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1 **Inflammatory bowel disease as a new risk factor for dementia**

2 Marco Zuin^{1,3}, Roberto De Giorgio^{1,3}, Eleonora Capatti^{1,3}, Elisa Boschetti², Giovanni Zuliani^{1,3}

3

4 1 Department of Translational Medicine, University of Ferrara, 44100 Ferrara, Italy

5 2 Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

6 3 Azienda Ospedaliero-Universitaria "S. Anna", Ferrara, Italy

7

8 **Abstract**

9 The prognostic impact of inflammatory bowel disease (IBD), chronic inflammatory conditions
10 consisting of ulcerative colitis (UC), and Crohn's disease (CD) on the risk of dementia has been
11 poorly investigated. We evaluated the risk of dementia in IBD patients by a systematic review and
12 meta-analysis of the available data. Three studies, enrolling 121.827 patients [14.839 IBD (12.1%)
13 and 106.961 (87.7%) controls, respectively] were included in the analysis. Of these, 57.7% ($n =$
14 8.571) had UC, while 42.2% ($n = 6268$) had CD. The mean follow-up period was 21.3 years. A
15 random effect model revealed an aHR of 1.52 (95% CI 1.04–2.020, $p = 0.01$; $I^2 = 91.1\%$) for
16 dementia in IBD patients. Sensitivity analysis confirmed yielded results. Subjects having a CD
17 showed an aHR for dementia of 1.48 (95% CI 1.07–2.03, $p = 0.001$, $I^2 = 68.9\%$), while the risk
18 among those with a history of UC did not reach the statistical significance (aHR: 1.47, 95% CI
19 0.95–2.82, $p = 0.81$, $I^2 = 89.9\%$). IBD males had an increased risk of dementia compared to
20 women. IBD patients and in particular those with CD have an increased risk of dementia in the
21 long-term period.

22

23 Corresponding author:

24 Marco Zuin, MD

25 Department of Translational Medicine,

26 University of Ferrara, 44100 Ferrara, Italy

27 E-mail: marco.zuin@edu.unife.it

28

29 **Introduction**

30 Dementia represents a growing health concern worldwide [1]. It is known that patients with
31 dementia have a high prevalence of comorbid medical conditions and related complaints, which
32 directly influence the disease progression and relative outcome [2, 3]. A prompt identification of
33 vulnerable populations at higher risk of dementia is key to identify those subjects who may benefit
34 from early prevention and timely intervention. Over the last 2 decades, different studies have
35 reported several medical conditions able to increase the risk of dementia. However, the prognostic
36 impact of inflammatory bowel disease (IBD), chronic inflammatory conditions consisting of
37 ulcerative colitis (UC), and Crohn's disease (CD) on the risk of dementia has been poorly
38 investigated. The aim of the present manuscript is to evaluate the risk of dementia in IBD patients
39 by a systematic review and meta-analysis of the available data.

40

41 **Materials and methods**

42 **Study selection and data extraction**

43 The study was performed in accordance with the Preferred Report Items for Systematic Reviews
44 and Meta-analyses (PRISMA) guidelines (Supplementary table S1) [4]. For this purpose, PubMed-
45 MEDLINE and Scopus databases were systematically searched for articles, published in English
46 language, from inception through September 15, 2021, using the following Medical Subject
47 Heading (MESH) terms: "Inflammatory bowel disease" OR "IBD" AND "dementia". Inclusion
48 criteria were: (i) studies enrolling subjects with a confirmed diagnosis of IBD, (ii) stratifying the
49 population as UC and CD patients, and (iii) reporting the risk of dementia as adjusted hazard ratio
50 (aHR) with relative 95% confidence interval. Conversely, case reports, review articles, editorials/
51 letters, and case series with less than 10 participants

52 as well as studies including duplicate populations, if any, were excluded. References from the
53 included studies were screened to potentially identify other investigations meeting the inclusion
54 criteria. Ethical approval and informed consent were not required, as this study did not directly
55 enrol human subjects. For each assessed study, we extracted the overall, controls, UC and CD
56 number of patients enrolled, the mean age, male gender, and the adjusted hazard ratio (aHR) for
57 dementia in IBD patients as well as for UC and CD subjects' subgroups. The quality of the included
58 studies was graded using the Newcastle–Ottawa quality assessment scale (NOS) [5].

59

60 **Data analysis**

61 From each study, the aHR with the related 95% confidence interval (CI) was pooled using a random
62 effect model, while a forest plot was adopted to visually evaluate the results. Heterogeneity among
63 studies was assessed using Higgins and Thomson I² statistic where I² values correspond to the
64 following levels of heterogeneity: low (< 25%), moderate (25%–75%), and high (> 75%),
65 respectively. Due to the low number of the included studies (< 10), small-study bias was not
66 examined, as our analysis was underpowered to detect such bias. A predefined sensitivity analysis
67 (leave-one-out analysis) was performed removing 1 study at the time, to evaluate the stability of our
68 results regarding the risk of dementia in IBD subjects. To further appraise the impact of potential
69 baseline confounders, a sub-analysis for UC and CD was performed. All metaanalyses were
70 conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA). A *p* value <
71 0.05 was considered statistically significant.

72

73 **Results**

74 Initial search resulted in 276 articles. After removing duplicates (*n* = 88) and applying our inclusion
75 criteria, only 3 studies [6–8] enrolling 121.827 patients [14.839 IBD (12.1%) and 106.961 (87.7%)
76 controls, respectively] were included in the analysis. Of these, 57.7% (*n* = 8.571) had UC, while

77 42.2% ($n = 6268$) had CD. The mean follow-up period was 21.3 years. Quality assessment showed
78 that all studies were of moderate–high quality according to the NOS scale (Table 1). A random
79 effect model revealed an aHR of 1.52 (95% CI 1.04–2.020, $p = 0.01$; $I^2 = 91.1\%$) for dementia in
80 IBD patients (Fig. 1, Panel A). The relative funnel plot is shown in Supplementary Table S2;
81 however, it cannot reassure about the presence of potential publication bias due to the lower number
82 of available studies. To evaluate the robustness of the association results, we performed a leave-
83 one-out sensitivity analysis by iteratively removing one study at a time and recalculating the
84 summary aHRs, which remained stable (ranging between aHR: 1.31, 95% CI 1.09–1.33, $p < 0.001$
85 and aHR: 1.38, 95% CI 1.23–1.56, $p < 0.001$), indicating that our results were not driven by any
86 single study. When the studies were stratified according to the type of IBD, those having a CD
87 showed an aHR for dementia of 1.48 (95% CI 1.07–2.03, $p = 0.001$, $I^2 = 68.9\%$) (Fig. 1, Panel B),
88 while the risk among those with an history of UC did not reach the statistical significance (aHR:
89 1.47, 95% CI 0.95–2.82, $p = 0.81$, $I^2 = 89.9\%$) (Fig. 1, Panel C). Intriguingly, IBD males had an
90 increased risk of dementia compared to women.

91

92 **Discussion**

93 The results of the present analysis showed that patients affected by IBD, and especially those with
94 CD, have a higher risk of dementia in the long-term period. However, due to the high heterogeneity
95 observed, our results must be cautiously considered as a preliminary account on the impact of IBD
96 on dementia. Probably, the heterogeneity observed is multifactorial. First, the limited number of
97 studies satisfying the inclusion criteria and the relative few numbers of enrolled patients represent,
98 per se, a potential source of heterogeneity. Second, inherited biases derived from the original
99 investigations may have further contributed to the observed heterogeneity level. In fact, different
100 levels of methodological quality and sampling bias by the competing risk of dementia may also
101 have affected the results of this analysis. To this regard, also the retrospective design used by Zingel
102 et al. [8] and therefore its lower methodological quality might have contributed to not firm results,

103 when compared with the other longitudinal investigations analysed. Moreover, the limited number
104 of studies satisfying the inclusion criteria did not allow us to perform meta-regression for potential
105 important confounders such as the length of IBD, the disease severity, previous surgical treatments,
106 and type of dementia. Nonetheless, the sensitivity analysis performed confirmed the validity of our
107 preliminary results. From a pathophysiological perspective, the mechanism promoting the risk of
108 dementia in IBD patients has not been yet understood. Probably, the chronic systemic inflammation
109 observed in IBD patients may represent a trigger for neuroinflammatory state, thereby driving
110 microglia activation with consequent oxidative stress and misfolding proteins, mechanisms known
111 to contribute to Alzheimer's disease [9]. The difference in dementia risk between CD and UC could
112 be probably explained by the different systemic inflammatory mediator profile involved [10];
113 however, further dedicated studies are needed to elucidate the implicated inflammatory pathways.
114 Furthermore, also the intestinal microbiota could represent another important mediator to linking
115 IBD with the development of cognitive impairment/dementia. Indeed, the altered gut microbiota,
116 which is commonly observed in IBD patients, can influence brain function and behaviour through
117 the microbiota–gut–brain axis via various pathways such as increased amyloid- β deposits and tau
118 phosphorylation, neuroinflammation, metabolic dysfunctions, and chronic oxidative stress [11, 12].
119 Our study has several limitations related to the design of the studies reviewed with all inherited
120 biases and the numbers of investigations on the issue. In fact, only a few studies have analysed the
121 relationship between IBD and dementia, limiting our results and conclusions. Moreover, the
122 relatively high heterogeneity observed, which probably depends on the inclusion criteria as well as
123 by the studies design, may have resulted in not firm conclusions. Finally, we cannot perform any
124 analysis to evaluate the potential role of different risk factors for dementia, since they were not
125 reported in the original investigations.

126

127 **Conclusions**

128 In conclusion, IBD patients and in particular those with CD have an increased risk of dementia in
129 the long-term period. The potential benefits of early screening for dementia in these patients should
130 be evaluated in the setting of randomized controlled trials.

131

132 **Supplementary Information**

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134 research, and data analysis. RDG: editing and revision of the manuscript, and data interpretation;
135 EC: literature research and visualization. EB: literature research and data interpretation; GZ: editing
136 and revision of the manuscript, data interpretation, and supervision.

137 All the authors read and approved the final version of the manuscript.

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139 **Declarations**

140 Conflict of interest The authors declare that they have no conflicts of interest. Authors declare no
141 competing financial, general, and institutional interests.

142 **Ethical approval** Not applicable.

143 **Informed consent** Not applicable.

144

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