# Statistical methods for observational studies

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# Overview

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# Introduction
## Context

- Clinical trials are the gold standard to demonstrate efficacy in clinical research
- Participants receive specific interventions according to the protocol
- 4 phases
  - Phase I: Evaluate safety, tolerance threshold, side effects on healthy volunteers
  - Phase II: Test efficacy (and continue safety): comparative studies
  - Phase III: Gather more information on safety and efficacy
  - Phase IV: After approval, detect possible rare undesirable side effects
- However, limitations need to be acknowledged (less appropriate for rare conditions, restricted generalization...)
- Observational studies can complete missing information of clinical trials

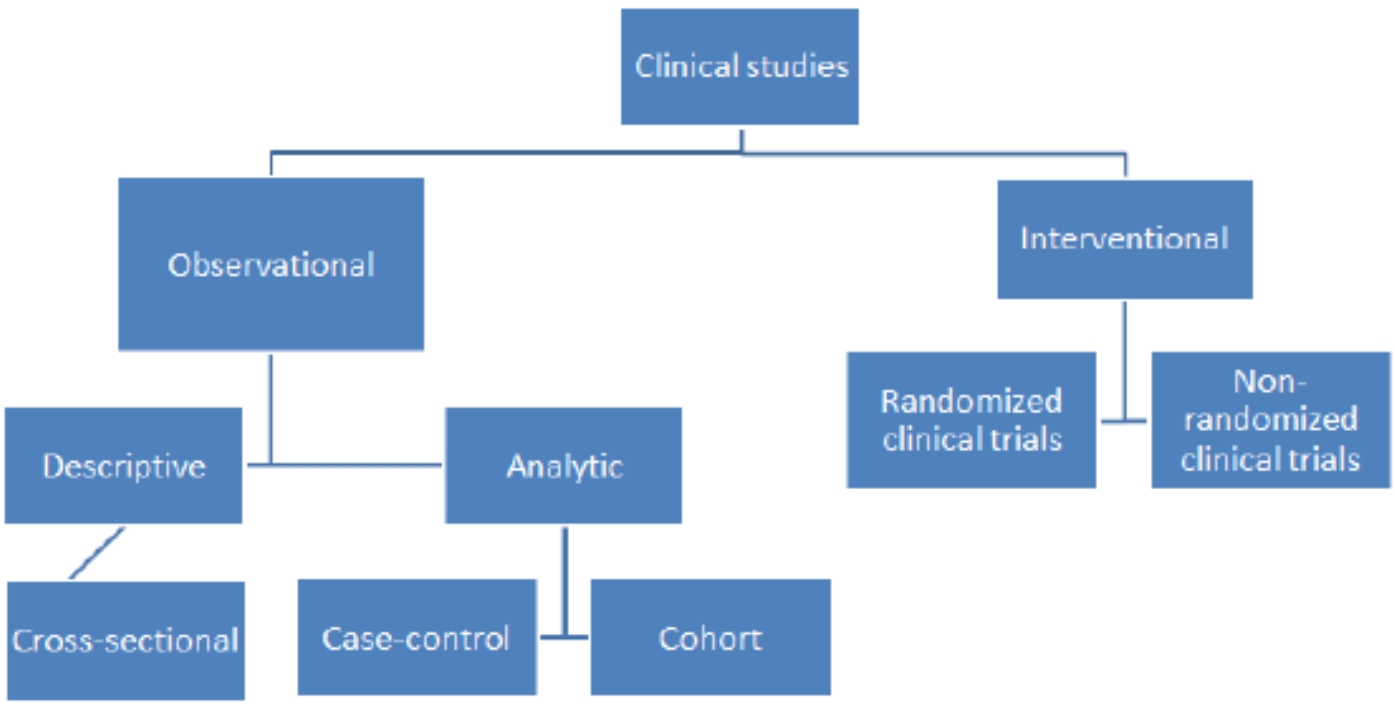
Any intervention studied is determined by clinical practice and not the protocol.

Useful to analyze

- Effectiveness: efficacy in real life
- Possible safety concerns and long-term complications
- Patients' compliance to treatment in real life
- Understudied populations
- Use of treatments (concomitant medication, off-label use,...)
- Rare conditions

# Introduction
## Observational studies

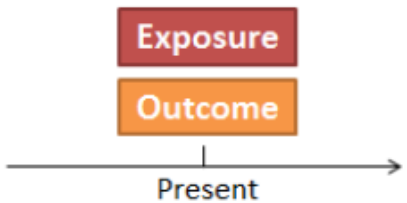
- Descriptive epidemiology: Monitoring the occurrence of a disease
- Analytic epidemiology: Studying the risk factors of a disease depending on an exposure



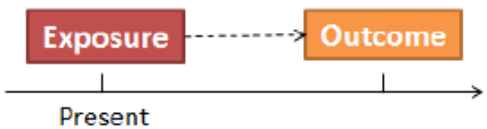
# Overview

# Observational studies
## The designs

**Cross-sectional studies**: Exposure and outcome determined simultaneously




**Cohort studies**: Inclusion of exposed and unexposed and analysis of whether or not they develop the outcome




**Case-control studies**: Inclusion of subjects with and without the outcome and collection of information on the past exposure

# Observational studies
## Potential biases

**Selection bias**:

- Distortion in estimating the association between the exposure and the outcome
- Consequence of how subjects are selected in the study

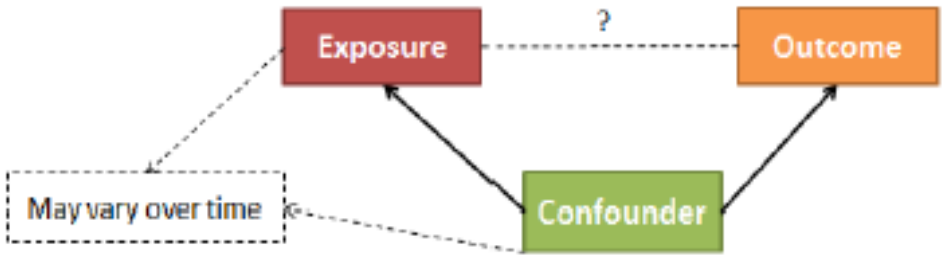
Example: Case-control study: influence of NSAIDs on colon cancer
Selection bias if the control chosen are patients hospitalized for arthritis
$\Rightarrow$ Both cases and controls will be exposed to NSAIDs

**Information bias**:

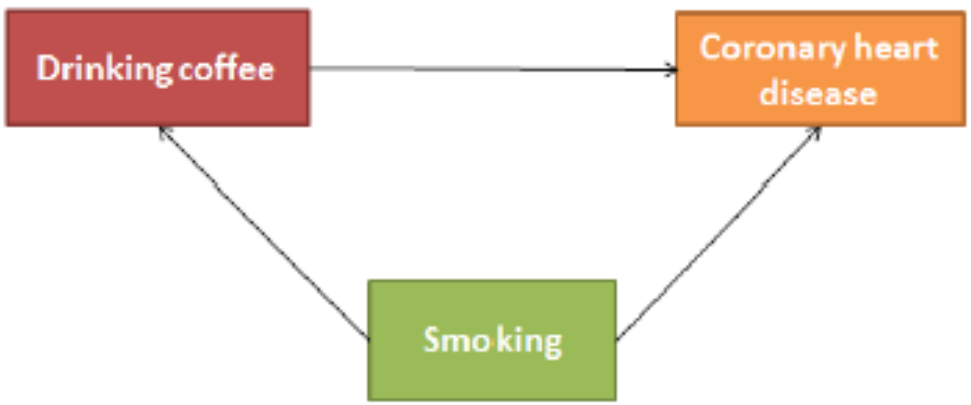
- Distortion in estimating which is the consequence of measurement errors or bad classifications of patients

# Observational studies
## Confounding

Confounders: factors associated with the exposure and with the outcome studied




Example:



# Overview

# Standard approaches
## Methodology

**Adjusting for confounding with multivariate regression**

- Include treatment and confounder in the model

**Stratification with the Cochran-Mantel-Haenszel method** (cmh)

- Comparing crude and stratum-specific associations

$$H_0 : OR_1 = OR_2 = ... = OR_K = 1$$

**Matching**

- Controlling confounding by forming homogeneous pairs regarding the confounder
- Statistical tests for matched data (ex: paired t-test for a continuous outcome )

# Standard approaches
## Propensity score methods

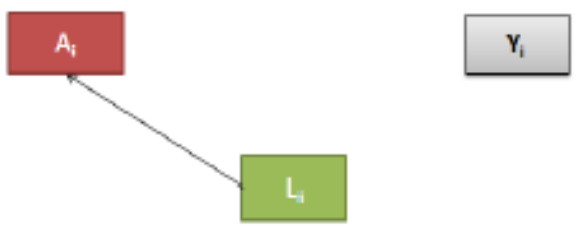
### Definition

Conditional probability for a patient to receive the treatment given his/her observed covariates

$$e_i = P(A_i = a_i | L_i)$$

where

- $e_i$: propensity score for subject $i$
- $A_i$: treatment of subject $i$
- $L_i$: covariate for subject $i$




$\rightarrow$ Estimate $e_i$ with logistic regression

# Standard approaches
## Propensity score methods

Methods using the propensity score:

- **Adjustment**: propensity score $\hat{e}_i$ is included in the regression model with the treatment $A$

$$E[Y_i] = \beta_0 + \beta_1 A_i + \beta_2 \hat{e}_i$$

- **Stratification**: propensity score is cut in percentiles and the association is observed in each stratum
- **Matching**: a treated patient is matched with an untreated patient with the closest propensity score
- Inverse Probability of Treatment Weighted (IPTW)

**Inverse Probability of Treatment Weighted (IPTW)**

- Calculate a weight from the propensity score for each subject:

$$IPTW_i = \frac{1}{P(A_i = a_i | L_i = l_i)} = \frac{1}{\hat{e}_i}$$

For a binary treatment: $IPTW_i = \frac{A_i}{\hat{e}_i} + \frac{1-A_i}{1-\hat{e}_i}$ (demo)

$\rightarrow$ In the weighted sample (pseudo-population): no confounding $\Rightarrow$ a usual regression model can be applied (demo)

- Stabilized weights to increase statistical efficiency

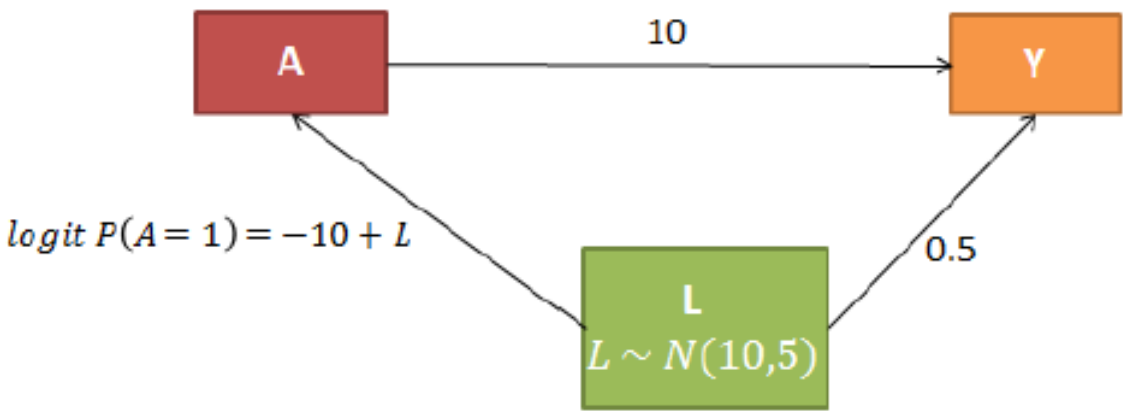
$$sw_i = \frac{P(A_i = a_i)}{P(A_i = a_i | L_i = l_i)} = P(A_i = a_i) \times IPTW_i$$

# Methodology
## Comparisons

| Methods | Strengths | Weaknesses |
|---|---|---|
| Multivariate adjustment | - Simultaneously adjustment for multiple confounders<br>- Use of all information in continuous variables | - Adequacy and assumptions of the model |
| Stratification | - Simple<br>- Estimation of the effects by stratum | - Difficult to interpret if multiple confounders with multiple levels<br>- Can cause loss of information or not remove enough confounding according to how the stratification is done |
| Matching | - Elimination of the influence of strong constitutional confounders<br>- Elimination of the influence of confounders that are hard to measure | - Difficult to acquire an adequate sample size<br>- Overmatching |
| Propensity score | - Simultaneously control for multiple confounders<br>- Ability to directly see confounding through distribution of the propensity score | - Difficult to understand the results<br>- Measurement of all relevant covariates |

# Standard approaches
## Applications: simulated data

- Point-treatment study
  - $L \sim \mathcal{N}(10, 5)$: a continuous confounder
  - *logit* $P(A = 1) = -10 + L$: a dichotomous treatment
  - $Y = 10A + 0.5L + \mathcal{N}(-10, 5)$: a continuous outcome
  - $i = 1, ..., n$ subjects with $n = 1000$
  - 200 simulations
- Objective: estimate the causal effect of $A$ on $Y$
- True value: 10



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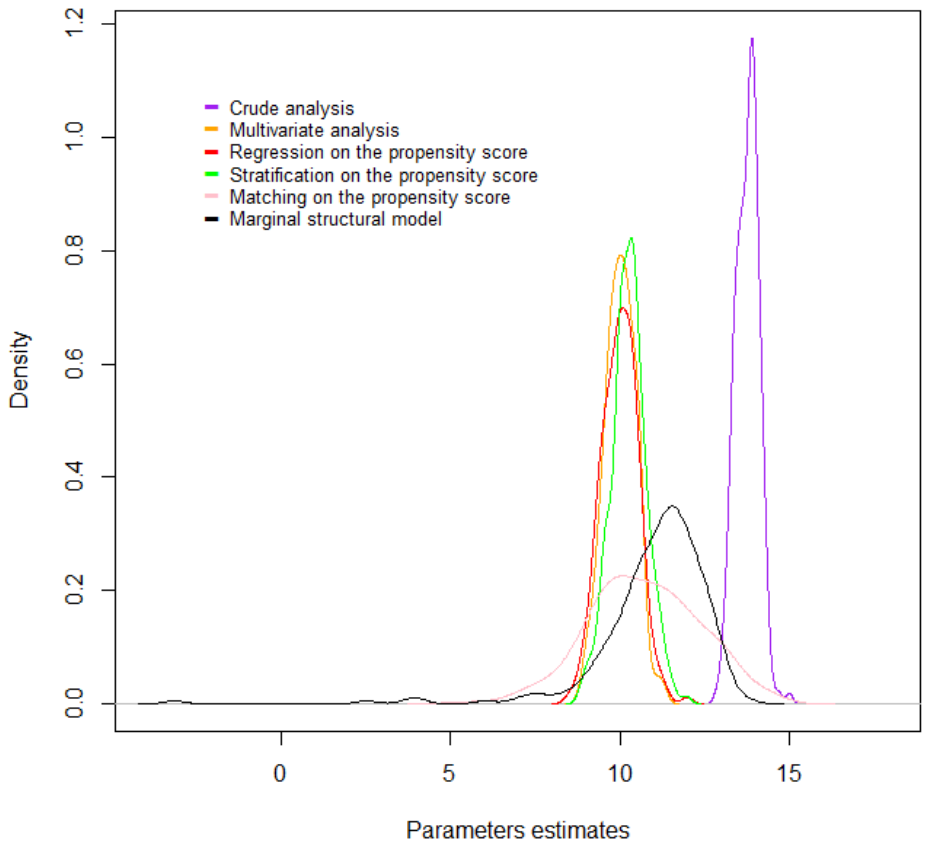
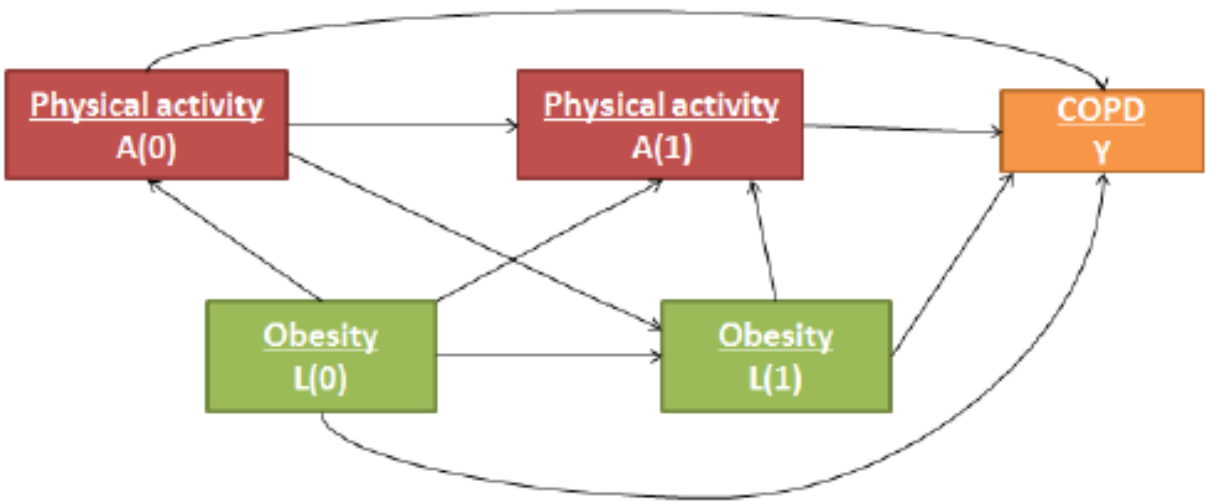



- Crude analysis overestimates the effect
- Adjusting on the confounder, adjusting on the propensity score, stratification on the propensity score: similar results with values centered around 10
- Matching on the propensity score and IPTW: more scattered estimates
  (Truncating method for the weights)

# Overview

# Marginal Structural models
## Introduction

- **Literature search:**
  - "Marginal structural models and causal inference in epidemiology", Robins JM, Hernan MA, Brumback B (2000), *Epidemiology*
  - "Marginal structural models to estimate the joint causal effect of nonrandomized treatments", Hernan MA, Brumback B, Robins JM (2001), *Journal of American Statistical Association*
- **Marginal structural models (MSMs) are useful when:**




**=> Relationship between treatment and outcome can be confounded**

# Marginal Structural Models
## Notations

**Notations**

- $A_i(t)$: treatment at time $t$ for subject $i$
- $\bar{A}_i(t) = (A_i(0), ..., A_i(t))$ for subject $i$, treatment history until $t$
- $L_i(t)$: confounder value at time $t$ for subject $i$
- $\bar{L}_i(t) = (L_i(0), ...L_i(t))$ for subject $i$, covariate history until $t$
- $V_i$: subset of time-fixed covariates ($V_i = L_i(0)$)
- $C_i(t)$: censoring indicator for subject $i$ at time $t$
- $K$: study duration
- Outcome: $Y_i$ for binary or continuous variables and $T_i$ for survival analysis

**Potential outcome**

- $Y_{\bar{a}}$: a subject's binary or continuous outcome had he/she been treated with $\bar{a}$ rather than his/her observed treatment $\bar{A}$
- $T_{\bar{a}}$: a subject's time-to-event if he/she had followed treatment history $\bar{a}$ from the start of follow-up rather than his/her observed treatment history

# Marginal Structural Models

## Weights

# Marginal Structural Models
## Weights

- Computing the Inverse Probability of Treatment Weights **IPTW**
  $t = 1, ..., K$ (implementation)

$$sw_i(t) = \prod_{k=0}^{t} \frac{f(A_i(k)|\bar{A}_i(k-1), V_i)}{f(A_i(k)|\bar{A}_i(k-1), \bar{L}_i(k))}$$

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- Computing the Inverse Probability of Censoring Weights **IPCW**

$$sw_i^{\dagger}(t) = \prod_{k=0}^{t} \frac{P[C_i(k) = 0|\bar{C}_i(k-1) = 0, \bar{A}_i(k), V_i]}{P[C_i(k) = 0|\bar{C}_i(k-1) = 0, \bar{A}_i(k), \bar{L}_i(k)]}$$

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- Computing the final weights

$$sw_i(t) \times sw_i^{\dagger}(t)$$

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- Computing the final weights

$$sw_i(t) \times sw_i^{\dagger}(t)$$

$\Rightarrow$ 1 weight per person and per time (sw)

# Marginal Structural Models
## Modeling

- **Binary outcome:** $\boxed{logit\ P(Y_{\bar{a}} = 1) = \beta_0 + \beta_1 cum(\bar{a})}$[1]
  measured at end of follow-up

$$sw_i(K) \times sw_i^{\dagger}(K)$$

- **Continuous outcome:** $\boxed{E[Y_{\bar{a}}] = \beta_0 + \beta_1 cum[\bar{a}]}$
  $\rightarrow$ Fit a standard GEE linear model giving the time-specific weight $sw_i(t) \times sw_i^{\dagger}(t)$ to each subject

- **Survival:** $\boxed{\lambda_{T_{\bar{a}}}(t) = \lambda_0(t) exp(\gamma_1 a(t) + \gamma_2 V)}$
  $\Rightarrow$ Weighted pooled logistic regression treating each person-time as an observation
  $\Rightarrow$ Use weights $sw_i(t) \times sw_i^{\dagger}(t)$ for
  $logit\ P[D(t) = 1 | D(t-1) = 0, \bar{A}(t-1)] = \theta_0(t) + \theta_1 A(t-1) + \theta_2 V$

[1] $cum(\bar{a}) = \sum_{k=0}^{K} a_k$

# Marginal Structural Model
## Assumptions

- **Exchangeability:**
  - No unmeasured confounding assumption
  - Measure enough joint predictors of exposure and outcome
  - Sensitivity analyses (asses the impact of adding further potential confounders
- **Consistency:**
  - Links the counterfactual data $Y_{\bar{a}}$ to the observed data $(Y, A)$
  - A subject's counterfactual outcome under his or her observed exposure history is his or her observed outcome

$$Y_{\overline{A}} = Y$$

- **Positivity:**
  - The experimental treatment assumption
  - Both treated and untreated patients at every level of the confounder
- **Specifications of the models:**
  - Models for initiation of treatment and censoring, given past covariate and treatment history need to be correctly specified

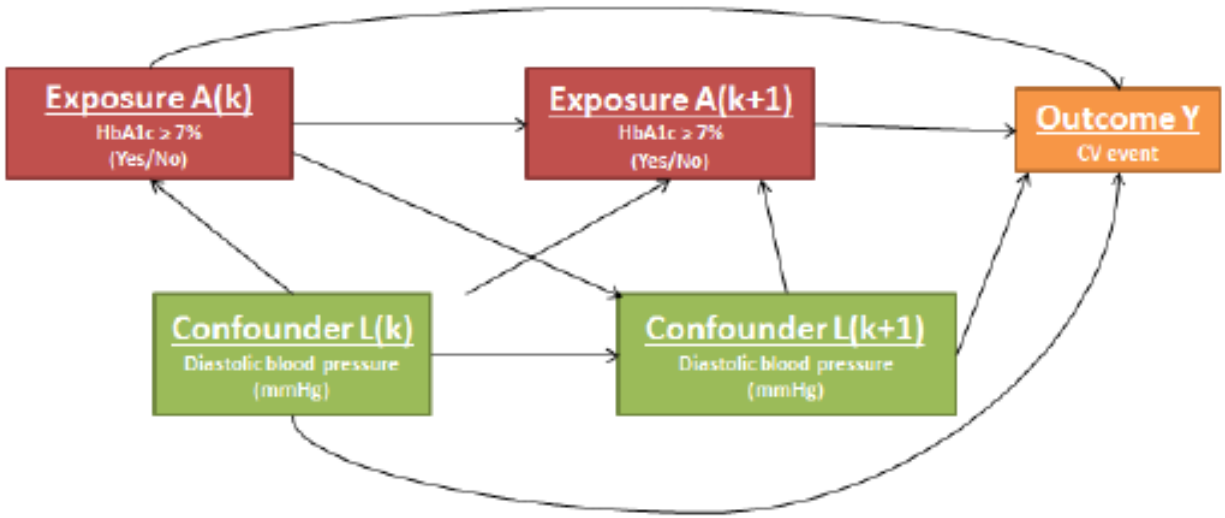
**The CREDIT study:** a long-term international non-interventional study in patients with type 2 diabetes, treated with insulin (Initial protocol)

**Clinical context**:

- Diabetes:
  - Chronic disease that can be controlled but for which there is no cure
  - Triggered by a shortage or a deficiency of insulin (hormone normally produced by the pancreas to help control blood glucose level)
- When glucose lacks of insulin
  $\Rightarrow$ glucose does not give energy to cells and is not absorbed by them
  $\Rightarrow$ its accumulation causes damages to the organs (retina, kidney,...)

# Marginal Structural Models
## Application: real-life data

**A binary analysis to study the relationship between CV events and glycemic control, in presence of a time-dependent confounder, the diastolic blood pressure**




- 2,524 patients followed up to 4 visits
- Dataset:
  - one row of data per patient for each visit until their time to CV event
  - if no CV event: one row of data per visit until censoring

# Marginal Structural Models

## Application: real-life data

| | HbA1c < 7% at baseline N=143 | HbA1c ≥ 7% at baseline N=2,381 | Total N=2,524 |
|---|---|---|---|
| **CV event** N (%) | 9 (6.3%) | 106 (4.5%) | 115 (4.6%) |
| **Age (years)** mean (SD) | 63.44 (10.01) | 61.30 (10.04) | 61.42 (10.05) |
| **Sex** **Men** | 78 (54.5%) | 1,172 (49.2%) | 1,250 (49.5%) |
| **Women** | 65 (45.5%) | 1,209 (50.8%) | 1,274 (50.5%) |
| **Diastolic blood pressure** mean (SD) | 79.81 (10.73) | 80.97 (11.53) | 80.90 (11.49) |

- Only 4.6% of the patients enrolled present a CV event during follow-up
- Diastolic blood pressure: time-dependent confounder
  - Relationship between diastolic blood pressure and cv event
  - Relationship between diastolic blood pressure and glycemic control

# Marginal Structural Models
## Application: real-life data

**Implementation:**

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   - same method but outcome: $C_i(k)$

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   - One weight per patient and per visit
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4. Fitting final marginal structural model: PROC LOGISTIC with the *weight* option: *logit* $P(Y_{\bar{a}} = 1) = \beta_0 + \beta_1 \sum_{k=0}^{K} a_k$
   - $\sum_{k=0}^{K} a_k$: duration of exposure to an HbA1c value $\geq 7\%$

# Marginal Structural Models

## Application: real-life-data

| Parameter | | Estimate | Standard Error | Pr > ChiSq |
|---|---|---|---|---|
| Intercept | | -3.7579 | 1.0118 | 0.0002 |
| Visit | 2 | -0.6392 | 0.2826 | 0.0237 |
| Visit | 3 | -1.2237 | 0.3384 | 0.0003 |
| Visit | 4 | -4.5909 | 0.4643 | <.0001 |
| HbA1c | | 0.2838 | 0.1233 | 0.0214 |
| Sex | M | 1.5312 | 1.3011 | 0.2392 |
| Age | | 0.0387 | 0.0151 | 0.0102 |
| Age*Sex | M | -0.0241 | 0.0199 | 0.2264 |

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- $OR = 1.32$ [1.01-1.69]

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- $OR = 1.32$ [1.01-1.69]
- Significant difference between the exposed and the unexposed

# Marginal Structural Models

## Application: real-life data

**Comparison with an unweighted model:**

| Parameter | | Estimate | Standard Error | 95% Confidence Limits | | Pr > ChiSq |
|---|---|---|---|---|---|---|
| Intercept | | -9.7361 | 1.3187 | -12.3207 | -7.1516 | <.0001 |
| Visit | 2 | -0.2105 | 0.2374 | -0.6758 | 0.2549 | 0.3754 |
| Visit | 3 | -0.2183 | 0.2442 | -0.6970 | 0.2604 | 0.3714 |
| Visit | 4 | -1.0216 | 0.3303 | -1.6690 | -0.3742 | 0.0020 |
| Sex | M | 2.2480 | 1.3572 | -0.4120 | 4.9080 | 0.0976 |
| Age | | 0.0579 | 0.0155 | 0.0276 | 0.0883 | 0.0002 |
| Age*Sex | M | -0.0289 | 0.0207 | -0.0694 | 0.0115 | 0.1611 |
| HbA1c | $\geq$ 7% | 0.3626 | 0.2317 | -0.0915 | 0.8168 | 0.1176 |
| DBP | | 0.0193 | 0.0089 | 0.0019 | 0.0367 | 0.0293 |

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| Sex | M | 2.2480 | 1.3572 | -0.4120 | 4.9080 | 0.0976 |
| Age | | 0.0579 | 0.0155 | 0.0276 | 0.0883 | 0.0002 |
| Age*Sex | M | -0.0289 | 0.0207 | -0.0694 | 0.0115 | 0.1611 |
| HbA1c | $\geq$ 7% | 0.3626 | 0.2317 | -0.0915 | 0.8168 | 0.1176 |
| DBP | | 0.0193 | 0.0089 | 0.0019 | 0.0367 | 0.0293 |

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- Assumptions:
  - Exchangeability $\Rightarrow$ sensitivity analysis
  - Positivity
  - Specification of the models

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## Discussion and perspectives

- Only a few patients with CV event
- Relevant time-dependent confounder
- Assumptions:
  - Exchangeability $\Rightarrow$ sensitivity analysis
  - Positivity
  - Specification of the models
- Other application: marginal structural Cox model vs unweighted method $\Rightarrow$ Similar results

# Overview

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- MSMs enable time-dependent confounders to be taken into account
- Point treatment study: difference between results obtained

# Conclusion

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- Looking through the litterature, the propensity score methods rapidly directed us towards the MSM with IPTW estimator
- MSMs enable time-dependent confounders to be taken into account
- Point treatment study: difference between results obtained
- Application on real-life data:
  - Results going in the same direction but,
  - Non-significant results for the unweighted method

# Conclusion

- Objective: Statistical methods for observational studies
- Looking through the litterature, the propensity score methods rapidly directed us towards the MSM with IPTW estimator
- MSMs enable time-dependent confounders to be taken into account
- Point treatment study: difference between results obtained
- Application on real-life data:
  - Results going in the same direction but,
  - Non-significant results for the unweighted method
- In literature: important difference between marginal structural models and unweighted methods

THANK YOU FOR YOUR ATTENTION !

# How to use Cochran-Mantel-Haenszel Test and Breslow-Day Test

- Calculate crude $OR_{Y-A}$
- Calculate stratum-specific OR's: $OR_{Y-A|L}$
- If $OR_{Y-A} = OR_k \Rightarrow$ L is unlikely to be a confounder
- If $Or_{Y-A} \neq$:
  - If $OR_1 = OR_2 = ... = OR_K \Rightarrow$ L may be a confounder
    - Apply CMH test of conditional independence: $H_0$: A and Y are conditionnally independent

$$CMH = \frac{(\sum_k n_{11k} - \mu_{11k})^2}{\sum_k \sigma^2_{11k}}$$

    - Calculate $OR_{MH}$ (if $H_0$ is rejected, $OR_{MH}$ should be $\neq 1$)
  - If stratum-specific Or's differ from each oether $\Rightarrow$ there might be an effect modification (interaction)
    - Apply Breslow-Day test of homogeneity of the OR's: $H_0$: stratum-specific OR's are equal (homogeneous)

$$Q_{BD} = \sum_k \sum_i \sum_j \frac{(n_{ijk} - m_{ijk})^2}{m_{ijk}} \sim Khi^2(K-1)$$

back

# Stratification

| | $L = k$ | | |
|---|---|---|---|
| | $Y = 1$ | $Y = 0$ | |
| $A = 1$ | $n_{11k}$ | $n_{10k}$ | $n_{1+k}$ |
| $A = 0$ | $n_{01k}$ | $n_{00k}$ | $n_{0+k}$ |
| | $n_{+1k}$ | $n_{+0k}$ | $n_k$ |

- CMH test statistic: $M^2 = \frac{[\sum_k (n_{11k} - \mu_{11k})]^2}{\sum_k Var(n_{11k})} \sim \chi^2(1)$, where
  - $\mu_{11k} = \frac{n_{1+k} n_{+1k}}{n_k}$ is the expected frequency of $A = 1$ and $Y = 1$ for $L = k$ assuming the conditional independence holds
  - $Var(n_{11k}) = \frac{n_{1+k} n_{0+k} n_{+1k} n_{+0k}}{n_k^2 (n_k - 1)}$
- Common odds ratio:

$$\widehat{OR}_{MH} = \frac{\sum_k (n_{11k} n_{00k})/n_k}{\sum_k (n_{10k} n_{01k})/n_k}$$

back

# Paired t-test

- Comparing 2 measures of a quantitative variable realized on the paired subjects
- Treating the 2 matched samples as one dataset on which the difference between both measures would have been computed

- $H_0$ : *themeandifferencebetweenbothmeasuresisnull*
- Test statistic: $t = \frac{\frac{1}{n}\sum_{i=1}^{n} \text{Diff}_i}{\sqrt{\frac{SCE_d}{n(n-1)}}} \sim St(n-1)$

  (where $SCE_d = \sum_{i=1}^{n} \text{Diff}_i^2 - \frac{(\sum_{i=1} \text{Diff}_i)^2}{n}$)

$H_0$ rejected $\Rightarrow$ significant difference between both outcomes

back

# Computation of the unstabilized weights

## Proof in a point treatment study

**Actual population**: $n_{ijk}$ is the number of patients with the outcome $i$, under treatment $j$ and with value covariate $k$ in the actual population

| | $L=1$ | | $L=0$ | | Total |
|---|---|---|---|---|---|
| | $A=1$ | $A=0$ | $A=1$ | $A=0$ | |
| $Y=1$ | $n_{111}$ | $n_{101}$ | $n_{110}$ | $n_{100}$ | $n_{1++}$ |
| $Y=0$ | $n_{011}$ | $n_{001}$ | $n_{010}$ | $n_{000}$ | $n_{0++}$ |
| Total | $n_{+11}$ | $n_{+01}$ | $n_{+10}$ | $n_{+00}$ | $n_{+++}$ |

**Pseudo-population**: $N_{ijk}$ is the number of patients with the outcome $i$, under treatment $j$ and with value covariate $k$ in the pseudo-population

| | $L=1$ | | $L=0$ | | Total |
|---|---|---|---|---|---|
| | $A=1$ | $A=0$ | $A=1$ | $A=0$ | |
| $Y=1$ | $N_{111}$ | $N_{101}$ | $N_{110}$ | $N_{100}$ | $N_{1++}$ |
| $Y=0$ | $N_{011}$ | $N_{001}$ | $N_{010}$ | $N_{000}$ | $N_{0++}$ |
| Total | $N_{+11}$ | $N_{+01}$ | $N_{+10}$ | $N_{+00}$ | $N_{+++}$ |

**Weights**:
For patients with $L = 1$: When $n_{+11}$ patients are treated, $n_{111}$ have $Y = 1 \Rightarrow$ if all patients with $L = 1$ ($n_{++1}$) would have been treated, we would have:

$N_{111} = \frac{n_{++1} \times n_{111}}{n_{+11}} = w_{11} \times n_{111}$, where $w_{11} = \frac{n_{++1}}{n_{+11}} = \frac{1}{P(A{=}1|L{=}1)}$

back

# Association between $A$ and $L$

| | $L=1$ | $L=0$ | |
|---|---|---|---|
| $A=1$ | $N_{+11}$ | $N_{+10}$ | $N_{+1+}$ |
| $A=0$ | $N_{+01}$ | $N_{+00}$ | $N_{+0+}$ |
| | $N_{++1}$ | $N_{++0}$ | $N_{+++}$ |

Objective: show that the proportion of treated who have $L=1$ is the same as the proportion of untreated who have $L=1$, i.e. $\frac{N_{+11}}{N_{+1+}} = \frac{N_{+01}}{N_{+0+}}$

$$\frac{N_{+11}}{N_{+1+}} = \frac{w_{11}n_{+11}}{w_{11}n_{+11}+w_{10}n_{+10}} = \frac{\frac{n_{++1}}{n_{+11}}\times n_{+11}}{\frac{n_{++1}}{n_{+11}}\times n_{+11}+\frac{n_{++0}}{n_{+10}}\times n_{+10}} = \frac{n_{++1}}{n_{+++}}$$

$$\frac{N_{+01}}{N_{+0+}} = \frac{w_{01}n_{+01}}{w_{01}n_{+01}+w_{00}n_{+00}} = \frac{\frac{n_{++1}}{n_{+01}}\times n_{+01}}{\frac{n_{++1}}{n_{+01}}\times n_{+01}+\frac{n_{++0}}{n_{+00}}\times n_{+00}} = \frac{n_{++1}}{n_{+++}}$$

back

# Mathematical dimension

- A process is "causally exogenous or ancillary" if

$$Y_{\bar{a}} \coprod A(t) | \overline{A}(t-1)$$

  $\Rightarrow$ $Y_{\bar{a}}$ is independent of $\overline{A}$

- A treatment is a "statistically exogenous or ancillary" process if

$$\overline{L}(t) \coprod A(t) | \overline{A}(t-1)$$

- $sw_i(t)$ quantifies the degree to which the treatment process is statistically nonexogenous through time $t$
  $\Rightarrow$ numerator = denominator for all $t$ with probability 1 if and only if treatment process is statistically exogenous
  $\Rightarrow$ weighted regression = unweighted analysis only if $A(t)$ is statistically exogenous

(back)

# Truncation method for the IPTW method

In the simulated study, some weights computed for the MSM are extreme:

- Summary of the weights for the $118^{th}$ simulated dataset:

| Min | $1^{st}$ qu. | Median | Mean | $3^{rd}$ qu. | Max |
|---|---|---|---|---|---|
| 0.46 | 0.49 | 0.54 | 5.59 | 0.62 | 4649 |

  $\Rightarrow$ Parameter estimate: -3.15 (true value: 10)

- Summary of the weights for the $1^{st}$ simulated dataset

| Min | $1^{st}$ qu. | Median | Mean | $3^{rd}$ qu. | Max |
|---|---|---|---|---|---|
| 0.48 | 0.51 | 0.53 | 0.91 | 0.63 | 74.7 |

  $\Rightarrow$ Parameter estimate: 10.65

(back)

# Initial study protocol of the CREDIT study

- Multicenter international non-interventional longitudinal study with a 4-year follow-up per patient carried out on 3,060 subjects
- Visits done according to clinical practice
- Original objectives:
  - Observation of medical practice in the real life, over a 4-year period, in people with type 2 diabetes treated with insulin
  - Evaluation of the evolution and relationship between glycemic control and the risk of cardiovascular events in type 2 diabetic patients treated with insulin, taking into account known cardiovascular risk factors

# Initial study protocol of the CREDIT study

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| - Male or female, age $>$ 40 years<br>- With type 2 diabetes<br>- Time from diagnosis of diabetes to insulin initiation $>$ 1 year<br>- Treated with insulin (all regimens*) for more than 1 month and less than 6 months prior to study entry<br>- With an HbA1c value within 3 months prior to insulin initiation<br>- Insulin initiated with an intention of a long term treatment<br>- Informed consent must be obtained in writing<br>- Patients able to be followed over a long period of time | - Type 1 diabetes<br>- Not insulin treated type 2 diabetes<br>- Secondary diabetes (pancreatic history, steroids therapy, endocrine diabetes)<br>- Current temporary insulin therapy (gestational diabetes, pancreas cancer, surgery, clinical trial)<br>- Pregnancy at inclusion |

(back)

# Marginal Structural Model
## Inverse Probability of Treatment Weights (IPTW)

- Binary treatment
- For the denominator of $sw_i(k)$:

$$logit\ P(A(k) = 0 | \overline{A}(k-1) = 0, \overline{L}(k)) = \alpha_0(k) + \alpha_1 L(k) + \alpha_2 V$$

$$\begin{cases} \prod_{u=0}^{k} \hat{p}_i(u) & \text{if subject } i \text{ did not start treatment up to time } k \\ (1 - \hat{p}_i(t)) \prod_{u=0}^{t-1} \hat{p}_i(u) & \text{if subject } i \text{ started treatment at time } t \text{ for } 0 < t \leq k \\ 1 - \hat{p}_i(0) & \text{if subject } i \text{ is treated at time 0} \end{cases}$$

- For the numerator of $sw_i(k)$: remove $L(k =$ from the logistic model

(back)

# Marginal Structural Models
## Application: real-life data

**A time-to-event analysis**

$\Rightarrow$ Application of a marginal structural Cox model

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## Application: real-life data

**A time-to-event analysis**

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1. Implementing final weights $sw_i(t) \times sw_i^{\dagger}(t)$: same method as previously

# Marginal Structural Models
## Application: real-life data

**A time-to-event analysis**

$\Rightarrow$ Application of a marginal structural Cox model

1. Implementing final weights $sw_i(t) \times sw_i^{\dagger}(t)$: same method as previously

2. Fitting final marginal structural Cox model

# Marginal Structural Models
## Application: real-life data

**A time-to-event analysis**

$\Rightarrow$ Application of a marginal structural Cox model

1. Implementing final weights $sw_i(t) \times sw_i^{\dagger}(t)$: same method as previously

2. Fitting final marginal structural Cox model

   - PROC GENMOD with the *scwgt* option
   - Unstructured correlation matrix
   - *repeated* option

(back)

# Applications and resutls
## Real-life data

| Parameter | | Estimate | Standard Error | 95% Confidence Limits | | Pr > \|Z\| |
|---|---|---|---|---|---|---|
| Intercept | | -7.7774 | 1.0893 | -9.9123 | -5.6424 | <.0001 |
| HbA1c | $\geq$ 7% | 0.2180 | 0.2726 | -0.3162 | 0.7522 | 0.4238 |
| Visit | 2 | -0.1487 | 0.2413 | -0.6217 | 0.3243 | 0.5378 |
| Visit | 3 | -0.1768 | 0.2554 | -0.6773 | 0.3238 | 0.4888 |
| Visit | 4 | -0.9356 | 0.3446 | -1.6110 | -0.2603 | 0.0066 |
| Sex | M | 2.2918 | 1.3606 | -0.3750 | 4.9586 | 0.0921 |
| Age | | 0.0527 | 0.0157 | 0.0219 | 0.0834 | 0.0008 |
| Age*Sex | M | -0.0301 | 0.0207 | -0.0706 | 0.0104 | 0.1457 |

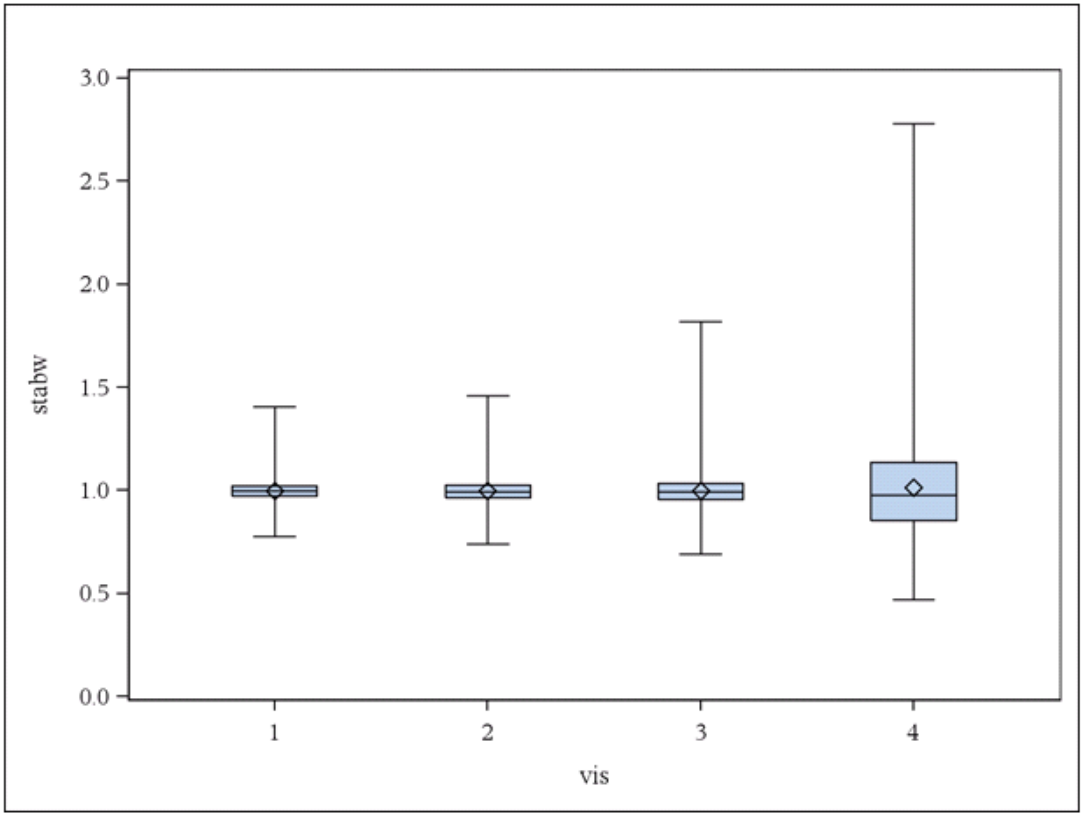
| Parameter | | Estimate | Standard Error | Pr > ChiSq | Hazard Ratio |
|---|---|---|---|---|---|
| Age | | 0.0414 | 0.0097 | < 0.0001 | 1.042 |
| Sex | M | 0.3641 | 0.1891 | 0.0541 | 1.439 |
| HbA1c | $\geq$ 7% | 0.3563 | 0.2309 | 0.1228 | 1.428 |
| DBP | | 0.0195 | 0.0089 | 0.0292 | 1.020 |

Table: Unweighted method

- Similar results (weights boxplot)

(back)

# Distribution of the final weights




back