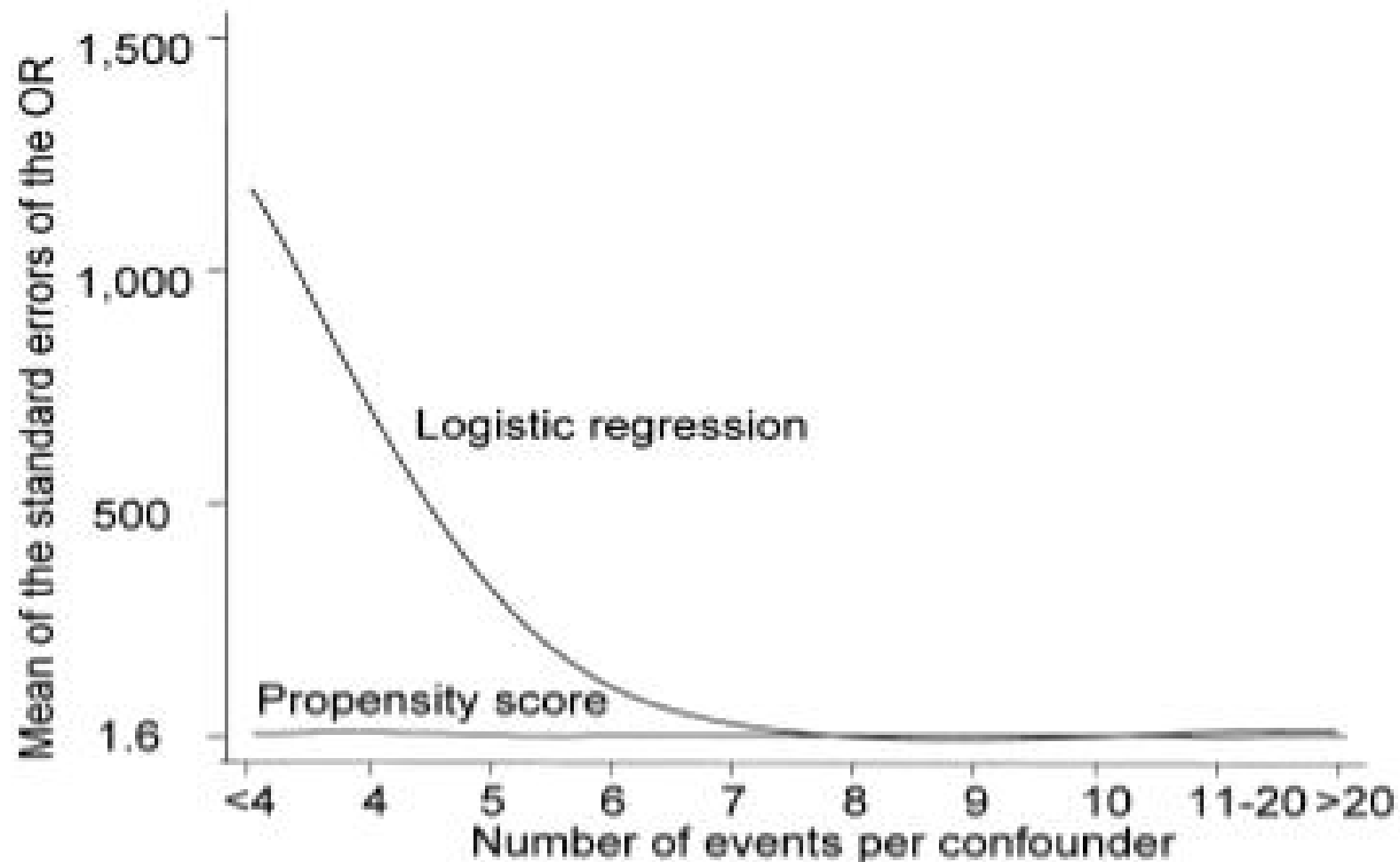
FIGURE 3. Mean of the standard errors of the odds ratio for the exposure, by number of events per confounder and by technique. The estimates of the propensity score are more precise (the standard errors are much smaller) than the estimates from logistic regression. As the number of events per confounder increases, the precision of the logistic regression increases. OR, odds ratio.