



L'origine des MICI se trouve t'elle dans l'alimentation?

Franck Carbonnel

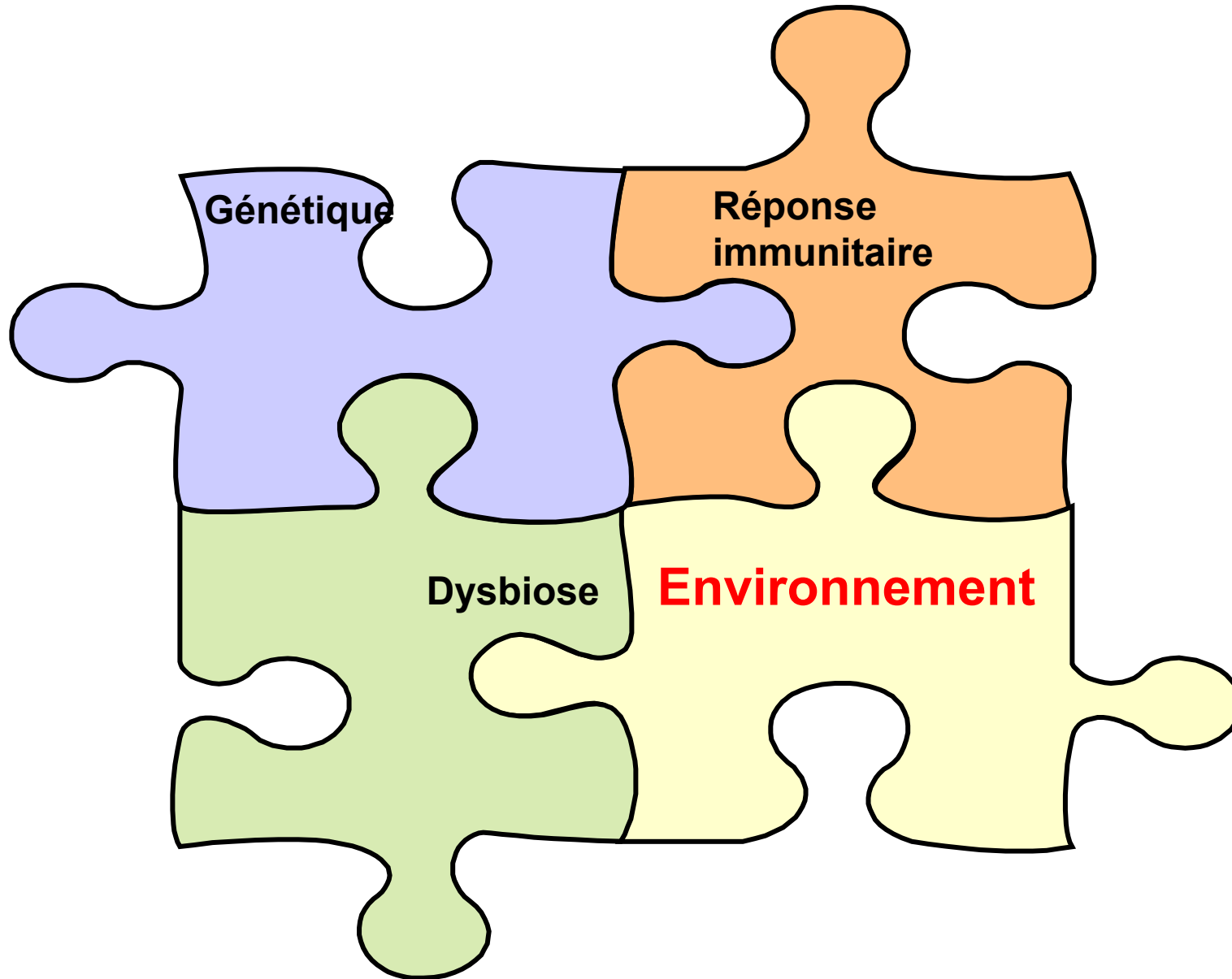
Service de Gastroentérologie
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Unité INSERM U1018 E3N-EPIC

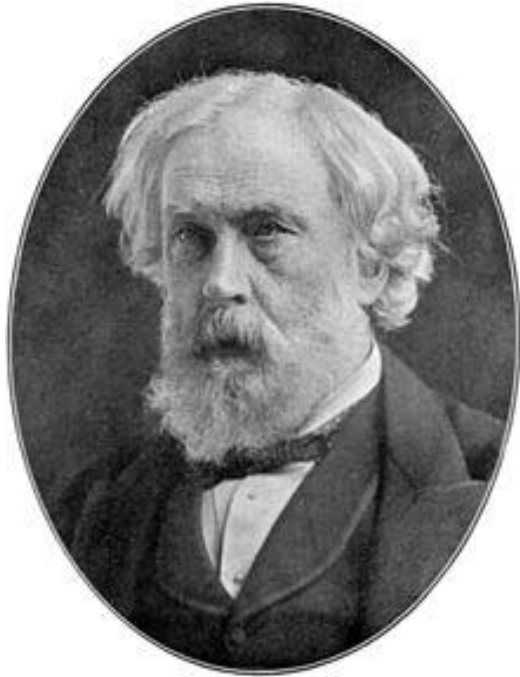


Liens d'intérêts

Abbvie, Alpha Wassermann , Arena, Biogen, Celltrion, Enterome, Ferring , Janssen, Nestlé, Nordic pharma, Pharmacosmos, Roche, Takeda, Tillotts

Le puzzle étiologique de la maladie de Crohn

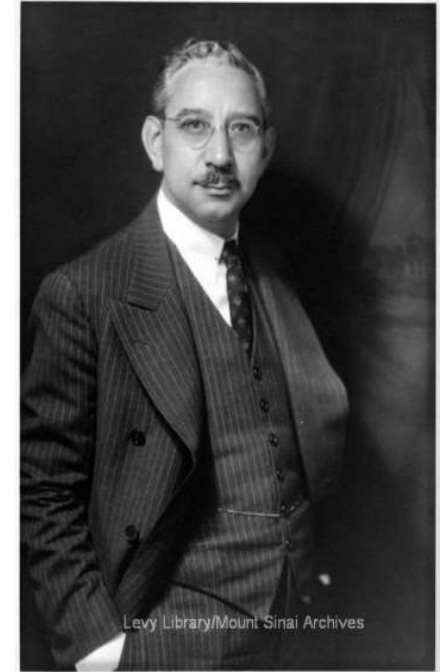




Samuel Wilks (1824-1911)
décrit la RCH en 1859

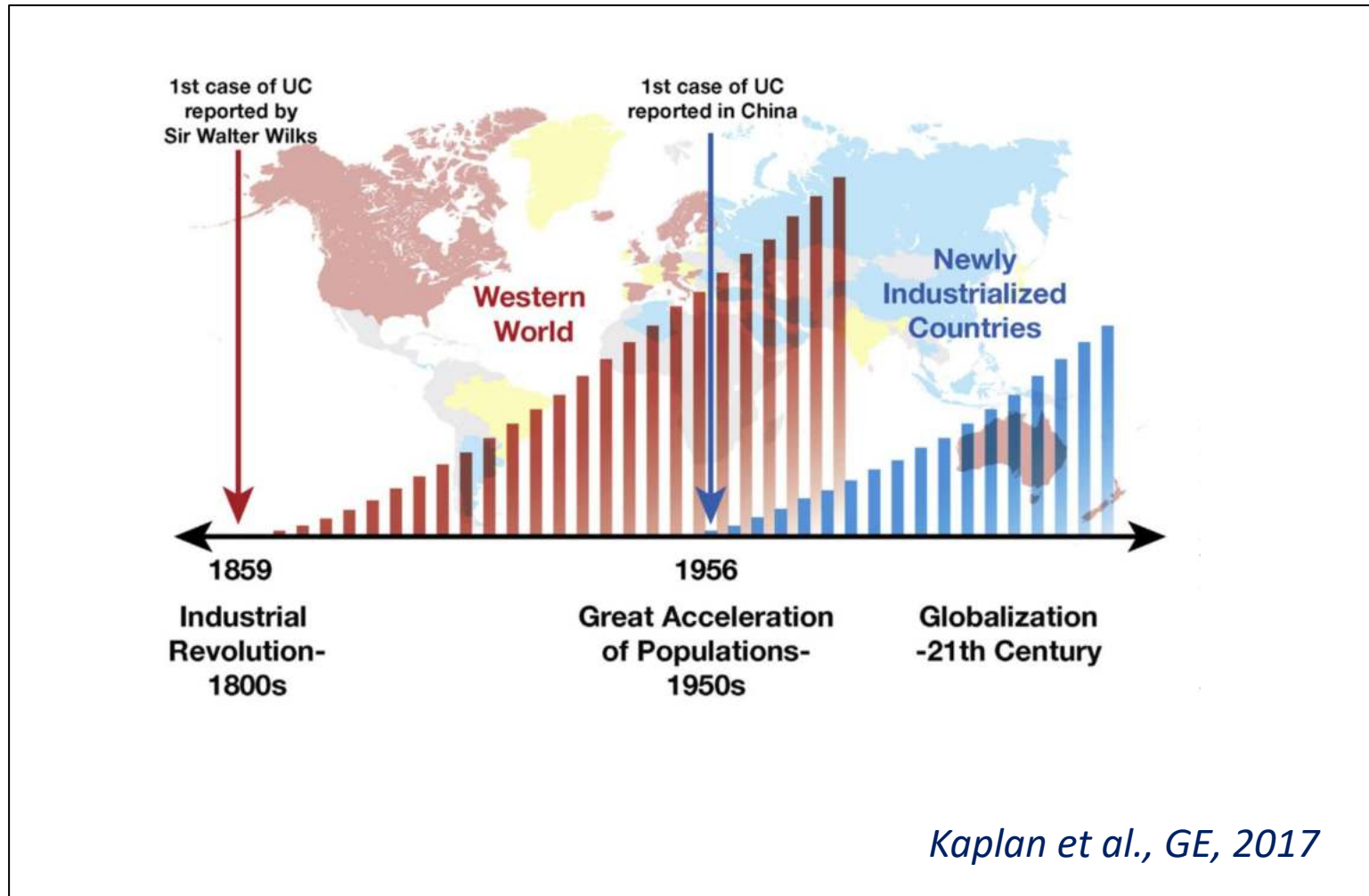


Thomas Dalziel (1861-1924) et
Burrill Crohn (1884-1983)
décrivent la maladie de Crohn
respectivement en 1913 et 1932



Introduction

Increasing trend of IBD in industrialized countries since the 19th century and in industrializing countries since the 20th century.



Evolution de l'incidence des MICI chez les Londoniens originaires du Bangladesh



	1981-1989	1997-2001	SIR
RCH	2.4	8.2	2.1 (0.9-3.9)
MC	2.3	7.3	2.5 (1.2-4.6)

Inflammatory Bowel Disease in Immigrants to Canada And Their Children: A Population-Based Cohort Study

Eric I. Benchimol, MD, PhD, FRCPC^{1,2,3,4}, David R. Mack, MD, FRCPC^{1,2}, Astrid Guttmann, MDCM, MSc, FRCPC^{4,5}, Geoffrey C. Nguyen, MD, PhD, FRCPC^{4,6}, Teresa To, PhD^{4,7}, Nassim Mojaverian, MSc⁴, Pauline Quach, MSc^{1,4} and Douglas G. Manuel, MD, MSc, FRCPC^{4,8,9}

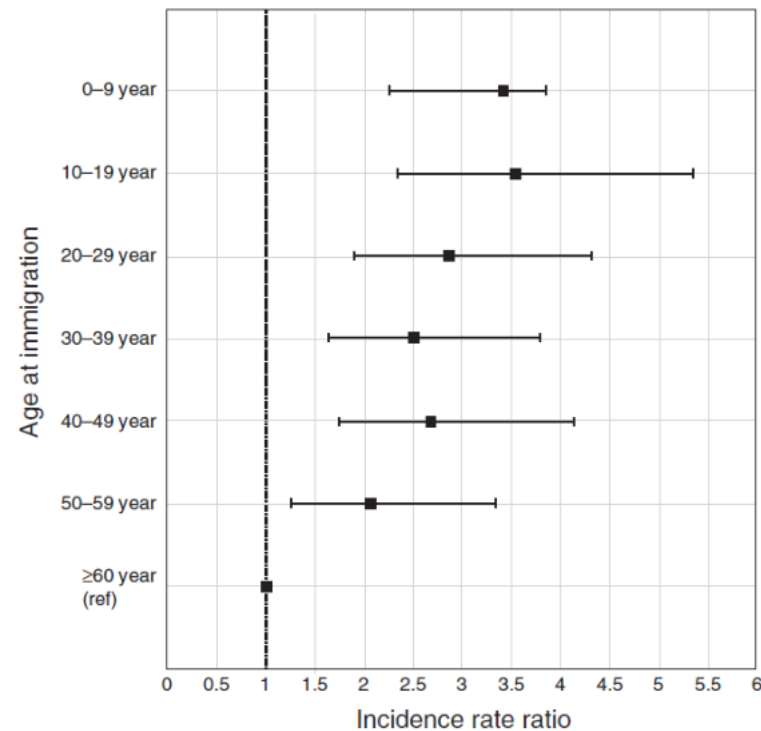


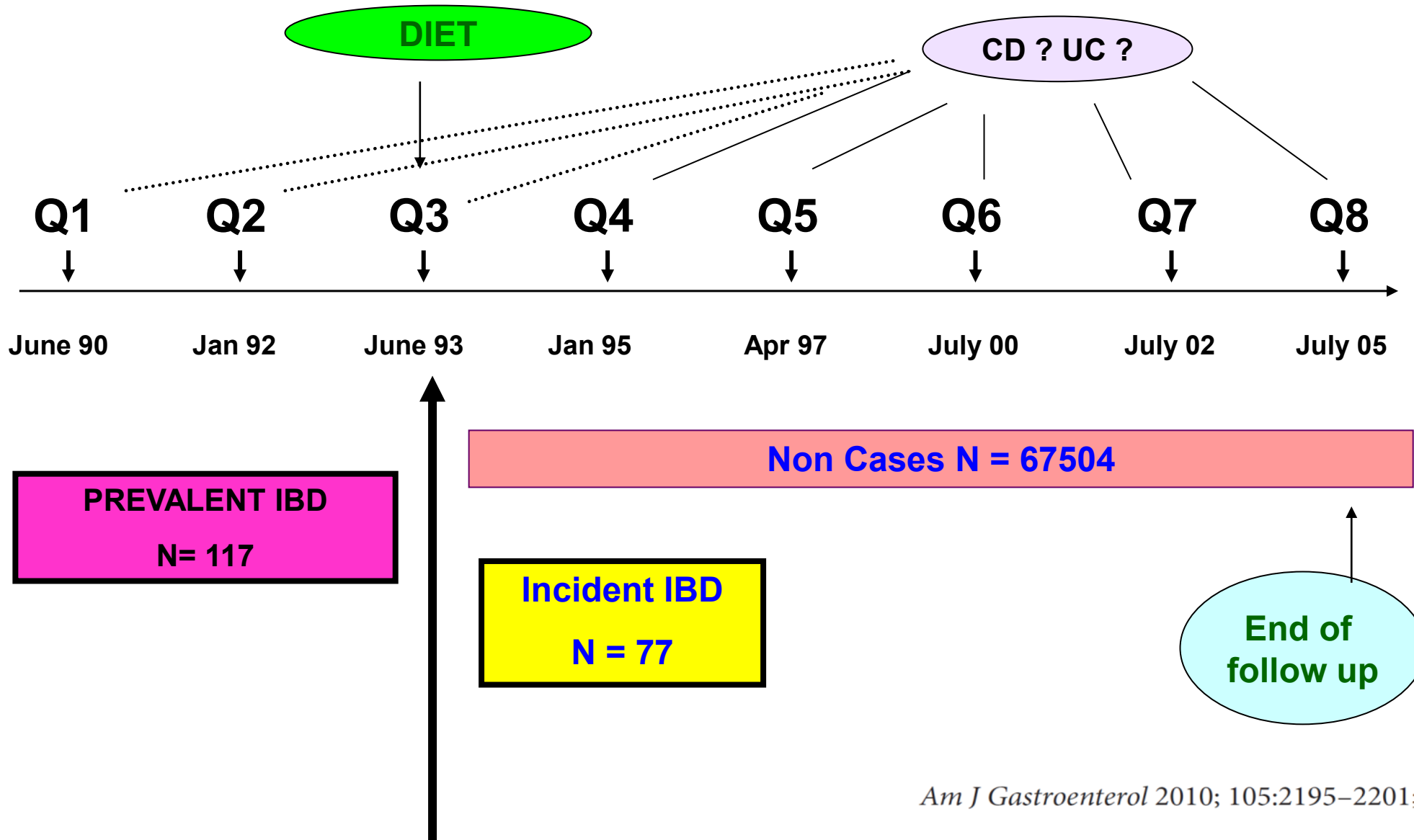
Figure 3. Adjusted incidence rate ratio for inflammatory bowel disease (IBD) by decade of age at arrival to Canada. Immigrants who arrived ≥ 60 years of age acted as the reference group (incidence rate ratio=1.0). Descriptive characteristics of the included populations. Ref, reference.

Facteurs d'environnement ayant un rôle suspecté ou avéré dans les MICI

- Perinatal infections
- Intestinal infections
- Listeria
- Helicobacter
- *Mycobacterium avium paratuberculosis*
- *Pseudomonas fluorescens*
- Adherent-invasive *E coli*
- Yersinia
- Norovirus
- Tabac
- Activité physique
- Appendicectomie
- Pollution de l'air
- Exposition solaire/vitamine D
- Antibiotiques, contraception orale, AINS, anti CTLA-4/anti PD-1, anti PI3K, IL17
- Allaitement maternel
- Alimentation

ASSOCIATIONS

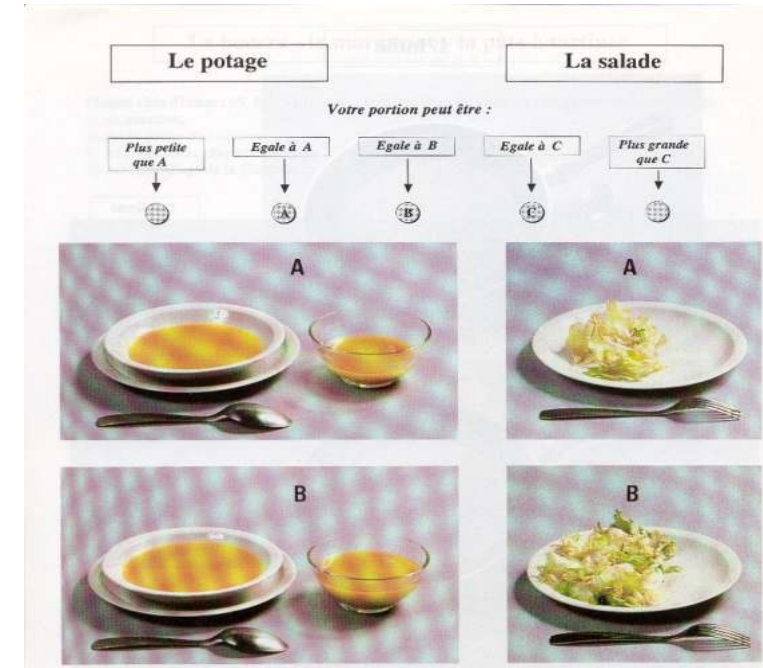
E3N : A cohort study



Data on diet in E3N cohort

- Semi quantitative food frequency questionnaire (1993)

Repas du soir	combien de fois ?			en quelle quantité ?
	jamais ou moins d'1 fois par mois	ou nombre de fois par mois	ou nombre de fois par semaine	Choisissez la taille de votre portion habituelle à l'aide du recueil de photos ou indiquez le nombre d'unités consommées
	Cochez	1 à 3 fois / mois	1 à 7 fois / sem.	Cochez ou inscrivez un chiffre ou une lettre
Plat d'accompagnement				
Pâtes, semoule de blé (y compris couscous)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 22 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>
Riz (y compris paëlla) ordinaire <input type="checkbox"/> complet <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 23 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>
Frites	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 23 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>
Pommes de terre, purée (frites exclues)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 24 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>
Légumes secs (haricots secs, lentilles, ...)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 25 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>
Légumes (à l'exclusion des légumes secs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Photo page 26 <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/>

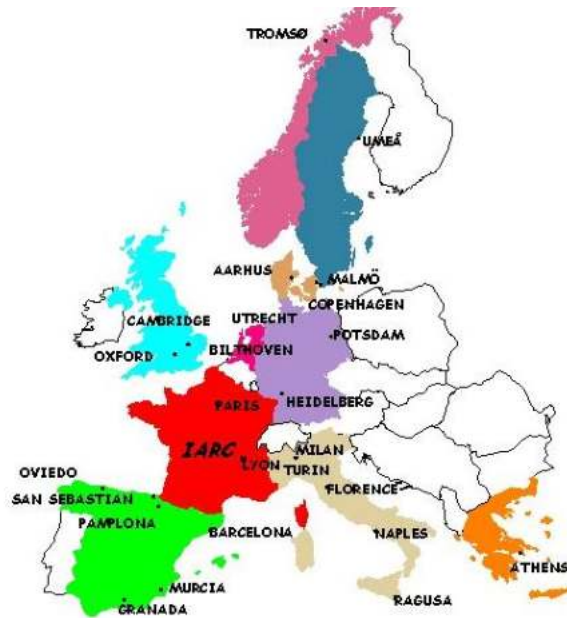


- Estimated consumption in 208 food items/beverages (g/j)
- + Calculation of the corresponding energy and nutrient intakes

Validation : Lucas et al. 1995 (Livret) ; Van Liere et al. 1997 (Questionnaire)

L'étude EPIC sur l'alimentation et la santé

	Tromsø
	Umeå Malmö
	Aarhus Copenhagen
	Oxford Cambridge
	Potsdam Heidelberg
	Utrecht Bilthoven
	Paris (nationwide)
	Turin Milan Florence Naples Ragusa
	Oviedo San Sebastian Pamplona Murcia Granada
	Athens (nationwide)



- N=500 000 volontaires sains, 23 centres dans 10 pays
- Suivis par questionnaires validés **depuis 1990**: mode de vie, régime alimentaire

- **Nested case-control studies**

Cas incidents validés de MICI appariés à 4 contrôles
n=360 000, 10 centres, 7 pays (Allemagne, Danemark, France, Italie, Pays-Bas, UK, Suède)

Association entre aliments ou nutriments et MICI



Prevo
Jantchou

	Europe	Nurses' Health Study (USA)
Apport élevé en viandes rouges	RCH (E3N, Epic)	NA
Apport élevé en acides gras polyinsaturés n-6, faible en n-3	RCH (Epic)	RCH
Apport faible en fibres (fruits, légumes)	MC (Epic)	MC
Apport faible en zinc	MC (nutrinet)	MC
Apport faible en potassium	NA NA	MC



Ashwin
Ananthakrishnan

Dong C, J Crohns Colitis 2022. Chan S, IBD 2014 ; Tjonneland A, Gut 2009 ; Andersen V, JCC 2018
Ananthakrishnan A, Gut 2014 ; Ananthakrishnan A, Gastroenterology 2013; Ananthakrishnan A, Int J Epidemiol
2015;44:1995–2005. Khalili H, Front Immunol 2016;7:554. Dugelay E, Am J Gastroenterol 2020



Meat Intake Is Associated with a Higher Risk of Ulcerative Colitis in a Large European Prospective Cohort Study

Dong C, et al J Crohns Colitis. 2022 Apr 9

Table 1. Characteristics of the cohort.

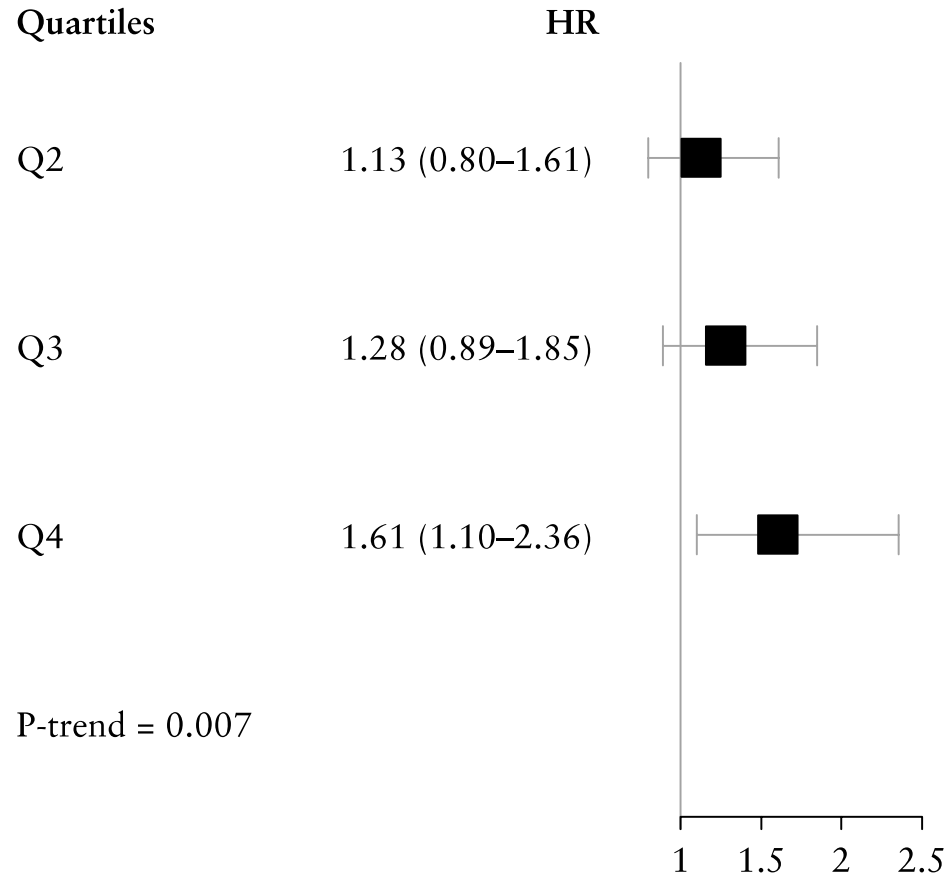
Country	Cohort size [n]	CD cases [n]	UC cases [n]	Mean age at recruitment [years]	Recruitment period range [year]	Mean follow-up [years]	Male [%]	Total energy intake [kcal/day]	Total protein intake [g/day]	Animal protein [g/day]	Vegetable protein [g/day]
All	413 593	177	418	52.5 [8.6]	1991–2001	16.8 [3.7]	31.42	2103.1 [618.8]	87.2 [27.7]	52.2 [23.0]	26.9 [10.6]
France	72 987	29	39	52.9 [6.7]	1993–1997	18.8 [2.7]	0	2151.6 [576.2]	94.1 [27.2]	59.2 [22.1]	26.6 [10.1]
Italy	29 108	7	29	50.2 [7.8]	1992–1998	15.7 [2.8]	40.84	2331.8 [688.6]	97.1 [29.2]	58.4 [21.6]	31.2 [12.3]
Spain	32 247	20	30	49.5 [8.0]	1992–1996	17.8 [2.6]	38.14	2163.8 [680.0]	102.9 [31.5]	66.4 [23.9]	30.7 [12.4]
UK	80 493	22	61	49.8 [14.4]	1993–2001	16.0 [3.4]	29.83	1985.0 [557.3]	80.5 [24.3]	40.2 [21.7]	30.7 [12.4]
The Netherlands	38 195	18	43	49.3 [11.9]	1993–1997	16.2 [2.9]	25.58	2047.9 [590.8]	86.7 [23.9]	52.8 [17.9]	26.2 [8.7]
Germany	52 011	20	42	50.4 [8.6]	1994–1998	13.6 [3.5]	43.02	2050.2 [643.8]	76.1 [24.9]	39.6 [17.0]	22.1 [7.4]
Sweden	52 736	31	63	52.4 [10.8]	1991-1996–	17.9 [4.2]	43.65	2039.4 [642.1]	76.6 [24.8]	48.3 [19.3]	21.6 [8.1]
Denmark	55 816	30	111	56.7 [4.4]	1993–1997	16.1 [3.3]	47.61	2202.4 [596.2]	94.6 [26.9]	63.9 [22.2]	27.0 [7.6]



Meat Intake Is Associated with a Higher Risk of Ulcerative Colitis in a Large European Prospective Cohort Study


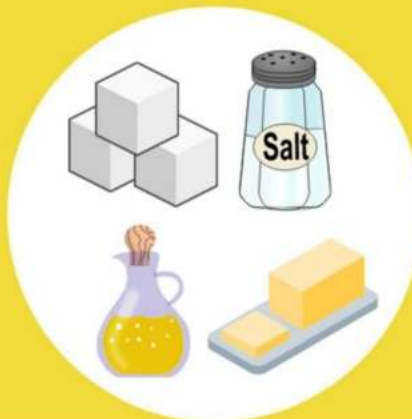


Dong C, et al
J Crohns
Colitis. 2022
Apr 9;jjac054

Association between red meat and risk of UC





NOVA Food classification

Unprocessed or minimally processed foods	Processed culinary ingredients	Processed foods	Ultra-processed foods
<p data-bbox="140 378 528 549">Foods which did not undergo processing or underwent minimal processing techniques, such as fractionating, grinding, pasteurization and others.</p> 	<p data-bbox="614 406 1024 521">These are obtained from minimally processed foods and used to season, cook and create culinary dishes.</p> 	<p data-bbox="1110 392 1519 592">These are unprocessed or minimally processed foods or culinary dishes which have been added processed culinary ingredients. They are necessarily industrialized.</p> 	<p data-bbox="1606 406 2015 549">These are food products derived from foods or parts of foods, being added cosmetic food additives not used in culinary.</p> 
<p data-bbox="97 1071 571 1163">Legumes, vegetables, fruits, starchy roots and tubers, grains, nuts, beef, eggs, chicken, milk</p>	<p data-bbox="592 1099 1067 1156">Salt, sugar, vegetable oils, butter and other fats.</p>	<p data-bbox="1088 1071 1563 1185">Bottled vegetables or meat in salt solution, fruits in syrup or candied, bread, cheeses, purees or pastes.</p>	<p data-bbox="1606 1056 2058 1185">Breast milk substitutes, infant formulas, cookies, ice cream, shakes, ready-to-eat meals, soft drinks and other sugary drinks, hamburgers, nuggets.</p>



413,590
participants
without IBD
in Europe



unprocessed/minimally
processed foods



ultra-processed
foods

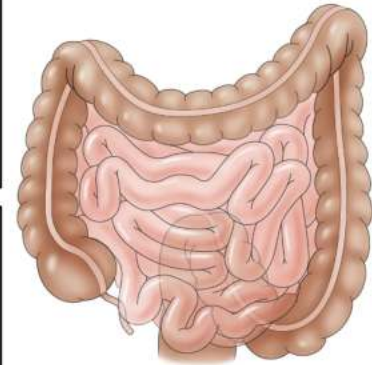
mean follow-up: 13.2 years, 179 incident cases of CD and 431 incident cases of UC

↓ risk of CD
Highest vs lowest quartile
aHR 0.57 (95%CI: 0.35-0.93)

= risk of UC
Highest vs lowest quartile
aHR 0.89 (95%CI: 0.65-1.21)

= risk of CD
Highest vs lowest quartile
aHR 1.48 (95%CI: 0.79-2.76)

= risk of UC
Highest vs lowest quartile
aHR 0.93 (95%CI: 0.61-1.43)



Clinical Gastroenterology
and Hepatology



Association entre profils alimentaires et MICI



Antoine Racine

	Europe	Nurses' Health Study (USA)
Non méditerranéen	NS (Epic) MC (cohortes suédoises)	NA
Riche en sucres/sodas et pauvres en légumes	RCH (Epic)	NA
Inflammatoire	NA	MC
Aliments ultra transformés	NS (Epic et nutrinet)	MC
Aliments non/peu transformés	MC (diminution du risque; EPIC)	MC (diminution du risque)

Lo C-H, Gastroenterology 2020;159:873-883.e1. Racine A., Inflamm Bowel Dis 2016;22(2):345–54 Vasseur P., Inflamm Bowel Dis 2021;27(1):65–73. Narula N., BMJ 2021;374:n1554. Khalili H., Gut 2020;69(9):1637–44. Ananthakrishnan A Gut 2014;63(5):776–84.

Alimentation favorable ou délétère et MICI

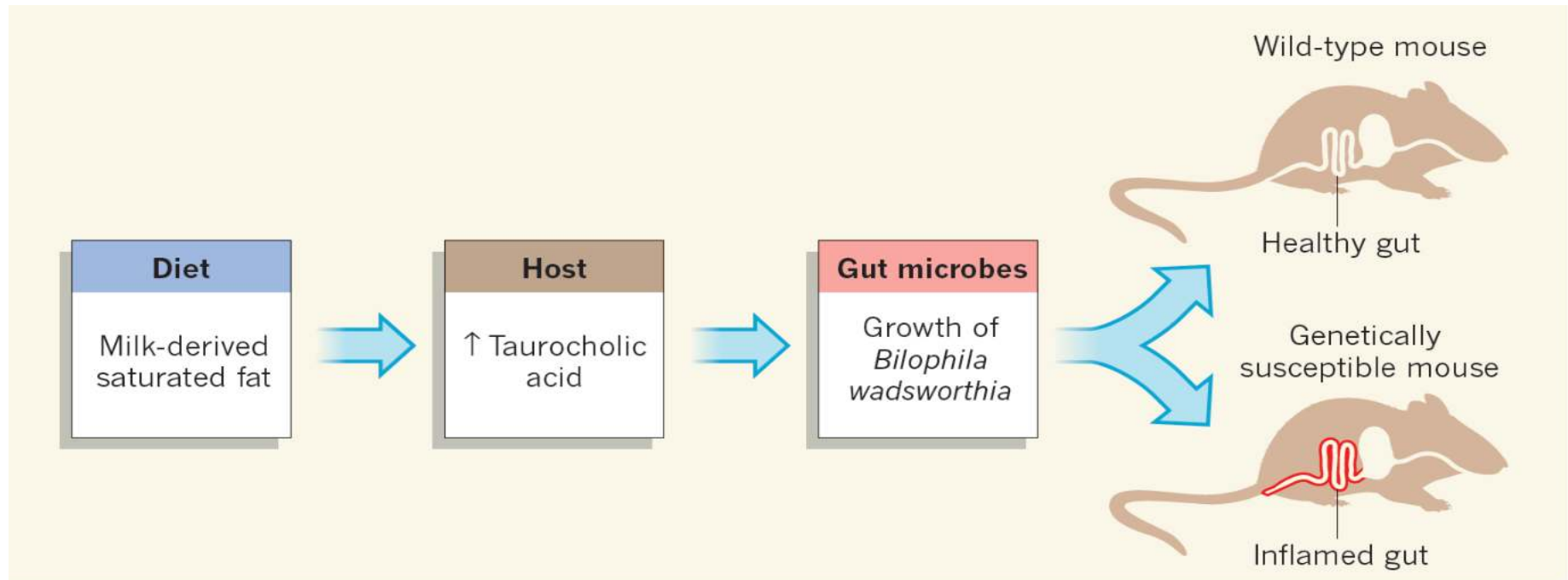
	MC	RCH
Favorable	Zinc, potassium, fibres (fruits, légumes) Aliments non/peu transformés Profil anti inflammatoire et méditerranéen	Omega 3, légumes
Délétère	Aliments ultratransformés	Viandes rouges Omega 6 Sucres/sodas

Dong C, J Crohns Colitis 2022. Chan S, IBD 2014 ; Tjonneland A, Gut 2009 ; Andersen V, JCC 2018 Ananthkrishnan A, Gut 2014 ; Ananthkrishnan A, Gastroenterology 2013; Ananthkrishnan A, Int J Epidemiol 2015;44:1995–2005. Khalili H, Front Immunol 2016;7:554. Lo C-H, Gastroenterology 2020;159:873-883.e1. Racine A., Inflamm Bowel Dis 2016;22(2):345–54 Vasseur P., Inflamm Bowel Dis 2021;27(1):65–73. Narula N., BMJ 2021;374:n1554. Khalili H., Gut 2020;69(9):1637–44. Ananthkrishnan A Gut 2014;63(5):776–84.

QUELQUES DONNEES EXPERIMENTALES

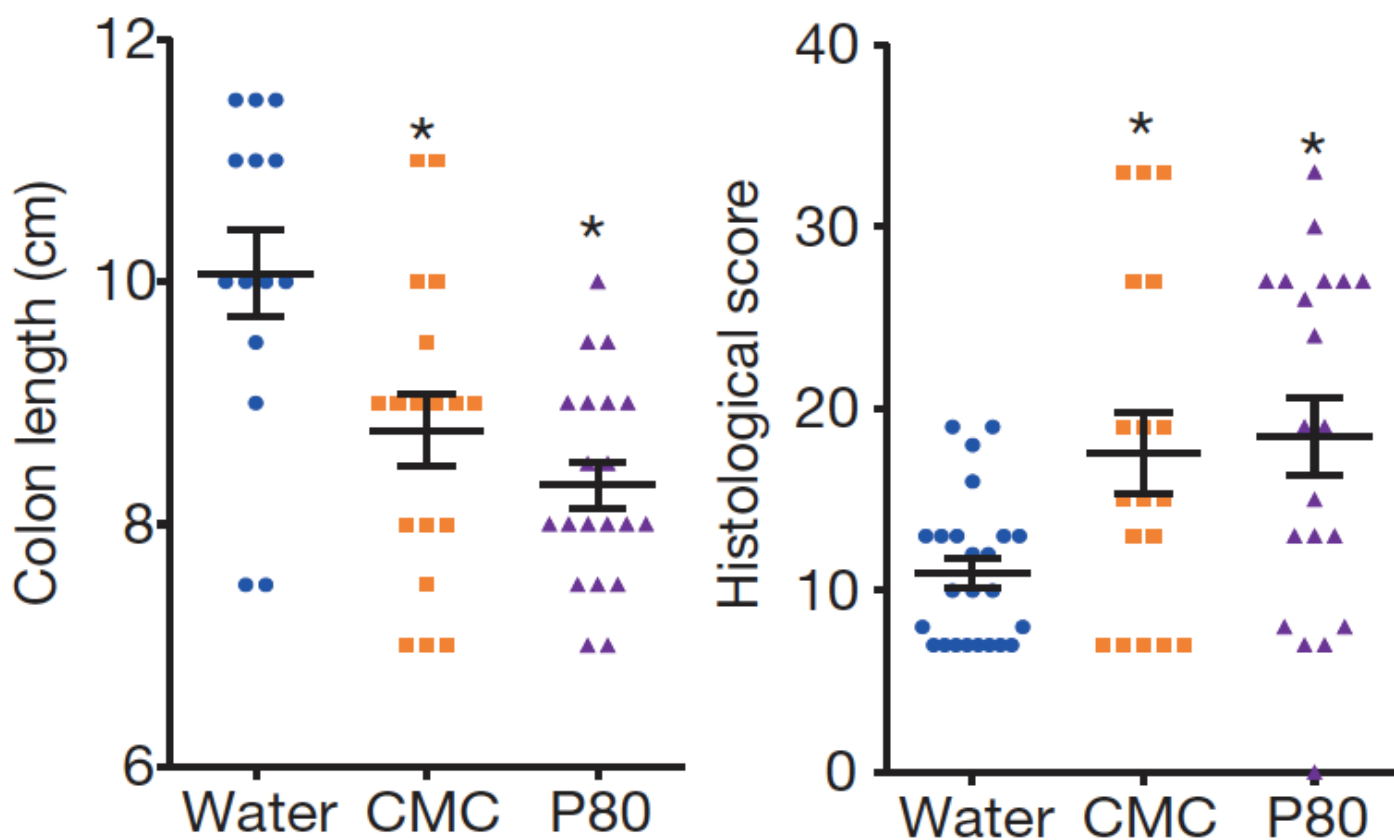
Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in $Il10^{-/-}$ mice

Suzanne Devkota¹, Yunwei Wang¹, Mark W. Musch¹, Vanessa Leone¹, Hannah Fehlner-Peach¹, Anuradha Nadimpalli¹, Dionysios A. Antonopoulos², Bana Jabri¹ & Eugene B. Chang¹

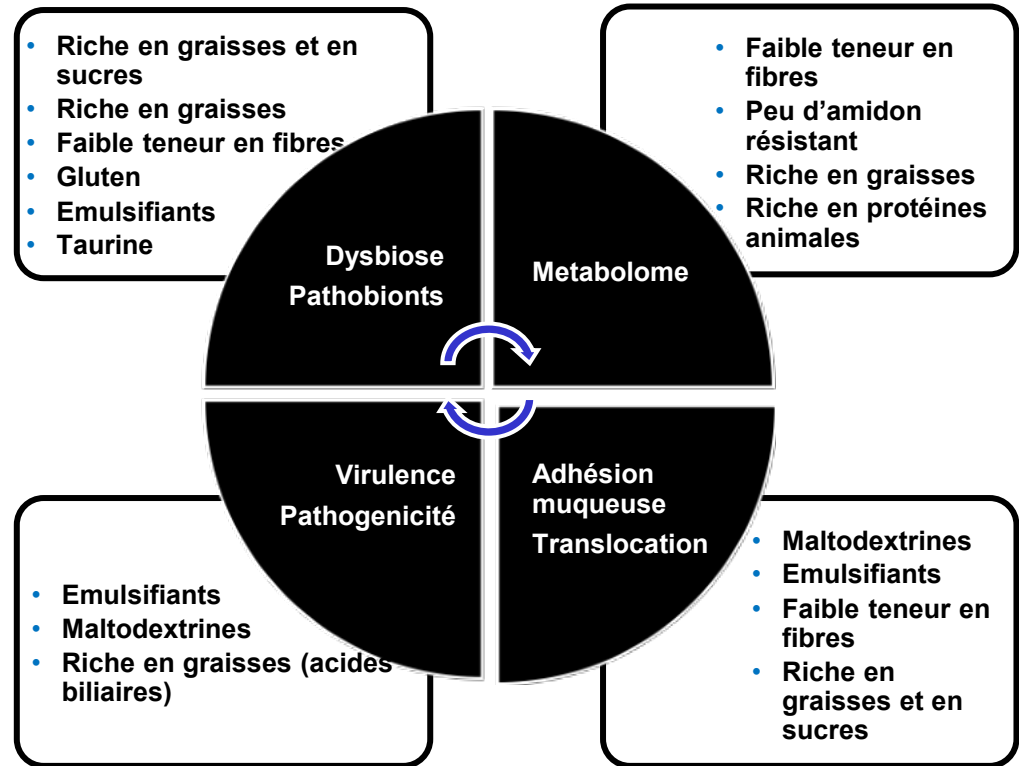
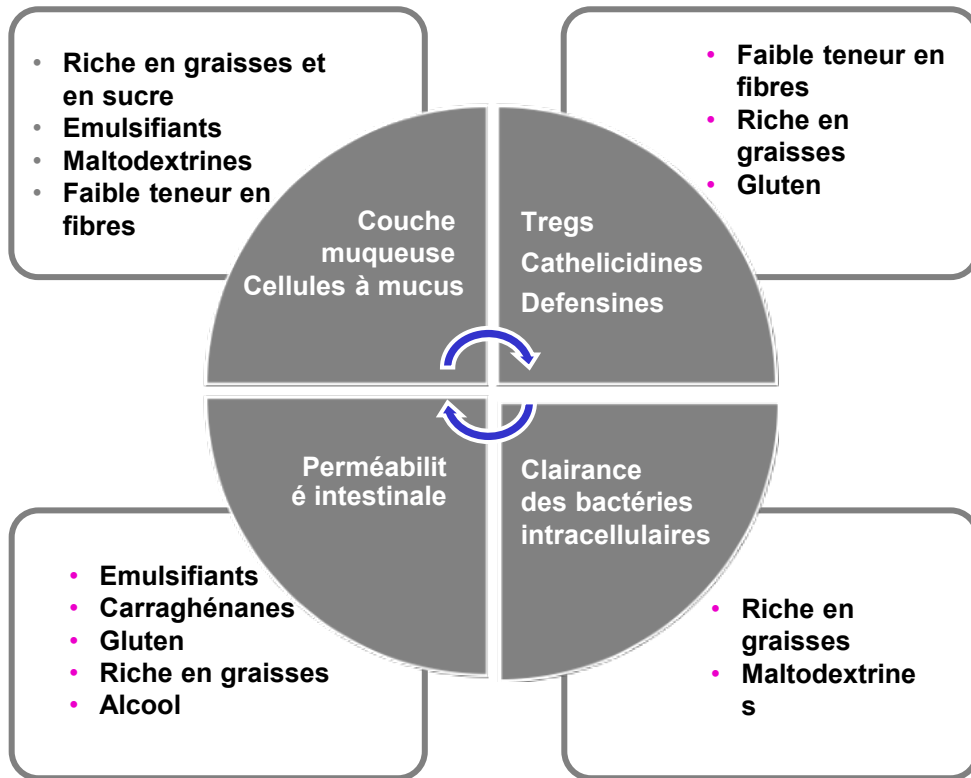


Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

Benoit Chassaing¹, Omry Koren², Julia K. Goodrich³, Angela C. Poole³, Shanthi Srinivasan⁴, Ruth E. Ley³ & Andrew T. Gewirtz¹



L'ALIMENTATION AFFECTE L'HOTE ET LE MICROBIOME



VERS LA CAUSALITÉ

Essai randomisé alimentation entérale vs corticoïdes chez des enfants atteints de maladie de Crohn

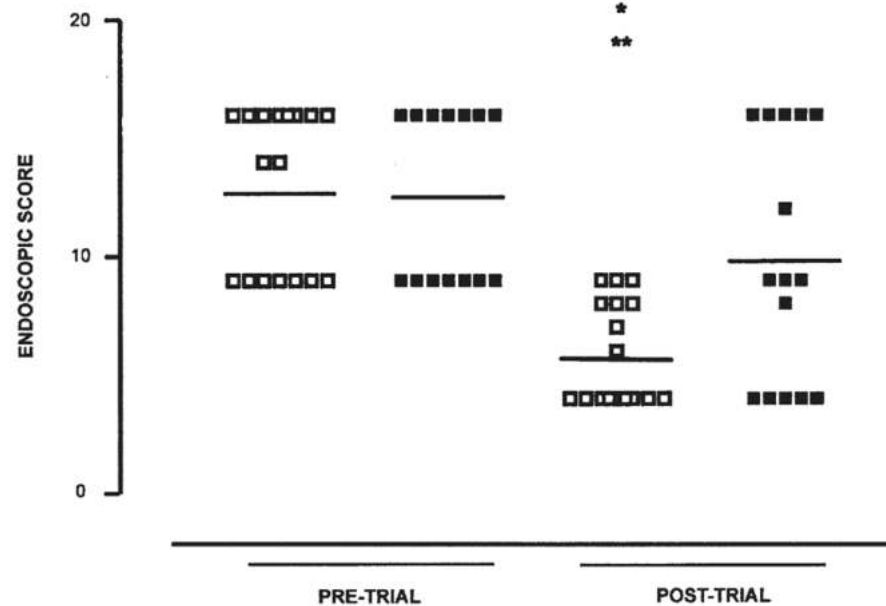


Figure 3. Crohn's Disease Endoscopic Index of Severity scores in the 2 groups of patients at baseline and at the follow-up evaluation (10 weeks after the beginning of therapy). * $P < .001$ vs CS group. ** $P < .001$ vs baseline. Horizontal bars indicate mean value. □, Polymeric group; ■, CS group.



NestléHealthScience

Modulen

IBD



Nutritional Management of Crohn's Disease

Nutritionally complete and balanced

Adaptable caloric density up to 1.5 kcal/ml

Neutral flavour for flexible use

Net Weight 400 g

Extensive Modulation of the Fecal Metagenome in Children With Crohn's Disease During Exclusive Enteral Nutrition

Am J Gastroenterol 2015; 110:1718–1729;

Table 2. Linear regressions of genus relative abundance against days on EEN

Genus	Slope	P value	P value adjusted
<i>Decreased during EEN</i>			
Unknown <i>Bifidobacteriaceae</i> genus	-0.011	7.17E-05	5.81E-03
<i>Dialister</i>	-0.0212	2.05E-04	6.12E-03
<i>Bifidobacterium</i>	-0.015	2.86E-04	6.12E-03
<i>Ruminococcus</i>	-0.0159	3.02E-04	6.12E-03
<i>Subdoligranulum</i>	-0.0154	5.34E-04	7.54E-03
Unknown <i>Actinomycetaceae</i> (<i>Actinomycetales</i>) genus	-0.0115	5.59E-04	7.54E-03
<i>Atopobium</i>	-0.0131	6.74E-04	7.80E-03
<i>Akkermansia</i>	-0.0155	1.02E-03	1.03E-02
<i>Solobacterium</i>	-0.0107	1.21E-03	1.09E-02
Unknown <i>Coriobacteriaceae</i> genus	-0.00919	1.64E-03	1.33E-02
<i>Megasphaera</i>	-0.0144	1.90E-03	1.40E-02
<i>Veillonella</i>	-0.0199	3.03E-03	1.91E-02
<i>Mogibacterium</i>	-0.00849	3.75E-03	1.91E-02
<i>Anaerococcus</i>	-0.0157	3.77E-03	1.91E-02
<i>Pseudobutyrvibrio</i>	-0.0103	3.90E-03	1.91E-02
<i>Peptoniphilus</i>	-0.0137	4.04E-03	1.91E-02
<i>Actinomyces</i>	-0.0108	4.22E-03	1.91E-02
<i>Prevotella</i>	-0.0153	4.24E-03	1.91E-02
<i>Staphylococcus</i>	-0.00978	9.30E-03	3.82E-02
<i>Faecalibacterium</i>	-0.0144	1.09E-02	3.82E-02
<i>Gordonibacter</i>	-0.00958	1.10E-02	3.82E-02



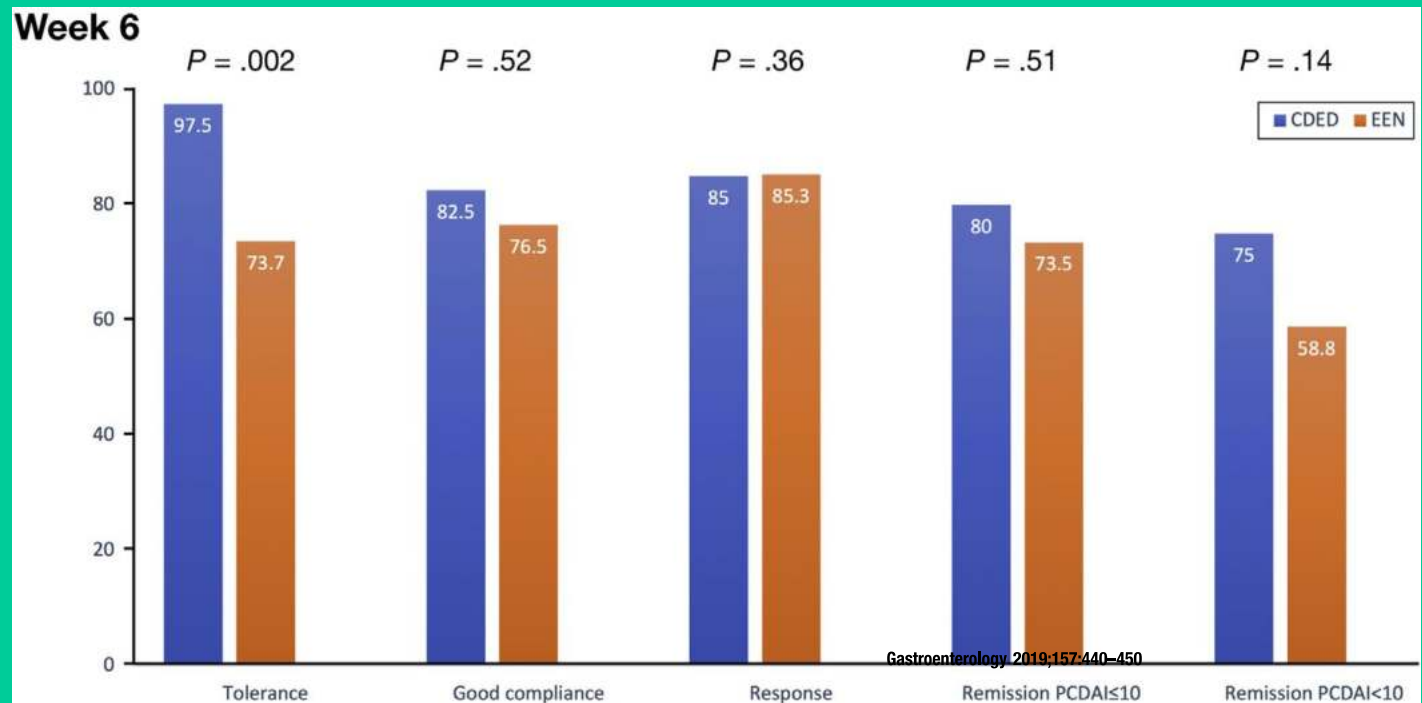
Le scepticisme est le commencement de la foi.

(Oscar Wilde)

Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial



Arie Levine,^{1,§} Eytan Wine,^{2,§} Amit Assa,^{3,4} Rotem Sigall Boneh,¹ Ron Shaoul,⁵ Michal Kori,⁶ Shlomi Cohen,⁷ Sarit Peleg,⁸ Hussein Shamaly,⁹ Avi On,¹⁰ Peri Millman,¹¹ Lee Abrams,¹ Tomer Ziv-Baran,⁴ Shannan Grant,^{12,13} Guila Abitbol,¹⁴ Katherine A. Dunn,¹⁵ Joseph P. Bielawski,¹⁵ and Johan Van Limbergen^{13,16,17,§}



Gastroenterology 2019;157:440-450

Figure 1. Primary and secondary endpoints CDED vs EEN-tolerance, compliance and ITT-response and ITT-remission.

Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial



Arie Levine,^{1,§} Eytan Wine,^{2,§} Amit Assa,^{3,4} Rotem Sigall Boneh,¹ Ron Shaoul,⁵ Michal Kori,⁶ Shlomi Cohen,⁷ Sarit Peleg,⁸ Hussein Shamaly,⁹ Avi On,¹⁰ Peri Millman,¹¹ Lee Abramamas,¹ Tomer Ziv-Baran,⁴ Shannan Grant,^{12,13} Guila Abitbol,¹⁴ Katherine A. Dunn,¹⁵ Joseph P. Bielawski,¹⁵ and Johan Van Limbergen^{13,16,17,§}

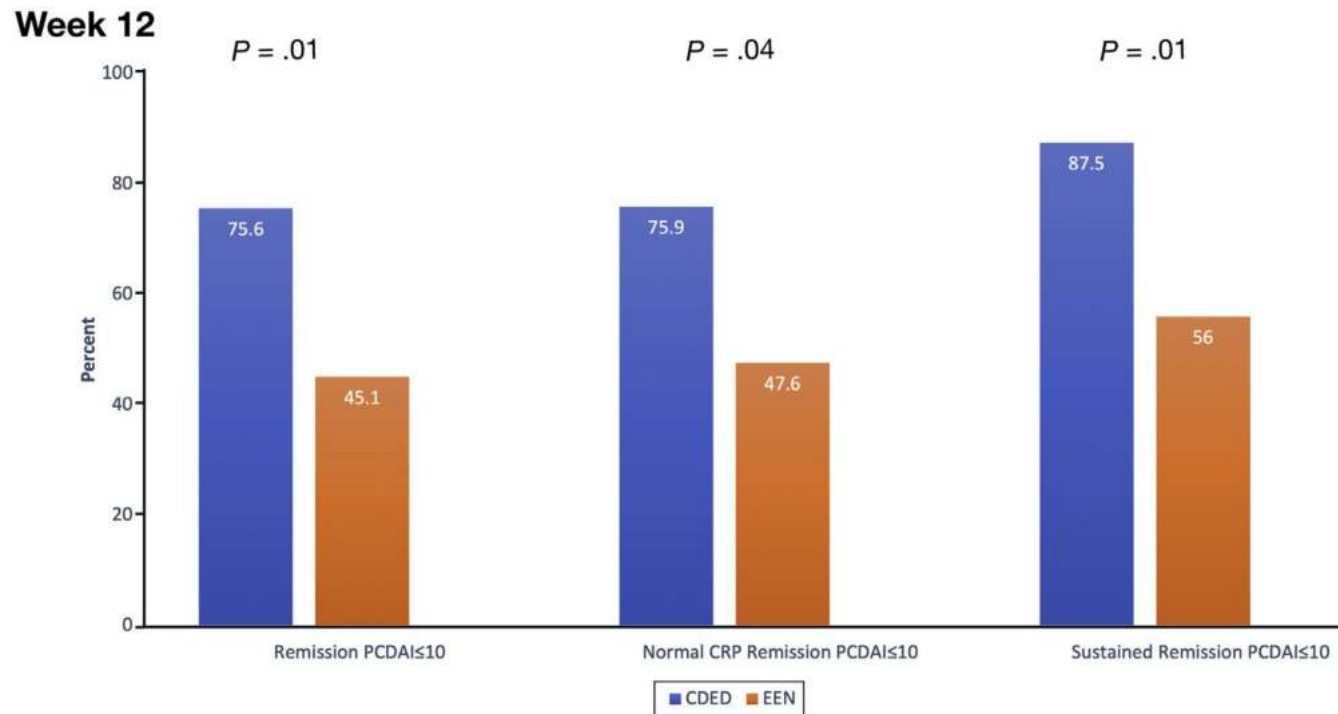


Figure 3. Week 12 remission, normal CRP remission, and sustained remission. enterology.2019;157:440-450

Principal Investigator

Prof Franck Carbonnel,
Université Paris Saclay,
APHP, France

Dutch coordinator

Prof Geert d'Haens,
University of Amsterdam,
Netherlands

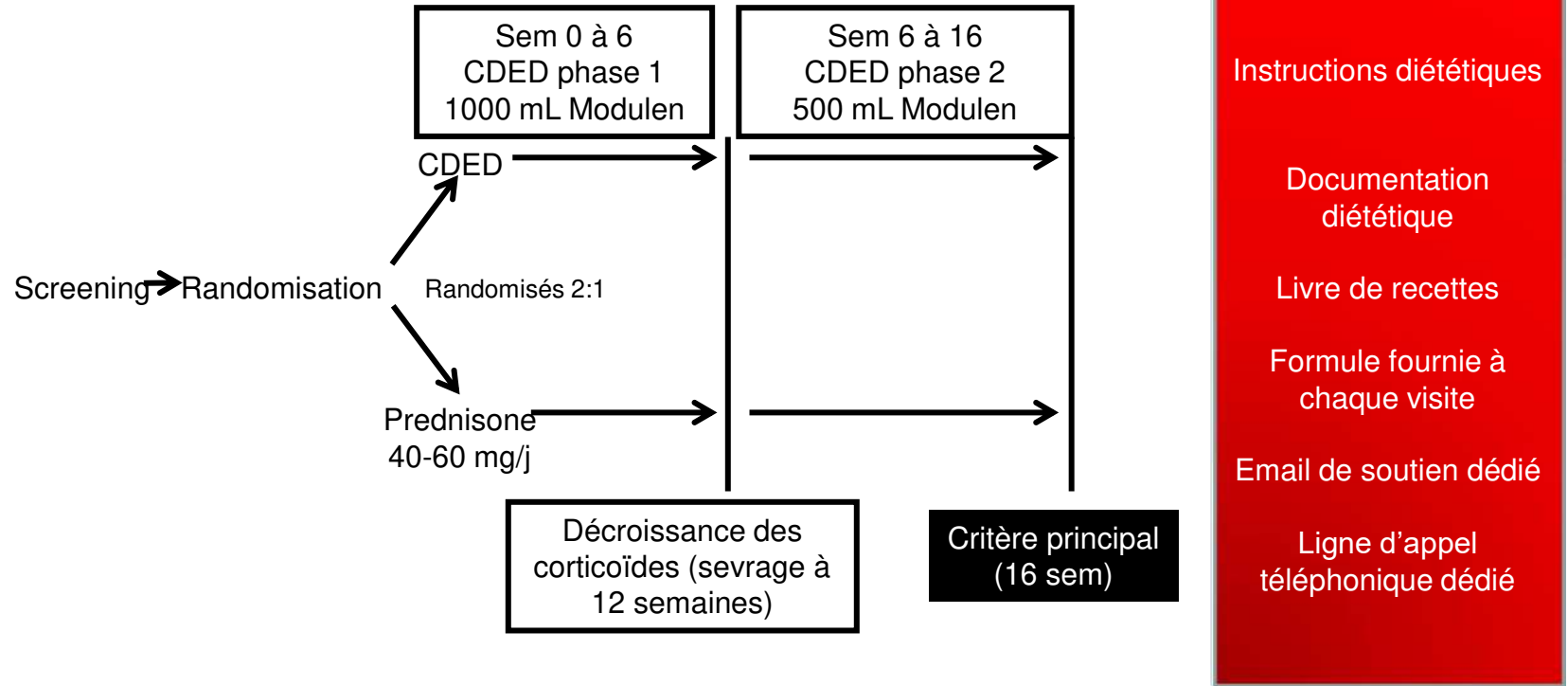
Israeli coordinator

Prof Nitsan Maharshak,
Ichilov medical center,
University of Tel Aviv,

**Prospective rAndomized controlled tRial of Crohn's
diseAse exclusion Diet vs corticosteroids in adults and
pediatric patientS with activE Crohn's disease**

**Essai thérapeutique prospectif randomisé dans la
maladie de Crohn active de l'enfant et de l'adulte:
Comparaison d'un régime alimentaire d'exclusion aux
corticoïdes**

Design de l'essai



Critère de jugement principal = Réponse endoscopique à 16 semaines sans corticoïdes ni biologiques, lecture centralisée et double des résultats de la capsule entérique PillCam

*L'origine des MICI se trouve t'elle dans
l'alimentation*



Il y a une association probablement causale entre MICI et alimentation

- Des études épidémiologiques et expérimentales montrent que l'alimentation de type occidental/moderne est associée à une augmentation du risque de MICI
- Les facteurs de risque alimentaires de MC et de RCH sont différents
- La nutrition entérale est efficace sur les symptômes et les lésions endoscopiques de MC
- Le CDED, est efficace sur les symptômes de MC chez l'enfant

L'est-il chez l'adulte? Y a-t-il un effet sur les lésions intestinales?

Merci !



Prevo Jantchou



Antoine Racine



Catherine Dong



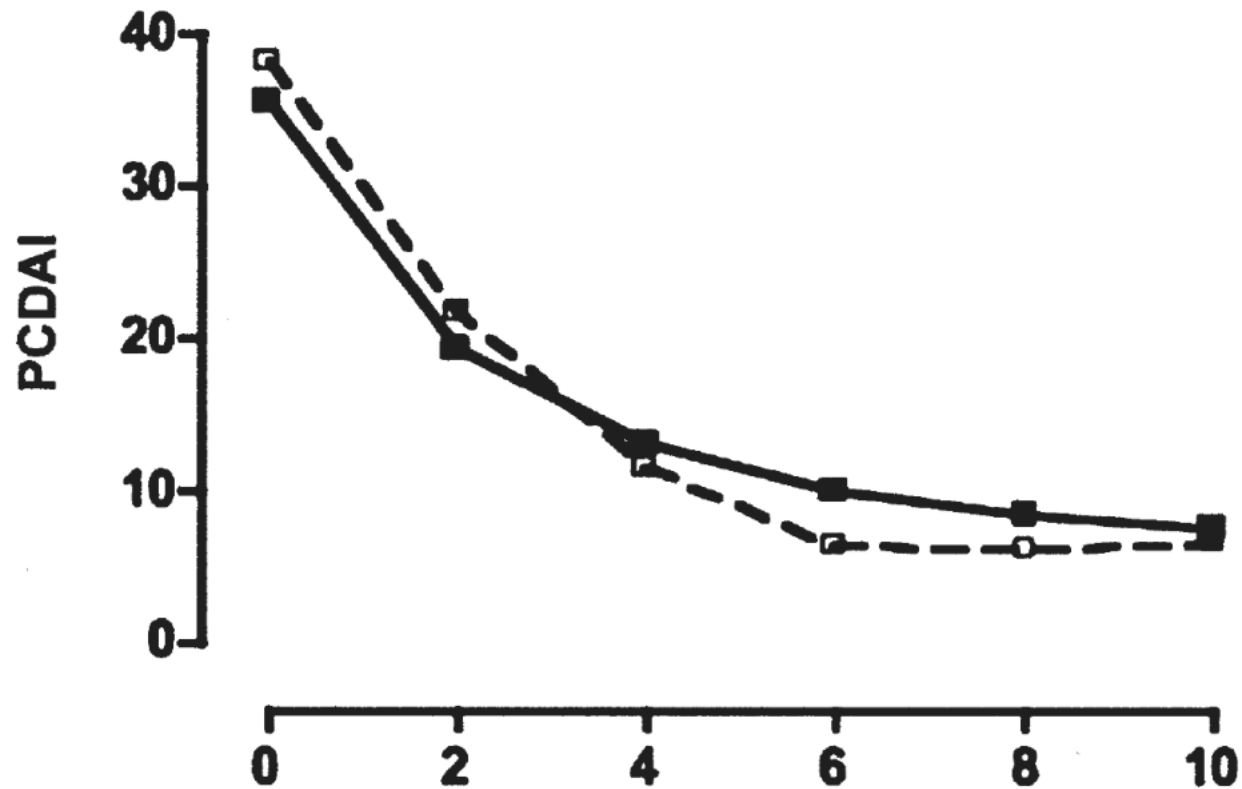
Antoine Meyer



Marie Christine Boutron



Essai randomisé alimentation entérale vs corticoïdes chez des enfants atteints de maladie de Crohn



CIBLER LES COMPOSANTS ALIMENTAIRES POUR TRAITER LES MÉCANISMES PATHOGÉNIQUES

FC

Phase 1 +2 Diet : Réduire/exclure

- **Teneur élevée en graisses animales**

- Muqueuse intestinale, dysbiose, acides biliaires

- **Teneur élevée en protéines animales, Heme**

- Dysbiose, métabolisme des sulfures, acides biliaires, biofilms

- **Blé et gluten**

- Dysbiose, perméabilité intestinale

- **Carence en fibres**

- Détérioration de la couche muqueuse, dysbiose

Additifs

- **Emulsifiants**

- Couche muqueuse, dysbiose

- **Maltodextrine sucres non absorbés**

- Couche muqueuse, biofilm, immunité innée

- **Sulphites**

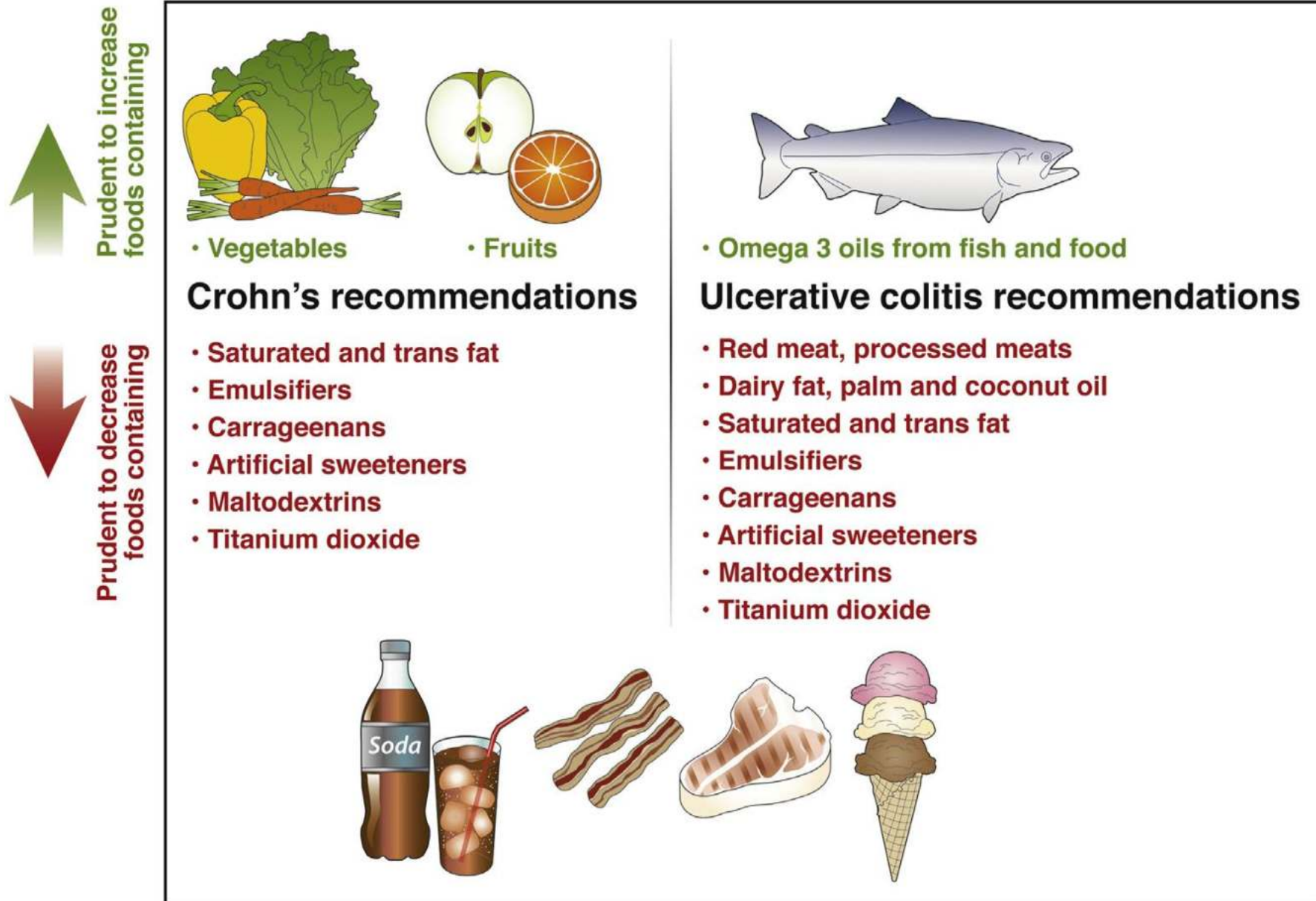
- Bactéries réductrices de sulphites

- **Carraghénanes**

- Dysbiose, lésions intestinales

Naturel

Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases (CGH 2020;18:1381–1392)



Projet MIKInautes

- L'alimentation influence t'elle le risque de **rechute** de MICI.
- 1047 malades inclus
- Investigateur principal : Pr Jean Pierre Hugot
- Promoteur : AFA