Modification d’effet

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Modification d'effet

*« When the incidence rate of disease in the presence of two or more risk factors differs from the incidence rate **expected** to result from their individual effects » (Mac Mahon)*

- Définition:

Variation de l'association entre 2 paramètres selon un 3e

  - Effet plus grand qu'attendu : interaction positive (synergisme)
  - Effet plus faible qu'attendu: interaction négative (antagonisme)

- Echelle additive, multiplicative…

- Comment l'explorer?
  - Etudier l'association par stratum du 3e paramètre

  - Présenter les résultats par stratum et non ajusté pour le 3e paramètre

Confusion versus ME

- ME pas d'estimation unique
- « compétition » confusion-ME: ME prime
- Rothman:
  - Confounding is a bias that you hope to prevent or control.
  - Interaction is just a more detailed description of the effect itself (in all its rich diversity).
  - Confounding is something to avoid.
  - Interaction is something to report.

Modification d’effet…

encore à la mode?

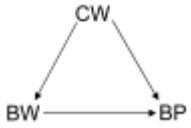
4 types de modification d'effet

VanderWeele T, Robins J. Four types of effect modification – a classification based on directed acyclic graphs. **Epidemiology 2007**.

Inférence causale

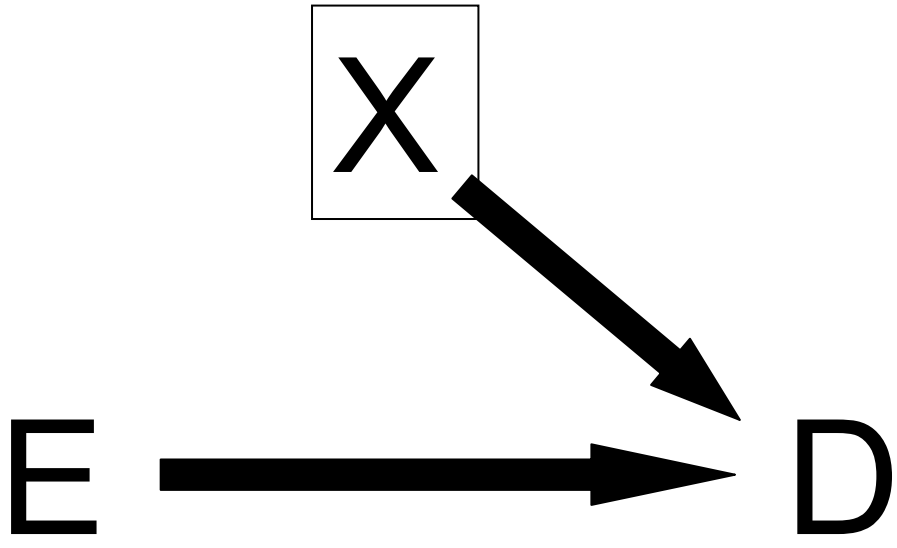
$$h[E(D|e_1,x_1)] - h[E(D|e_0,x_0)] \neq h[E(D|e_1,x_0)] - h[E(D|e_0,x_0)] + h[E(D|e_0,x_1)] - h[E(D|e_0,x_0)]$$

Graphiques directs acycliques (DAG)

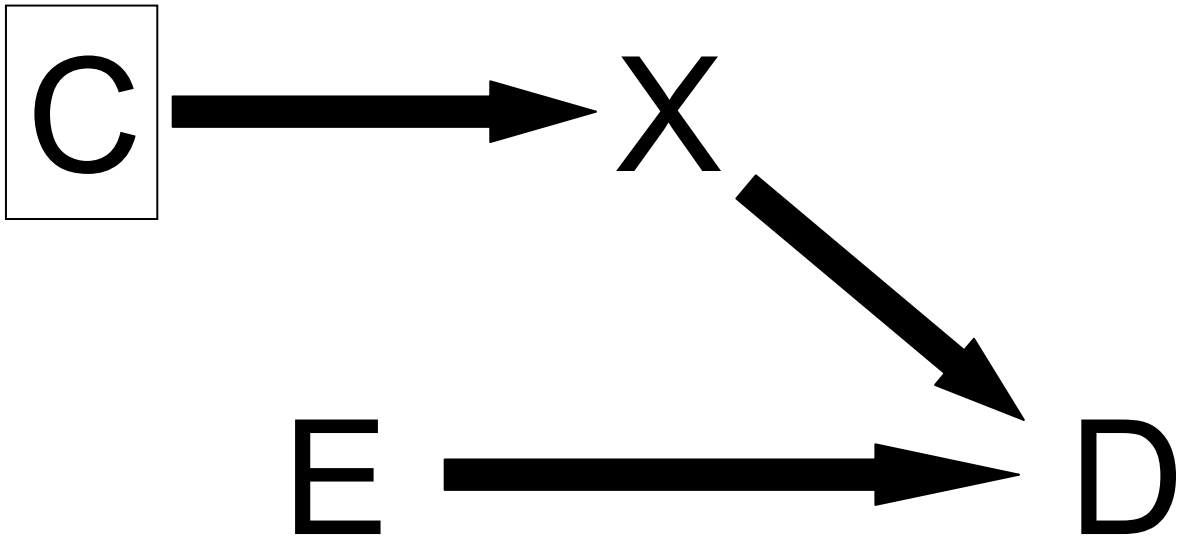


- ME directe
- ME indirecte
- ME par proxy
- ME par cause commune

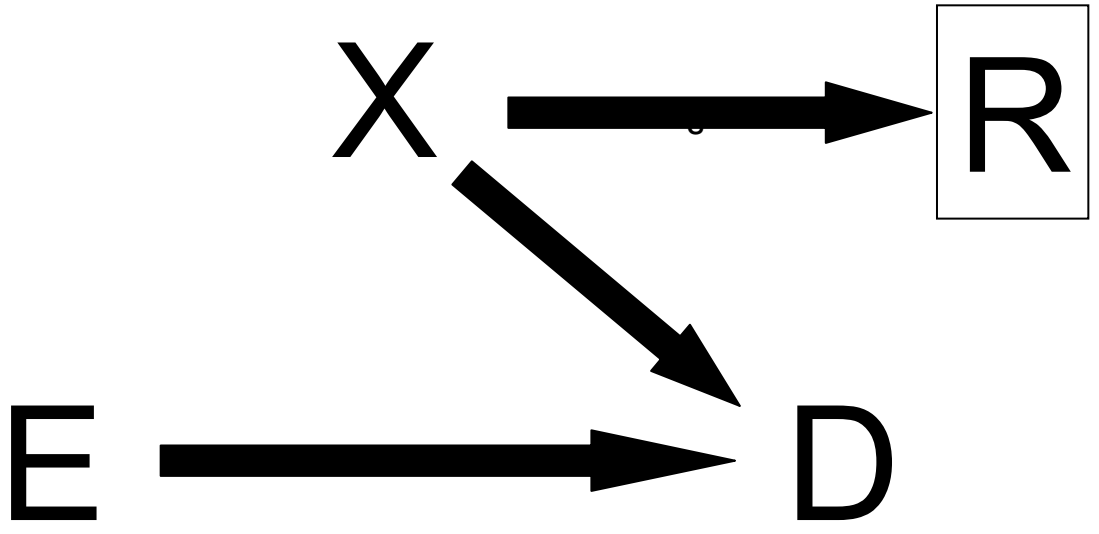
ME directe



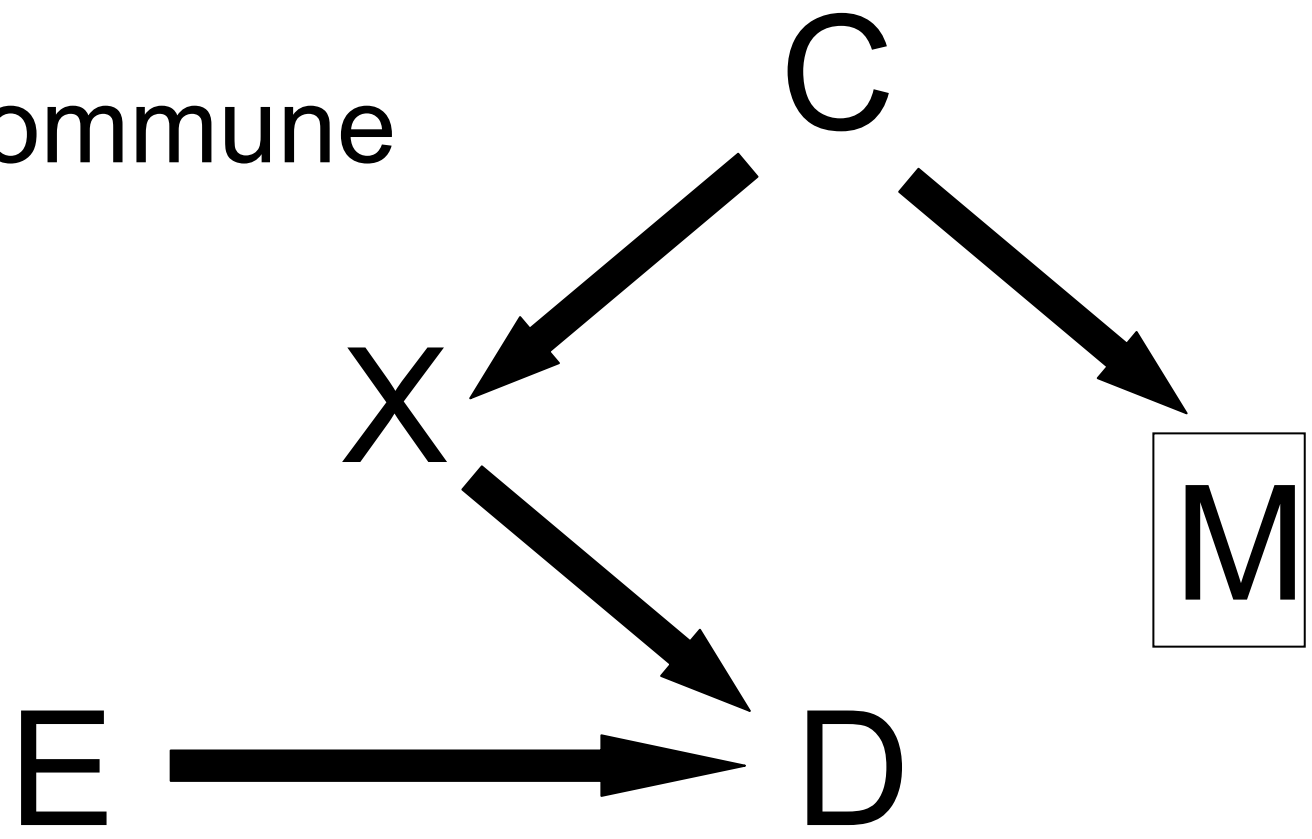
ME indirecte



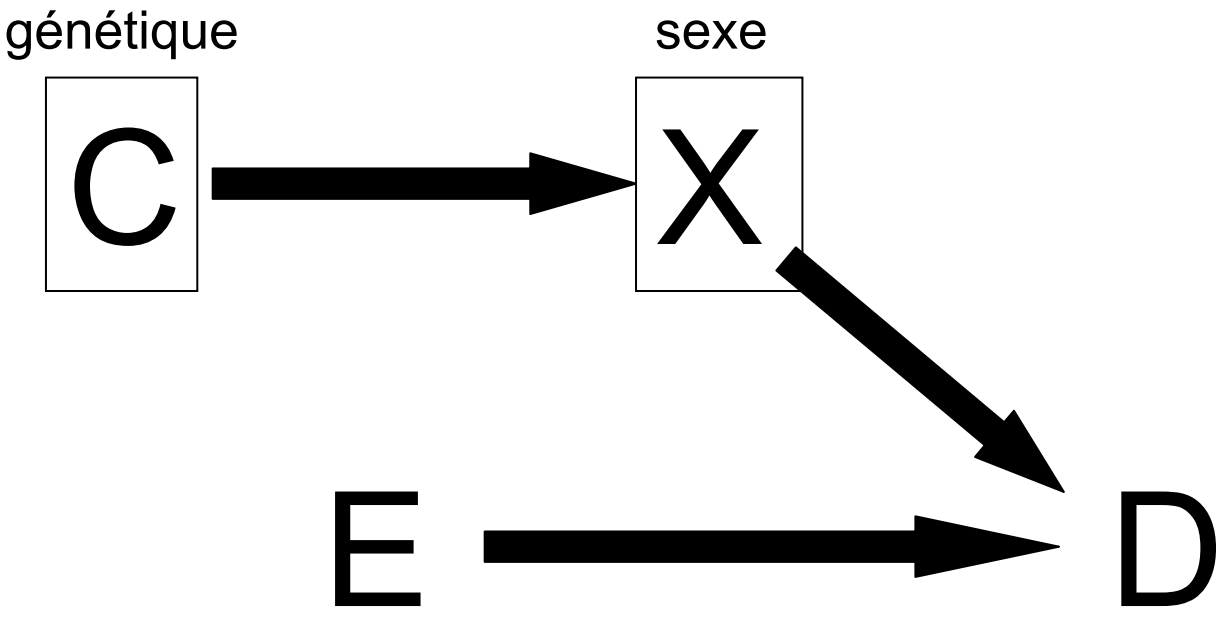
ME par proxy



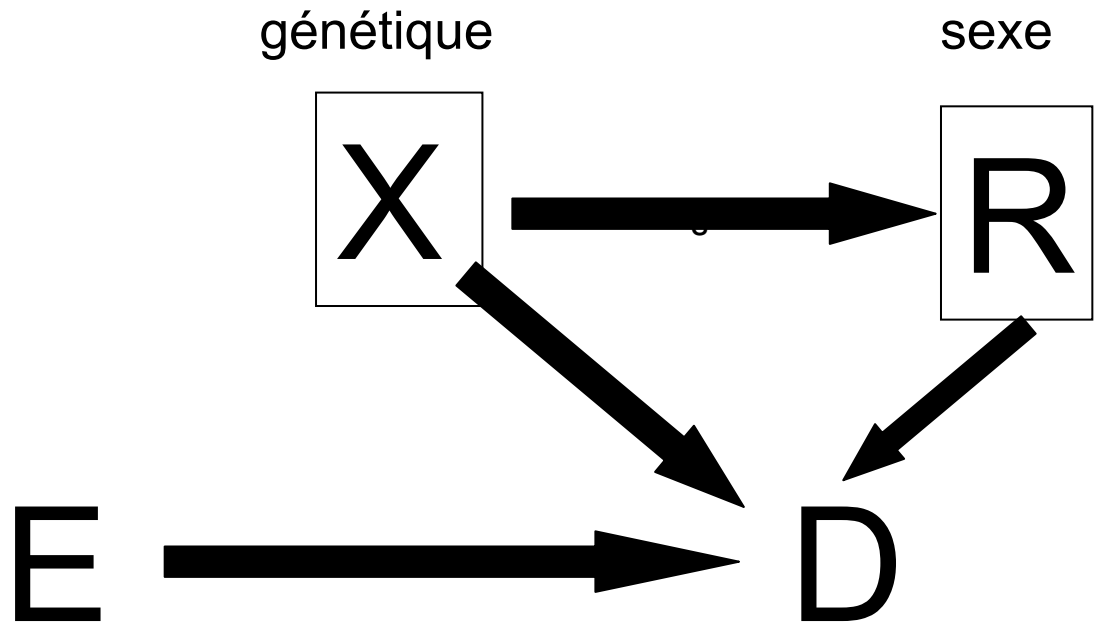
ME par cause commune

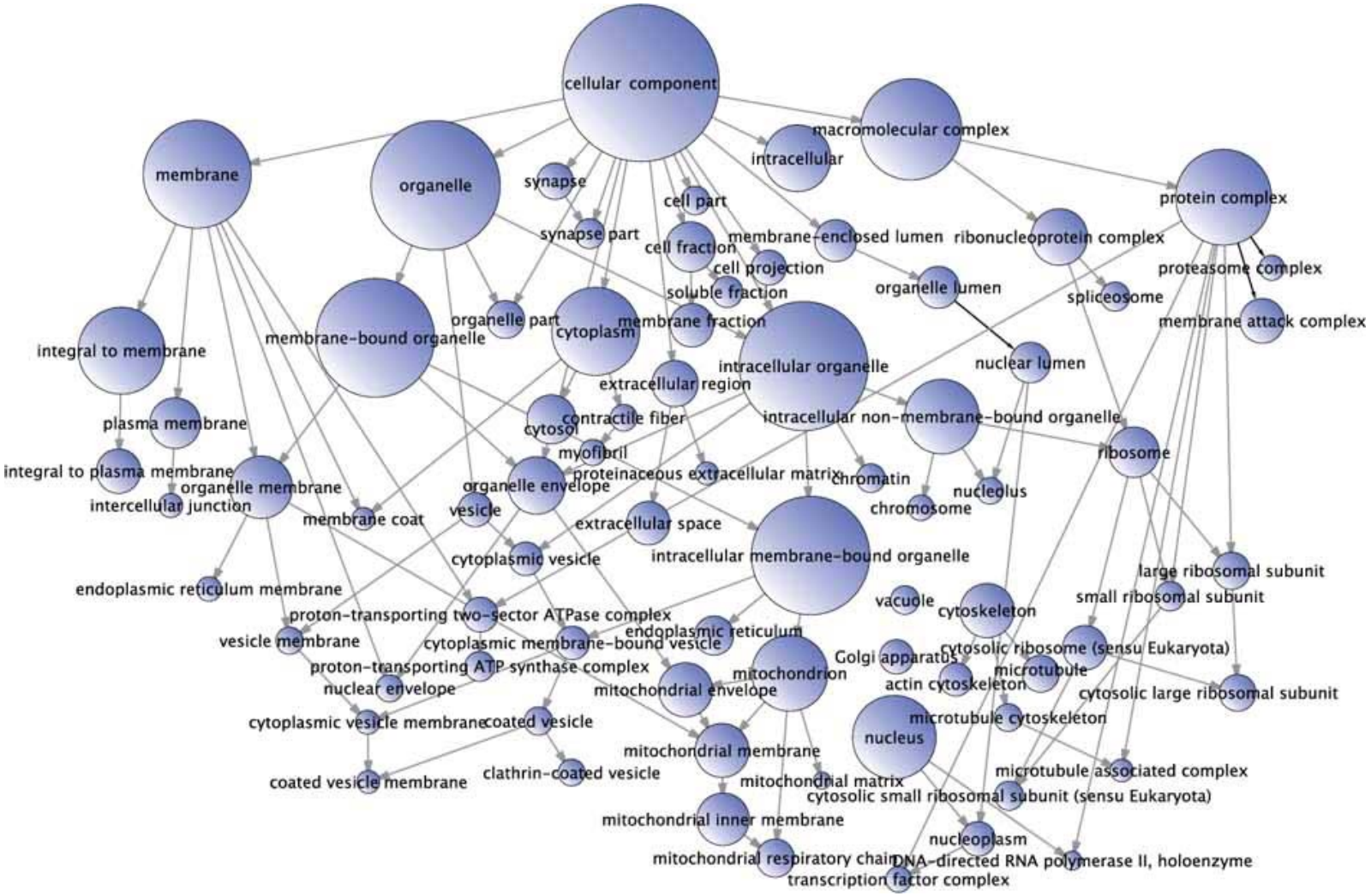


Génétique + sexe



Génétique + sexe




cellular component
membrane
organelle
synapse
cell part
intracellular
macromolecular complex
protein complex
synapse part
cell fraction
membrane-enclosed lumen
ribonucleoprotein complex
cell projection
proteasome complex
soluble fraction
organelle lumen
spliceosome
membrane attack complex
integral to membrane
membrane-bound organelle
organelle part
cytoplasm
membrane fraction
intracellular organelle
nuclear lumen
extracellular region
plasma membrane
contractile fiber
cytosol
intracellular non-membrane-bound organelle
ribosome
myofibril
integral to plasma membrane
organelle membrane
proteinaceous extracellular matrix
organelle envelope
chromatin
nucleolus
intercellular junction
membrane coat
vesicle
chromosome
extracellular space
cytoplasmic vesicle
intracellular membrane-bound organelle
large ribosomal subunit
endoplasmic reticulum membrane
small ribosomal subunit
vacuole
cytoskeleton
proton-transporting two-sector ATPase complex
endoplasmic reticulum
vesicle membrane
cytoplasmic membrane-bound vesicle
cytosolic ribosome (sensu Eukaryota)
Golgi apparatus
proton-transporting ATP synthase complex
mitochondrion
microtubule
nuclear envelope
mitochondrial envelope
actin cytoskeleton
cytosolic large ribosomal subunit
cytoplasmic vesicle membrane
coated vesicle
microtubule cytoskeleton
nucleus
mitochondrial membrane
microtubule associated complex
clathrin-coated vesicle
coated vesicle membrane
mitochondrial matrix
cytosolic small ribosomal subunit (sensu Eukaryota)
mitochondrial inner membrane
nucleoplasm
mitochondrial respiratory chain
DNA-directed RNA polymerase II, holoenzyme
transcription factor complex

Modification d'effet = Interaction?

VanderWeele T. On the Distinction Between Interaction and Effect Modification. Epidemiology 2009.

- Interaction et modification d'effet souvent utilisés de façon interchangeables
- Pas équivalents!…
- Interaction: causalité double

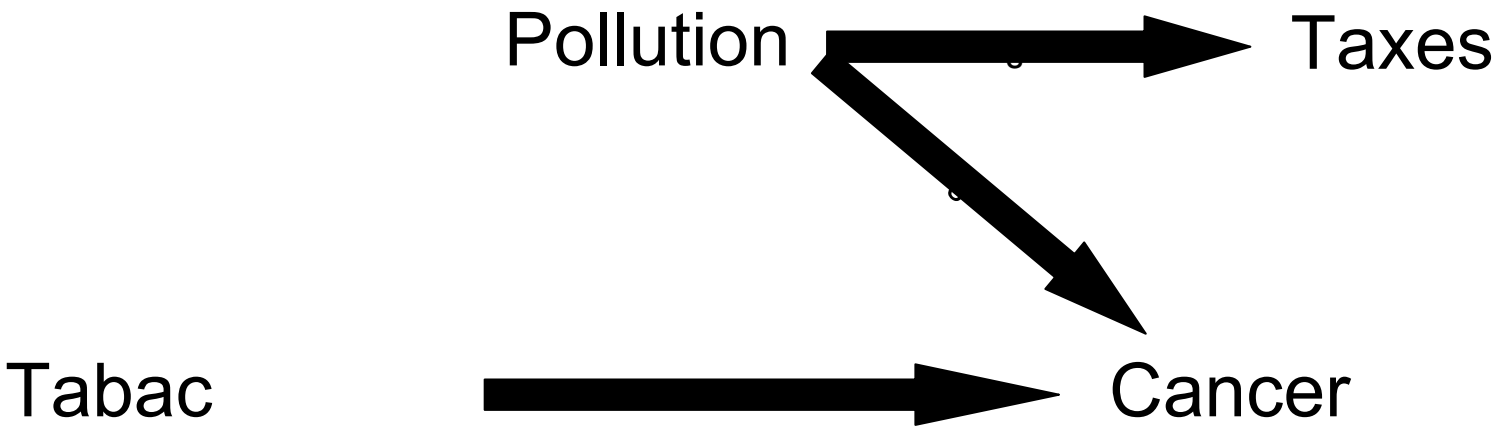
Ex: Tabac + alcool => cancer ORL

- Modification d'effet: différence par strate

Ex: Tabac + domicile => cancer ORL

Interaction

Modification d'effet



Quand chercher?
Comment savoir?

1) Y penser! => **dans la conception de l'étude**

2) Hypothèses causales

3) Analyser par strates (tables, graphique…)

4) Mesurer l'effet

statistique	oui, mais
épidémiologique	**importance réelle?**

=> Tester l'homogénéité des mesures de chaque strate (χ^2 de Wald)

=> **Tester l'hétérogénéité globale**

Ho : RR1 = RR2 = RR3 = RR4

Ha : au moins un RR d'une strate ≠

Tests: Breslow-Day test of homogeneity
Analyse multivariée (test global)
Ajustement pour tests multiples (Bonferroni?)

TV Perneger, What's wrong with Bonferroni adjustments, *BMJ* 316 (1998), pp. 1236–1238.

5) Rapporter toutes les ME, résultats par strates

PTCA versus tt conservateur

	PTCA	Conservateur
Décès	300	300
Survie	300	300
Total	**600**	**600**

OR=1

PTCA versus tt conservateur

	<50 ans		>50ans	
	PTCA	Conservateur	PTCA	Conservateur
Décès	100	200	200	100
Survie	200	100	100	200
Total	**300**	**300**	**300**	**300**

OR=0.25 **OR=4.0**

TABLE 14–17. *Deaths From Lung Cancer (per 100,000) Among Individuals With and Without Exposure to Cigarette Smoking and Asbestos*

Cigarette Smoking	Asbestos Exposure	
	No	*Yes*
No	11.3	58.4
Yes	122.6	601.6

Adapted from Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473–490, 1979.

Incidence additive :

58.4 + 122.6 – 11.3 = 169.7

Table 9–1. Hypothetical 1-year risk of lung cancer according to exposure to cigarette smoke and to asbestos (cases per 100,000)

	No Asbestos Exposure	Asbestos Exposure
Nonsmokers	1	5
Smokers	10	50

Différence des risques :

Non fumeurs : 5 – 1 = **4** / 100.000

Fumeurs : 50 – 10 = **40** / 100.000

Rapport des risques :

Non fumeurs : 5/1 = **5**

Fumeurs : 50/10 = **5**

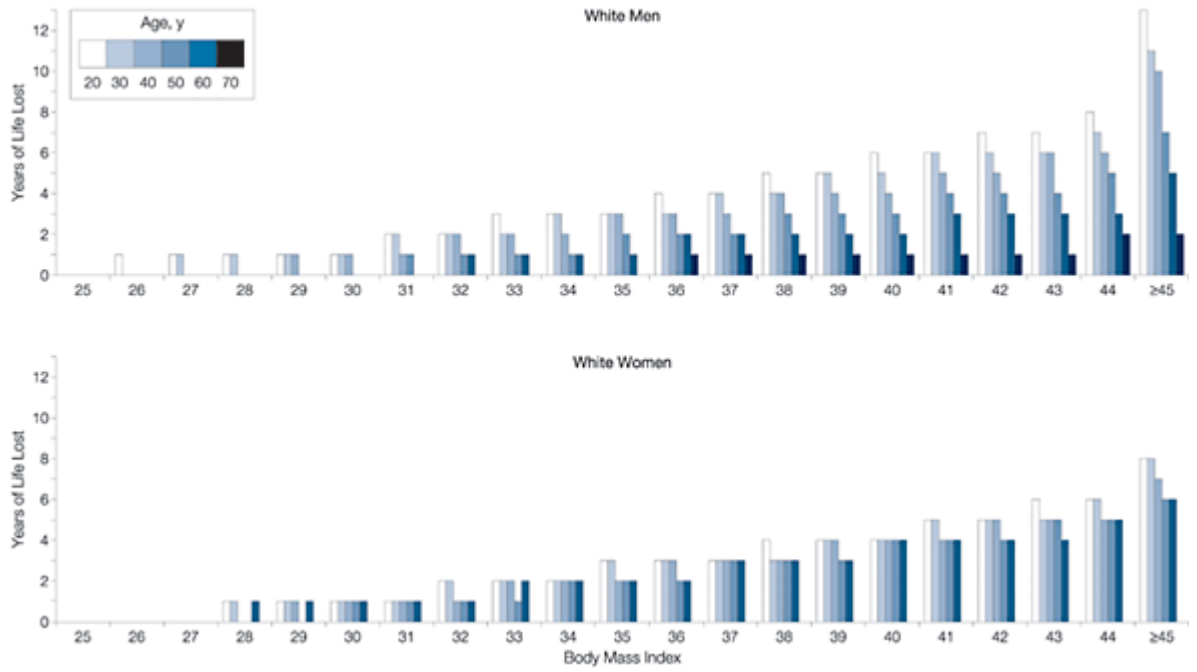
10 x : Tabac modifie l'effet de l'asbestose

Tabac NE modifie PAS l'effet de l'asbestose

TABAC = modificateur d'effet ????

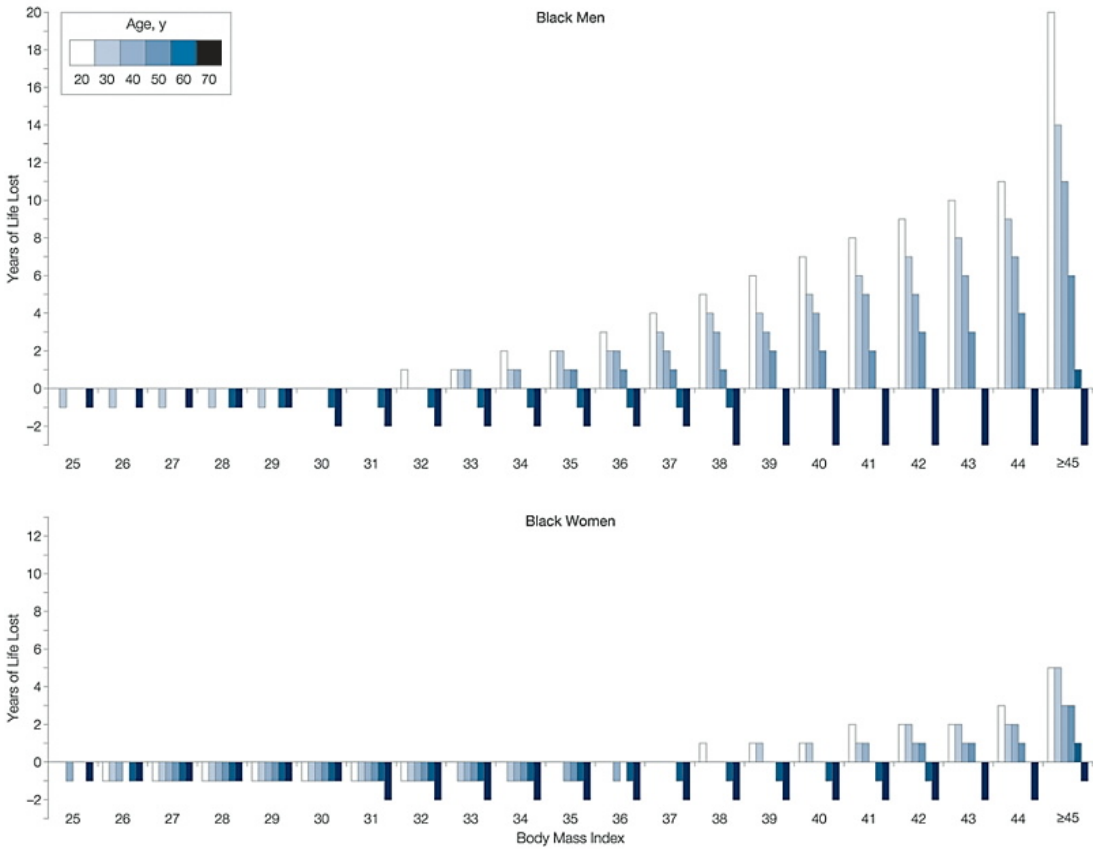
Dépend de la mesure utilisée

Obésité et années perdues de vie



JAMA. Jan 8 2003;289:187-193

Obésité et années perdues de vie



JAMA. Jan 8 2003;289:187-193

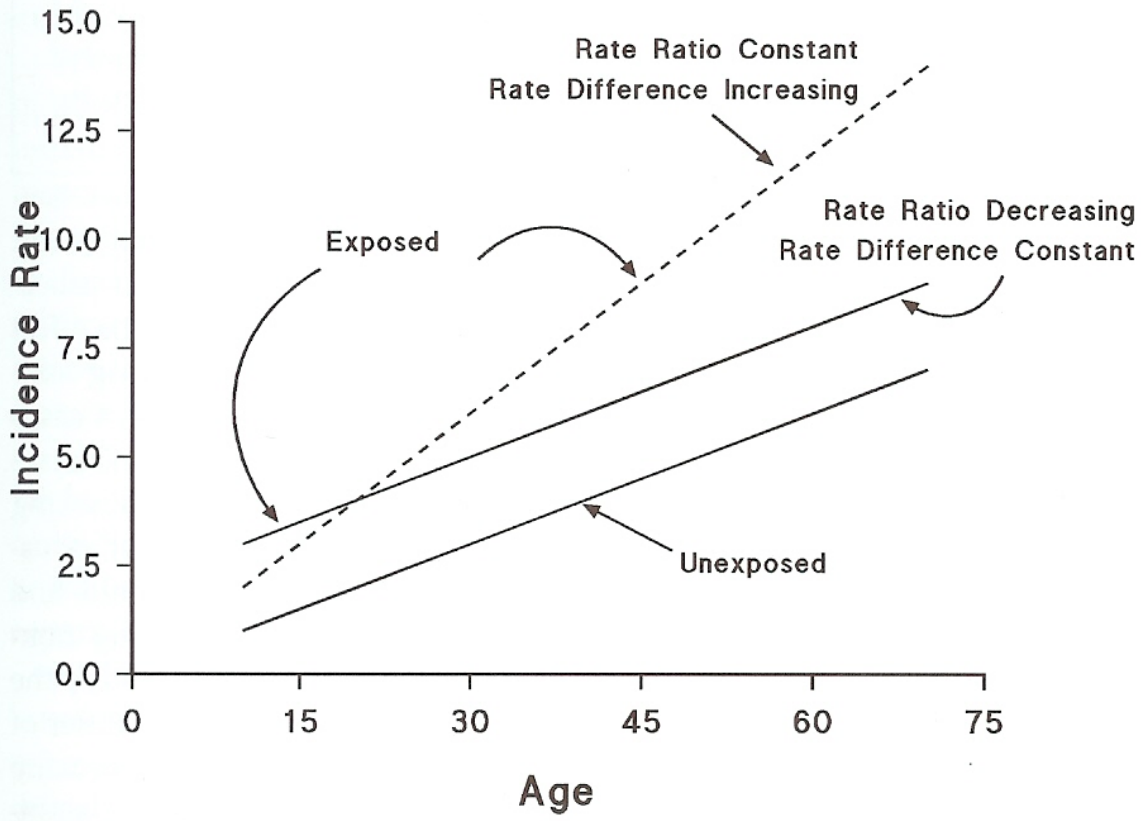


Figure 9–1. Age-incidence curves showing disease incidence increasing linearly with age for unexposed and two possible linear relations over age for exposed.

Modification d'effet, ou aller à la pêche…

- Puissance nécessaire pour détecter un effet

  => Erreur β

  échantillon 10x ?

- Chance de trouver par hasard une ME?

  => Erreur α

  Particulièrement à risque si non planifiées, multiples, pas de rationnel scientifique

- Exemple: analyses de sous-groupe

Schulz K., et al. Lancet 2005; 365: 1657–61

ISIS 2 ou le signe du zodiac…

- Lancet 1988, 17,187 patients
- Aspirine dim mortalité après infarctus myocarde (p=0.00001)
- 40 analyses de sous-groupe demandées par éditeurs?

⇒ Signes zodiac!
Gémeaux et balances risque augmenté de décès (+9% ns)

⇒ Autres signes astrologiques: effet bénéfique
(-28%, p=0.00001).

ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **2:**349–60.


STAR
SIGN
LIBRA

	Febrile morbidity			Rate ratio (95% CI)
	Yes	No	Total	
Age 20–24 years				
New antibiotic	11	84	95	1·4 (0·6–3·2)
Standard antibiotic	8	86	94	
Age 25–29 years				
New antibiotic	8	69	77	1·2 (0·4–3·1)
Standard antibiotic	7	72	79	
Age 30–34 years				
New antibiotic	3	48	51	0·3 (0·1–0·9)
Standard antibiotic	11	38	49	
Age 35–39 years				
New antibiotic	10	32	42	1·1 (0·5–2·5)
Standard antibiotic	9	33	42	
Total				
New antibiotic	32	233	265	0·9 (0·6–1·4)
Standard antibiotic	35	229	264	

Test for statistical interaction (Breslow-Day) non-significant (p=0.103)

Schulz K., et al. Lancet 2005; 365: 1657–61

SF Assmann, et al. Lancet 2000

	Number of trials
Were subgroup analyses reported?	
Yes	35
No	15
Number of baseline factors included	
1	17
2	3
3	3
4	5
5	1
6	1
⩾7	5
Number of outcomes for subgroup analysis	
1	17
2	6
3–5	6
⩾6	6
Total number of subgroup analyses	
1	8
2	4
3–5	8
6–8	9
9–11	0
12–24	4
Unclear	2
Statistical method used for subgroup analysis	
Descriptive only	7
Subgroup p values	13
Interaction test	15
Subgroup differences claimed	
Yes	21
No	14
Subgroup claim features in summary or conclusion	
Yes	13
No	8

Review of 50 reports from general medical journals (New England Journal of Medicine, The Lancet, JAMA, and BMJ):

70% reported subgroup analyses.

40% did at least six subgroup analyses (24!).

<50% tests of interaction

Hôpitaux Universitaires de Genève

Is atrial fibrillation associated with pulmonary embolism ?

Grégoire Gex[1,2], Eric Gerstel[1], Arnaud Perrier[1]

[1] Service de Médecine Interne Générale, Hôpitaux Universitaires de Genève
[2] Service de Pneumologie, Hôpitaux Universitaires de Genève

BACKGROUND

"Pulmonary embolism can cause a new-onset atrial fibrillation" : widespread idea

"Chronic AF could be a risk factor for PE"

→ In case of PE suspicion, AF often increases the intuitive pre-test probability of PE

BACKGROUND

Epidemiologic evidence of PE-AF association :

Series of patients with PE suspicion…

- No one found any significant difference in prevalence of AF in both groups.
- No systematic ECG for all patients
- No adjustments (in all but one study)
- Numbers of patients were low (max. 500 patients)

METHODS

Study population

- Patients included in 2 European prospective multicentre RCTs on PE diagnosis (CTEP-3 + CTEP-4)
- Inclusion criteria :

  All consecutive patients who presented to the ER with a clinical suspicion of PE, defined as :
  - acute onset of new or worsening dyspnea
  - **or** chest pain
  - **without** another obvious cause

RESULTS

- 2449 patients included
- 22% PE (n=551)
- **4.6% AF (n=25) in patients with PE**
  5.8% AF (n=108) in patients without PE (p=0.28)
- OR for PE in case of AF : **0.68** (CI95% 0.42-1.11, p=0.12)
  (adjustments for age, sex, cardiac failure, COPD, history of stroke, neoplasm, diabetes and creatinine clearance).

Effet protecteur!

	All patients suspected of PE N=2449
AF	**0.68** (0.42-1.11) p=0.122 n=133
COPD	**0.43** (0.28-0.65) p<0.001 n=247
Heart failure	**0.53** (0.31-0.88) p=0.014 n=144

Critères d'inclusion:

Dyspnée

Adjusted for age, sex and presence of AF, heart failure, COPD, stroke or cancer in the past and creatinine clearance

DISCUSSION : Role of dyspnea

	All patients suspected of PE N=2449	**New dyspnea at presentation** N=1756	**No new dyspnea at presentation** N=693	**p-value for interaction with dyspnea**
AF	Adjusted OR of PE in case of AF*			**p=0.003**
	0.68 (0.42-1.11), p=0.122 n=133	**0.47** (0.26-0.84) p=0.010 n=104	**2.42** (0.97-6.07) p=0.059 n=29	
COPD	Adjusted OR of PE in case of COPD*			**p=0.009**
	0.43 (0.28-0.65) p<0.001 n=247	**0.32** (0.20-0.51) p<0.001 n=217	**1.40** (0.51-3.87) p=0.515 n=30	
Heart failure	Adjusted OR of PE in case of heart failure*			**p=0.095**
	0.53 (0.31-0.88) p=0.014 n=144	**0.43** (0.25-0.73) p=0.002 n=135	**1.80** (0.36-8.99) p=0.475 n=9	

* Adjusted for age, sex and presence of AF, heart failure, COPD, stroke or cancer in the past and creatinine clearance

The End of Life Care Research Program

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EOL aux SI?

- 20% des décès aux SI (ou 3 jours suivant)
- Qualité de la fin de vie est importante pour les patients, mais aussi pour les familles (séquelles) et les soignants
- Majeur partie des décès aux SI se produisent à la suite d'un retrait thérapeutique (**life-support withdrawal**)
- Prolongation du retrait thérapeutique n'est pas justifié médicalement, éthiquement, économiquement

⇒ « stuttering withdrawal » est un marqueur d'indécision médicale et de mauvaise qualité des soins?

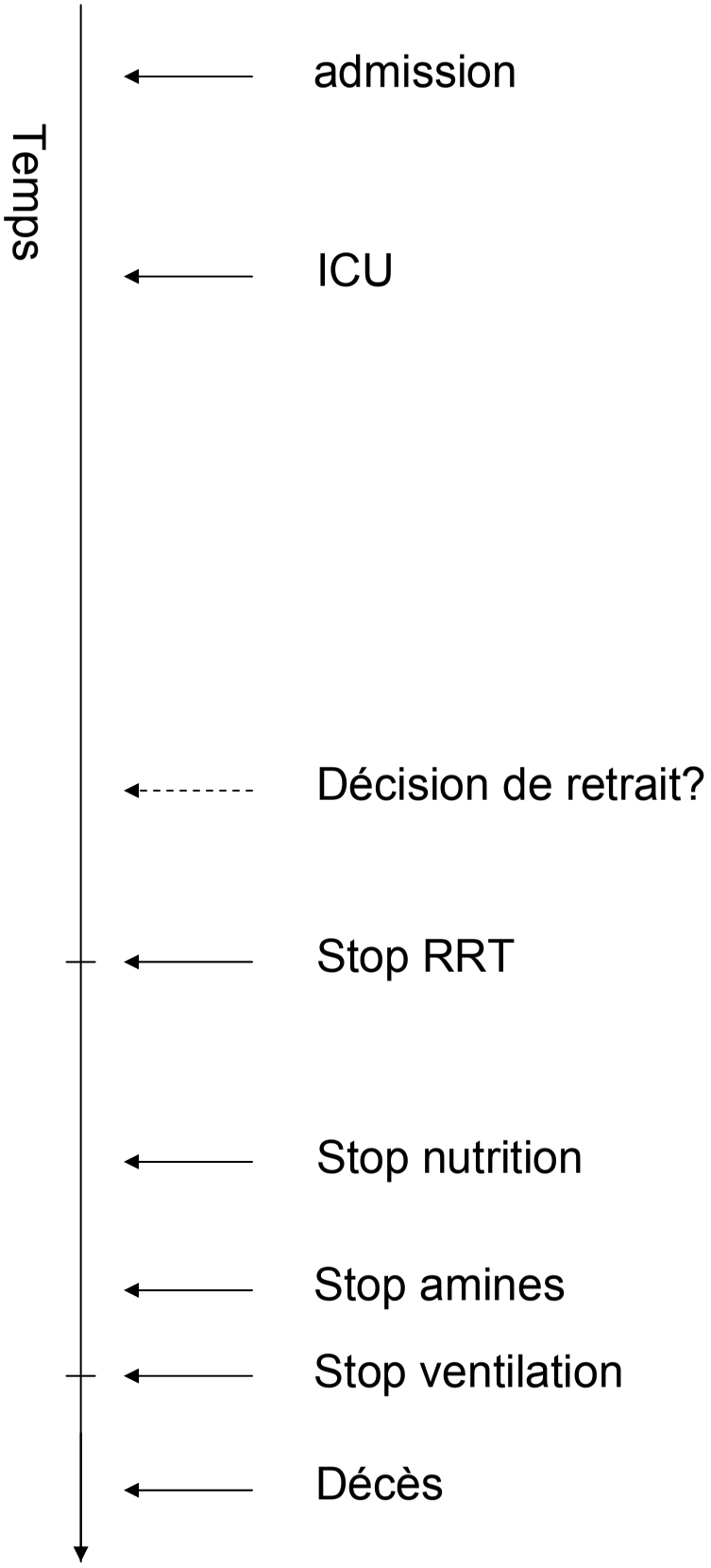
=>Améliorer la qualité de la fin de vie aux SI est un objectif important

Duration of Withdrawal of Life Support in the Intensive Care Unit and Association with Family Satisfaction

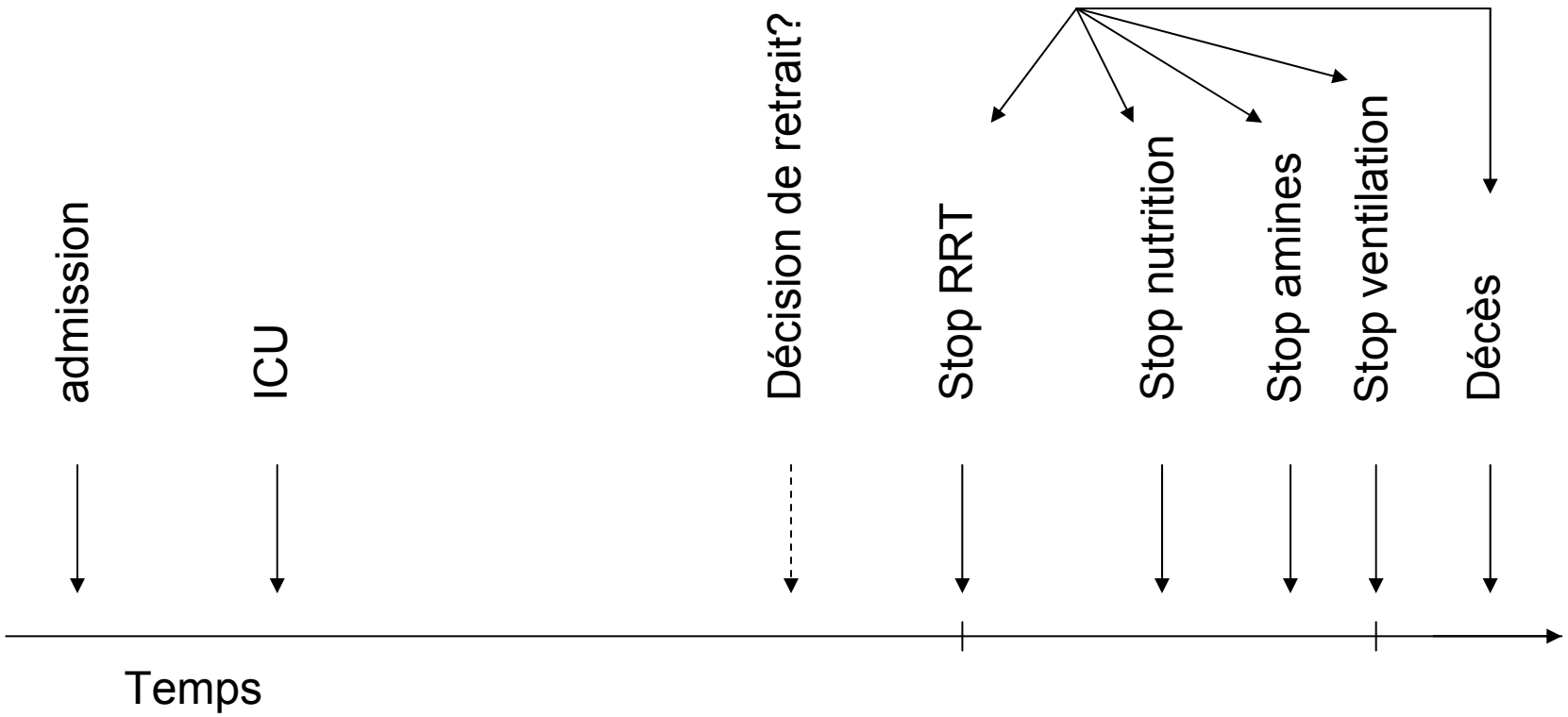
Eric Gerstel, Ruth A. Engelberg, Thomas Koepsell, J. Randall Curtis

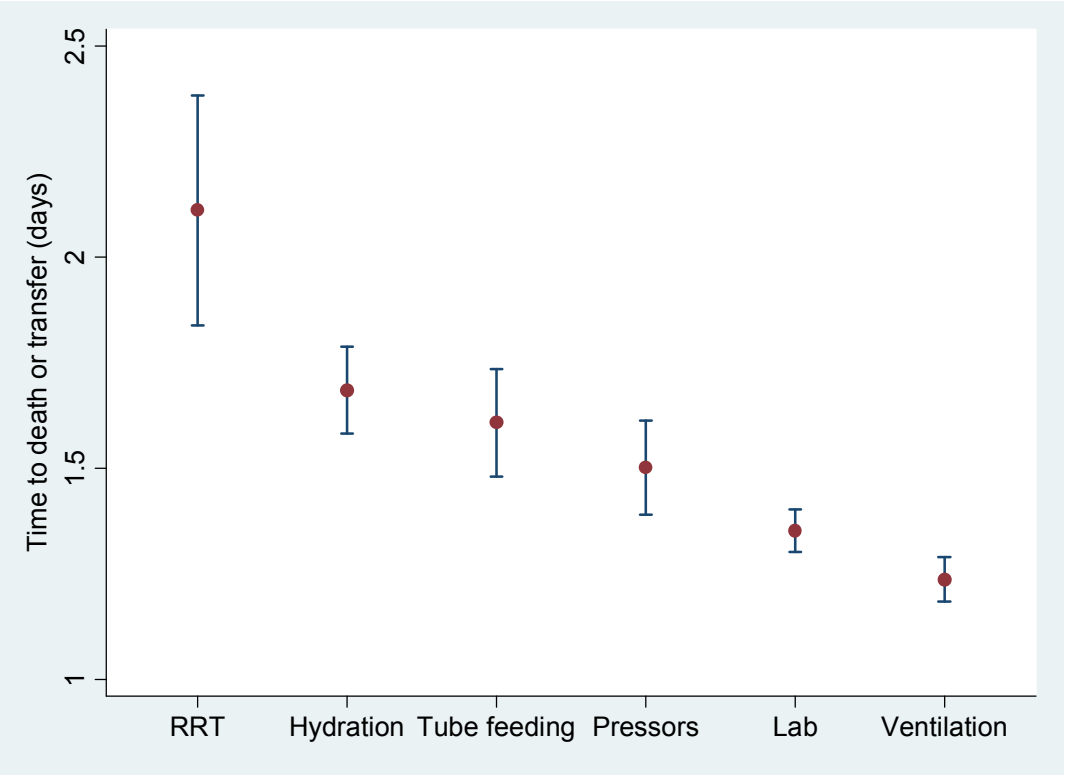
AJRCCM 2008

- Cohorte prospective multicentrique
- 15 centres (WA), 2003-2006 – **2100 patients**
- Critères d'inclusion: tous les patients décédés pendant ou dans les 24h suivant une admission aux SI
- Exclusion: durée séjour SI<6h, patients décédés en « full-support »
- Abstraction prospective des dossiers + questionnaires FS-ICU adressés aux familles 1 mois après décès

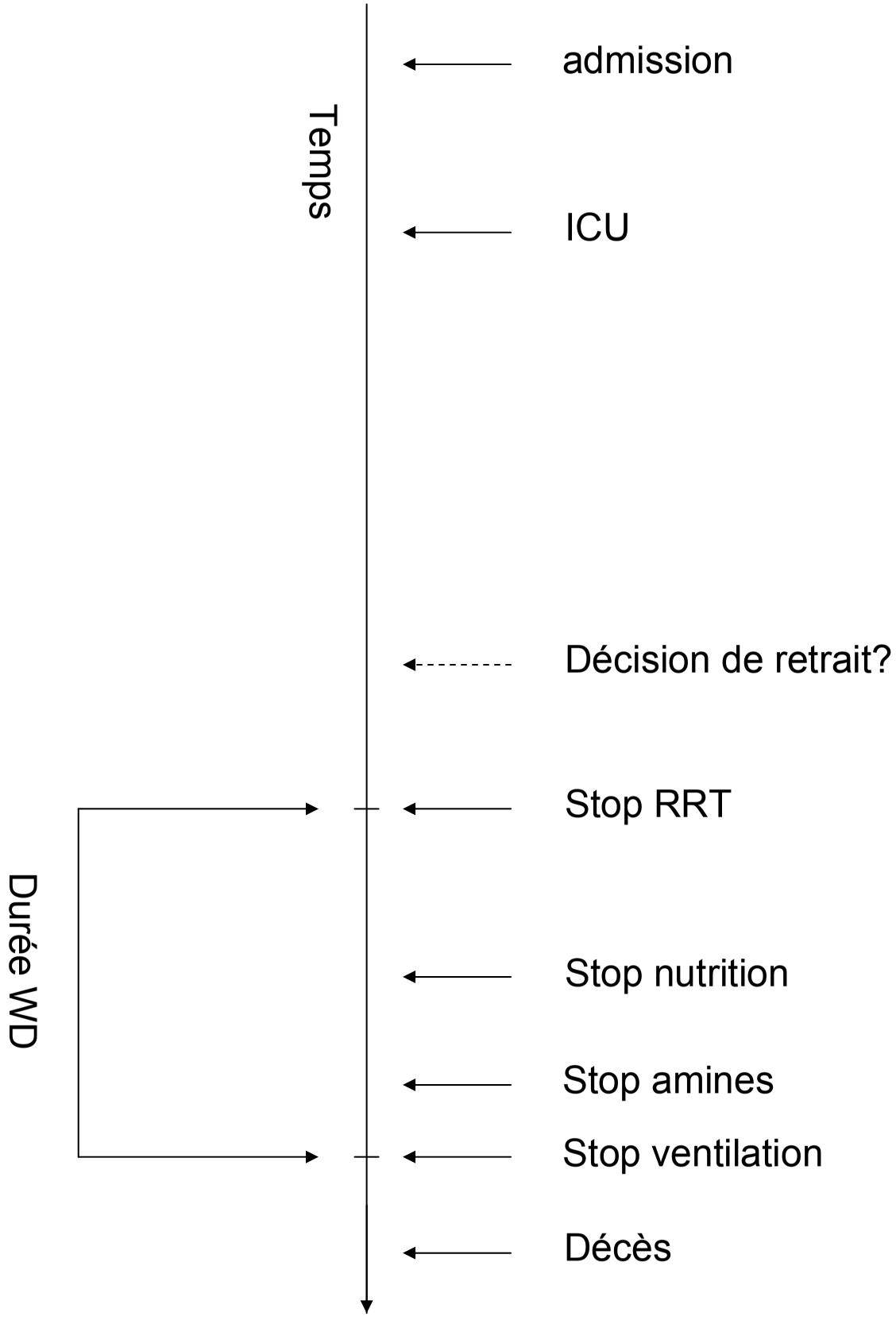

Temps
admission
ICU
Décision de retrait?
Stop RRT
Stop nutrition
Stop amines
Stop ventilation
Décès

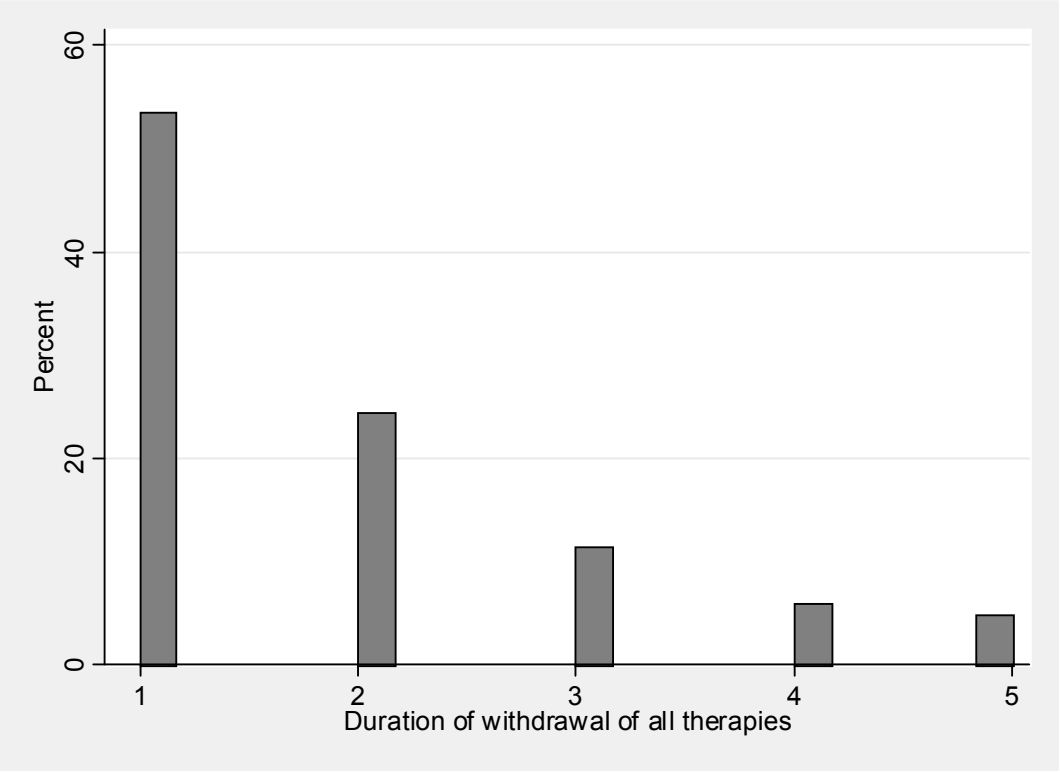
Séquence WD

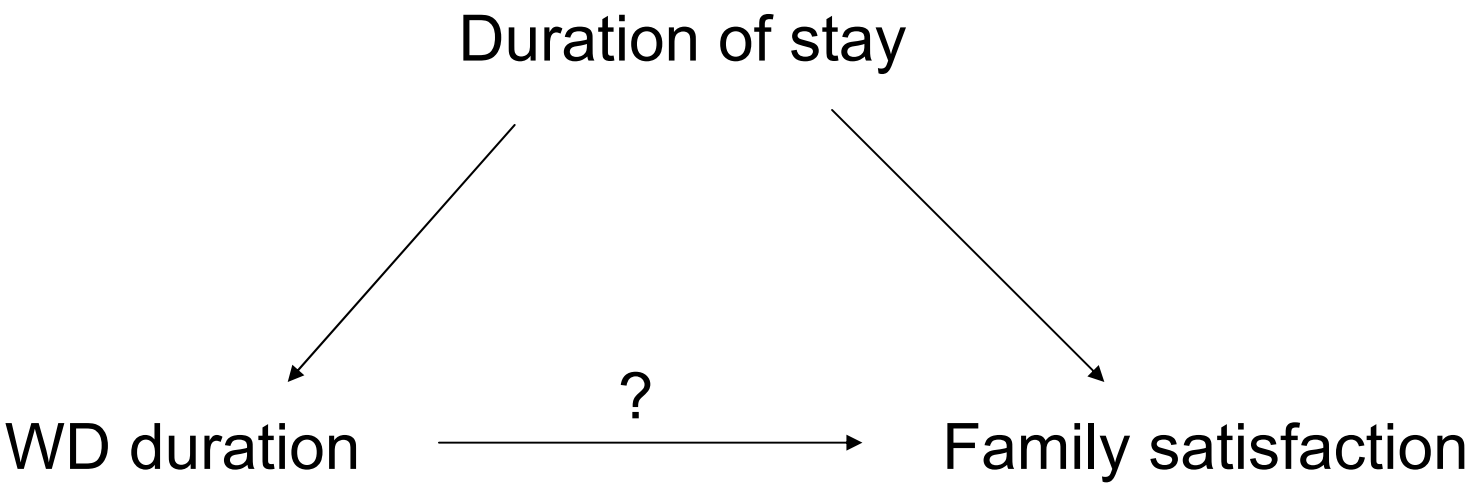

admission
ICU
Décision de retrait?
Stop RRT
Stop nutrition
Stop amines
Stop ventilation
Décès
Temps

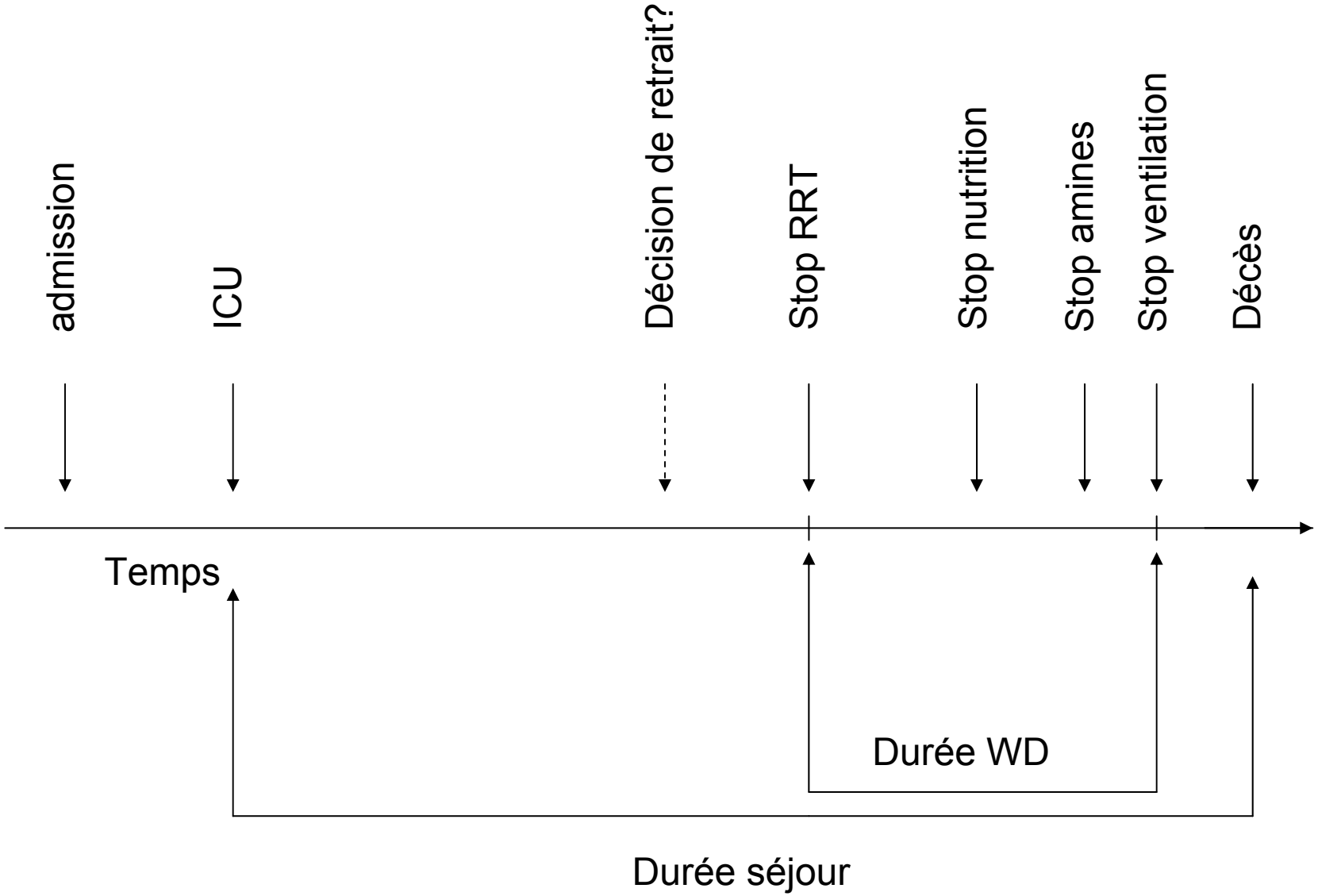


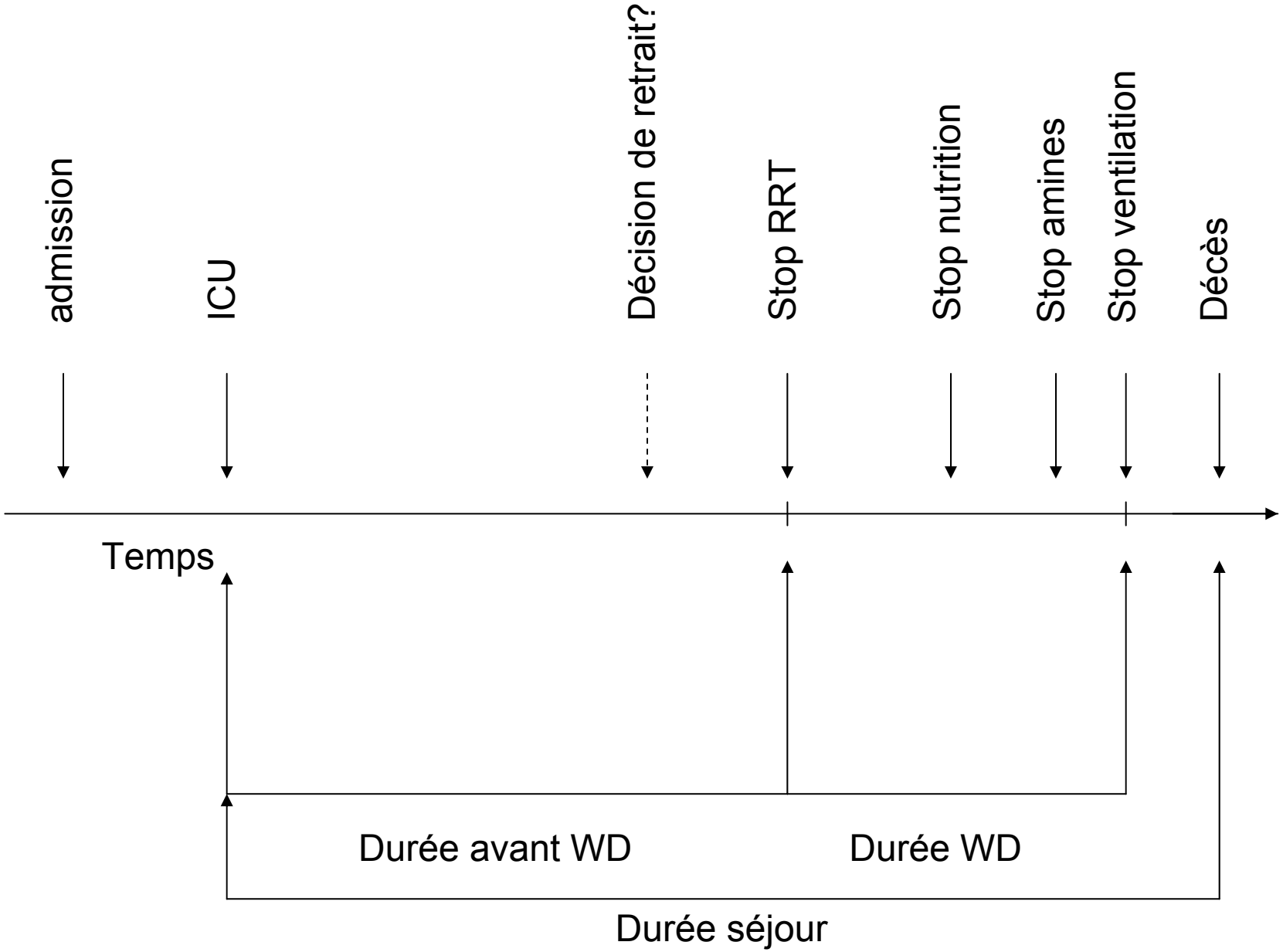
p-value*	RRT	Hydration	Tube feeding	Pressors	Lab
Hydration	0.32†				
Tube feeding	0.14†	0.0007			
Pressors	0.0079	0.63	0.89		
Lab	<0.0001	<0.0001	0.0001	0.042	
Ventilation	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

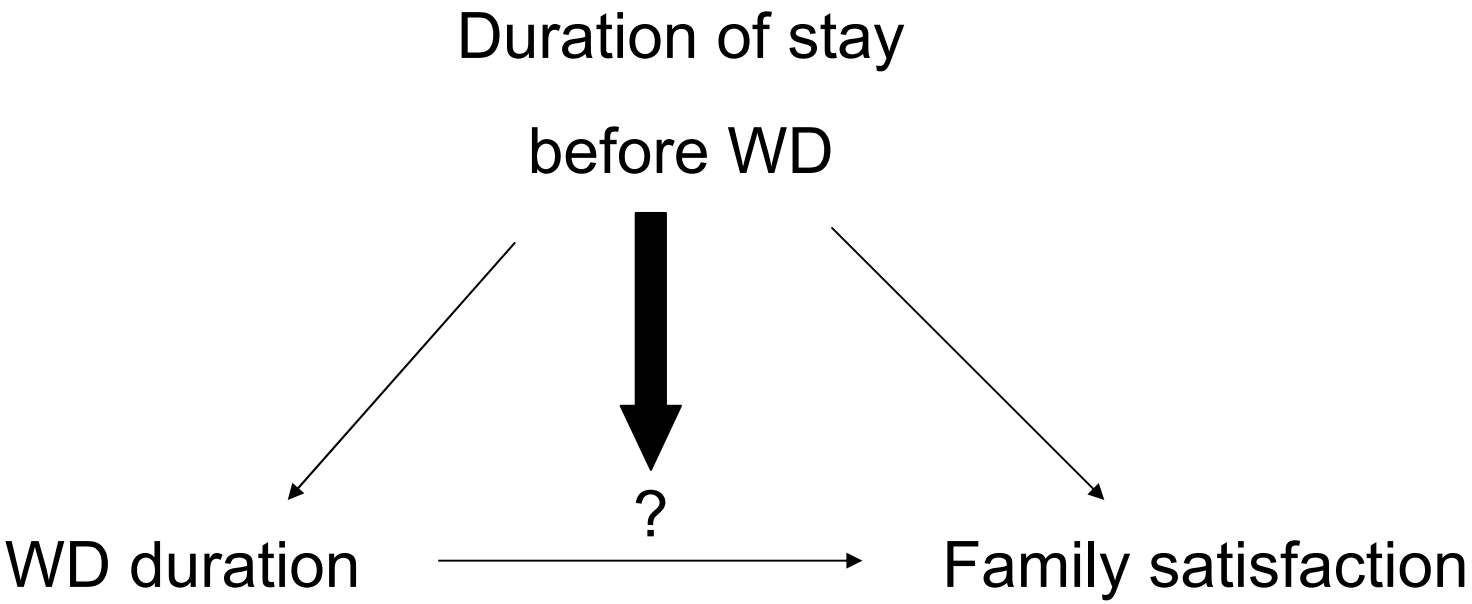

Temps
admission
ICU
Décision de retrait?
Stop RRT
Stop nutrition
Stop amines
Stop ventilation
Décès
Durée WD


Percent
0
20
40
60
1
2
3
4
5
Duration of withdrawal of all therapies


Duration of stay
?
WD duration
Family satisfaction


admission
ICU
Décision de retrait?
Stop RRT
Stop nutrition
Stop amines
Stop ventilation
Décès
Temps
Durée WD
Durée séjour


admission
ICU
Décision de retrait?
Stop RRT
Stop nutrition
Stop amines
Stop ventilation
Décès
Temps
Durée avant WD
Durée WD
Durée séjour


Duration of stay
before WD
?
WD duration
Family satisfaction

Withdrawal duration – associated factors

Associated factors		Withdrawal duration (days) N	Mean	SD	p-value
		584	1.84	1.13	
Age (years)					0.022
<65		161	1.97	1.28	
65-74		114	1.94	1.16	
75-84		184	1.82	1.07	
?85		125	1.62	1.00	
Race/ethnicity					0.73
White		444	1.81	1.16	
Non White		47	1.81	1.14	
Insurance Status					0.21
Private/Commercial		168	1.80	1.10	
Government/Public		73	1.96	1.26	
Medicare		228	1.76	1.06	
Medicaid		30	2.23	1.57	
None		11	2.00	1.10	
LOS in the ICU before withdrawal of life support (days)					<0.001
0-4		375	1.71	1.04	
5-9		115	1.98	1.22	
10-14		30	2.20	1.37	
>14		64	2.20	1.27	
Primary diagnosis category					0.066
Cardiovascular		112	1.95	1.16	
Infectious		83	1.89	1.15	
Gastro-intestinal and hepatic		42	1.86	1.20	
Neurologic		72	1.63	1.01	
Trauma		42	2.29	1.50	
Respiratory		128	1.70	1.02	
Cancer		42	1.69	1.00	
Miscellaneous		47	1.96	1.16	
Number of therapy/interventions					<0.001
1		20	1.00	-	
2		69	1.36	0.71	
3		185	1.56	0.86	
4		222	1.94	1.21	
5		81	2.73	1.28	
6		7	3.00	1.29	
Ventilation					
Intubated last week of life	yes	431	1.92	1.20	0.004
	no	153	1.61	0.90	
Extubated before death	yes	351	1.90	1.22	0.42
	no	72	2.03	1.13	
Mental status and presence of symptoms in the patient's last 24 hours					
Alert/oriented	yes	183	1.64	1.02	0.003
	no	371	1.96	1.20	
Pain	yes	190	1.75	1.10	0.034
	no	307	1.94	1.17	
Dyspnea	yes	182	1.77	1.09	0.56
	no	121	1.85	1.18	
Living will					0.91
	yes	272	1.83	1.06	
	no	156	1.81	1.19	

Withdrawal duration – associated factors

Associated factors		N	Withdrawal duration Mean	SD	p-value
Number of family decision makers					0.001
1		36	1.58	1.05	
2-3		434	1.77	1.06	
>3		111	2.16	1.35	
Documentation of family conference					
Prognosis discussed	yes	362	1.89	1.15	0.16
	no	222	1.76	1.11	
Family wishes to WD/WH	yes	519	1.86	1.15	0.18
	no	65	1.66	1.00	
Patient wishes to WD/WH	yes	107	1.83	1.09	0.97
	no	476	1.84	1.14	
Decision to WD/WH	yes	366	1.83	1.14	0.84
	no	217	1.85	1.14	
Patient's wishes expressed	yes	258	1.79	1.08	0.36
	no	325	1.87	1.17	
Family discord	yes	18	2.28	1.45	0.092
	no	565	1.82	1.11	
Family present at death					0.17
	yes	476	1.82	1.13	
	no	73	2.01	1.25	
Spiritual advisor involved					0.075
	yes	293	1.92	1.20	
	no	289	1.75	1.05	

Association WD and family satisfaction

Satisfaction score	Duration of stay in the ICU	Effect on satisfaction* (% change†)	95% CI	p-value
Family satisfaction with care domain score (14 items)	3 days	-2.0	-12.3 – 7.4	0.037
	8 days	3.5	-5.7 – 11.8	
	16 days	11.6	0.4 – 21.5	
Family satisfaction with decision making domain score (10 items)	3 days	-0.3	-11.1 – 9.4	0.007
	8 days	6.3	-3.3 – 14.9	
	16 days	15.9	4.6 – 25.9	
Family satisfaction total score (24 items)	3 days	-0.9	-10.2 – 7.7	0.004
	8 days	5.3	-2.8 – 12.9	
	16 days	14.5	4.7 – 23.2	

* model adjusted for age, gender, race, number of life-sustaining therapies, intubation status, and including an interaction term with duration of stay

ME - conclusions

- Décider a priori
- Reporter tous les résultats
- Importance épidémiologique

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- Importance et clarté statistique (test global)
- Plausibilité