

The chicken or the egg?

Mente e IBD

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& Endoscopisti Digestivi Ospedalieri

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Dr. Francesco Ferrara

*CARO RICCARDO, AVREI
PENSATO A TE PER LA
RELAZIONE «THE
CHICKEN OR THE EGG?
MENTE E IBD»*



Dr. Riccardo Solimando

IN CHE SENSO???



World Health
Organization

SALUTE

Stato di completo benessere FISICO, *MENTALE* e SOCIALE

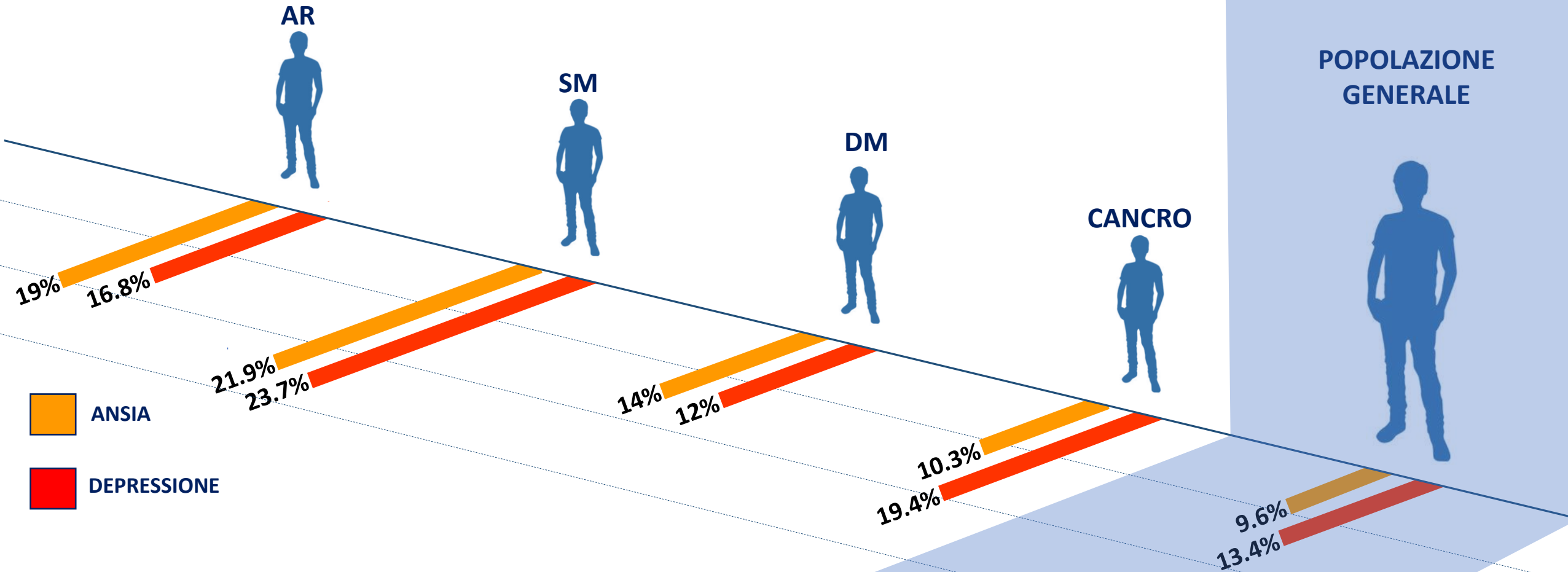
UNMEET NEEDS IN IBD

- Better risk stratification
- Tailored therapy
- Better monitoring
- **Restoring quality-of-life (fatigue, anxiety, depression)**

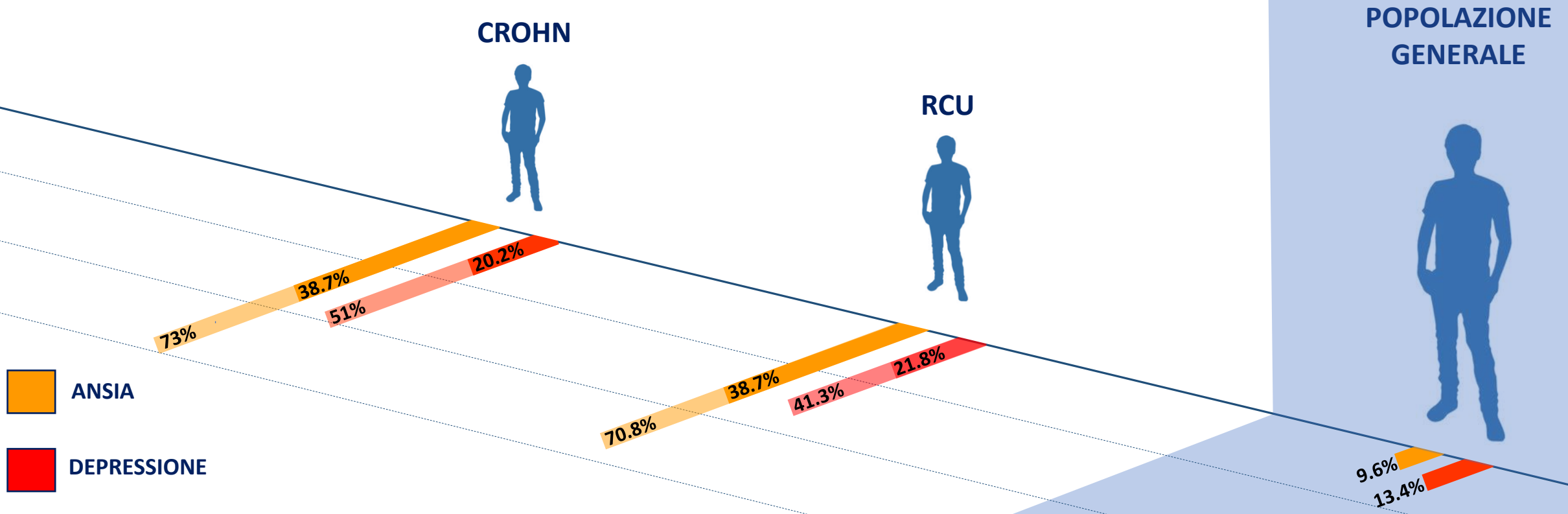


**MENTE
E
IBD**

Prevalenza disturbi psicologici nelle patologie croniche



Prevalenza dei disturbi psicologici nelle IBD



- **FATTORI DI RISCHIO:** malattia attiva, fenotipo aggressivo, sesso femminile, problematiche economico-lavorative
- **CONSEGUENZE NEGATIVE:** stigma, isolamento sociale, cambio abitudini di vita, minore aderenza a tx, maggiore ricorso ad accertamenti

MODELLO PSICOLOGICO

Disturbi psicologici come reazione secondaria al «peso» delle IBD (assenza cura, cronicità, compromissione qualità di vita e relazioni sociali).

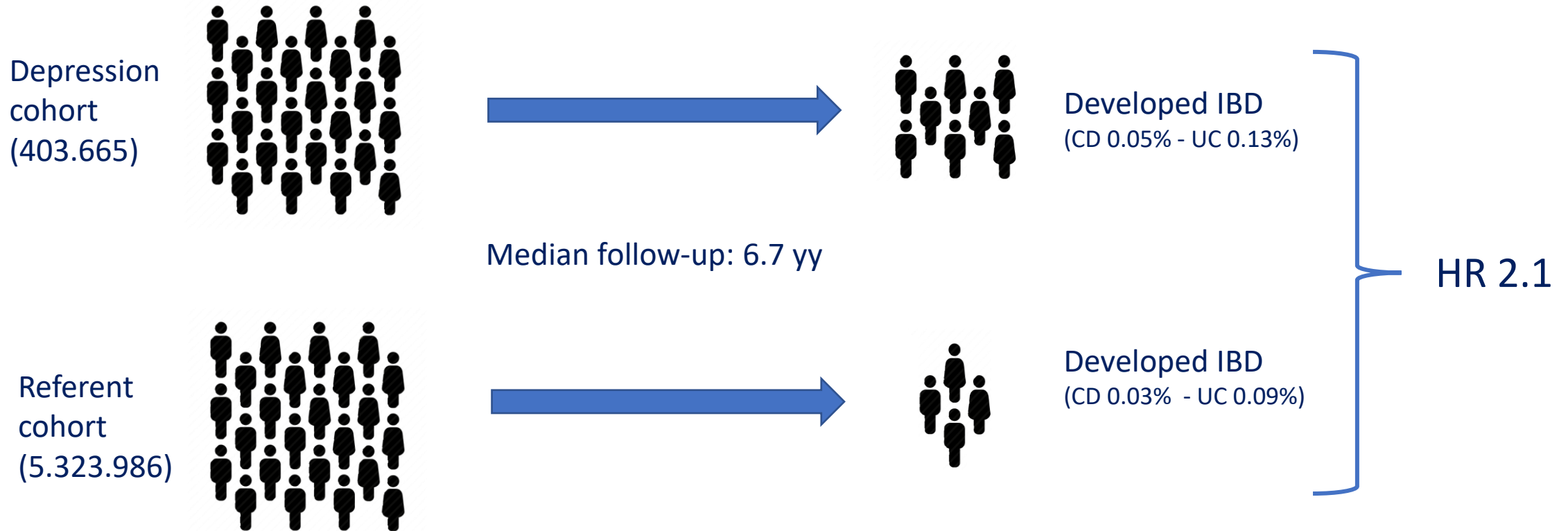


MENTE
E
IBD

The image features a large iceberg floating in a blue ocean under a blue sky with scattered white clouds. The top of the iceberg is visible above the water line, while the vast majority of its mass is submerged below the surface. The text 'MENTE E IBD' is centered on the submerged portion of the iceberg, illustrating the concept that psychological issues are often the much larger, hidden part of the overall condition.

I disturbi psicologici predispongono allo sviluppo di IBD

Retrospective cohort UK study



- I disturbi psicologici possono precedere la diagnosi di IBD di almeno 5 anni
- **Trattamenti antidepressivi risultano selettivamente protettivi per lo sviluppo di IBD**

Disturbi psicologici pre-esistenti correlano con outcome peggiori in IBD



NEURO-IMMUNE INTERACTIONS: HOW THE NERVOUS AND IMMUNE SYSTEMS INFLUENCE EACH OTHER Depressive symptoms in inflammatory bowel disease

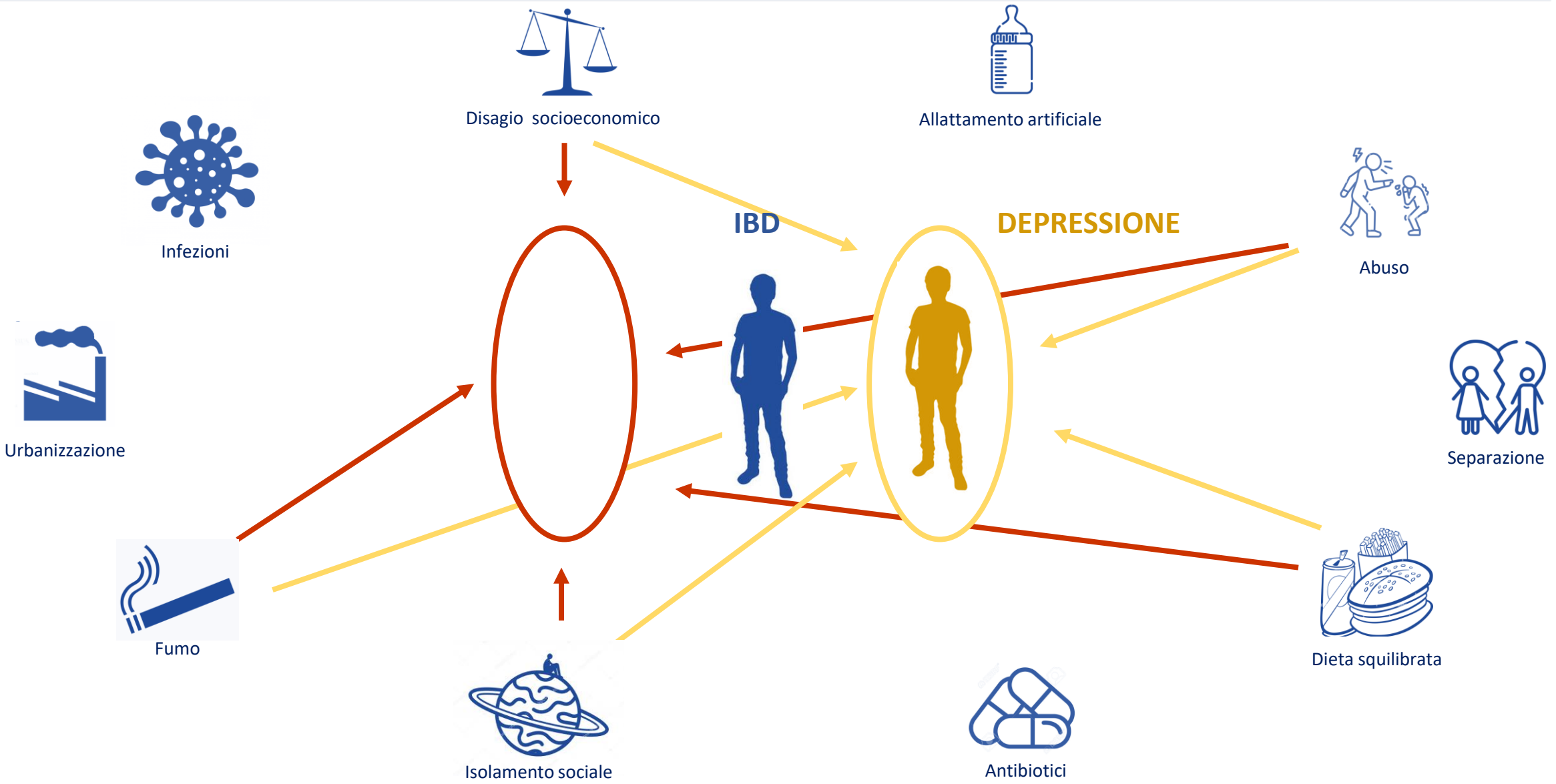
Table 2. Association between depression and biomedical outcomes in large longitudinal studies* of people with IBD

Outcome	Measure of depression	Crohn's disease	Ulcerative colitis
Readmission to hospital	Medical records coding of ICD depression diagnosis	OR = 1.89 (1.06–3.40) in children [35] and OR = 1.27 (1.07–1.50) in adults [34]	No increased odds in children [35] but OR = 1.35 (1.07–1.70) in adults [34]
Relapse**	PHQ-8 score \geq 5	RR = 1.3 (1.2–1.5) in adults [9]	RR = 1.3 (1.1–1.5) in adults [9]
Recurrent disease***	PHQ-8 score \geq 5	RR = 2.3 (1.9–2.8) in adults [9]	RR = 1.8 (0.9–1.7) in adults [9]
Requirement for biologicals	HADS > 7	Reduced time to clinical recurrence in adults ($P < 0.001$) [37]	Reduced time to clinical recurrence in adults ($P = 0.005$) [37]
Requirement for surgery	PHQ-8 score \geq 5	RR = 1.8 (1.4–2.3) [9]	RR = 1.6 (1.1–2.3) [9]
	Medical records coding of ICD depression diagnosis	OR = 1.28 (1.03–1.57) in one cohort [36], RR = 1.3 (1.1–1.6) in another [9]	No increased risk of surgery in one cohort [36] but RR = 1.8 (1.2–2.6) in another [9]

*All longitudinal studies with ≥ 1000 patients were included and all results are adjusted for potential confounders.

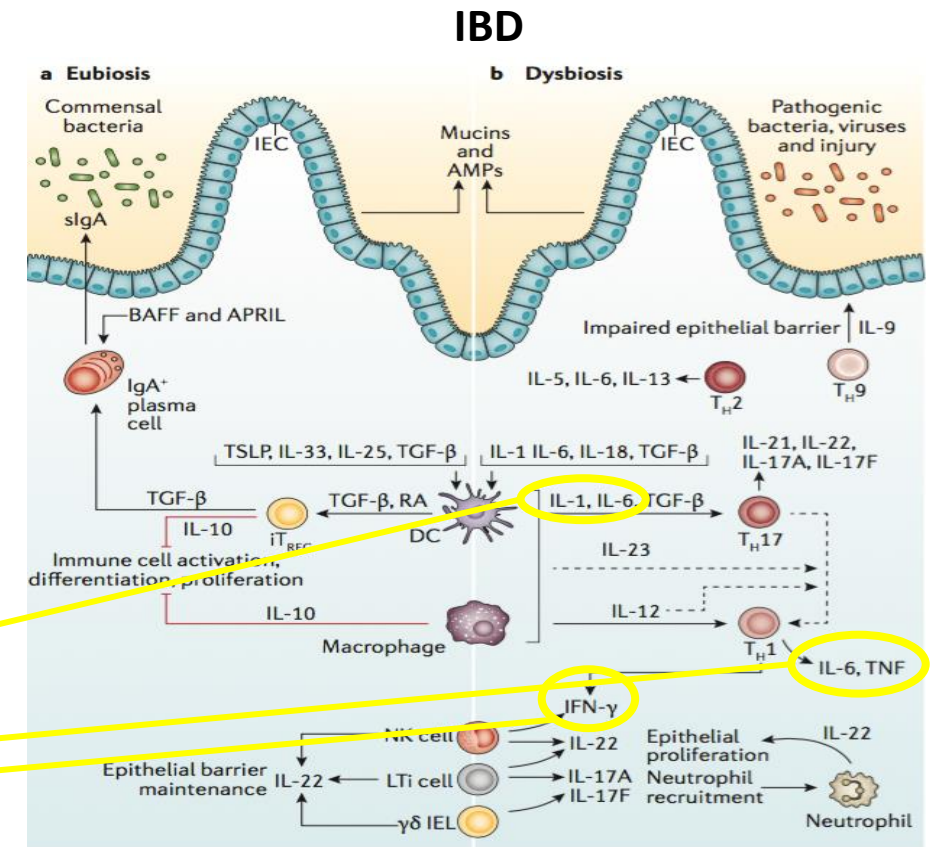
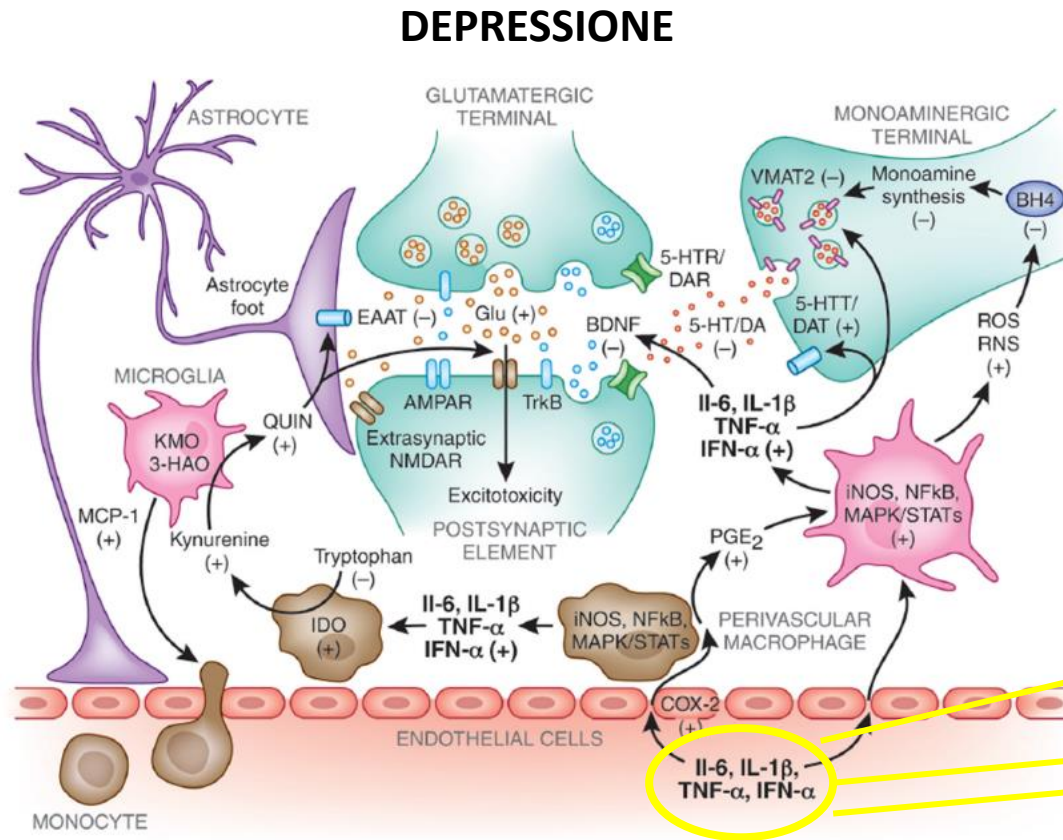
Il decorso della IBD in pz con progressi disturbi psicologici è gravato da un maggior numero di ricoveri, flare di malattia, ricorso a tx biologica e chirurgia.

Convergenza fattori di rischio tra IBD e disturbi psicologici



Danese A. Arch Pediatr Adolesc Med 2009; Jacobsen C. JCC 2013; Molendijk M. J Affect Disord 2018; Anathakrishnan AN. Nat Rev Gastroenterol Hepatol 2015; Pasco Ja Br J Psychiatry 2008

Convergenza immunopatogenesi IBD e disturbi psicologici



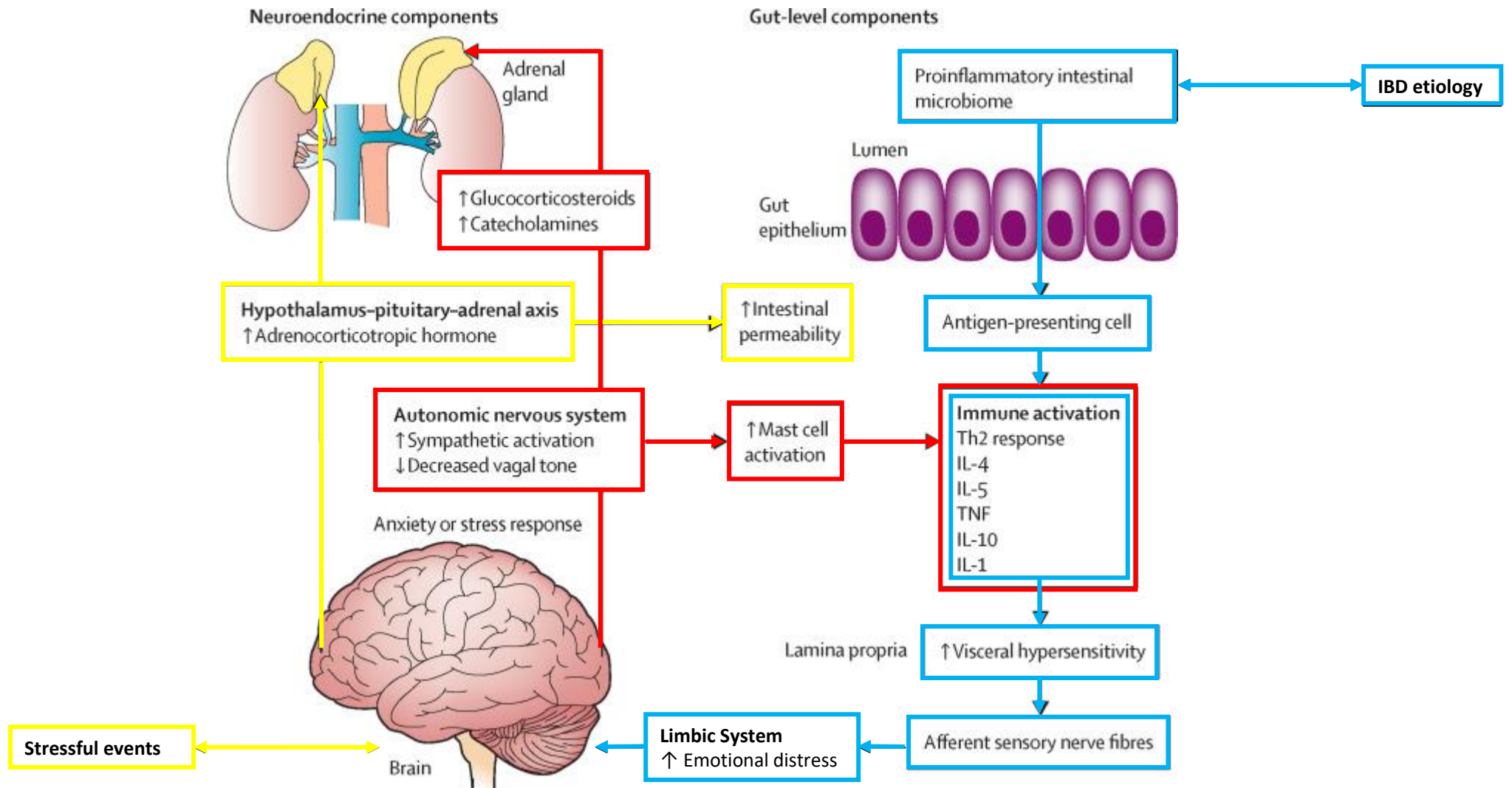
DISREGOLAZIONE IMMUNITARIA CONDIVISA

aumento PCR, attivazione linfociti Th1 (IL-1, IL-6, IL-12), TNF-α, IFN-γ

Interazione bidirezionale tra mente e IBD



Axis Gut-Brain Axis



Axis Gut-Brain Axis

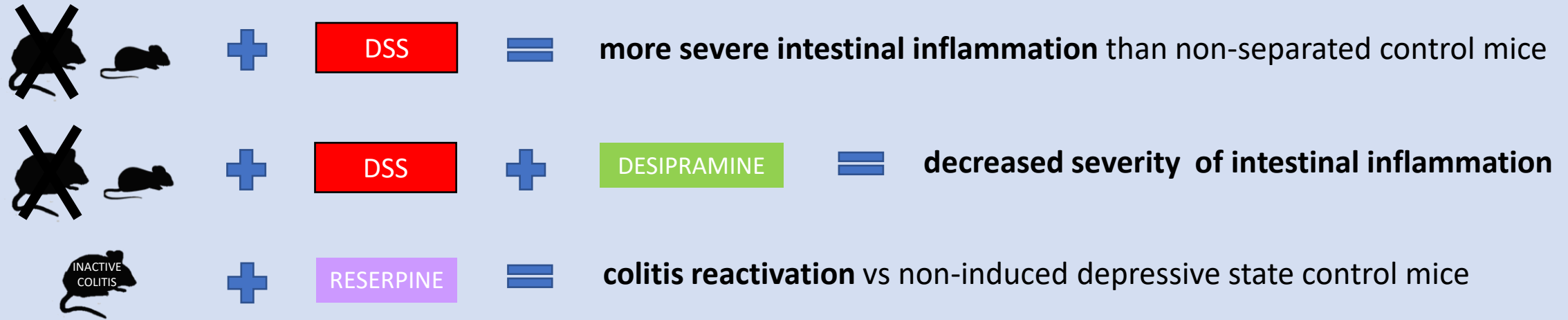
IBD



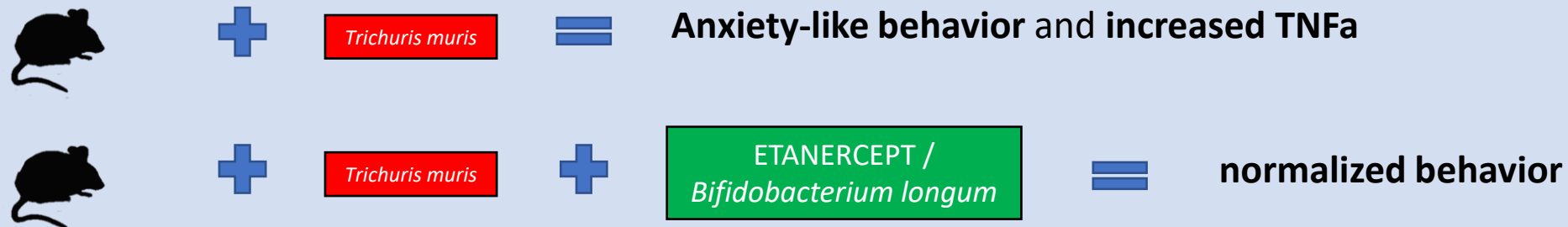
MENTE

Relazione bidirezionale mente e IBD (modelli animali)

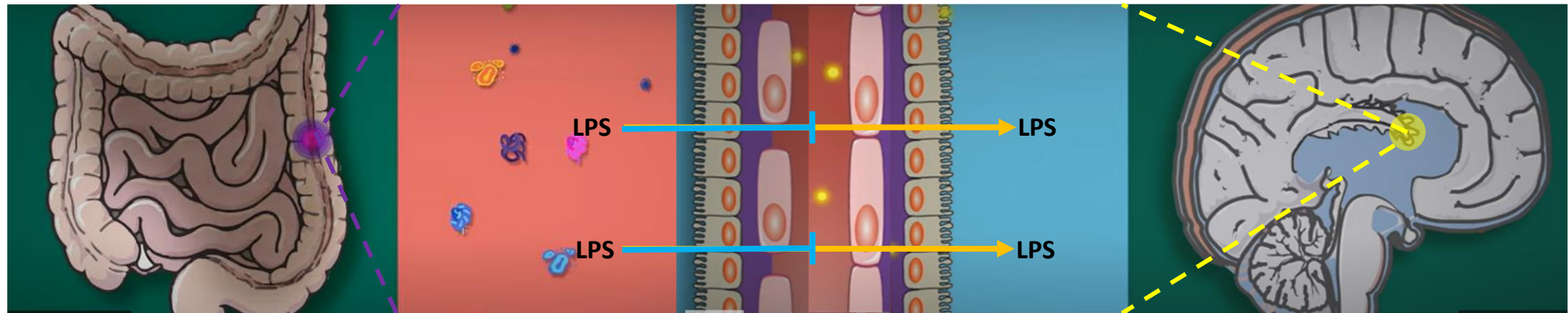
Brain-to-Gut Signaling



Gut-to-Brain Signaling



Relazione bidirezionale mente e IBD (modelli animali)



BARRIERA EMATO-INTESTINALE

BARRIERA EMATO-ENCEFALICA (PLESSO CORIOIDEO)



CHIUSURA PLESSO CORIOIDEO
GENETICAMENTE INDOTTA

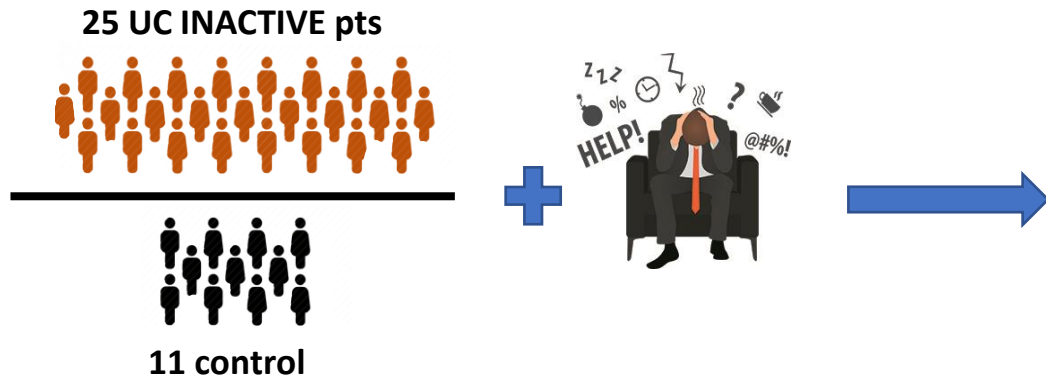


Comportamento ansioso

I disturbi psicologici potrebbero essere la conseguenza di un meccanismo di difesa

Relazione bidirezionale mente e IBD (modello umano)

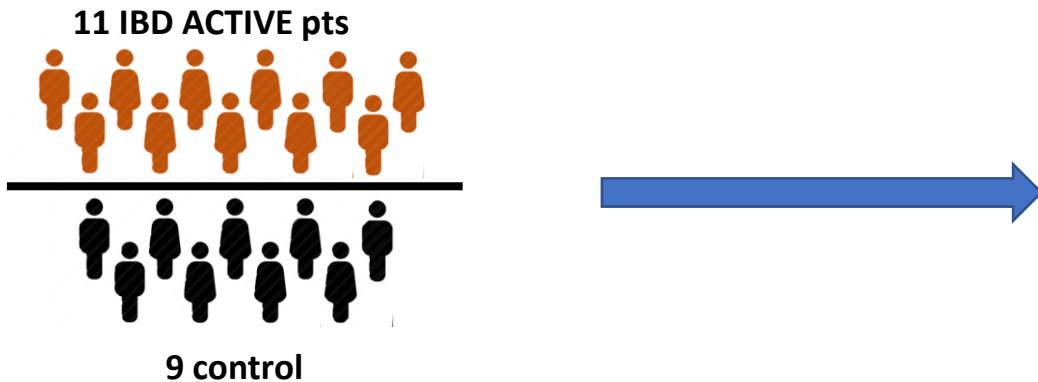
Brain-to-Gut Signaling



Acute psychologic stress induces systemic and mucosal proinflammatory responses in UC vs control:

- Increased mucosal expression of TNF α
- Increased circulating TNF α and IL-6

Gut-to-Brain Signaling



Highest **depressive** and **anxiety** scores correlate with:

- Increased mucosal expression of IL-6
- Increased circulating IL-6 and CRP

Relazione bidirezionale mente e IBD (modello umano)

Neurogastroenterology & Motility

ORIGINAL ARTICLE

A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease



PREMESSE

- Proprietà anti-infiammatorie del nervo vago (studi animali)
- Il tono vagale risulta diminuito nei pz con Crohn

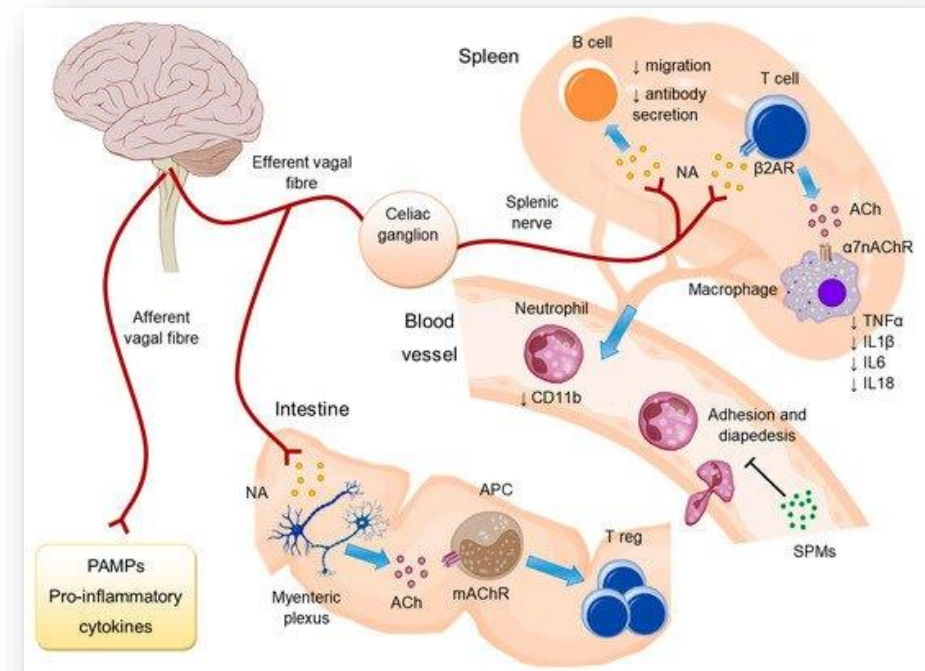
DISEGNO DELLO STUDIO

- Impianto di elettrostimolatore del nervo vago in 9 pz con malattia di Crohn attiva moderata, naïve a tx farmacologiche

OBIETTIVI

- Primario: valutare efficacia su attività clinica (CDAI)
- Secondario: valutare efficacia su attività biochimica (PCR e calprotectina), mucosale (CDEIS) e disturbi psicologici

RIFLESSO VAGALE ANTI-INFIAMMATORIO

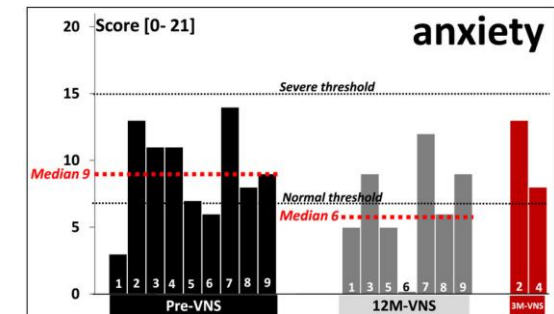
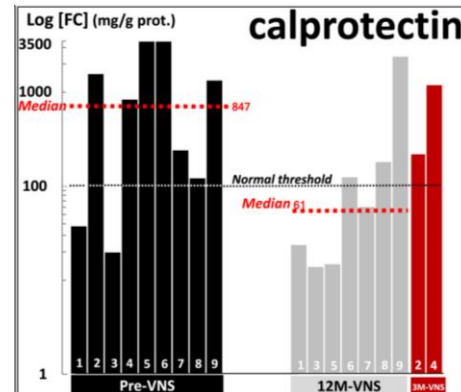
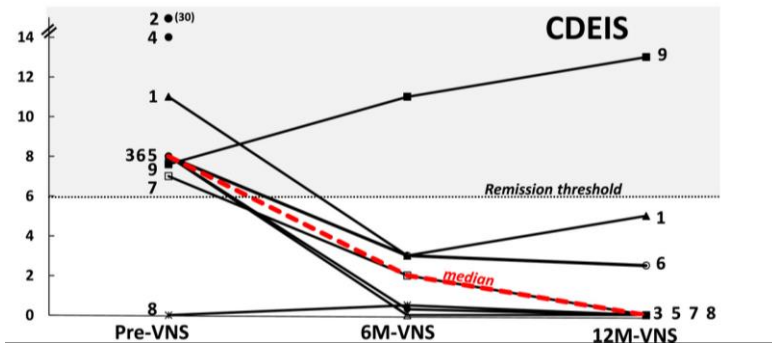
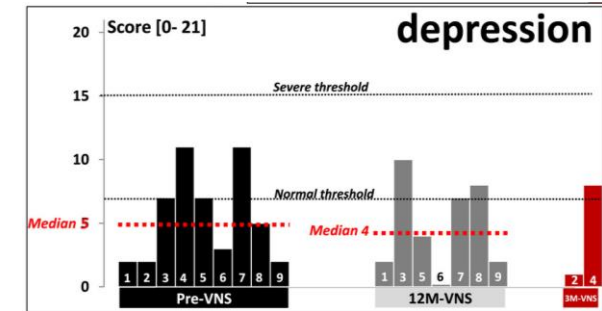
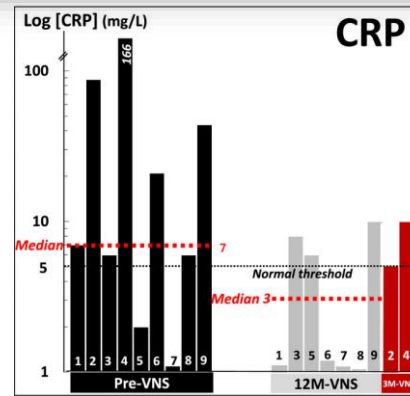
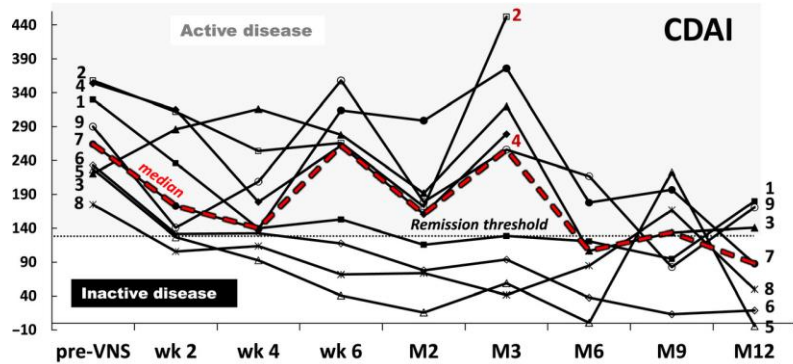
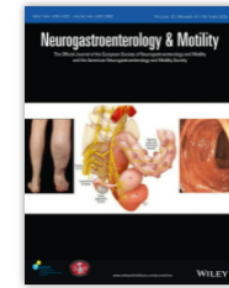


Relazione bidirezionale mente e IBD (modello umano)

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A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease



MODELLO PSICOLOGICO

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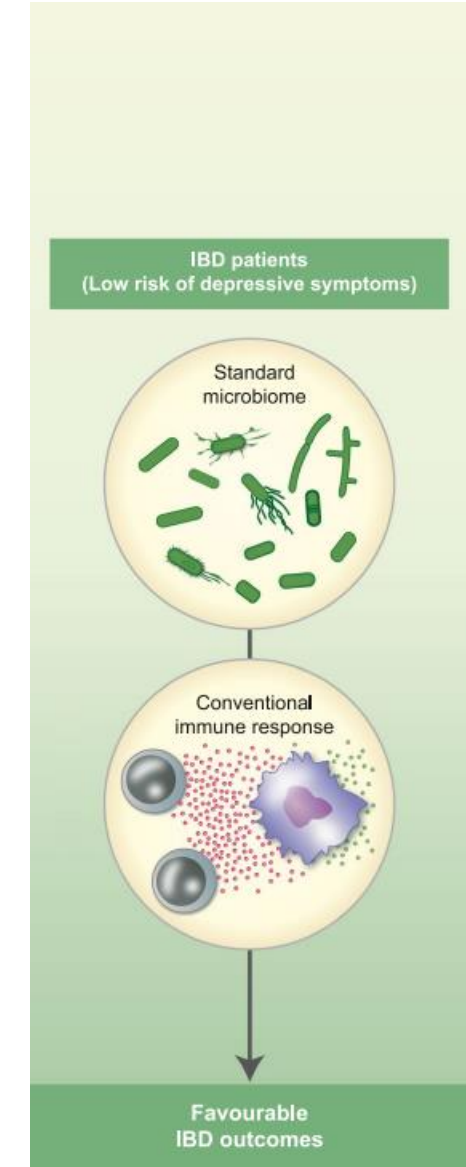
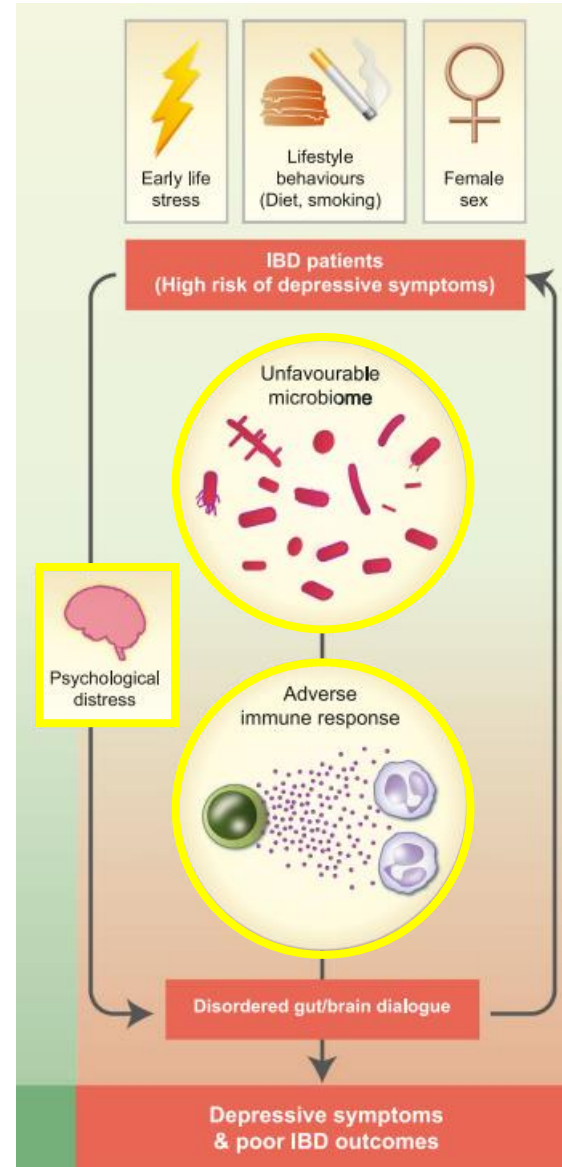
MODELLO NEUROBIOLOGICO

Lo stato infiammatorio contribuisce alla patogenesi delle IBD e dei disturbi psicologici (manifestazioni extraintestinali), attraverso una disregolazione del gut-brain axis



**MENTE
E
IBD**

Circolo vizioso IBD e MENTE: risvolti terapeutici?



Evidenze su terapia

RCT in corso: low FODMAPS diet, amitriptilina, terapia cognitivo-comportamentale, ...

	Type of study	Specific therapy identified as effective	Tested in patients reporting IBS-type symptoms?	Tested in patients with psychological disorders?
Biological therapies	RCTs ³⁶⁻³⁸	Anti-tumour necrosis factor- α	Indirectly; limited response in symptomatic patients with low inflammatory burden ³⁶⁻³⁸	No
Probiotics	Meta-analysis of RCTs ⁷⁵	VSL#3 probiotic formula in ulcerative colitis only	No	No
Faecal microbial transfer	Meta-analysis of RCTs ⁷⁶	NA	No	No
Low FODMAP diet	RCTs ^{77,78}	NA	Yes; improved quality of life and IBS symptom severity ^{77,78}	No
Antidepressants	Meta-analysis of case series and RCTs ³²	Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants	Possibly (patients with ongoing symptoms despite having adequate* therapy for ulcerative colitis ⁷⁹)	No
Psychological therapies	Meta-analysis of RCTs ³¹	Cognitive behavioural therapy	Yes; improved quality of life in subgroup analysis in one RCT ⁸⁰	Yes; no effect compared with waiting list control in one RCT ⁸⁰

IBS=irritable bowel syndrome. RCT=randomised controlled trial. NA=not applicable. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. *Defined by the treating physician.

Table 1: Evidence base for the treatment of IBS-type symptoms and psychological disorders in patients with inflammatory bowel disease

IBD e MENTE: the chicken or the egg?



White Paper AGA: *provision of care that encompasses medical care plus psychosocial, environmental and behavioral interventions to improve health has been termed “**whole person care**” and may result in achieving highest health value.*

DALLA CURA DELLA MALATTIA ALLA CURA DELLA PERSONA

Szigethy EM. Clinical Gastroenterol Hepatol 2017

Modello di cura integrato (medico-psicologo): migliore qualità di vita del pz



Dr. Riccardo Solimando

*CARO FRANCESCO,
L'APPROCCIO
BIOPSIICOSOCIALE
E' LA SOLUZIONE!*



Dr. Francesco Ferrara e audience

IN CHE SENSO???

It is unclear whether psychiatric co-morbidities directly influence disease activity by exacerbating inflammation, or whether the negative outcomes are indirectly caused by medication, non-adherence to medication or a generally worse subjective feeling that is ascribed to IBD without the presence of objective inflammation

Modello biopsicosociale per IBD

Qualità di vita

Inflammatione mucosale

Comorbidità psicologiche

Sintomi IBS-like

Disbiosi

(circolo)

Terapie: immunomodulatori, probiotici, trapianto fecale, antidepressivi,
terapie psicologiche (powell terapie)

Tabella 1

IFX su depressione

Observational evidence suggests that anti-inflammatory treatments for IBD may improve co-morbid depressive symptoms correlating with reduction in inflammation

Terapie psicologiche

31

Nessun beneficio sulla attività infiammatoria

Terapie dietetiche (low FODMAPS diet)

93

No effetto su disturbi psicologici e attività infiammatoria

Studio antidepressivi in IBD

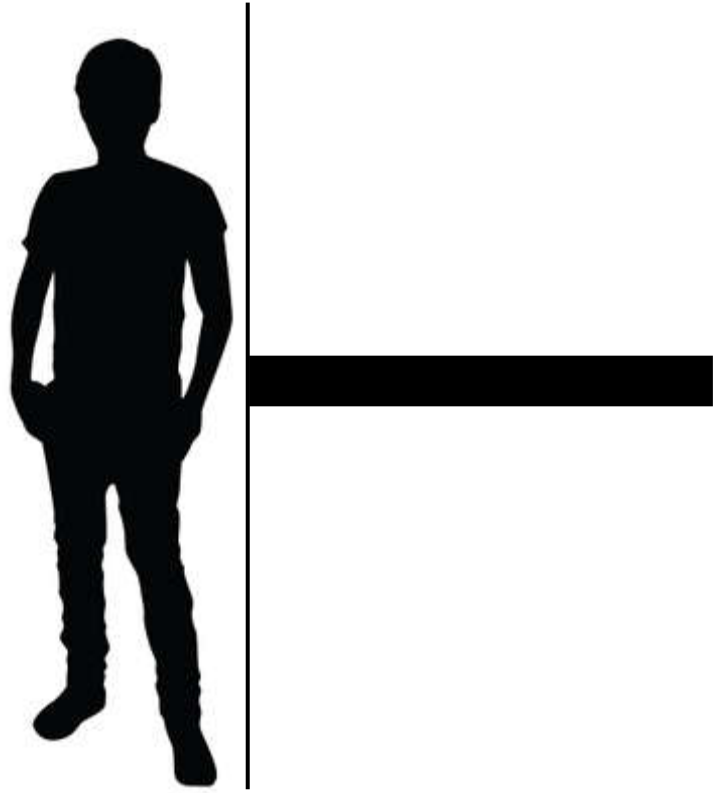
62

Bennebroek Evertsz F, Bockting CL, Stokkers PC, et al. The effectiveness of cognitive behavioral therapy on the quality of life of patients with inflammatory bowel disease: multi-center design and study protocol (KL!C- study). BMC Psychiatry. 2012;12:227. 13.

National Audit Report of Inflammatory Bowel Disease Service Provision: Adult National Report. London, United Kingdom: Royal College of Physicians; 2014.

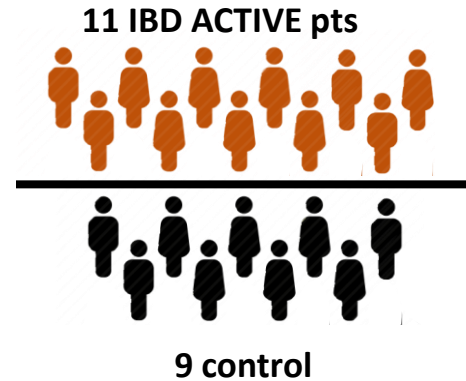
Conclusioni

Modello di cura integrato: migliore qualità di vita



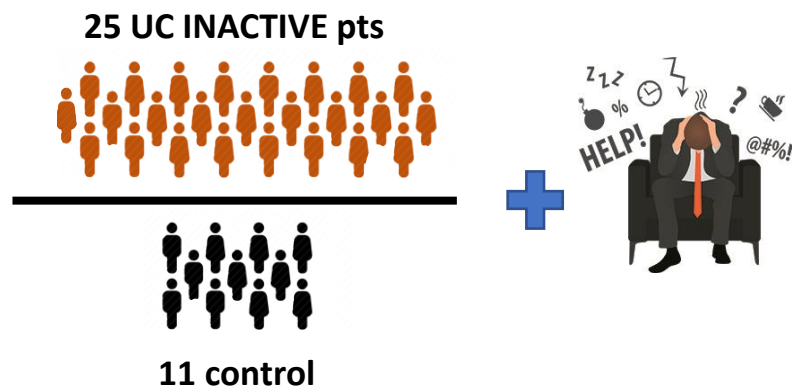
Relazione bidirezionale mente e IBD (modelli umani)

- *Gut-to-Brain Signaling*



- Highest **depressive** and **anxiety** scores
- Increased mucosal expression of **IL-6** and **IL-1 β**
- Increased circulating **IL-6** and **CRP**

- *Brain-to-Gut Signaling*



- Acute psychologic stress induces systemic and mucosal proinflammatory responses in UC vs control:
- Increased mucosal expression of **TNF α** and **O₂ metabolites**
 - Increased circulating **TNF α** and **IL-6**

Relazione bidirezionale mente e IBD (modelli umani)



A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease

Premesse:

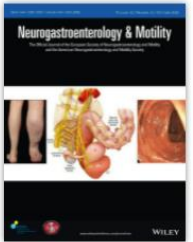
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Disegno dello studio:

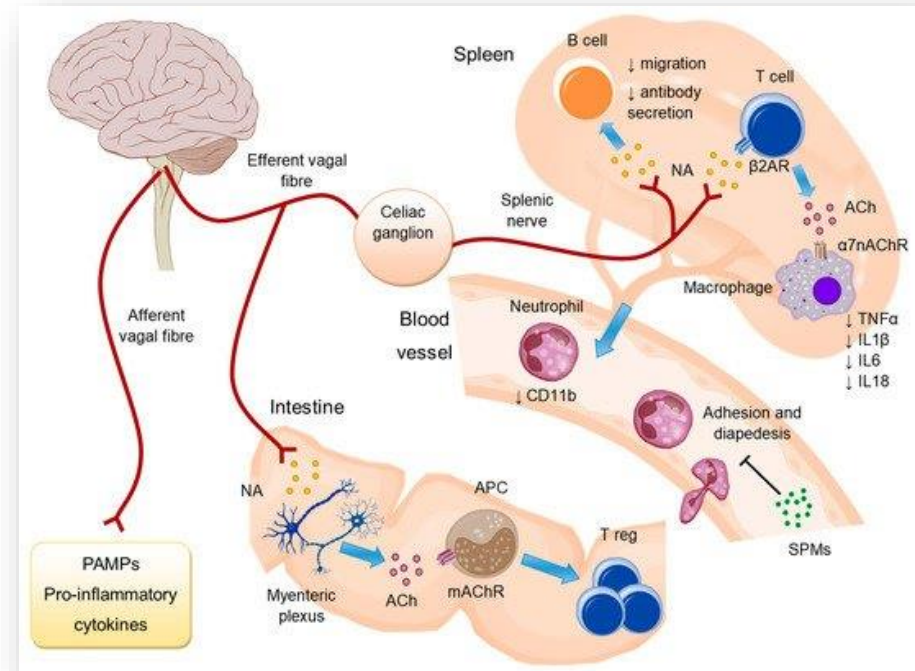
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Obiettivi:

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RIFLESSO COLINERGICO VAGALE ANTI-Infiammatorio



Relazione bidirezionale mente e IBD (modelli umani)



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