Conference on ‘Nutrition at key life stages: new findings, new approaches’
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Food patterns and the prevention of depression

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An emerging field of research in nutritional epidemiology is the assessment of several links between nutritional quality and mental health. Specifically, some studies have pointed out that several food patterns could be associated with a reduced risk of depression among adults. This association seems to be consistent across countries, cultures and populations according to several systematic reviews and meta-analyses of observational studies. Some previously described food patterns, specifically the Mediterranean Food Pattern, the Alternative Healthy Eating Index, the Prudent diet or the Provegetarian Food Pattern may be effective to reduce the future risk of depression. Among them, only the Mediterranean Food Pattern has been tested for primary prevention in a large randomised trial, but the inverse association found was not statistically significant. The scientific report of the 2015 Dietary Guidelines for Americans Advisory Committee concluded that current evidence is still limited. Notwithstanding, this field is promising and, according to large and well-conducted observational studies, food patterns potentially associated with reduced risk of depression are those emphasising seafood, vegetables, fruits and nuts. There is a need to assess whether differences in the intake of some micro or macronutrients between these dietary patterns can make a difference in their association with a lower risk of depression. Moreover, the shape of the dose–response curve and the potential existence of a nonlinear threshold effect have not yet been established.

Dietary inflammatory index: CVD: PREDIMED: SUN cohort: Inflammation

Burden of disease by major depressive disorder

Depressive disorders generally consist of major depressive disorder, dysthymia and minor depression, but not other conditions that include depressive features, such as bipolar disorder. Major depressive disorder is the most serious clinical entity in the depressive spectrum and it is one of the most commonly diagnosed psychiatric illnesses. Major depressive disorder represents a priority for potential preventive interventions, because it is highly prevalent and it represents a serious recurrent condition associated with lower quality of life, elevated costs of medical treatments, a huge burden of personal and familial suffering, frequent co-morbidities, increased risk of suicide and elevated overall mortality. The yearly prevalence of major depression in adults is at least 5 %. The lifetime prevalence is 13 % with higher rates among females than males1,2. Symptoms of depression include low mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of

Abbreviations: HEI, Healthy Eating Index; MDS, Mediterranean Dietary Score; MeDiet, Mediterranean diet; RR, relative risk; SUN, Seguimiento Universidad de Navarra.
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According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), released in May 2013, the diagnostic criteria for major depressive disorder are those shown in Table 1. According to Matters and Loncar, unipolar depressive disorders were ranked the fourth global cause of disability-adjusted life years lost in 2002 and they were projected to become the second leading cause of disability-adjusted life years lost in 2030 in the world, and its first cause in high-income countries (3). Consequently, depressive disorders pose heavy health and economic burdens and thus their prevention is a global public health priority.

Age-adjusted rates of depression and suicide are known to be lower in Southern Europe (Spain, Italy and Greece) than in Northern or Central European countries (4). This South-to-North gradient has been hypothetically related to the diversity of food patterns between Mediterranean and non-Mediterranean countries. This difference also indirectly suggests that some aspects of the traditional Mediterranean diet (MeDiet) might have contributed to lower the risk of depression.

### Aetiological hypothesis of depression

Major depressive disorder is considered to be a multifactorial disease. Therefore, a wide array of potential causes including biological, psychological and environmental factors are likely to be involved in the aetiology of depression. The interaction among these elements needs also to be taken into account (5). Alterations in multiple neurobiological pathways, and not a single mechanism, are probably responsible for clinical cases of depression. Recent advances in neuroimaging procedures, including functional neuroimaging studies, have allowed a better understanding of some of these mechanisms.

Well-defined clinical and laboratory evidence supports a hormonal role in depression. This hypothesis holds that repeated or maintained stress-induced hypercortisolae mia will eventually lead to down-regulation of glucocorticoid receptors in the central nervous system. The normal negative feedback on cortisol consisting of inhibition of corticotropin-releasing hormone and adrenocorticotropic hormone as a response to high cortisol levels will be eventually reversed in depression. As a consequence, an alteration of the hypothalamic-pituitary-adrenal axis is frequently seen in depressed patients with positive instead of negative feedback. This creates a vicious cycle with cortisol levels permanently elevated. The consequence of this vicious circle is that the levels of cortisol, adrenocorticotropic hormone and corticotropic-releasing hormone are often simultaneously elevated in the depressed patients. This vicious circle has also been supposedly implicated in reduced volume of the hippocampus, reduced rates of neurogenesis, accumulation of visceral fat, abdominal obesity and a higher propensity to insulin resistance. This mechanism is compatible with the coexistence of major depression and a higher cardiovascular risk related to abdominal obesity, low-grade inflammatory status and insulin resistance. In this context it seems logical to think that depression and cardiovascular risk are very likely to share similar risk factors and aetiological mechanisms.

Another widely accepted aetiological theory is the monoamine hypothesis of depression. It suggests that depression is related to a dysfunction in serotonergic or noradrenergic systems in the central nervous system. The crucial step is reduced availability of these monoamines in the synapse. The ability of some antidepressants to increase monoamine availability in the synapse by blocking their catabolism (for example, monoamine oxidase inhibitors) or by inhibiting their reuptake by the presynaptic neuron (for example, serotonin-reuptake inhibitors) are strong bases for this hypothesis (5). Also, a test of oral tryptophan depletion (the subject is given a drink containing all amino acids except tryptophan, and therefore body stores of tryptophan are depleted) will not cause depression in healthy subjects, but will cause a relapse of some previously depressed subjects because tryptophan is the rate-limiting substrate for serotonin synthesis in the brain. In this context, an adequate intake of vitamin B₆, folate, and vitamin B₁₂ can be speculated to be associated with lower depression risk, because they are involved in the metabolism of S-adenosyl methionine and methionine (an essential amino acid). These latter two compounds are critical to the production of monoamines (serotonin and noradrenaline) and methylation in the brain. An interesting hypothesis of depression suggests that deficiencies in vitamin B₆, folate and vitamin B₁₂ can lead to reduced synthesis of these monoamines and decreased availability.

### Table 1. Diagnostic criteria for depression

<table>
<thead>
<tr>
<th>Core symptoms</th>
<th>Additional symptoms</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Depressed mood most of the day</td>
<td>Clinically significant weight loss or significant</td>
<td>≥Five symptoms, including at least two core</td>
</tr>
<tr>
<td>Markedly decreased interest or pleasure in almost</td>
<td>increase or decrease in appetite</td>
<td>symptoms during almost every day in a 2-week</td>
</tr>
<tr>
<td>all activities (anhedonia)</td>
<td>Insomnia or hypersomnia</td>
<td>period</td>
</tr>
<tr>
<td></td>
<td>Psychomotor agitation or retardation</td>
<td></td>
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<tr>
<td></td>
<td>Fatigue or loss of energy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feelings of worthlessness or excessive or inappropriate</td>
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</tr>
<tr>
<td></td>
<td>guilt</td>
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<tr>
<td></td>
<td>Diminished ability to think or concentrate, or indecisiveness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent thoughts of death or suicidal ideation</td>
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**Note:** DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
of them in the synapse. The repeatedly reported association between elevated levels of homocysteine and depression seems to corroborate this hypothesis because suboptimal levels of folate and B vitamins are associated with higher homocysteine levels and higher homocysteine levels have been associated with depression(6). A food pattern that ensures an optimal nutritional adequacy of these micronutrients (B vitamins and folate) would be likely to exert a preventive action on depression.

Food patterns as a component cause of sufficient causal pathways leading to depression

According to the classical model of causation in epidemiology proposed by Kenneth Rothman(7), the occurrence of a specific disease will always have several contributing determinants that may act together in conjunction to produce the disease outcome of interest. There are several sufficient causes or causal pathways, each of them composed of several elements. The Rothman’s model defined sufficient causes as complete causal mechanisms that will inevitably produce the disease. These complete causal mechanisms or ‘sufficient’ causes will never be isolated or single factors. On the contrary, each of them needs to include a set of different elements and circumstances that, once all of them are present, will unavoidably determine the production of the disease. This is the reason why the Rothman’s model is sometimes called a modified deterministic causal model.

In contrast to sufficient causes, Rothman defined a component cause as each of the many elements that are included in at least one of the sufficient causal mechanisms or pathways. Usually, epidemiologists consider component causes as actual and proper causes of disease because the disease will not occur by that sufficient causal mechanism or pathway unless all the component causes of that pathway are present. Speaking in positive terms, if only one of its component causes is removed, that causal pathway will not produce the disease. This is a powerful approach for preventive medicine because, under the assumptions of this model, it is not necessary to tackle all of the component causes which are included in a sufficient cause or pathway in order to prevent the disease. Only with the elimination of one of them, the disease will be prevented.

In the context of the Rothman’s model of causation in epidemiology, there is a growing body of evidence to support that some unhealthy food patterns can be considered as component causes of depression. Indeed, this assertion does not imply that unhealthy food patterns will be always a cause of depression (they are not a sufficient cause) neither that in all cases of depression an unhealthy food pattern was involved in the causal pathway (they are not a necessary cause of depression). Food patterns merely represent one of several component causes present in at least one of the multiple sufficient causes (causal pathways) of depression. Nevertheless, they can be appropriately referred to as causes of depression.

Biological plausibility for the link between cardioprotective diets and reduced risk of depression

One important criterion for causality in epidemiology is biological plausibility. There are many reasons to support the biological plausibility that cardioprotective food patterns are also protective against major depression(6). Reasons to support this biological plausibility include the following mechanisms exerted by a cardioprotective diet: Anti-inflammatory effects; A high content of antioxidants, which can produce neuroprotection; Improved insulin sensitivity and reduced risk of metabolic syndrome; Improved endothelial function being the endothelium responsible for neurotrophins synthesis, including brain-derived neurotrophic factor; Potential for enhanced synaptogenesis and neurogenesis as a consequence of better availability and function of neurotrophins; Better nutritional adequacy and availability of B vitamins and folate related to the synthesis of monoamines; Improvement of lipid subtypes (n-3 fatty acids and other unsaturated fatty acids instead of trans fatty acids or SFA) in cell membranes, and consequently increased fluidity and permeability of cell membranes, where receptors for neurotransmitters are located; Counteracting of the adverse metabolic effects and increased visceral fat due to the abnormal regulation of the hypothalamic–pituitary–adrenocortical axis that occurs in depression.

In this context, a wide body of clinical and epidemiological evidence supports a strong mutual link between depression and CVD. Sometimes the occurrence of depression precedes a cardiovascular event; in other instances a cardiovascular event is associated with a future higher risk of depression. It is very likely that depression and CVD may share common pathophysiological factors. For example, the seven health cardiovascular metrics proposed by the American Heart Association in 2010(6) were predictive of a substantially lower risk of depression in 5110 participants of the Aerobics Study cohort followed-up for 6-1 years(10). Also in the Seguimiento Universidad de Navarra (SUN) cohort, after following-up more than 16 000 participants initially free of depression and CVD during an average of 9 years, several predictive equations for cardiovascular risk built with baseline values of cardiovascular risk factors were strongly associated with the future risk of developing depression during the follow-up period (P Molero, unpublished results).

Advantages of food patterns in nutritional epidemiology

Several nutrients or foods have been associated with the risk of depression in longitudinal epidemiologic studies. They include a reduced risk of depression associated with an increased intake of folate(11,12), n-3 fatty acids and n-3:n-6 fatty acids ratio(13–15), olive oil(16,17) or moderate alcohol intake(18,19), whereas an increased risk of depression has been associated with higher intake of trans fatty acids(17), fast food and commercial bakery(20).
However, in nutritional epidemiology, two different situations need to be differentiated. Sometimes, the disease of interest is likely to be caused by a single nutrient or food. In contrast, and much more frequently, the disease will be probably associated with several dietary factors. For the first (and rare) situation the focus on a single nutrient or food may be adequate. However, for the most common situations of multifactorial dietary causes of a disease, the focus on a single nutrient or food will be wrong. In these very common situations, the food pattern approach represents the best-fitted methodology according to the current state of the art in nutrition research. The reason is that to assess the overall food pattern may be more useful because it goes beyond nutrients or foods and examines the effects of the overall diet. The focus on isolated nutrients or single foods is usually inappropriate because it would be unrealistic to assume that a single food or nutrient will have an important effect. In addition, the assessment of isolated food components makes it difficult to take into account any interaction between them. Food patterns allow capturing a wide range of potential interactions between different nutrients and foods. Moreover, the assessment of isolated foods or nutrients will be frequently confounded by other dietary factors.

The analysis of food patterns instead of isolated foods or nutrients overcomes most of the earlier-mentioned problems. Conversely, from an epidemiologic point of view, the sociological reality that many foods are usually consumed together provides an interesting approach per se. Therefore, in the study of the relationships between nutritional factors and the risk of depression, to change the focus to overall food patterns is more useful than the reductionist view of attributing all the effect to a single food or nutrient (21). The advantages and limitations of the use of food patterns in nutritional epidemiology are presented in Table 2.

Table 2. Strengths and limitations of the food pattern approach

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Interaction between nutrients is captured</td>
<td>Two general approaches: which is better?</td>
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<tr>
<td>Synergies</td>
<td>Hypothesis-oriented (a priori)</td>
</tr>
<tr>
<td>Antagonisms</td>
<td>Data-driven (a posteriori)</td>
</tr>
<tr>
<td>Confounding by other dietary factors is prevented</td>
<td>Cluster</td>
</tr>
<tr>
<td>Increased statistical power</td>
<td>Factor analysis</td>
</tr>
<tr>
<td>The isolated effect of a nutrient is too small</td>
<td>The reproducibility is impossible or suboptimal</td>
</tr>
<tr>
<td>Cumulative exposure has a stronger effect</td>
<td>Sample-specific medians v. normative scores</td>
</tr>
<tr>
<td>It avoids multicollinearity</td>
<td>Factor or cluster analyses are not reproducible</td>
</tr>
<tr>
<td>It avoids issues of multiple comparisons</td>
<td>Heterogeneity in dietary assessment tools</td>
</tr>
<tr>
<td>It describes a sociological reality of interest per se</td>
<td>It may introduce new sources of confounding</td>
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</table>

Food patterns cannot be directly measurable. However, they have been defined as the quantities, proportions, variety or combinations of different foods and beverages in diets, and the frequency with which they are habitually consumed (22, 23).

The methodology to ascertain food patterns can follow four different general approaches: (i) Selective diets: The procedure involves classifying subjects according to whether or not they meet several criteria (e.g. avoidance of meat or meat products to classify them as vegetarians); (ii) Indexes or scores: They are built according to individuals’ scores on quality of the food pattern and its components. They are sometimes referred to as a priori food patterns (e.g. the Mediterranean Dietary Score (MDS) proposed by Trichopoulou et al., (24)); (iii) Cluster Analysis: Statistical analysis conducted to build groups of similar individuals according to their food patterns. These are examples of a posteriori or empirically derived food patterns; (iv) Factor Analysis: Statistical identification of factors explaining variation in individuals’ scores (e.g. the Western Food Pattern originally proposed by Hu et al. (25). As the previous analysis, this approach identifies a posteriori or empirically derived food patterns.

The second approach represented by a dietary index tries to assess overall diet quality. The use of a dietary index is considered as an a priori approach because the scoring systems for such indexes or scores are based on previous knowledge of what constitutes a healthy diet or what represents a traditional or geographical model for a typical combination of food habits (e.g. a Mediterranean-type diet). Sometimes, the dietary index/score approach might be limited by the gaps in current knowledge and current understanding of the food-disease relationship. Further examples, beyond the MeDiet, of some a priori-defined food patterns using indexes or scores are the Healthy Eating Index (HEI), a single summary measure of the degree of conformity between an individual’s diet and the recommendations of the US Department of Agriculture Food Guide Pyramid for five major food groups and to specific recommendations in the US Dietary Guidelines for Americans, the Healthy Diet Score, the Recommended Food Score or the Alternative HEI.

Available longitudinal evidence on food patterns and the risk of depression

Some studies have pointed out that several food patterns could be associated with the risk of depression among...
adults. This association seems to be consistent across countries, cultures and populations according to several systematic reviews and meta-analyses. These systematic reviews included not only adults but also other populations, included retrospective or cross-sectional studies without longitudinal data and finally, occasionally included studies that really did not assess the effect of an overall food pattern, but only of food items or food groups. Table 3 provides a summary of available longitudinal prospective studies assessing the risk of adult depression associated with overall food patterns.

Only one large randomised trial (the PREDIMED study) has tested the effects on the risk of incident cases of clinical depression during 5-4-years follow-up of two MedDiet in comparison with a control group receiving advice to follow a low-fat diet in an elderly population at high cardiovascular risk. The point estimates for the relative risks (RR) associated with the intervention using a MedDiet supplemented with extra-virgin olive oil (RR = 0.91) or a MedDiet supplemented with mixed tree nuts (RR = 0.78) in the PREDIMED trial suggested an inverse association. However, the CI for both estimates were wide and they showed that the results were compatible with a null result. Even when both MedDiet were merged together and analysed as a single group, the multivariable-adjusted RR was 0.85 (95% CI 0.64, 1.13). Only when the analysis was limited to participants with type 2 diabetes (approximately 50% of the sample), a significantly reduced risk of depression was observed and only for participants assigned to the MedDiet + nuts (RR = 0.59; 95% CI 0.36, 0.98; P = 0.04) but not for participants randomly allocated to MedDiet + extra-virgin olive oil. A second available trial of a small sample size and short duration tested a diet in line with the model of the Dietary Approaches to Stop Hypertension and moderately reduced in sodium. The outcome was the amelioration of symptoms of postmenopausal depression. A beneficial effect was observed for both the active intervention and the control group, without significant differences between them.

Among observational studies, an inverse association between a priori defined Mediterranean-type diets and the incidence of depression has been found in two large cohorts. In the largest of them (the SUN study) a reduced risk of depression associated with closer
Conformity to the traditional MeDiet was found\(^{31}\). The conformity to the MeDiet was operationally defined using the MDS proposed by Trichopoulou et al.\(^{33}\). The MDS assigned 1 point to subjects whose consumption was at or above the sex-specific median of six components in agreement with the traditional MeDiet (vegetables, fruits/nuts, legumes, fish/seafood, cereals and MUFA:SFA lipid ratio). The participant received also 1 point if her/his intake was below the median for the two components not in line with the traditional MeDiet (meat/meat products and dairy products). For ethanol, 1 point was assigned only for moderate amounts of intake (5–25 g/d for women or 10–50 g/d for men). Consequently, the MDS could theoretically range from the highest possible conformity to MeDiet (9 points) to the minimum possible conformity (0 points reflecting no adherence at all). Adherence to the MDS was categorised into five categories: low (score 0–2), low–moderate (score 3), moderate–high (score 4), high (score 5) and very high (6–9). The RR of incident clinical depression (480 new diagnoses during 4-4 years follow-up) were 0.74, 0.66, 0.49 and 0.58 for low-moderate, moderate-high, high and very high conformity \(v\), low conformity, respectively, all of them statistically significant in fully adjusted models and with a significant linear trend \((P = 0.002)\). To allay fears related to a potential reverse causality bias (i.e. depressed patients may have poorer dietary habits as a consequence of their depression), the authors repeated their analyses after excluding those cases of depression reported in the first 2 years of follow-up \((n = 243)\). Contrarily to the hypothesis of reverse causation that would predict an attenuation of the association after the exclusion of early cases, the inverse associations for the two upper categories of conformity to the MeDiet were not attenuated, but they even exhibited stronger inverse associations with \(RR = 0.42\) (95% CI 0.27, 0.66) and \(R = 0.50\) (95% CI 0.33, 0.74) for MDS = 5 and MDS ≥ 6, respectively.

Nevertheless, it should be pointed out that a smaller cohort study in Greece, did not find any significant advantage of the MeDiet\(^{34}\). However, it is necessary to highlight that the present study was based on a sample of only 732 elders. The point estimate for the RR associated with the MeDiet was protective although not significant probably due to a lack of statistical power.

The association between the adherence to other quality dietary indexes beyond the MeDiet and depression has also been analysed. Whereas no significant effect between the adherence to the HEI and changes in depressive symptoms was found after 3 years of follow-up in the NuAge study\(^{35}\), Akbaraly et al. showed a significant association between a higher score in the alternative HEI and a lower risk of depression in women, but not in men, from the Whitehall-II cohort study\(^{36}\). Also in the SUN cohort, several other quality dietary indexes, specifically the alternative HEI and the Pro-vegetarian Dietary Pattern showed an inverse association with the incidence of depression and suggested the potential existence of a nonlinear threshold effect\(^{37}\). This last finding suggests that the risk of depression can be reduced when a subject moves from very low to moderate adherence to a diet quality index. However, there is not much extra benefit in terms of reduced risk of depression for further improvements in adherence when the subject moves from moderate to high or very high scores. This dose–response pattern is compatible with the hypothesis that suboptimal intake of some micronutrients (present in the lower levels of adherence to diet quality scores) is involved in the risk of developing depression.

Principal component analysis (Factor Analysis approach) has also been developed in several cohort studies to identify post-hoc (empirically derived) food patterns\(^{38–44}\). Results obtained for MeDiet are consistent with those reported using a priori-defined food pattern\(^{38}\). Other examples include the results reported by Akbaraly et al. within the Whitehall-II study\(^{39}\) that found that an empirically derived food pattern rich in sugary desserts, fried foods, processed meats, refined grains and high-fat dairy products was associated with a significantly increased risk of depression, whereas an empirically derived food pattern rich in vegetables, fruits and fish was associated with a significantly lower risk of depression. In contrast with the significant protection against depression found for a Prudent food pattern empirically identified in the Kuopio cohort\(^{40}\) or in the Australian PATH cohort study\(^{41}\) or the detrimental role of Western, snacking and fat-sweet food patterns obtained in the GAZEL cohort study\(^{42}\), other studies have failed to report statistically significant results for the analysis of the association between a post-priori food patterns and depression\(^{43}\). In this sense, it is remarkable to highlight the results reported in the Nurses’ Health Study. In this large cohort, the Prudent (high in vegetables) or Western (high in meats) food patterns also identified by using principal component analysis did not show any significant association with the incidence of depression\(^{44}\). However, another posterior assessment in the Nurses’ Health Study using reduced rank regression methods found that a pro-inflammatory food pattern was significantly associated with a higher risk of depression\(^{45}\) supporting the hypothesis of the biological plausibility for the link between cardioprotective diets and reduced risk of depression mentioned earlier.

In line with these findings, the SUN cohort has also recently reported a similar magnitude of the increment in the risk of depression related to a pro-inflammatory food pattern assessed through the Dietary Inflammatory Index, a scoring algorithm based on an extensive review of the literature linking articles focusing on the effect of diet on inflammatory biomarkers\(^{46}\).

Though further longitudinal studies and trials are needed to confirm several aspects such as the link between depression and cardiometabolic conditions or the shape of the dose–response curve between adherence to a diet quality index and the risk of depression, we can conclude stating that there is a growing body of sound epidemiological evidence to support that food patterns with a high content in fruit and vegetables, olive oil, tree nuts, fish and whole grains, but low in meats, meat products, commercial bakery, trans fats, sugary desserts and sugar-sweetened beverages are associated with a reduced risk of depression.
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Conflicts of Interest
None.

Authorship
Both the authors contributed equally to the writing of this work.

References


