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COMMENTARY

Evolution from pseudodementia to dementia: is depressive symptom an optional extra?

A growing interest in pseudodementia sheds light on further explorations of the underlying mechanism on the progress of cognitive impairment and subsequent development of dementia. Pseudodementia is defined as cognitive dysfunction co-occurring with depression, with especially high prevalence in older adults (Yaffe *et al.*, 1999). Extant literature has noted that pseudodementia acts as a prodromal stage leading to dementia, frequently related to an increased risk of cognitive impairment (Alexopoulos *et al.*, 1993; Sáez-Fonseca *et al.*, 2007; Sohrabi *et al.*, 2019). Featured by detectable, treatable, and preventable, intervention on pseudodementia may provide a window for earlier diagnosis and slower deterioration of the insidious dementia. Though a bunch of studies have been dedicated to exploring the relationship between geriatric depression and cognitive impairment, in the presence or absence of cognitive dysfunction, there is still a far way to reach the agreement on the association between these three disorders. Statically significant association between cognitive difficulties and cognitive impairment (Jessen *et al.*, 2014; Reisberg *et al.*, 2010), and between geriatric depression and cognitive impairment (Kang *et al.*, 2014; Ownby *et al.*, 2006) have been described in recent literature, yet no significant results also have been reported in several community-based cohort studies (Becker *et al.*, 2009; Ganguli *et al.*, 2006). Moreover, long-term indifference to older adults suffering cognitive dysfunction combined with depression can be proportionally attributed to this unsolved relationship, since they are considered as "not really dementia", which is beyond the clinical threshold. Therefore, it is in great need to detangle the underlying mechanism wherein pseudodementia deteriorates to dementia on the perspective of depression, for maximizing the likelihood of a preventive strategy for dementia. A well-designed prospective large cohort focusing on community-based elder population would be a robust comparison to former researches.

In this issue of *International Psychogeriatrics*, Shin (2020) provided novel insights into the geriatric depressive symptoms to test its relationship with the 12-year later cognitive impairment, in the presence or absence of cognitive dysfunction. The author hypothesized that depressive symptoms might have a long-term impact on future cognitive impairment among community-dwelling older adults, and this adverse situation accompanied by cognitive dysfunction would result in a significant increase in the development of dementia. The study was based on the Korean Longitudinal Study of Aging (KLoSA), a nationwide longitudinal panel cohort in South Korea, focusing on a total of 10,254 community-dwelling older adults aged 45 years or older. Shin examined 4547 individuals in the cohort who were free from depressive symptoms and cognitive dysfunction at baseline (the first wave conducted in 2006), completing up to seventh wave by 2018. To clarify the individual impact and joint effort of depressive symptoms and cognitive dysfunction on cognitive impairment, four groups were subdivided using the CES-D10 Scale, a 10-item short-form version of the Center for Epidemiological Studies-Depression Scale (Andresen *et al.*, 1994), and the K-MMSE, a Korean version of the Mini-Mental State Examination (Kang *et al.*, 1997), respectively. To highlight, four stable groups were reclassified depending on whether the depressive condition and cognitive status of each individual remained in the same category at the second and third waves. If so, they would be deemed as stable. A comparison of survival curves between original and stable grouping was then performed aiming at adjusting the potential influence of short-term exposure fluctuations on the key event.

The point of Shin's study was the hazard calculation of four exposure groups in the contest of survival analysis. The pseudodementia group experienced the highest hazard ratio and the severest loss of survival, suggesting that depressive symptoms accompanied by cognitive dysfunction play a significant role in predicting long-term cognitive impairment. Nonetheless, older adults subject to depressive symptoms while free from cognitive dysfunction reported no significant difference in terminal events compared with the control group. Therefore, this study drew a conclusion that depressive symptoms co-occurred with cognitive dysfunction did pose threats to long-term cognitive impairment, even though depressive symptoms alone demonstrated no significant causal effect.

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However, this paper leaves out essential processes that are highly relevant to the reliability of results. The study did not make a comparison between the large number excluded population and samples finally included into the analysis. It is a huge gap from the original 10,254 population shrunk to 4547 population for final analysis. Despite the choice of survival analysis, it is still an open question whether the analyzed individuals could be representative for its KLoSA population, since information will always be lost whatever statistical methods are applied to analyze censored data (Leung *et al.*, 1997). Moreover, the crude control on confounding factors in this study lowered the representativeness of samples in each subdivision and its results in the survival analysis. Application of more apposite confounding adjustment like propensity score matching, rather than simply adding them together in the regression model, would reinforce the comparability between groups and reliability of results.

Baseline analysis showed that sociodemographic characteristics were of consequence in grouping depressive symptoms and cognitive dysfunction. Individuals overwhelmed by both depressive symptoms and cognitive dysfunction (pseudodementia, Dep-CD group) were more likely to be older, less educated, unemployed, less remained married, rural residents, and victims of metabolic diseases. However, as the study confessed, many confounding factors closely associated with a cognitive function such as emotional status, physical exercise, diet were unavailable in the KLoSA data. This omission in these unmeasured confounding factors may also question the comparability between four exposure groups. In addition, we think this omission would be a mirror of a wider problem on aging, medical, and economic burden. Especially, significant differences involving metabolic diseases like diabetes mellitus and hypertension in this study indicated that there might be an underlying mechanism among physiological metabolism, psychological well-being, and cognitive function. Evidence in terms of metabolic disorders such as abnormal levels of glucocorticoid, nerve growth factors has been stated in previous reviews to explain the mechanism between depression and dementia (Byers and Yaffe, 2011). The concept of metabolic depression having been raised in recent years also provides support that metabolic dysregulation may act as a predictor for the deterioration of late-life depression (Marijnissen *et al.*, 2017). Besides, a recent meta-analysis reported that metabolic diseases were associated with an increased risk of dementia (Atti *et al.*, 2019; Pal *et al.*, 2018), owing to both physiological disorders and social-economic factors, since poverty caused by unaffordable medical expense on metabolic diseases would subsequently lead to inaccessibility to sustainable medical treatments. Ultimately, this vicious circle may end up in the irreversible cognitive impairment. It is in high likelihood that metabolic dysregulation, depressive symptoms, and dementia may share a chain reaction or interaction with each other, however, few studies have taken all these three valuables into condition together. Future research may consider this possibility to better understand the relationship between the persistence of depressive symptoms and the occurrence of dementia.

Another problem that needs to be further explored is frequent fluctuations in cognitive dysfunction and depression. This contributes much to the blurred zone of pseudodementia as well as the complicated course from pseudodementia to dementia, making it tougher to clarify the long-term impact of depressive symptoms on cognitive impairment. What's more, lag effects (also called residual symptoms) could be frequently founded in depressive symptoms, wherein the higher frequency, the severer depression. Therefore, extant guidelines support that both history conditions and changes in the process are required to differentiate the status of pseudodementia and dementia (Zapotoczky, 1998). In Shin's study, four stable groups were defined free from fluctuation according to the second and third waves. Huge population changes in each group compared with the original classification demonstrated that unstable exposure of depressive symptoms and cognitive function existed among older adults. As for the fluctuations, this preliminary strategy using only two-round classification was not robust enough. Adding more waves to indicate the long-term fluctuation might be helpful to solve this limit, while constraints on sample size made it difficult to realize. Hence, considering the time effect on depressive and cognitive status and regarding them as time-dependent variables may better explain the variations in grouping and subsequent relationship exploration.

Apart from study design and data analysis, a discrepancy in measurements and study population may partly account for the difference in results from previous literature on the same topics. Great variations in assessment on cognitive functioning, ranging from mental examination to short memory test and from single-scale measurement to combined applications, may support the difference in the judgement of the outcome and their long-term relationship. One systematic review composed of cohort studies mainly using National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) to assess the cognitive function reported that those who

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suffered depression in the past were exposed a higher risk in developing Alzheimer's disease, the commonest cause of dementia (Ownby *et al.*, 2006). Besides, in Shin's literature, the K-MMSE assessment on cognitive function for the Korean community-dwelling elderly was in low sensitivity and specificity. In other words, this assessment on cognitive dysfunction and later impairment would result in the wrong classification of individuals, thus casting doubt on the final conclusion. As to assessment for depressive symptoms, Shin underscored the harmful effect of self-detected depressive symptoms, rather than depression diagnosed clinically, on the development of cognitive impairment among community-dwelling elders. Nonetheless, an insignificant relationship between depressive symptoms and later cognitive impairment was reported in accordance with previous community-based cohort studies. Possible reasons may be the low proportion of moderate and severe depressive population from community-based backgrounds and the classification in the survival analysis beginning from depression. Small samples in subdivided groups may provide this information, in that depressive symptoms occurring after cognitive dysfunctions might be overlooked. However, the explanation about shifting the scale from self-reported assessment on depressive symptoms to clinical diagnosis on depression may be short of evidence, since previous studies have stated that cognitive impairment developed from pseudodementia always shows coexisting depressive symptoms (Fischer *et al.*, 2002). Therefore, the insignificant result between long-term depressive symptoms and dementia needs to be taken cautiously.

Though more sophisticated design and analysis should be taken to strengthen the results, its relatively large cohort sample size, specific predicted factors, and preliminary solutions to exposure fluctuations are all key merits in this study. More importantly, Shin's study presents extremely high attention to early diagnosis of pseudodementia, which is one of the utmost curable stages for later irreversible dementia. The author brings a novel touch on the current hazy association between persisting depressive symptoms combined with cognitive dysfunction and cognitive impairment. Insignificant outcome between depressive symptoms and cognitive impairment is also reported, in line with previous literature in the context of community. More weights should be attached to explorations on cognitive deteriorating progress and medical support for pseudodementia among older adults, which would reduce the risk of later cognitive impairment.

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