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Editorial

Obesity, Cardiovascular Disease, Alzheimer's Disease/Dementia, and COVID-19: The Collision of Unrecognized and Current Pandemics

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According to the World Health Organization (WHO), individuals who are overweight and obese have nearly tripled since 1975 [1]. More than 1.9 billion adults across the globe were deemed overweight (39%) in 2016. Of these, more than 650 million adults were considered obese (13%) [1]. During the same year, it was also reported that more than 340 million children and adolescents (aged 5 - 19 years old) were either overweight or obese. And in 2020, more than 39 million children bellow the age of 5 were considered overweight or obese. The difference between an individual considered to be overweight and/or obese is based on the body-mass index (BMI) value, calculated as the ratio between a person's weight in kilograms divided by his/her height in meters squared. The normal BMI range values are between 20 and 25, while a BMI over 25 defines overweight and a further increase in the BMI over 30 is clinically used as a cut off to identify obesity. Importantly, even though the presence of specific rare genetic variants can increase the risk to develop obesity in certain individuals and ethnicities [2], weight gain and its consequences (overweight and obesity) are mainly driven by societies' obesogenic environments and therefore, are potentially preventable.

As the prevalence of obesity is increasing worldwide, obesity has become pandemic (one of the biggest in human history) due to the obesogenic environments in which we live, where a large proportion of people over-consume increased amounts of inexpensive, high-calorie density food. Other contributors include technology and structure of our communities that have dramatically reduced the requirements for physical activity. Extensively available passive entertainment (like video games, TV watching, online news, social media and other forms of entertainment like streaming) contribute to and reinforce a non-active lifestyle [3].

Obesity (or Adiposity-Based Chronic Disease (ABCD)) is defined by an increase of fat mass that is dysfunctional and that adversely affects health [4]. It is a bio-psycho-social chronic inflammatory disease that has been recognized as such by the American Medical Association since 2013 [3]. Although it's commonly perceived by many as just a physical attribute of potential discrimination, obesity is a component and a driver of metabolic syndrome, which includes dyslipidemia, decreased insulin sensitivity (insulin resistance), hyperinsulinemia, hyperglycemia, and hypertension. Because of its high prevalence and inflammatory nature, obesity has also been recognized as one of the main co-morbidities for cardiovascular disease, different forms of cancer, neurodegenerative diseases, and even COVID-19.

Obesity has also been previously related to neurological alterations, where the metabolic dysfunction, dyslipidemia and inflammation caused by obesity contribute to the development of a wide variety of disorders and effects on the nervous system [4]. Although the specific mechanisms involved remain undetermined, mechanistic insights obtained from obese animal models suggest that excess dietary fat compromises the hypothalamic control of energy homeostasis [5]. This mechanism might contribute to adipose tissue dysfunction, which can lead to elevated concentrations of free fatty acids (FA), systemic dyslipidemia, and the consequent free fatty acid lipotoxicity, all

resulting in changes in intracellular signaling and/or lipid use that can result in neurological dysfunction. These factors (excessive calorie intake, increased fat accumulation, free FA lipotoxicity) activate the production of cytokines and cells that are primarily involved in immune function but are also pro-inflammatory [3]. Because of its nature, the metabolic inflammation described in obesity may also be a major contributor to the impairment of the nervous system function through neuro-inflammation. The CNS impairment associated with obesity includes many diverse clinical presentations that range from mild cognitive impairment to severe cognitive compromise including vascular dementia and Alzheimer's Disease (AD). Several meta-analyses have shown a strong association between obesity and AD and other dementias, where obesity doubles the risk of AD when compared with that of individuals with healthy, normal body weight [6,7] and that a higher BMI in middle life predicts greater risk of dementia in later life [8].

In the context of an aging global population living in obesogenic environments and experiencing co-morbidity with cardiovascular disease, COVID-19 (the pandemic that begun in early 2020 and is still ongoing (WHO)) presents an even more current complicated scenario with regards to world-wide health. There have been several reports where an increase in AD and other forms of dementia and cognitive impairment in the presence of SARS-CoV-2 have been reported [9]. A question that remains unanswered is what is the relationship between age, obesity, inflammation, AD and SARS-CoV-2? Many studies have presented evidence that revealed the neuro-invasive potential of SARS-CoV-2 and discussed the potential ways by which the virus could compromise or even invade the CNS, including along nerves or through the bloodstream and hematogenous spread. Based on the wide range of presentation of neurological syndromes reported in the literature, Fotuhi., *et al*. proposed a conceptual framework of "NeuroCovid staging", where **stage I** refers to the invasion of SARS-CoV-2 binding to ACE2 receptors and is limited to nasal and gustatory epithelial cells, **stage II** adds a strong cytokine response with high levels of cytokines, ferritin, C-reactive protein and D-dimers, and finally **stage III** includes cytokine storm that compromise the integrity of the blood brain barrier and results in infiltration of inflammatory factors and other blood content (including viral particles) in the cerebral milieu [10,11]. Fotuhi., *et al*. speculate that the three stages of CNS compromise by SARS-CoV-2 can result in neuro-cognitive alterations that can increase the risk to develop neuro-degenerative diseases like AD (which accounts for more than 60% of all dementia cases) in the long term (post-COVID-19). In the context of a preexistent pandemic like obesity that has been relegated to the background for many years now, the questions that now remain unanswered are what are the specific mechanisms involved in CNS compromise and how do preexistent conditions (like obesity, cardiovascular disease, and chronic inflammation) contribute to facilitate CNS dysfunction in the presence of SARS-CoV-2 infection? Most recently, Albornoz et al. have reported that SARS-CoV-2 can promote microglial NLRP3 inflammasome activation (which is a hallmark and a major driver of neuro-degeneration) in transgenic mice expressing human ACE2 [12]. We hypothesize that the virus, in its most severe form of infection known as COVID-19, can act as a catalyst ("accelerant") and/or trigger in a system previously primed by the other conditions (current co-pandemics) described herein (obesity, chronic inflammation, cardiovascular disease), and accelerates the progression and manifestation of neurological conditions like AD and dementia that were already at a higher risk due to a compromised baseline. These questions remain unanswered, but the collision of the pandemics currently in place should bring our attention to the fact that most of them (if not, in their totality) may be preventable by applying primary and secondary measures by which prevention could be achieved.

Bibliography

1. Obesity and overweight (who.int).

2. Grarup NN, Sandholt CH, Hansen T, Pedersen O. "Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond". *Diabetologia* 57 (2014): 1528-1541. DOI: 10.1007/s00125-014-3270-4

3. Meldrum DR, Morris MA, Gambone JC. "Obesity pandemic: Causes, Consequences, and Solutions - But do we have the will?" *Fertility and Sterility* 107 (2017): 833-839. DOI: 10.1016/j.fertnstert.2017.02.104

4. O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. "Neurological consequences of obesity". *Lancet Neurology* 16 (2017): 465-477. DOI: 10.1016/S1474-4422(17)30084-4

5. Velloso LA and Schwartz MW. "Altered hypothalamic function in diet-induced obesity". *International Journal of Obesity* 35.12 (2011): 1455-1465. DOI: 10.1038/ijo.2011.56

6. Anstey KJKJ, Cherbuin N, Budge M, Young J. "Body mass index in middle and late-life as a risk factor for dementia: a meta-analysis of prospective studies". *Obesity Reviews* 12 (2011): e426-e437. DOI: 10.1111/j.1467-789X.2010.00825.x

7. Pedditizi E, Peters R, Beckett N. "The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies". *Age Ageing* 45 (2016): 14-21. DOI: 10.1093/ageing/afv151

8. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. "Central obesity and increased risk of dementia more than three decades later". *Neurology* 71 (2008): 1057-1064. DOI: 10.1212/01.wnl.0000306313.89165.ef

9. Fu YW, Xu HS, Liu SY. "Covid-19 and neurodegenerative diseases". *European Review for Medical and Pharmacological Sciences* 26 (2022): 4535-4544. DOI: 10.26355/eurrev_202206_29093

10. Fotuhi M, Mian A, Meysami S, Raji CA. "Neurobiology of COVID-19". *Journal of Alzheimer's Disease* 76.1 (2020): 3-19. DOI: 10.3233/JAD-200581

11. Xia X, Wang Y, Zheng J. "COVID-19 and Alzheimer's disease: How one crisis worsens the other". *Translational Neurodegeneration* 10 (2021): 15.DOI: 10.1186/s40035-021-00237-2

12. Albornoz EA, Amarilla AA, Modhiran N, Parker S, Li XX, Wijesundara DK, Aguado J, Pliego Zamora A, McMillan CLD, Liang B, Peng NYG, Sng JDJ, Saima FT, Fung JN, Lee JD, Paramitha D, Parry R, Avumegah MS, Isaacs A, Lo MW, Miranda-Chacon Z, Bradshaw D, Salinas-Rebolledo C, Rajapakse NW, Wolvetang EJ, Munro TP, Rojas-Fernandez A, Young PR, Stacey KJ, Khromykh AA, Chappell KJ, Watterson D, Woodruff TM. "SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein". *Nature Molecular Psychiatry*. (2022). DOI: 10.1038/s41380-022-01831-0

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