**Name of Journal:** *World Journal of Psychiatry*

**Manuscript NO:** 78264

**Manuscript Type:** LETTER TO THE EDITOR

**Why do we not reverse the path? Stress can cause depression, reduction of brain-derived neurotrophic factor and increased inflammation**

Claro AE *et al*. Depression and inflammation

Angelo Emilio Claro, Clelia Palanza, Marianna Mazza, Alessandro Rizzi, Linda Tartaglione, Giuseppe Marano, Giovanna Muti-Schuenemann, Marta Rigoni, Paola Muti, Alfredo Pontecorvi, Luigi Janiri, Gabriele Sani, Dario Pitocco

**Angelo Emilio Claro, Marianna Mazza, Giuseppe Marano, Luigi Janiri, Gabriele Sani,** Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Clelia Palanza,** Istituto Italiano di Antropologia, IsiTa, Rome 00185, Italy

**Alessandro Rizzi, Linda Tartaglione,** Department of Medical and Surgical Sciences, Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Giovanna Muti-Schuenemann,** Health Research Methods, Evidence and Impact Department, McMaster University, Ontario K9V 0A0, Canada

**Marta Rigoni, Paola Muti,** Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan 20126, Italy

**Alfredo Pontecorvi,** Department of Endocrine-Metabolic and Dermo-Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Dario Pitocco,** Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Author contributions:** Claro AE and Palanza C designed the study and wrote the first draft of the manuscript; Mazza M, Marano G, Rizzi A, Tartaglione L, Muti-Schuenemann G, Rigoni M, Muti P, Pontecorvi A, Janiri L, Sani G and Pitocco D supervised and added important contributions to the paper; All authors have read and agreed to the published version of the manuscript.

**Corresponding author: Marianna Mazza, MD, PhD, Assistant Professor,** Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, Rome 00168, Italy. marianna.mazza@policlinicogemelli.it

**Received:** June 16, 2022

**Revised:** July 20, 2022

**Accepted: August 16, 2022**

**Published online:**

**Abstract**

The aim of this paper is to describe the direction of the link between stress, depression, increased inflammation and brain-derived neurotrophic factor (BDNF) reduction. We hypothesize that severe stress or prolonged stress can be the driving factor that promote the onset of depression. Both stress and depression, if not resolved over time, activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines. This cascade fosters systemic chronic inflammation and reduced plasma BDNF levels. Since people with depression have a 60% increased risk of developing type 2 diabetes (T2D) and show high levels of inflammation and low levels of BDNF, we hypothesize possible reasons that might explain why T2D, depression and dementia are often associated in the same patient.

**Key Words:** Depression; Inflammation; Brain-derived neurotrophic factor; Type 2 diabetes mellitus; Dementia; Psychological stress

Claro AE, Palanza C, Mazza M, Rizzi A, Tartaglione L, Marano G, Muti-Schuenemann G, Rigoni M, Muti P, Pontecorvi A, Janiri L, Sani G, Pitocco D. Why do we not reverse the path? Stress can cause depression, reduction of brain-derived neurotrophic factor and increased inflammation. *World J Psychiatry* 2022; In press

**Core Tip:** This paper proposes a distinct interpretation of the link that exists between increased inflammation and reduction of brain-derived neurotrophic factor (BDNF). We describe why most of the people with altered inflammatory status and low BDNF do not automatically have depression, and why some people become depressed without diverging from average serum levels of these markers. We also suggest a reason why the use of tumor necrosis factor-α inhibition has no effect as a therapy in patients with resistant depression and high inflammatory levels.

**TO THE EDITOR**

We read with great interest the work of Porter and O’Connor[1] describing how brain-derived neurotrophic factor (BDNF) and inflammation are considered key players in the pathogenesis of depression.

We found the ideas of our colleagues very interesting and sharable. In this letter, we would like to suggest a different way to evaluate the link between BDNF, inflammation and depression. Following the “*social signal transduction theory of depression”*[2] we consider stress as the main cause of development of depressive symptoms; depression, in turn, is able to induce increased inflammation and reduced BDNF production.

It has been demonstrated that when a person lives in an environment characterized by numerous stressful situations (physical and social threat, or internal perceived stressors, like internal thoughts) that are severe or prolonged over time and he is not able to eliminate or psychically rework them, he displays a greater risk of developing depression[2,3].

Stress and depression, if not resolved over time, can activate brain regions connected with pain. These areas will project into lower regions that regulate inflammation *via* the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system (SNS)[3]. The SNS, in the first stage of modulation, will set up the production of epinephrine and norepinephrine. These neurotransmitters will activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines that will foster major inflammation or Systemic Chronic Inflammation (SCI)[2]. If this state is sustained for years, there is a high risk of developing inflammation-related disorders, quickened biological aging, infections, and premature mortality[4].

Moreover, stress and chronic inflammation are capable of inducing reduction of BDNF and indeed plasma BDNF levels are significantly lower in depressed patients compared with matched controls[5].

These considerations might explain why most of the people with altered inflammatory status and low BDNF do not automatically develop depression, and why some people become depressed without presenting the serum levels of either of the two markers far from the average[1]. It is neither the reduced BDNF nor the increased inflammation that induces depression, but rather it is stress itself that is able to promote the onset of depression. Moreover, if stress and depression last over time they can lead to increased inflammation and decreased BDNF[1]. Following this reasoning, it appears clearer why pharmacological intervention with tumor necrosis factor-α antagonist as an anti-depressant treatment in patients with resistant depression and high inflammation does not give positive results, while the same type of intervention is quite effective in treatment resistant patients with high inflammation and without depression[6,7]. That is because in patients with inflammatory diseases inflammation recognizes physical causes as an origin while in patients with depression it recognizes stress as the underlying cause of inflammation. If patients are not able to eliminate the source of stress, this will continue to generate depression, inflammation and reduced BDNF.

The article by Porter and O’Connor[1] allowed us to move even further and to hypothesize a possible link between stress, depression, inflammation, development of type 2 diabetes (T2D), BDNF reduction, and dementia.

Patients suffering from depression have high levels of stress which lead them to overeating, in particular food rich in carbohydrates or snacks, because this high-calorie food acts as a self-medication and is able to increase serotonin levels[8,9]. These patients are accordingly more prone to develop overweight and obesity, the strongest risk factors for the onset of T2D[10-12]. It has been showed that people with depression have a 60% increased risk of developing T2D[13] and 25% of patients with T2D have depression[14]. Nevertheless, depression in T2D patients is frequently unrecognized and therefore not treated[15-17].

Thus depression, untreated for years, contributes to maintain T2D and both depression and T2D can lead to increased SCI and decreased BDNF. In this way, the reduction of neurogenesis and synaptogenesis, a reduction of the vascular bed and vascular support and neuroinflammation are determined, finally leading to an increasing risk of dementia onset. Low BDNF levels are present in dementia patients[18,19] and patients with T2D are approximately two to four times more likely to develop dementia than individuals without T2D. These associations might explain why T2D, depression and dementia are often associated in the same patient[20-23]. We are aware that these are hypotheses, but we can consider them as useful reflections inspired by the article by Porter and O’Connor[1] to be validated in future studies.

**ACKNOWLEDGEMENTS**

The authors are grateful to Maria Rita Scardocci and Paolo Palanza for their technical support.

**REFERENCES**

1 **Porter GA**, O'Connor JC. Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime? *World J Psychiatry* 2022; **12**: 77-97 [PMID: 35111580 DOI: 10.5498/wjp.v12.i1.77]

2 **Slavich GM**, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* 2014; **140**: 774-815 [PMID: 24417575 DOI: 10.1037/a0035302]

3 **Kendler KS**, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 1999; **156**: 837-841 [PMID: 10360120 DOI: 10.1176/ajp.156.6.837]

4 **Irwin MR**, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol* 2011; **11**: 625-632 [PMID: 21818124 DOI: 10.1038/nri3042]

5 **Furman D**, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019; **25**: 1822-1832 [PMID: 31806905 DOI: 10.1038/s41591-019-0675-0]

6 **Bath KG**, Schilit A, Lee FS. Stress effects on BDNF expression: effects of age, sex, and form of stress. *Neuroscience* 2013; **239**: 149-156 [PMID: 23402850 DOI: 10.1016/j.neuroscience.2013.01.074]

7 **Raison CL**, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 2013; **70**: 31-41 [PMID: 22945416 DOI: 10.1001/2013.jamapsychiatry.4]

8 **Barrea L**, Pugliese G, Framondi L, Di Matteo R, Laudisio D, Savastano S, Colao A, Muscogiuri G. Does Sars-Cov-2 threaten our dreams? Effect of quarantine on sleep quality and body mass index. *J Transl Med* 2020; **18**: 318 [PMID: 32811530 DOI: 10.1186/s12967-020-02465-y]

9 **Mills JG**, Thomas SJ, Larkin TA, Deng C. Overeating and food addiction in Major Depressive Disorder: Links to peripheral dopamine. *Appetite* 2020; **148**: 104586 [PMID: 31926176 DOI: 10.1016/j.appet.2020.104586]

10 **Claro AE**, Palanza C, Tartaglione L, Mazza M, Janiri L, Pitocco D. COVID-19 and the role of chronic inflammation in patients with type 2 diabetes and depression. *Minerva Endocrinol (Torino)* 2022; **47**: 128-129 [PMID: 33979072 DOI: 10.23736/S2724-6507.21.03492-8]

11 **Schnurr TM**, Jakupović H, Carrasquilla GD, Ängquist L, Grarup N, Sørensen TIA, Tjønneland A, Overvad K, Pedersen O, Hansen T, Kilpeläinen TO. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. *Diabetologia* 2020; **63**: 1324-1332 [PMID: 32291466 DOI: 10.1007/s00125-020-05140-5]

12 **US Preventive Services Task Force.**, Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Krist AH, Kubik M, Li L, Ogedegbe G, Owens DK, Pbert L, Silverstein M, Stevermer J, Tseng CW, Wong JB. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021; **326**: 736-743 [PMID: 34427594 DOI: 10.1001/jama.2021.12531]

13 **Lindekilde N**, Rutters F, Erik Henriksen J, Lasgaard M, Schram MT, Rubin KH, Kivimäki M, Nefs G, Pouwer F. Psychiatric disorders as risk factors for type 2 diabetes: An umbrella review of systematic reviews with and without meta-analyses. *Diabetes Res Clin Pract* 2021; **176**: 108855 [PMID: 33965448 DOI: 10.1016/j.diabres.2021.108855]

14 **Mezuk B**, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008; **31**: 2383-2390 [PMID: 19033418 DOI: 10.2337/dc08-0985]

15 **Khaledi M**, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetol* 2019; **56**: 631-650 [PMID: 30903433 DOI: 10.1007/s00592-019-01295-9]

16 **Owens-Gary MD**, Zhang X, Jawanda S, Bullard KM, Allweiss P, Smith BD. The Importance of Addressing Depression and Diabetes Distress in Adults with Type 2 Diabetes. *J Gen Intern Med* 2019; **34**: 320-324 [PMID: 30350030 DOI: 10.1007/s11606-018-4705-2]

17 **CDC.** Depression Diabetes Distress Brief. [cited 10 March 2022]. Available from: https://www.cdc.gov/diabetes/pdfs/managing/Depression\_Diabetes\_Distress\_Brief\_508.pdf

18 **Spitzer RL**, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; **282**: 1737-1744 [PMID: 10568646 DOI: 10.1001/jama.282.18.1737]

19 **Palasz E**, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G. BDNF as a Promising Therapeutic Agent in Parkinson's Disease. *Int J Mol Sci* 2020; **21** [PMID: 32050617 DOI: 10.3390/ijms21031170]

20 **Tanila H**. The role of BDNF in Alzheimer's disease. *Neurobiol Dis* 2017; **97**: 114-118 [PMID: 27185594 DOI: 10.1016/j.nbd.2016.05.008]

21 **Biessels GJ**, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; **5**: 64-74 [PMID: 16361024 DOI: 10.1016/S1474-4422(05)70284-2]

22 **Katon W**, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. *Arch Gen Psychiatry* 2012; **69**: 410-417 [PMID: 22147809 DOI: 10.1001/archgenpsychiatry.2011.154]

23 **Chow YY**, Verdonschot M, McEvoy CT, Peeters G. Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2022; **185**: 109227 [PMID: 35122905 DOI: 10.1016/j.diabres.2022.109227]

**Footnotes**

**Conflict-of-interest statement:** All theauthors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** June 16, 2022

**First decision:** July 13, 2022

**Article in press:**

**Specialty type:** Psychiatry

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A, A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Dai RP, China; Kotlyarov S, Russia **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Fan JR