Trajectories of dietary habits and body mass index in prodromal phase of dementia : dynamic approach with latent process

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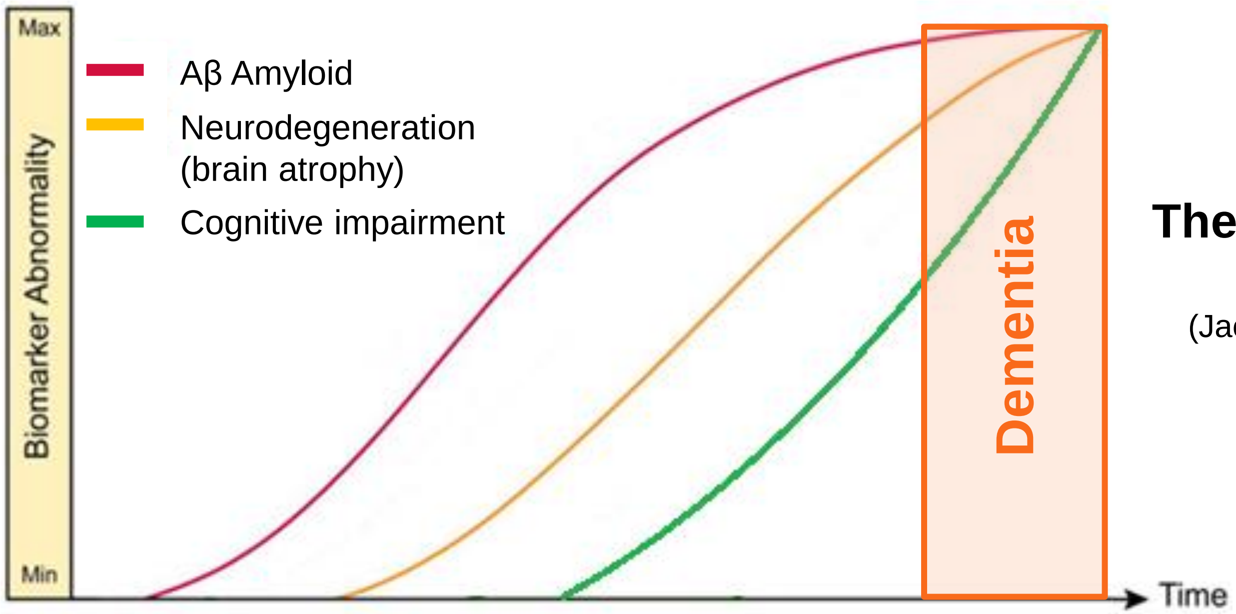
Dementia

- 2016 : **47.5 million** affected worldwide [1]
- 2020 : **1 in 4 french people** (≥ 65 years) could be demented [2]
- Alzheimer's disease (AD) : main form of **dementia**
- Risk factors : age, genetics
  cardiovascular factors, lifestyle (nutrition)
- No etiological treatment → **Prevention**
- Long preclinical phase → **Long-term prevention**



Theoretical pathological cascade
(Jack *et al*., Lancet Neurol., 2010)

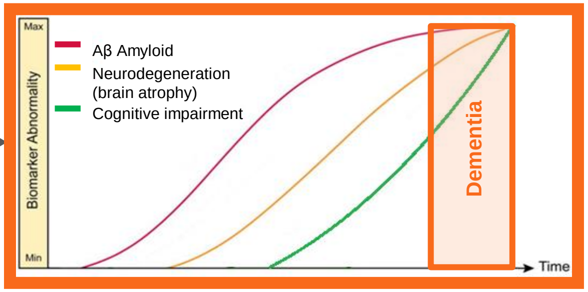
Nutrition and dementia

- Lifelong exposure
- Modulates cardiovascular factors
- Anti-inflammatory and antioxydant properties

Féart C, 2009

Causal relation

Nutrition



Reverse causation

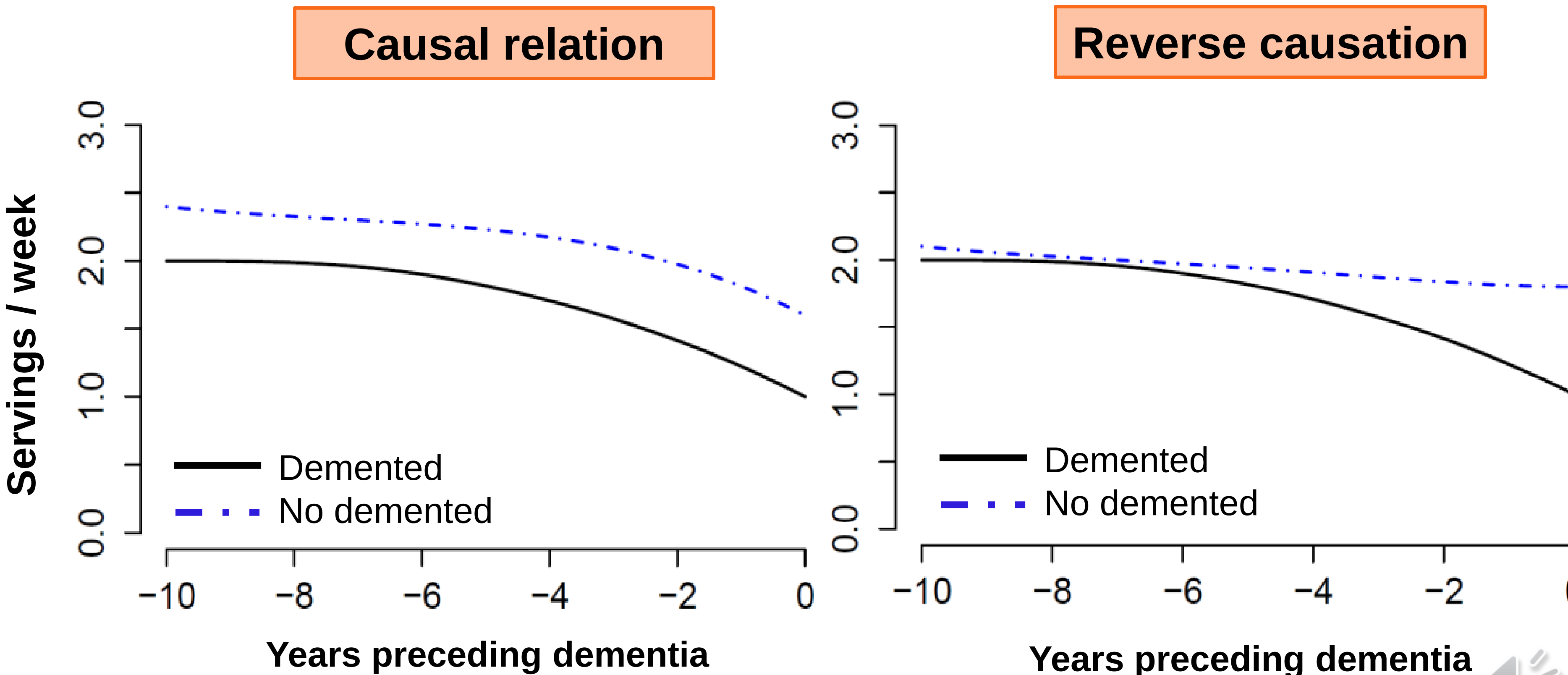
Guérin O, 2005

→ Difficult interpretations in terms of causality

→ Longitudinal studies most appropriate

Causality assumptions

- Expected trajectories of a **protective food**



Objective

Compare the consumption trajectories of major foods and body mass index
in the 10 years prior to the diagnosis visit of dementia
among demented cases and control subjects
in the Three-City (3C) Study – Bordeaux

Statistical issues

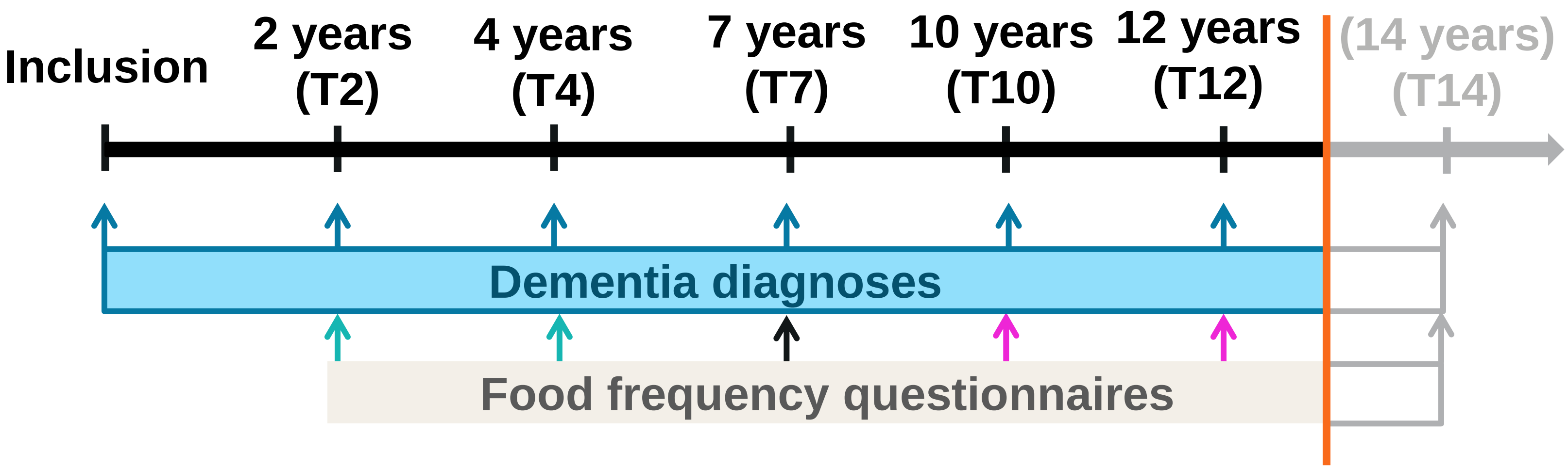
Comparison of trajectories

- Selection of nested case-control study sample

Complexity of data

- Change of food frequency questionnaire (FFQ) during the follow-up
- Potential non-gaussian data
  → Latent process multivariate mixed models

Study sample (1)



Population (N = 1425)

- Included in 3C – Bordeaux
- No demented at T2 (study baseline)
- Followed at least up to T4
- Nutritional evaluation at T2

Subsample of demented (n = 212)

- Diagnosed with dementia at T4, T7, T10 or T12
- ≤ 1 follow-up visit missed before diagnostic

Study sample (2)

Case-control sample (n = 615)

Potential controls

- All subjets no demented at the diagnosis visit of case

Matching method

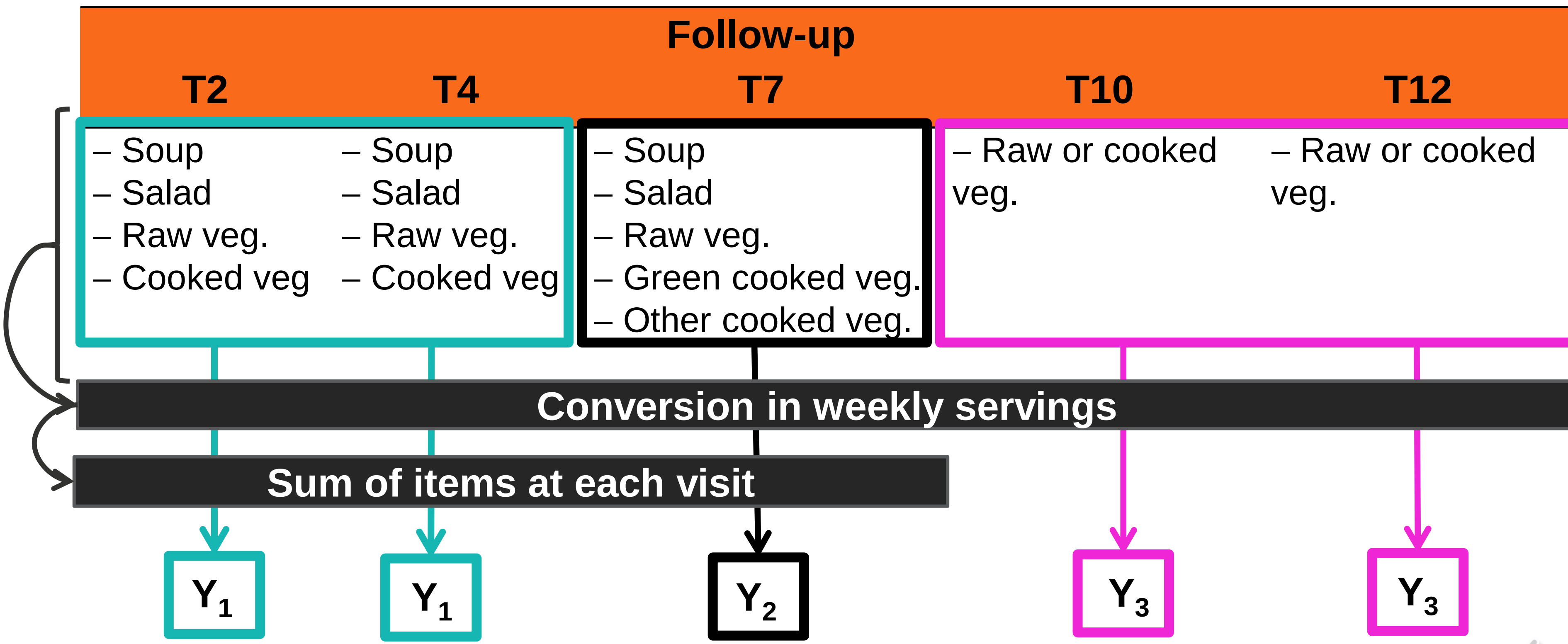
- Random sampling with replacement
- Control subjects possibly matched several times to different follow-ups

Matching variables

- Gender
- Initial age (± 3 years)
- Educational level (≤ secondary school vs. higher)
- Number of food frequency questionnaire (FFQ) reply (± 1)

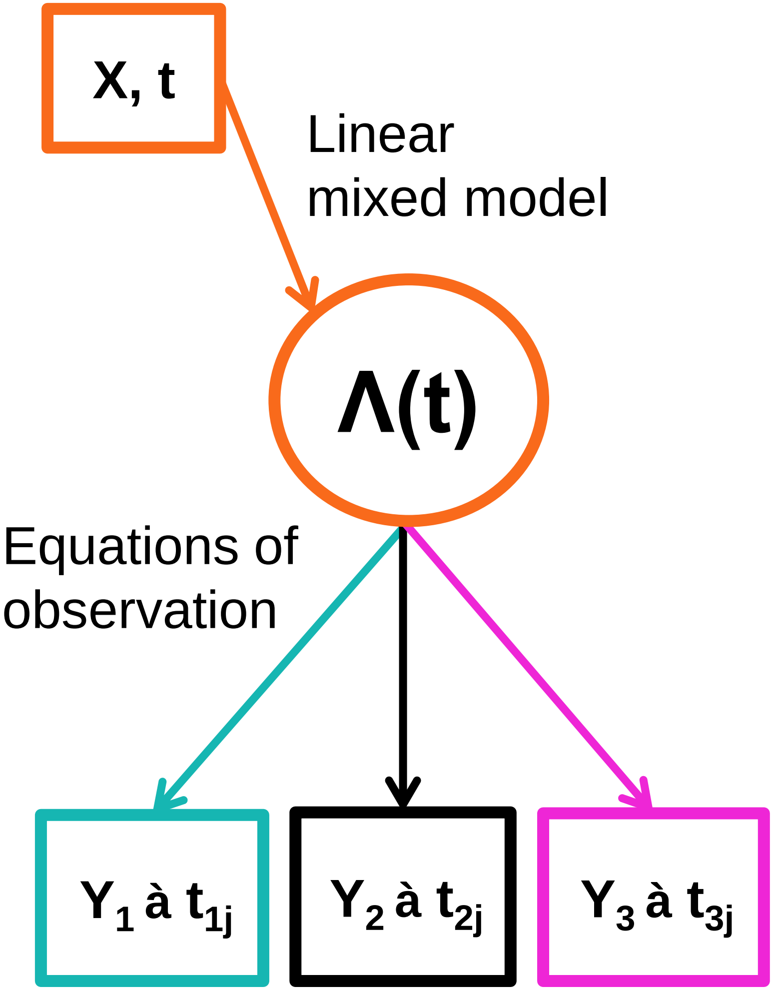
3C – Bordeaux data

- Nutritional evaluation from T2 (comprehensive dietary survey) to T12
- **5 food families of interest** : Fruits, Vegetables, Meat, Fish, Carbohydrate-rich foods (cereal, rize, pasta, potatoes, dried vegetables)



→ 3 different measurement tools (k = 1, 2, 3)

Latent process mixed model



Latent consumption for a given food familly

$$\Lambda_i\,(t) = X_i(t)^T\beta + Z_i(t)^T b_i$$

$$i = (1, \ldots, N);\ b_i \sim N(0, B);\ t \in \mathbb{R}$$

Measurement tools observed (k = 1, 2, 3)

- linear or non-linear (splines) transformations

$$H_k\,(Y_{kij}\,;\,\eta_k) = \Lambda_i(t_{kij}) + \varepsilon_{kij}$$

$$\varepsilon_{kij} \sim N(0, \sigma^2_{\varepsilon k});\ \varepsilon_{kij} \perp \varepsilon_{kij'}\,;\ b_i \perp \varepsilon_i;\ j = (1, \ldots, n_{ik})$$

- thresholds transformations

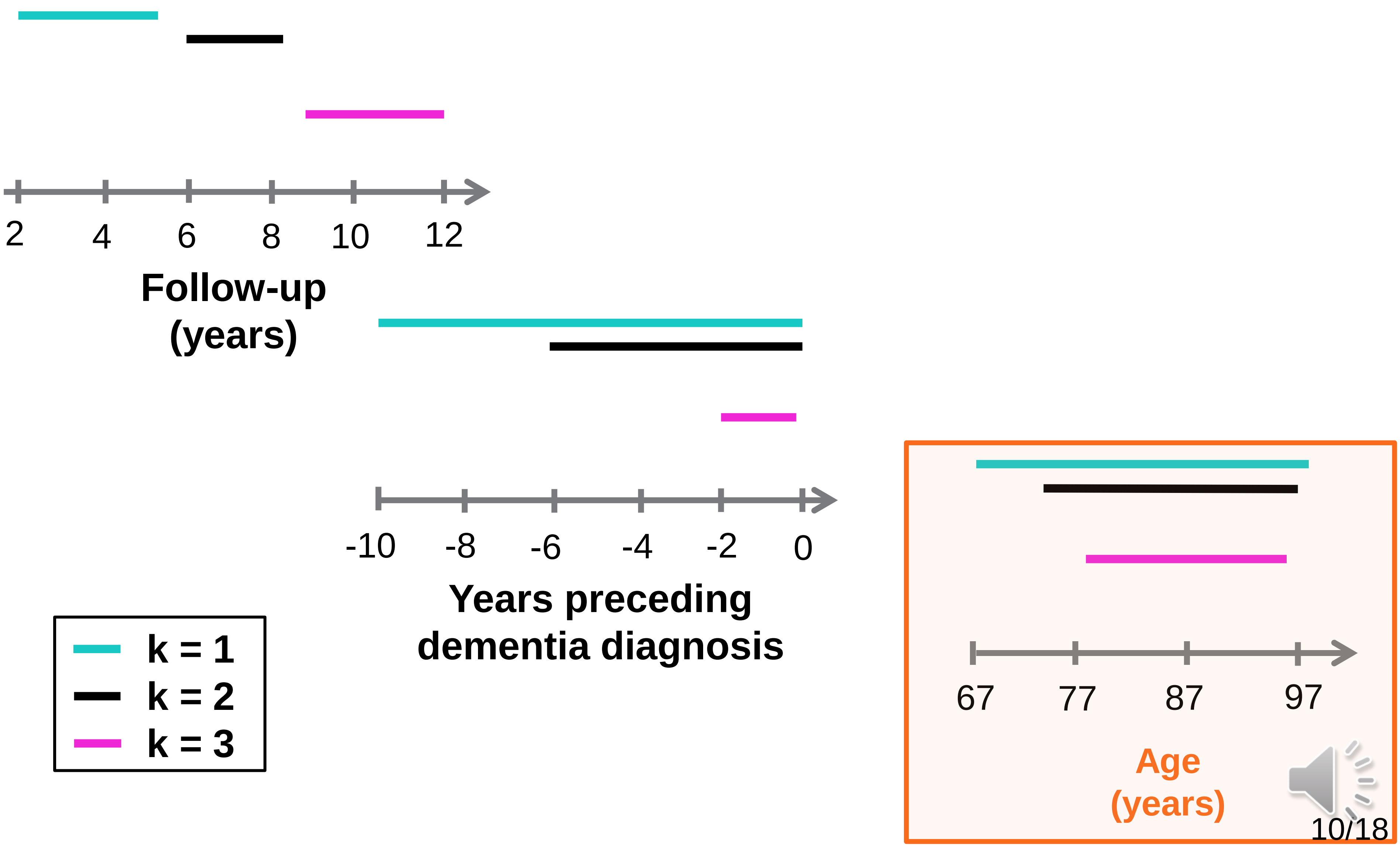
  → distributions < 10 different levels

$$Y_{kij} = m \Leftrightarrow \eta_m < \Lambda_i\,(t_{kij}) + \varepsilon_{kij} \leq \eta_{m+1}$$

$$\varepsilon_{kij} \sim N\,(0, \sigma^2_{\varepsilon k})\ ;\ \varepsilon_{kij} \perp \varepsilon_{kij'}\ ;\ b_i \perp \varepsilon_i\,;\ j = (1, \ldots, n_{ik})$$

- Function **multlcmm** of the **lcmm** package developed in **R**

Sequential change of FFQ over time



Modelling strategy

1) Estimation of transformation parameters $\hat{\eta}$ by food familly

- Timescale : age

$$\Lambda_i\,(t = \text{age67}) = \beta_1 t + \beta_2 t^2 + \beta_3 \text{age0}_i + b_{0i} + b_{1i}\, t$$
$$\text{age67} = (\text{age0} - 67)/100\ ;\ bi \sim N\,(0, B)$$

$$\left.\begin{aligned} H_1\,(Y_{1ij};\ \eta_1) &= \Lambda_i(t_{1ij}) + \varepsilon_{1ij} \\ H_2\,(Y_{2ij};\ \eta_2) &= \Lambda_i(t_{2ij}) + \varepsilon_{2ij} \\ H_3\,(Y_{3ij};\ \eta_3) &= \Lambda_i(t_{3ij}) + \varepsilon_{3ij} \end{aligned}\right\}\ \text{Vegetables}$$

2) Estimation of trajectories

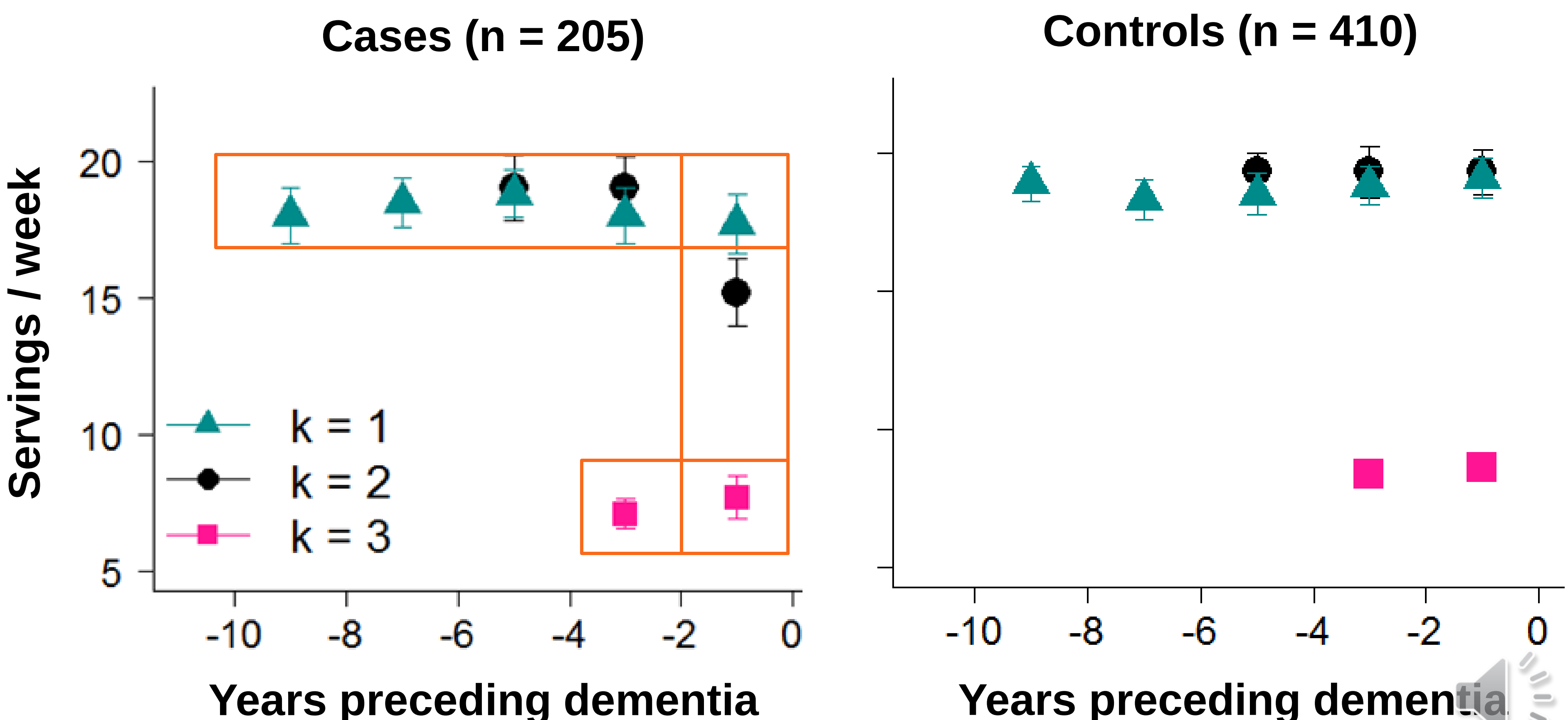
- Timescale : delay = (age at a given visit – age at the matching visit)/100
- Retrospective analyzes since the matching visit
- Fixed transformations : $\eta = \hat{\eta}$

$$\Lambda_i\,(t = \text{delay}) = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \text{case}_i + \beta_4 \text{case}_i{*}t + \beta_5 \text{case}_i{*}t^2 + \beta_6 \text{age0}_i + \beta_7 \text{gender}_i$$
$$+ \beta_8 \text{education}_i + \beta_9 \text{age0}_i{*}t + \beta_{10} \text{gender}_i{*}t + \beta_{11} \text{education}_i{*}t + b_{0i} + b_{1i}{*}t \quad \text{with} \quad bi \sim N(0, B)$$

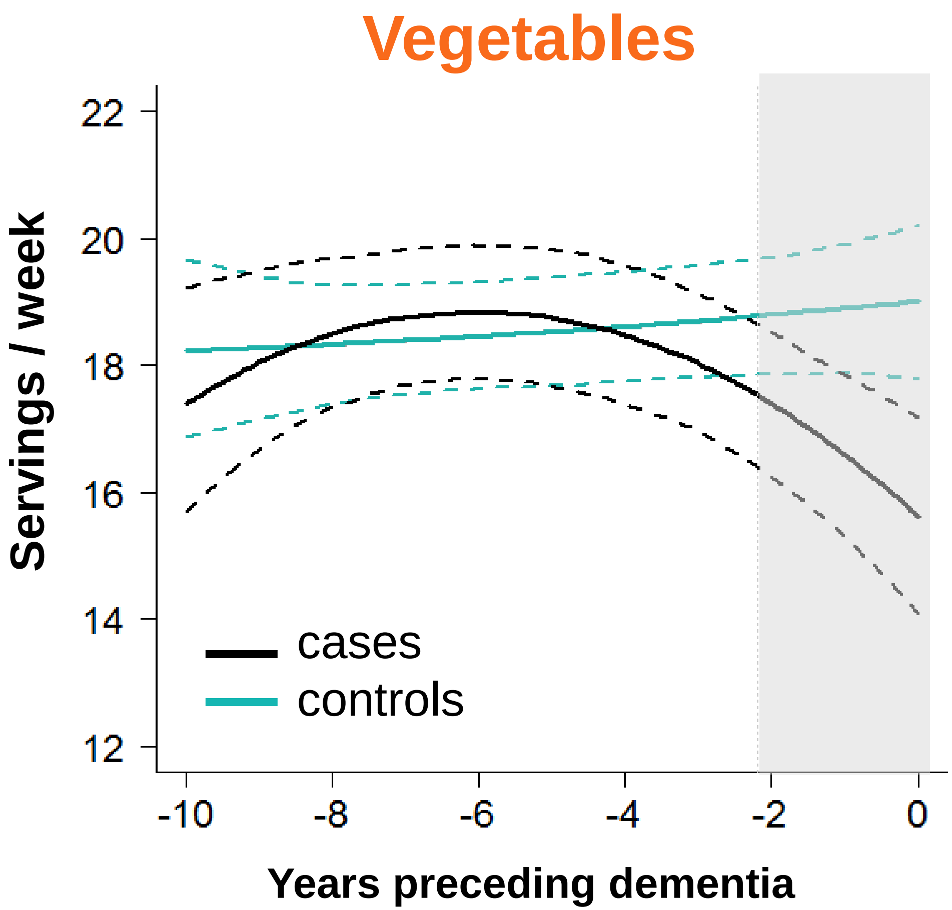
Results

- Means and 95% confidence intervals of the observed intakes by period of 2 years

Vegetables



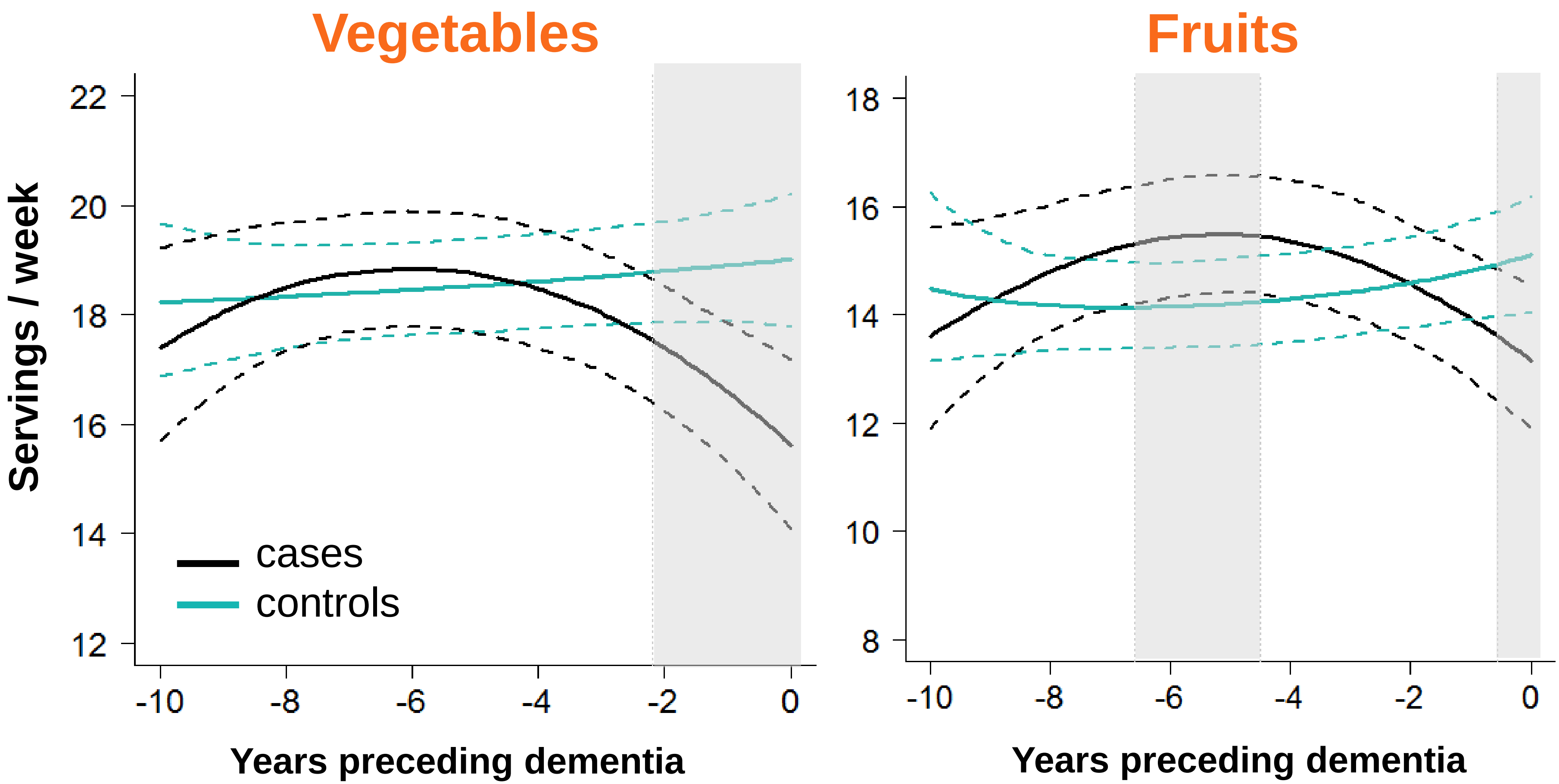
Predicted trajectories of Vegetables



P-value test de Wald	0.43	0.82	0.51	0.83	**0.03**	**<0.001**

- Scale of the first FFQ
- Profile : woman, 77 years at T2, educational level < secondary school

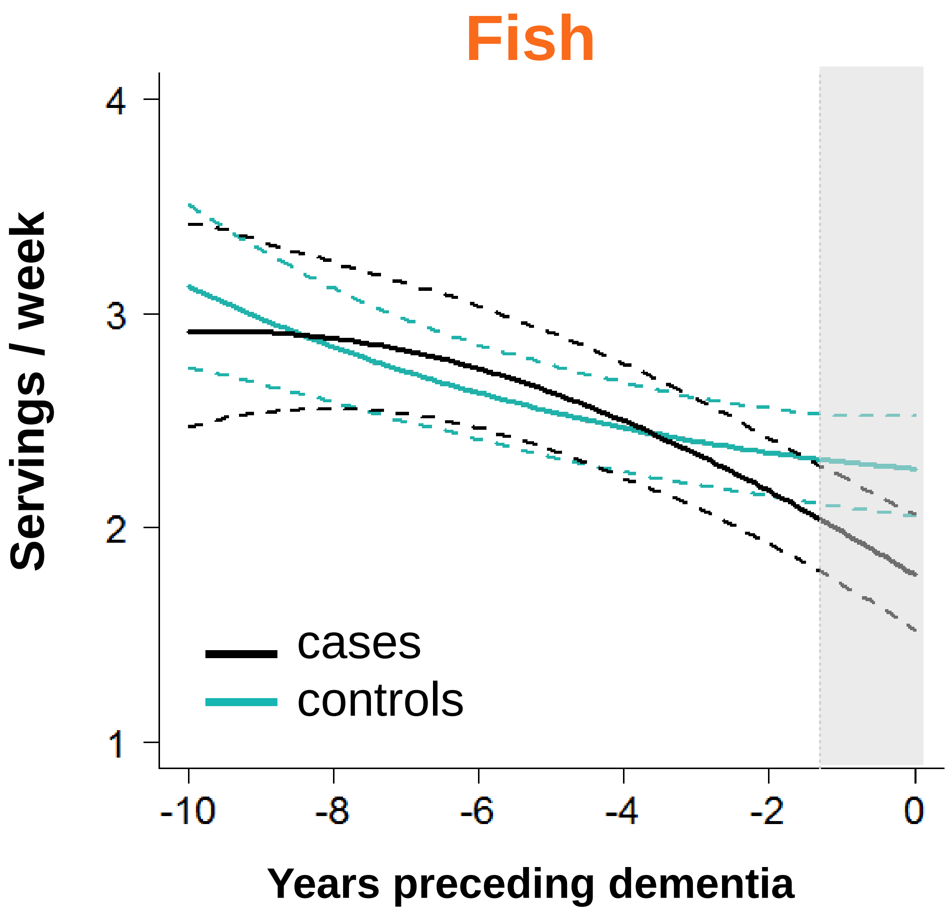
Predicted trajectories of Vegetables & Fruits



P-value test de Wald	0.43	0.82	0.51	0.83	**0.03**	**<0.001**	0.37	0.33	**0.03**	0.08	0.97	**0.009**

- ► Scale of the first FFQ
- ► Profile : woman, 77 years at T2, educational level < secondary school

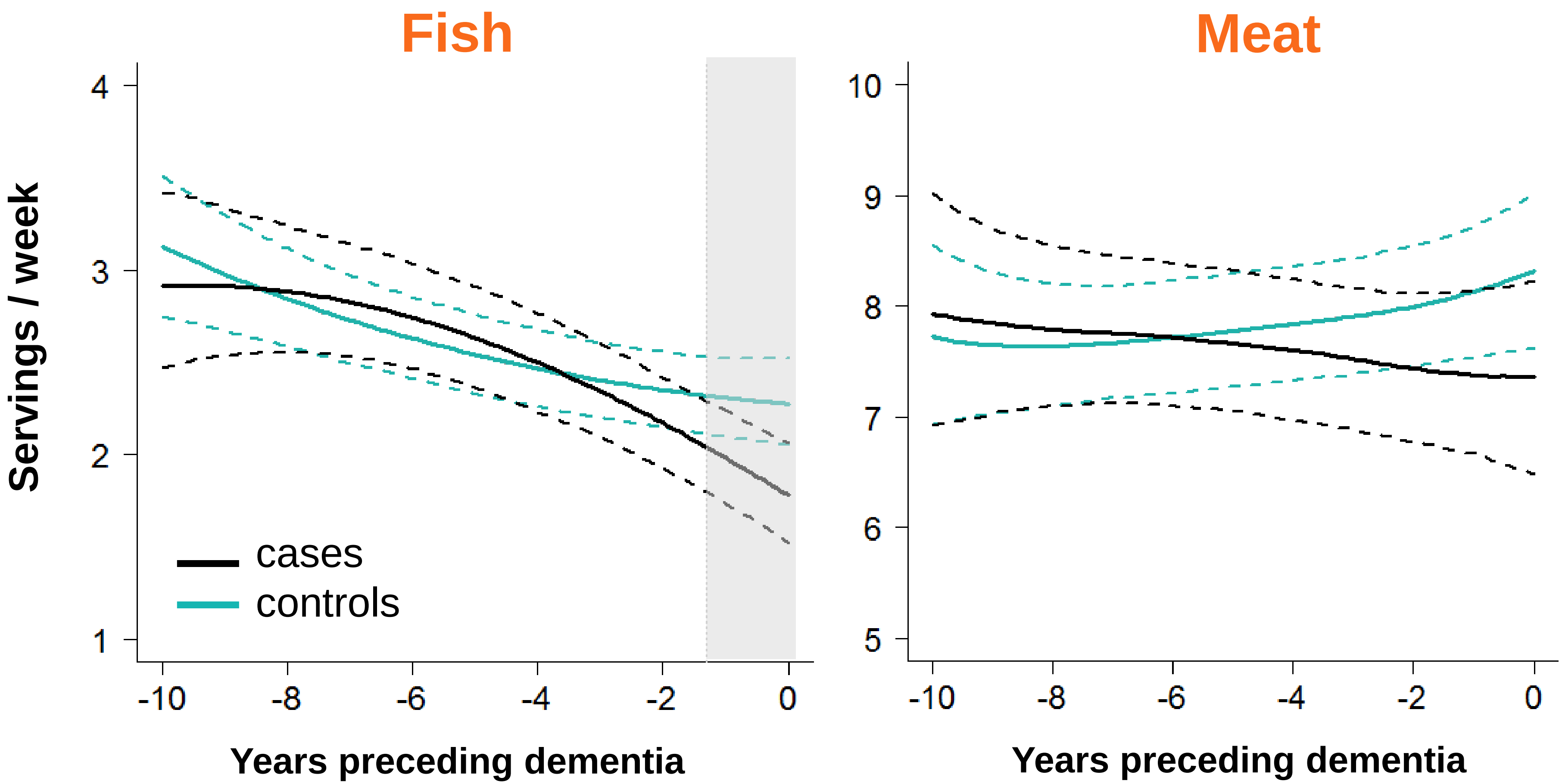
Predicted trajectories of Fish



P-value test de Wald	0.47	0.85	0.51	0.86	0.20	**0.002**

- Scale of the first FFQ
- Profile : woman, 77 years at T2, educational level < secondary school

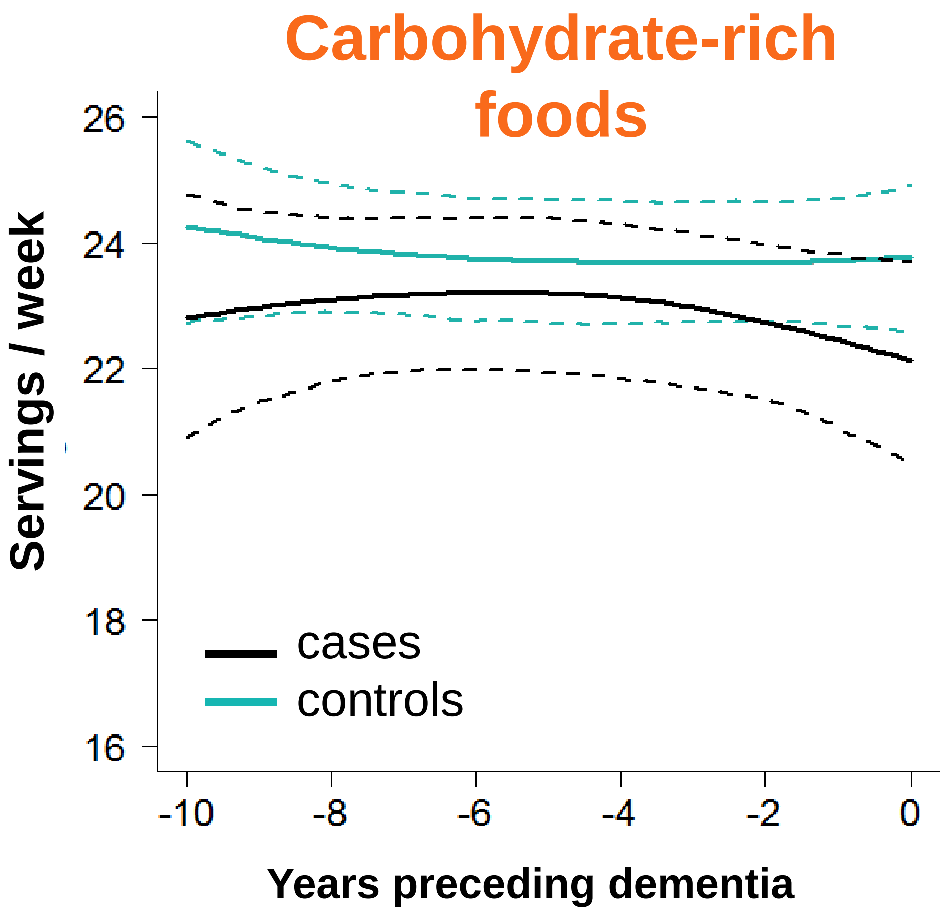
Predicted trajectories of Fish & Meat



P-value test de Wald											
0.47	0.85	0.51	0.86	0.20	**0.002**	0.71	0.69	0.99	0.53	0.14	0.06

- ► Scale of the first FFQ
- ► Profile : woman, 77 years at T2, educational level < secondary school

Predicted trajectories of Carbohyd.

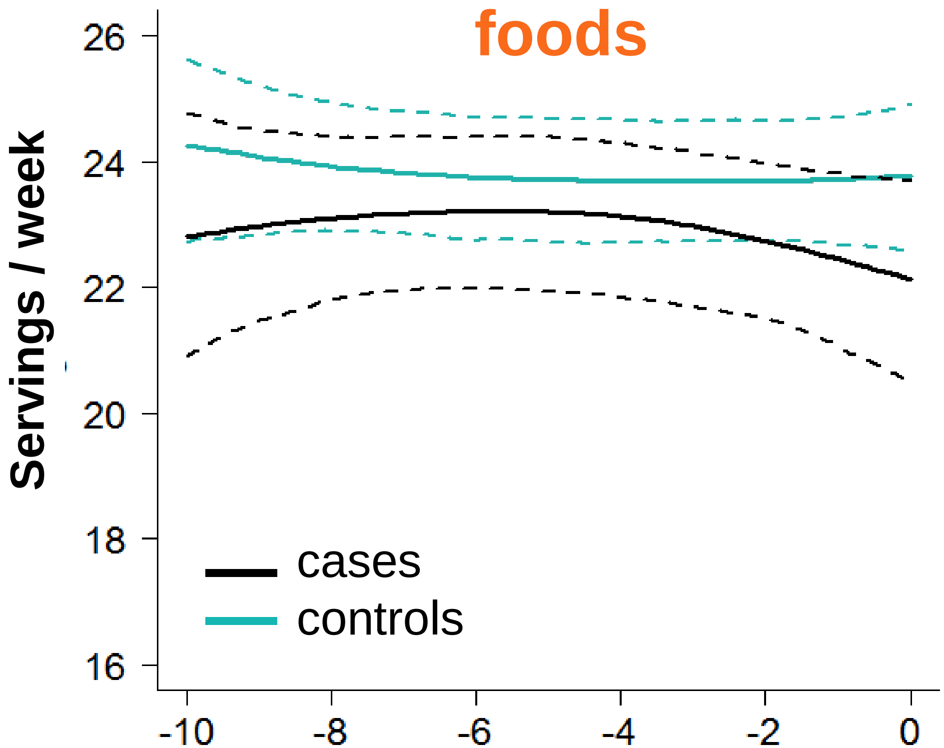


P-value test de Wald	0.19	0.25	0.43	0.41	0.17	0.07

- ► Scale of the first FFQ
- ► Profile : woman, 77 years at T2, educational level < secondary school

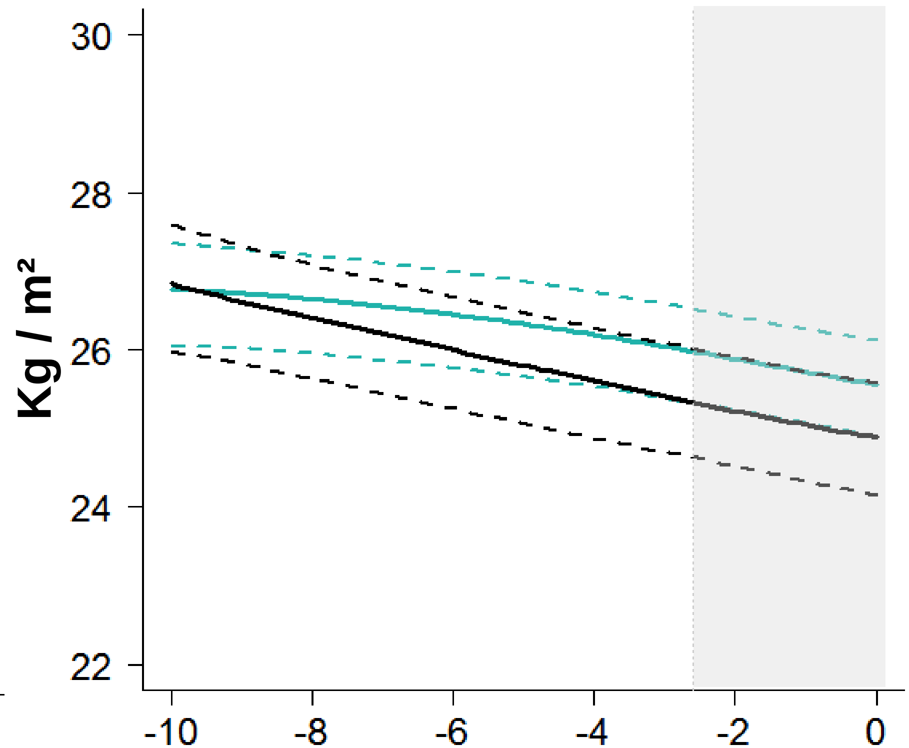
Predicted trajectories of Carbohyd. & BMI

Carbohydrate-rich foods



Years preceding dementia

BMI



Years preceding dementia

P-value test de Wald						
Carbohydrate-rich foods	0.19	0.25	0.43	0.41	0.17	0.07
BMI	0,97	0,45	0,17	0,07	**0,04**	**0,04**

- ► Scale of the first FFQ
- ► Profile : woman, 77 years at T2, educational level < secondary school

Epidemiological discussion

- **Foods** : significant differences between groups few years before diagnosis
- **BMI** : progressive decline but faster among cases
- No evidence of **causal relationship** between T-10 and T-2
- Possible **inverse causality** near diagnosis (Vegetables, Fish, Fruits)

- Foods analyzed separately: no comprehensive approach to diet
  → Overall diet (e.g., mediterranean diet)

Statistical discussion

- Complexity of the data : necessary application of **latent process models**
- Takes into account :
  - the **sequential change** of the FFQ
  - the **deviation from the normality** of the data

- Case-control approach
  - **Directly compares** trajectories in prodromal phase of dementia and in normal aging
  - Lets **test the difference** with a multivariate Wald test

  → What joint model does not allow

- Study baseline = diagnosis visit of dementia (not age of dementia)

  → Possibly increase the reverse causation effect

Perspectives

Epidemiological

- Mediterranean diet – Denutrition score
- Biological parameters link to lifestyle
- Longlife data from midlife ($\simeq$ 40 years)

Statistical

- Evaluation of the modelling strategy in two-steps by simulations
- Coevolution with neuro-anatomics trajectories

Thank you for your attention

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References

[1] WHO. Dementia. A public health priority. 2012 [cité 25 novembre 2016]; Disponible sur: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf?ua=1

[2] INSERM. Alzheimer. [cité 25 novembre 2016]. Disponible sur:

http://www.inserm.fr/thematiques/neurosciences-sciences-cognitives-neurologie-psychiatrie/dossiers-d-information/alzheimer

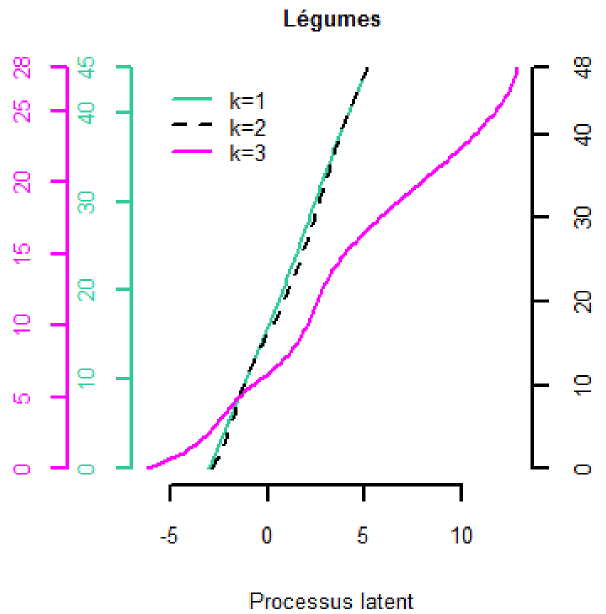
[3] Jack JrCR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet. 2010; (9): 119-28.

[4] Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues J-F, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA. 2009;302(6):638-48.

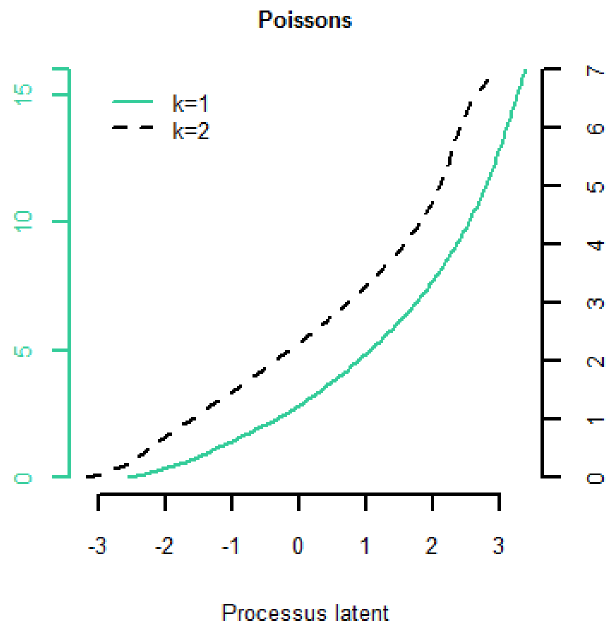
[5] Guérin O, Andrieu S, Schneider SM, Milano M, Boulahssass R, Brocker P, et al. Different modes of weight loss in Alzheimer disease: a prospective study of 395 patients. Am J Clin Nutr. 2005;82(2):435-41.

Food Frequency Questionnaires

	T2 (2001-2002)	T4 (2003-2004)	T7 (2006-2007)	T10 (2009-2010)	T12 (2011-2012)	
Fish	**Fi**1 (4)	**Fi**1 (4)	**Fi**1 (4)	**Fi**2 (1)	**Fi**2 (1)	K = 2
Meat	**M**1 (10)	**M**2 (4)	**M**2 (4)	**M**3 (1)	**M**3 (1)	K = 3
Fruits	**Fr**1 (18)	**Fr**1 (18)	**Fr**1 (18)	**Fr**2 (1)	**Fr**2 (1)	K = 2
Vegetables	**V**1 (8)	**V**1 (8)	**V**2 (10)	**V**3 (1)	**V**3 (1)	K = 3
Carbohydrate-rich foods	**C**1 (22)	**C**2 (8)	**C**2 (8)	**C**3 (3)	**C**3 (3)	K = 3



Pourcentage de variation expliquée			
Délai pré-diagnostic (années)	k=1 (%)	k=2 (%)	k=3 (%)
0	64,9	51,7	13,4
-2	62,8	49,3	12,3
-4	61,2	47,6	11,6
-6	60,2	46,6	11,2
-8	60,1	46,5	11,1
-10	60,8	47,2	11,4



Pourcentage de variation expliquée		
Délai pré-diagnostic (années)	k=1 (%)	k=2 (%)
0	70,3	52,7
-2	69,5	51,7
-4	69,1	51,2
-6	69,3	51,4
-8	70,0	52,3
-10	71,1	53,6