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An INFOGEST international consensus static in vitro digestion model adapted to the general older adult population and its application to dairy products

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INRAE

- An INFOGEST international consensus static in vitro digestion model adapted to the general older adult population and its application to dairy products

Didier Dupont, Anais Lavoisier, Olivia Menard, Stefano Nebbia and Martine Morzel

The logo for INFOGEST, featuring the word "INFOGEST" in a bold, black, sans-serif font. There are two orange dots: one at the top left and one at the bottom right of the text.

INFOGEST

The logo for JPI (Joint Programme in Innovation), featuring a stylized figure in green and yellow with a red dot above its head. Below the figure, the text "JPI" is written in a bold, green, sans-serif font, and the tagline "a healthy diet for a healthy life" is written in a smaller, green, sans-serif font.

JPI
*a healthy diet
for a healthy life*

Improving health properties of food by sharing our knowledge on the digestive process

International Research Network

Dr. Didier DUPONT, Senior Scientist, INRAE, France

INFOGEST

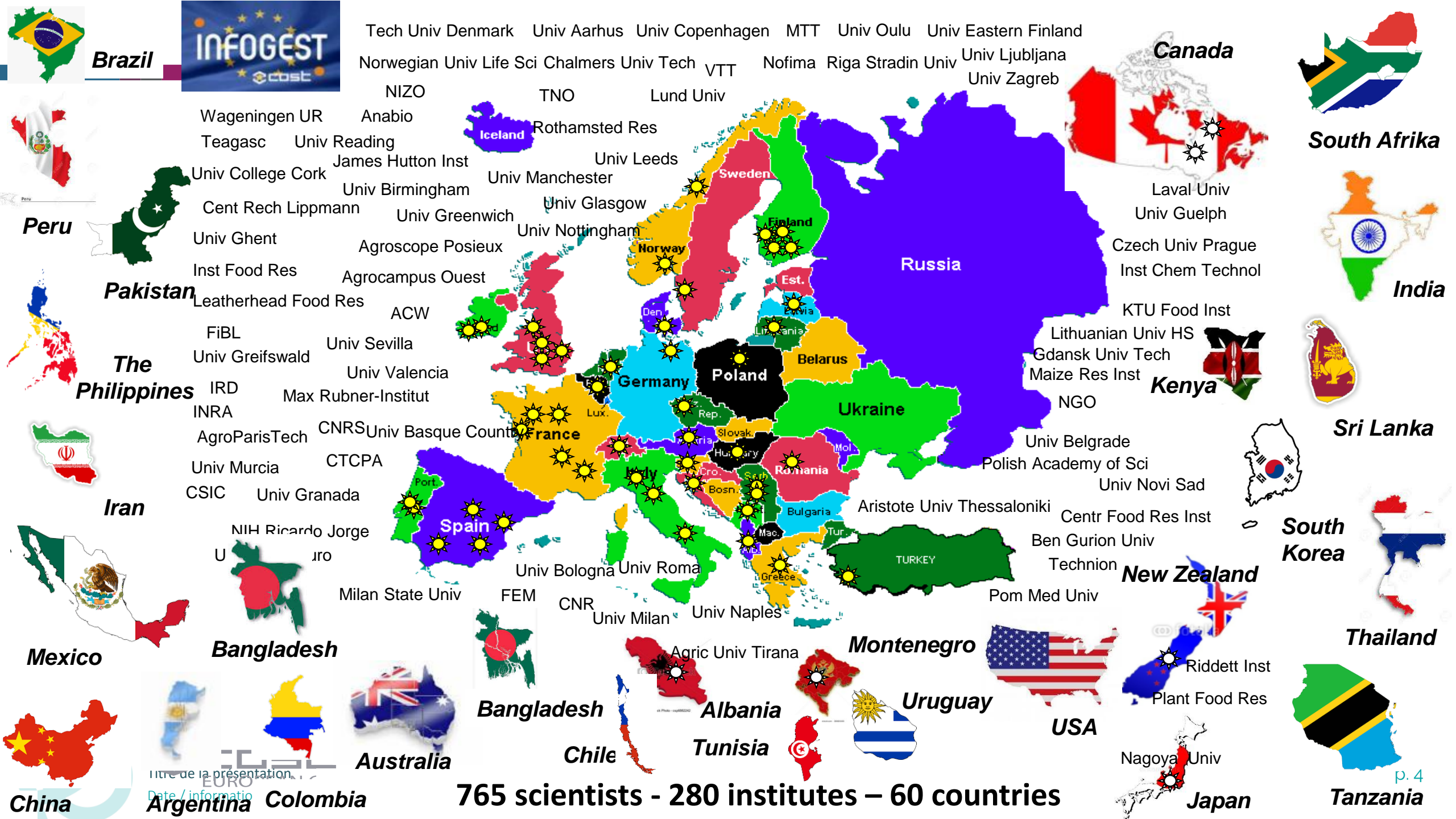


Scientific objectives

- Compare the existing digestion models, harmonize the methodologies and propose guidelines for performing experiments
- Develop *in vitro*, *in vivo* and *in silico* models of digestion.
Validate *in vitro* models towards *in vivo* data (animal and/or human).
- Identify the beneficial/deleterious components that are released in the gut during food digestion
- Determine the effect of the matrix structure on the bioavailability of food nutrients and bioactive molecules

But these goals can only be reached by...

- Gathering scientists from different disciplines (food science, nutrition, gastroenterology, immunology...) to share and improve our knowledge on food digestion



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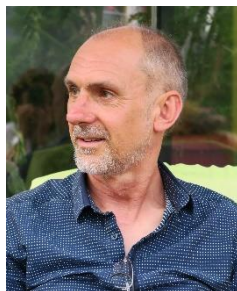
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> Industry involvement

☞ ~ 60 private companies are following INFOGEST





Chair
Didier Dupont - France
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www.cost-infogest.eu

**In vitro
models of
digestion
WG1**



Isidra Recio

**Food
interaction –
meal digestion
WG2**



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**Absorption
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lipases and
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**Digestive
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**In silico
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**Imaging
Technologies
applied to
digestion
WG7**



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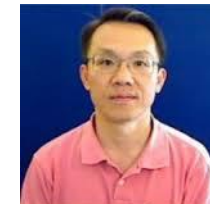
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Marion Letisse



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Choi-Hong Lan



Luca Marciani



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Date / nom de l'auteur

> Introduction - Digestive functions decline with age

* 10% of the world population is over 65, but this number reaches 16% in the US, 21% in Europe and even 30% in Japan

* In 2050, this number should increase from 10% to 16%

* Gastrointestinal motor function, food transit, chemical food digestion, and functionality of the intestinal wall have been previously shown to be affected by ageing (see Rémond *et al.* 2015)

* *In vitro* digestion models must take these changes into account to remain physiologically relevant

* Several *in vitro* digestion models of the elderly have been proposed in the literature by different groups: Levi & Lesmes, 2014; Hernandez-Olivas *et al.* 2020; Plante *et al.* 2020; Aalaei *et al.* 2021; Lee *et al.* 2022

* But all these models are different and harmonization is needed in order to allow comparison between studies



Oncotarget 

ONLINE ISSN: 1949-2653

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Reviews: Gerotarget (Focus on Aging):

 86 **Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition**

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Oncotarget. 2015; 6:13858-13898. <https://doi.org/10.18632/oncotarget.4030>

Metrics: PDF **4010 views** | HTML **8931 views**

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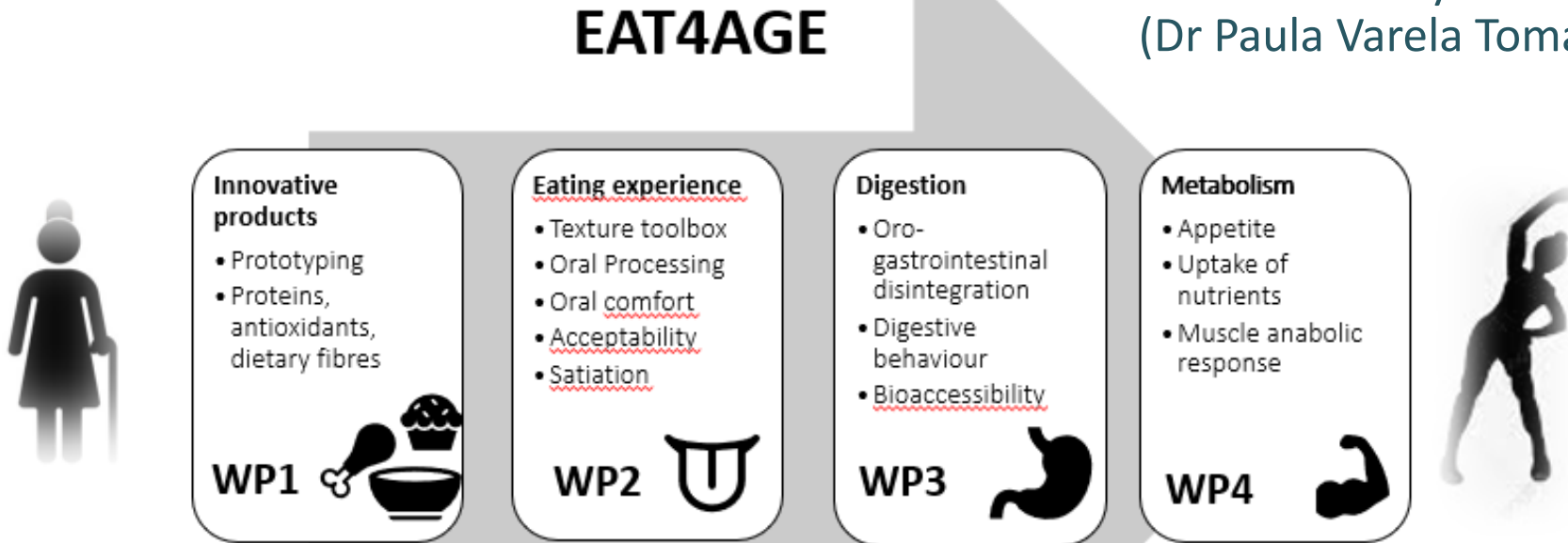
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EAT4AGE - Palatable, nutritious and digestible foods for prevention of undernutrition in active aging

Coordinated by NOFIMA
(Dr Paula Varela Tomasco)



Fighting undernutrition in elderly through innovative, palatable products that are liked, consumed, easily digested, and increase muscle mass

6 academic partners:

NOFIMA



Paula Varela

University of Leeds



INRAE Alan Mackie

Teagasc



Andre Brodkorb

Technion



Uri Lesmes

INRAE



Didier Dupont

Norwegian School of Sport Sciences




Raastad Truls



Methodology

Objective: gathering data from the literature in order to build static, semi-dynamic and dynamic *in vitro* digestion models simulating the gastrointestinal tract of the elderly

- 
- 1st of April 2021
- 1 List of the physiological parameters to find in the literature
 - 2 Exhaustive review of the literature to find data**
- 6th of October 2021
- 3 First meeting within the EAT4AGE consortium to identify the gaps of knowledge
 - 4 New literature search targeted on parameters
- 18th of January 2022
- 5 Second plenary meeting to discuss the missing information
 - 6 Creation of 3 subgroups (oral, gastric, intestinal) and more literature search...
 - 5 New subgroup and plenary meetings to discuss the model
- 11th of April 2022
- 7 All the data available put together into a presentation – Sharing with international experts
- 2nd and 3rd of May 2022
- 8 Workshop in Cork for reaching an international consensus**
- 22nd of May 2023
- 9 Publication of the model
- November 2023
- 10 Application of the consensus *in vitro* digestion model for elderly and comparison with the adult model for 3 categories of food studied (cereal, dairy, meat)



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Parameters to set up

Oral Phase

- * SSF composition
- * Dilution with SSF
- * pH
- * Duration
- * Mastication to achieve in order to reach a desired mean particle size
- * Salivary amylase

Gastric Phase

- * SGF composition
- * Dilution with SGF
- * pH
- * Duration
- * Pepsin
- * Gastric lipase

Intestinal Phase

- * SIF composition
- * Dilution with SIF
- * pH
- * Duration
- * Pancreatic lipase
- * Pancreatic amylase
- * Trypsin
- * Chymotrypsin
- * Bile

- First question to answer: what is an « older adult »? >60? >65?
- The literature analysis showed that, ideally we would need different models for different ages (the digestive conditions of a 65 y old are different than that of a 95 y old adult) but the literature is poor for some parameters after 70 y.
- So it was decided to build one model of adults older than 65



3-5 days
Preparations

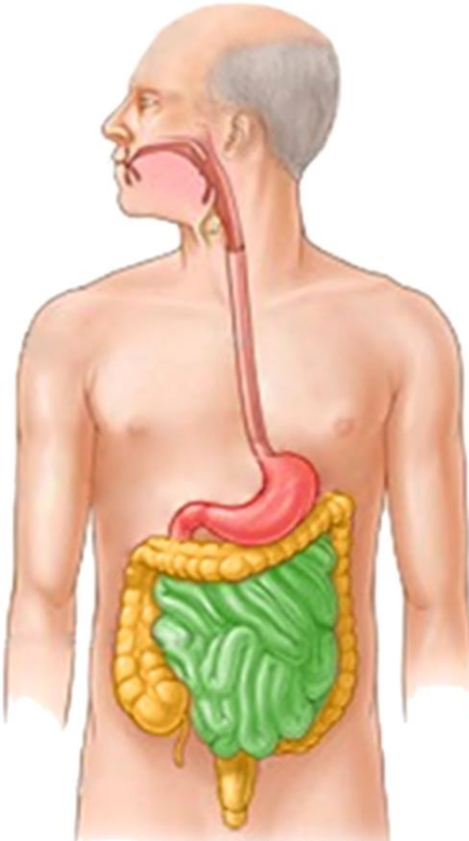
Prep-work

- Assay enzyme activity and bile salts concentration
- Prepare SSF, SGF and SIF, and CaCl₂ stock solution
- Perform pH adjustment pre-experiment

Parameters differing from the young adult model are in bold

Oral

Elderly (>65y)



Dry food : SSF ratio (V/V)	1:1
Salivary amylase (U/mL)	75
Duration (min)	2
pH	7.0

Stomach

Oral bolus : SGF ratio (V/V)	1:1
Pepsin (U/mL)	1200
Gastric lipase (U/mL)	36
Duration (hour)	3
pH	3.7

Intestine

Gastric effluent : SIF ratio (V/V)	1:1
CaCl ₂ [mM]	1

Pancreatin & Bile

Pancreatin (U/mL)-	
By trypsin	80
By lipase	1600
Bile salt [mM]	6.7

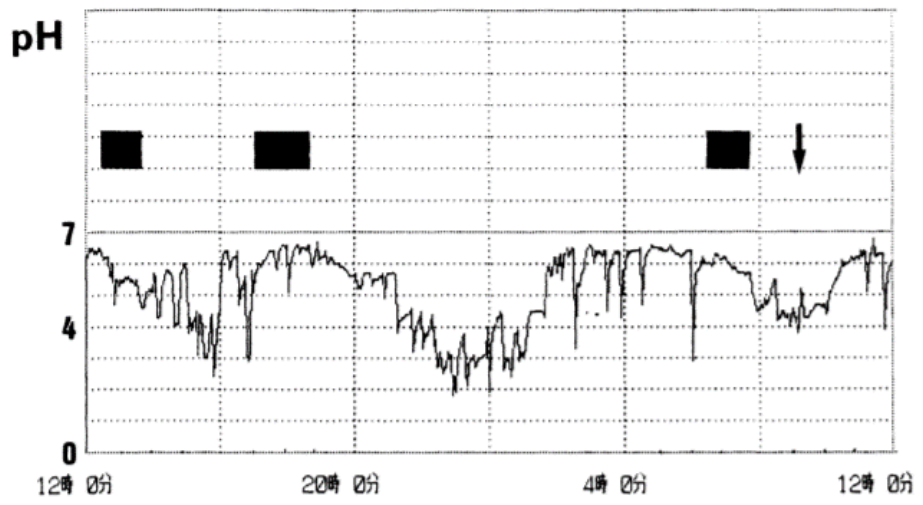
OR Individual components

Trypsin (U/mL)	80
α-chymotrypsin(U/mL)	20
Pancreatic α-amylase(U/mL)	160
Pancreatic lipase (U/mL)	1600
Sodium glycodeoxycholate [mM]	3.35
Taurocholic acid sodium salt hydrate[mM]	3.35

Duration (hour)	2
pH	7.0

Sampling, inactivate enzymes and analyses

➤ Gastric pH What is the pH at $T_{1/2}$?



INFOGEST proposal:
pH at $T_{1/2} = 3.7$

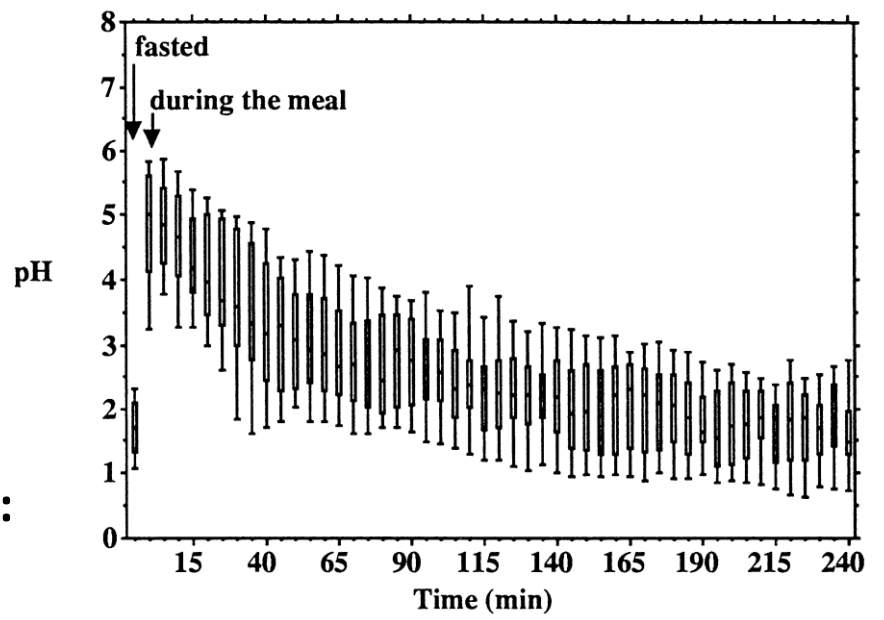
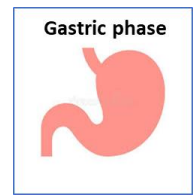
Moriyama et al. 2001
Extrapolation from these data, pH at $T_{1/2} \sim 3.9$

TABLE 2
Secretin Test Data: Patients without Pancreatic Disease, by Age Decade

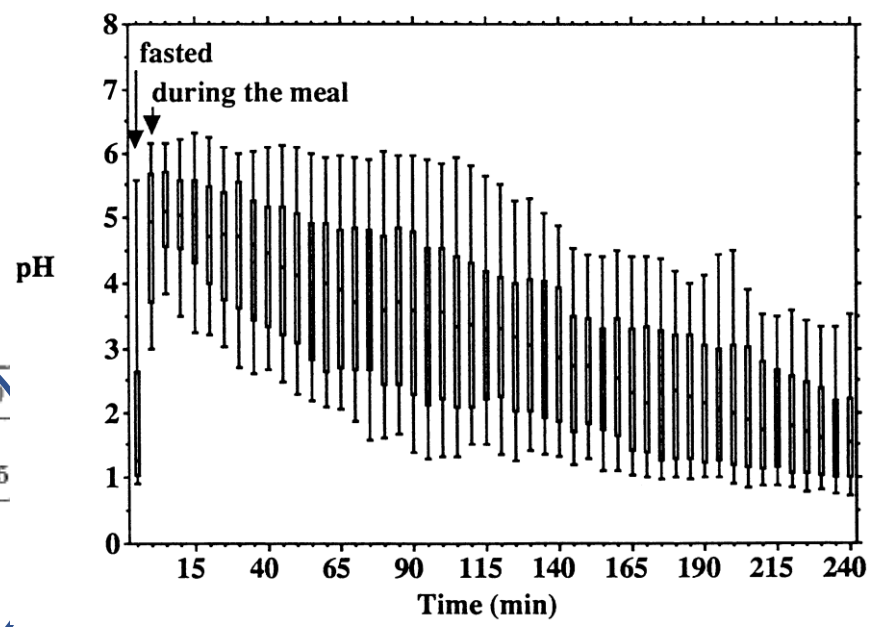
Age range (yrs)	F:M/Total No.	Age (yrs)	Duodenal (mean ± SD)				Gastric (mean ± SD)	
			Volume (ml/kg)	HCO ₃ (mEq/l)	Amylase (u/kg)	Blood amylase (IU)	pH	% pts pH < 3.5
50-59	469:300/769	54 ± 3	3.5 ± 1.2	109 ± 12	17.0 ± 7.9	76 ± 33	3.5 ± 2.3	64
60-69	352:291/643	64 ± 3	3.5 ± 1.1	109 ± 13	17.0 ± 7.6	68 ± 30	3.7 ± 2.4	60
70-79	108:80/188	73 ± 3	3.5 ± 1.2	109 ± 14	22.8 ± 12.9	77 ± 37	4.4 ± 2.6	50
>80	4:11/15	83 ± 3	3.4 ± 1.0	105 ± 19	19.4 ± 10.7	69 ± 39	4.4 ± 2.1	47

Dreiling et al. 1985

3.7 < gastric pH < 4.4



Russel et al. 1993



Extrapolation from these data, pH at $T_{1/2} = 3.7$

➤ Duration – Gastric phase

Brogna et al. 1999

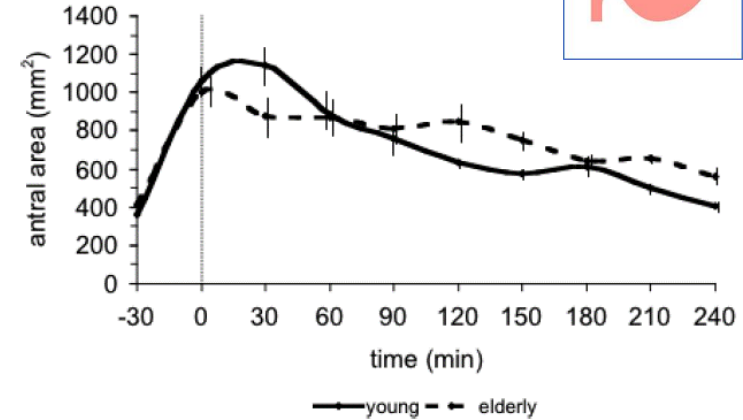
$T_{1/2}$ = 335 min **elderly**
 $T_{1/2}$ = 245 min **young**

+37%
Gastric
Emptying Time

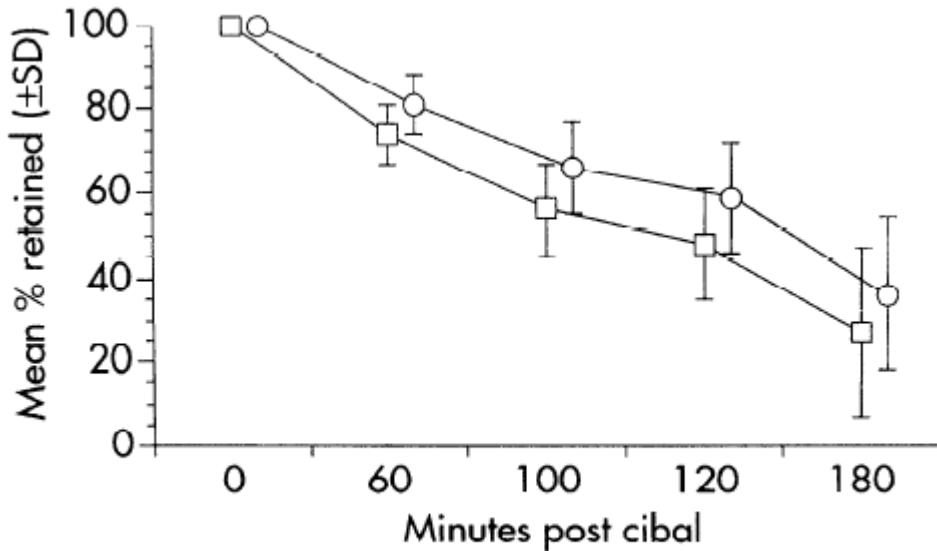
Table 1. Gastric Motility Parameters

Parameter	Elderly (N = 10)	Young (N = 9)	p
Fasting antral area, cm ²	416 ± 182	364 ± 77	.84
Maximal postprandial area, cm ²	878 ± 315	1143 ± 363	.06
Emptying time, min	448 ± 104	306 ± 57	.00

The meal consisted of 60 grams of “macaroni alla bolognese” with 70 grams of meat sauce, 50 grams of ham, 50 grams of soft fatty cheese, one roll, and 250 ml of water. Total energy was 800 kcal (15% proteins, 45% fat, 40% carbohydrates).



Antral area assessed by ultrasonography



448 min in **elderly** vs 306 min in **adult**: **+46%**

Di Francesco et al. 2005

Table 2. *Gastrointestinal transit in young and healthy elderly subjects*

	Young	Elderly	P
Gastric emptying			
Solid $T_{1/2}$, min	127 ± 13	182 ± 26	<0.05
Liquid $T_{1/2}$, min	35 ± 3	47 ± 4	<0.05

Elderly/young
+43% solid

Clarkston et al. 1997

INFOGEST proposal: Gastric phase = 3h

Fig. 2. Gastric emptying of solid component of meal in young (□) and elderly (○) subjects for total stomach. Data are mean values ± SD.

➤ Pepsin



	Young (18–34 years old) (n = 85)	Middle-aged (35–64 years old) (n = 99)	Elderly (65 years or older) (n = 22)
Men (%)	51 (60.0)	56 (56.6)	11 (50.0)
Black/white/other	57/23/5	62/35/2	2/20/0 ^{a,b}
Weight (lb)	180 ± 46 (170)	177 ± 35 (170)	161 ± 31 (160)
Height (in)	68 ± 4 (68)	67 ± 4 (68)	66 ± 4 (66) ^a
Smoking now (%)	42 (49.4)	56 (56.6)	1 (4.5) ^{a,b}
Smoking now or in the past (%)	52 (61.2)	68 (68.7)	11 (50.0)
<i>H. pylori</i> seropositive (%)	38/84 (45.2)	57/98 (58.2)	18/22 (81.8) ^{a,b}
<i>H. pylori</i> titer	49 ± 100 (0)	52 ± 80 (29)	125 ± 131 (76) ^{a,b}
Inflammation in biopsy sample (%)	32 (37.7)	44 (44.4)	14/20 (70) ^{a,b}
CASG (%)	29 (34.1)	40 (40.4)	9 (45)
CSG (%)	3 (3.5)	2 (2)	0 (0)
CAG (%) ^c	0 (0)	2 (2)	5 (25) ^{a,b}
<i>H. pylori</i> in biopsy sample (%)	32 (37.7)	49 (49.5)	10/20 (50.0)
BAO (mmol/h)	3.5 ± 3.8 (2.0)	3.7 ± 4.1 (2.8)	3.1 ± 5.1 (1.8)
PAO (mmol/h)	29.3 ± 12.7 (29.0)	29.9 ± 14.1 (29.6)	19.0 ± 13.2 (21.2) ^{a,b}
BPO (IU × 10 ³ /15 min)	2.0 ± 1.4 (1.7)	1.9 ± 1.4 (1.5)	1.3 ± 1.3 (1.0) ^{a,b}
PPO (IU × 10 ³ /15 min)	4.6 ± 2.1 (4.5)	4.6 ± 2.7 (4.2)	2.4 ± 1.9 (2.4) ^{a,b}
Gastrin level (pg/mL)	59 ± 38 (49)	60 ± 35 (46)	69 ± 62 (48)

Feldman, et al. 1996

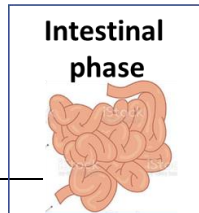
Basal Pepsin Output:
1.9 vs 1.3 📉 31.%

Pentagastrin Pepsin Output:
4.6 vs 2.4 📉 47%

Considering 1) a decrease of **40%** (average) in pepsin output
2) adult pepsin level 2000 U/ml (Brodkorb et al. 2019)

EAT4AGE proposal: 1200 U of pepsin/ml of gastric content

➤ Summary of the data for pancreatic enzyme activities



Reference	Population	Control group?	Lipase	Trypsin	Chymotrypsin	Amylase
Fikry, 1968	60-72 y. (n = 23)	No, compared with data for healthy adults from previous studies	= (activity)	↘ 30 % (activity)	/	↘ 30 % (activity)
Bartos & Groh, 1969	61 – 76 y. (n = 10)	Yes, adults 17 – 33 y. (n = 10)	/	/	/	= (output)
Gullo et al., 1983	2 groups: 61-68 y. (n = 15) and 71-78 y. (n = 10)	Yes, adults 18-54 y. (n = 30)	= (c			
Dreiling et al., 1985	4 groups: 50 - 59 y., 54 ± 3 (n = 769) 59 - 69 y., 64 ± 3 (n = 643) 69 - 79 y., 73 ± 3 (n = 188) > 80 y., 83 ± 3 (n = 15)	Yes, Adults 20 – 40 y. (n = 300)				
Vellas et al., 1988	72 ± 3.2 y. (n = 28)	Yes, adults 36 ± 7.8 y. (n = 27)		↘ (conc ↘ 43.6		
Ishibashi et al., 1991	65 – 78 y. (n = 18)	Yes, 2 groups: adults < 40 y. and 40 – 65 y.				
Laugier et al., 1991	16 – 83 y. (n = 180) >65 y. n = 20	/		↘ (conc U		



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Static *in vitro* digestion model adapted to the general older adult population: an INFOGEST international consensus

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*^c and [D. Dupont](#) [ID](#) *^a

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INFOGEST: decrease of

Application of the older adult model to dairy products

- **Whey-based dessert (WBD)**
- Ratio whey proteins/caseins = 80/20
- 10 % proteins, 2 % lipids, lactic ferments
- Heat treatment at 72°C for 2 min, acidified to pH 4.5 and stirred

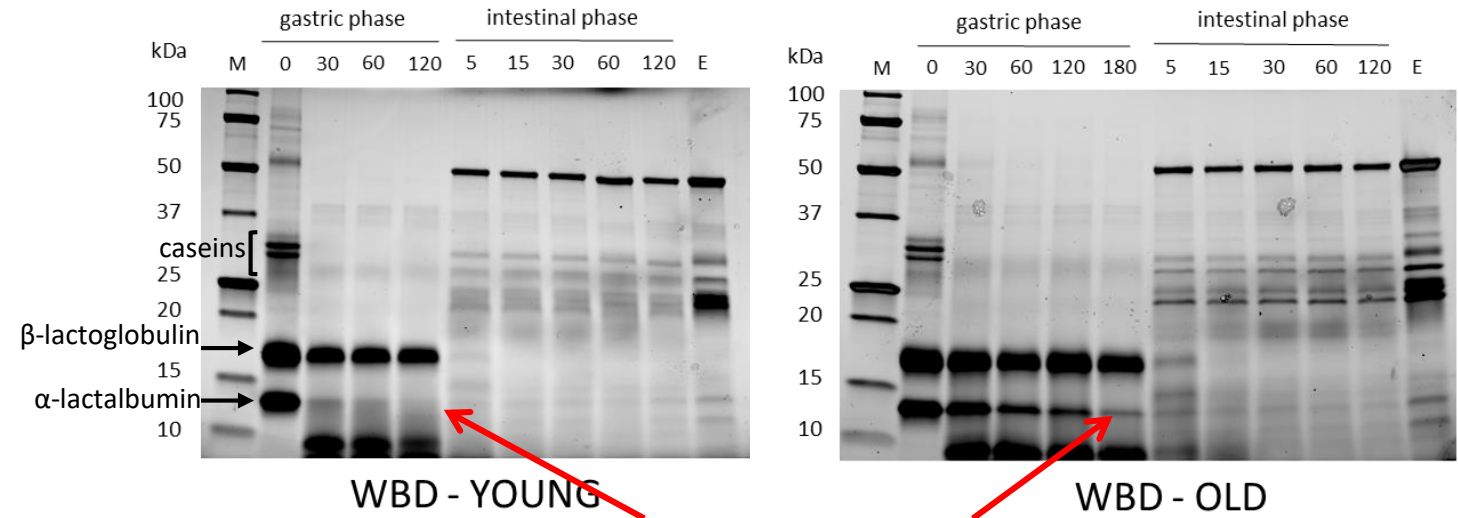
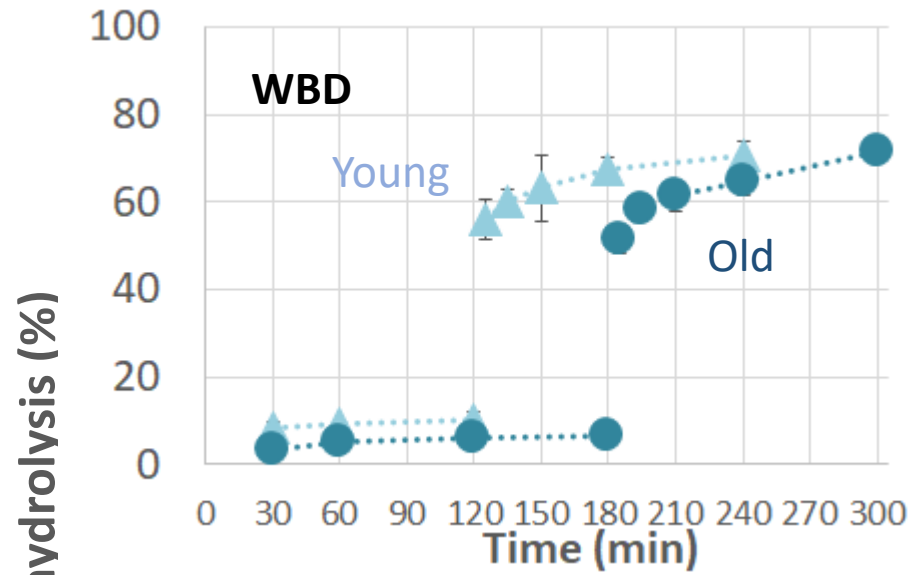


VS

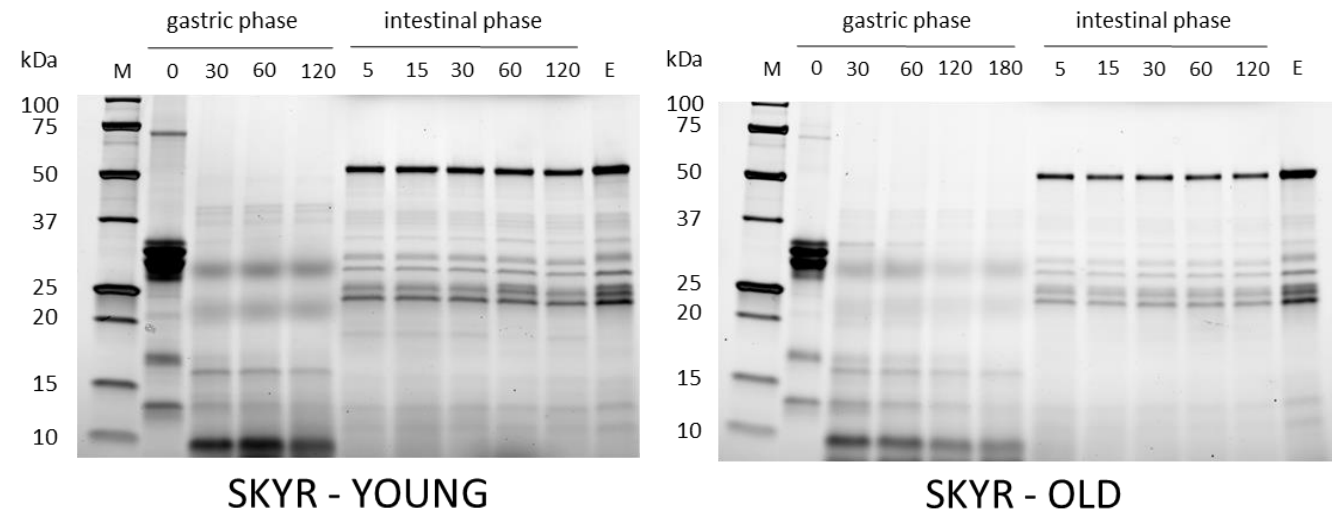
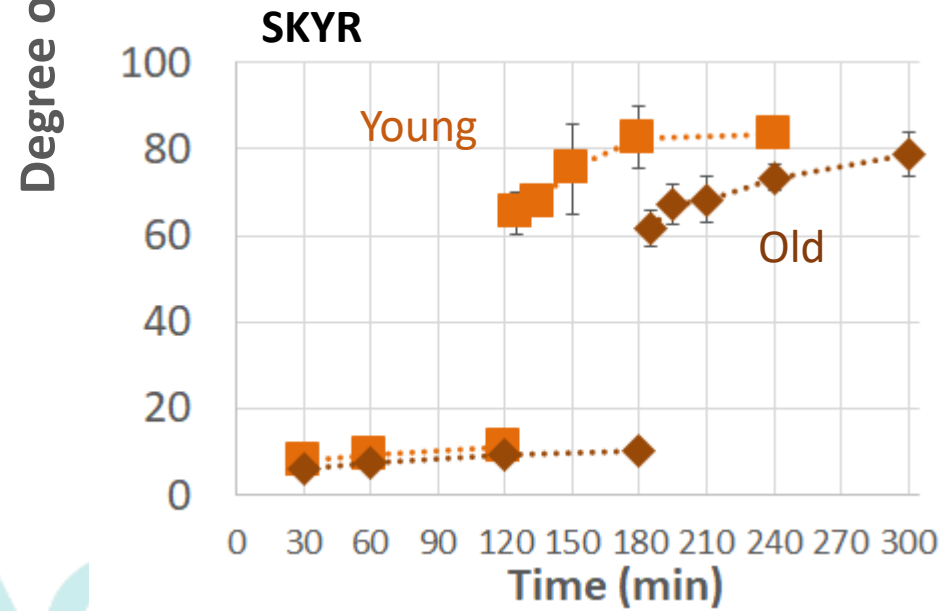
- **Control = commercial Skyr**
- Ratio whey proteins/caseins = 20/80
- 10 % proteins, 2 % lipids, lactic ferments



Protein hydrolysis

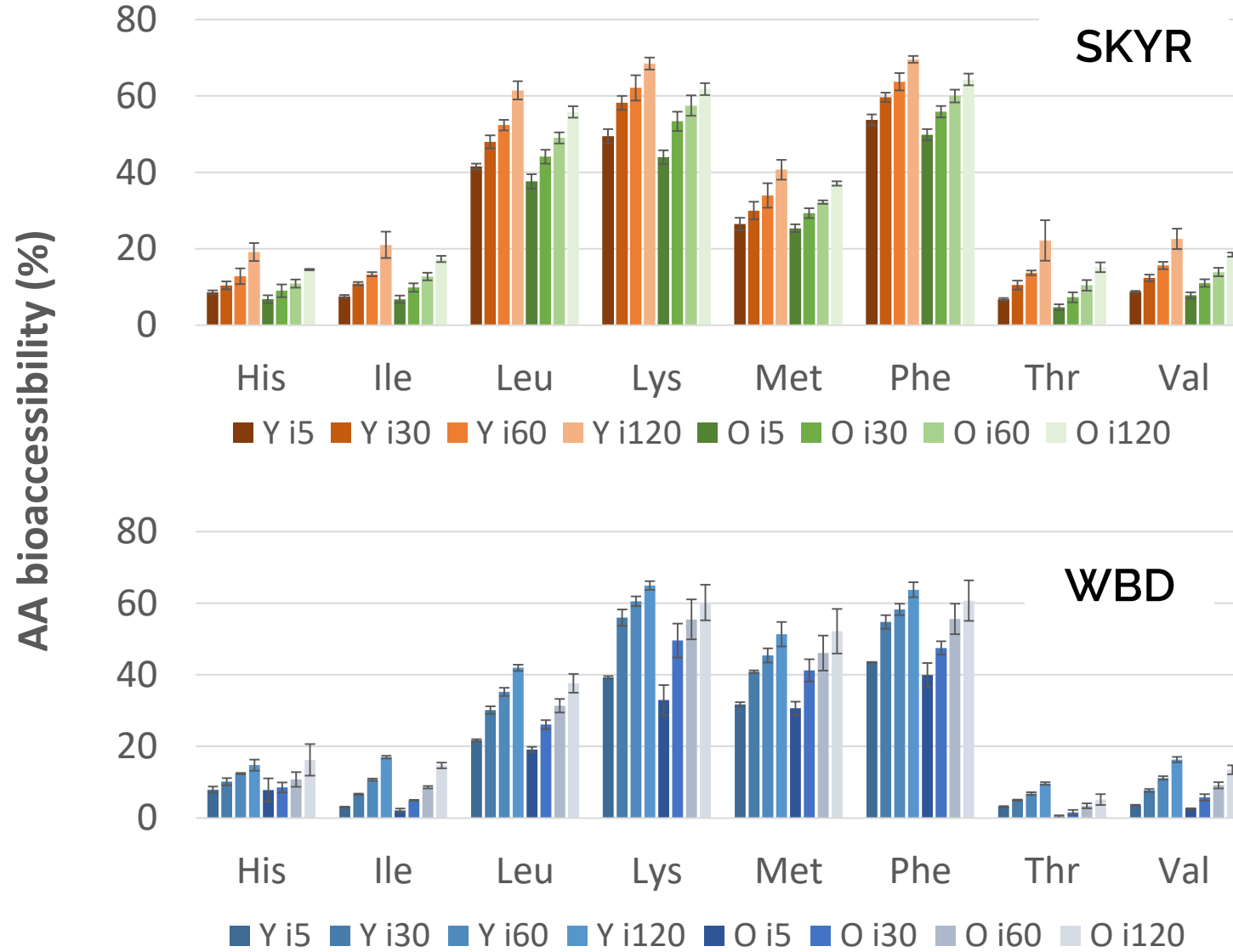


α -la more resistant
to pepsin in
elderly



Lower values for elderly in the gastric phase – Digestion of milk protein will be completed but after a longer time

Amino acid bioaccessibility



A 10% decrease in leucine bioaccessibility is observed for older adults but overall the designed dairy products exhibit a high digestibility

Conclusion

- A consensus static *in vitro* digestion model has been proposed by the INFOGEST network to simulate the gastrointestinal conditions of adults over 65
- Compares to the adult model, it exhibits :
 - An increase in the duration of the gastric phase (from 2h to 3h)
 - An increase in gastric pH (from 3.0 to 3.7)
 - A decrease in pepsin activity (from 2000 UI/mL to 1200 UI/mL)
 - A 20% decrease in pancreatic enzymes
 - A 40% decrease in bile salts concentration
- The model was applied to dairy products specifically designed for elderly people and showed a good protein digestibility and amino acid bioaccessibility
- It is currently being applied to the digestion of cereal-based and meat-based products within the EAT4AGE European project
- Parameters obtained from the literature are currently being used for building a semi-dynamic and a dynamic *in vitro* digestion model



We are pleased to announce the next
8th International Conference on Food Digestion

