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Levels of IL-6 in peripheral blood and cerebrospinal fluid of Alzheimer's disease: a meta-analysis

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Abstract: *BACKGROUND: Alzheimer's disease (AD) is a common degenerative disease of the central nervous system in the elderly. Several reports have described the serum levels of interleukin (IL-6) in AD. In order to elucidate the status of IL-6 in AD, the article conducted a meta-analysis of previously published results to assess the levels of IL-6 from different tissue sources in AD. METHODS: The levels of Th17 related cytokines (IL-6) in peripheral blood or cerebrospinal fluid (CSF) of AD were systematically reported in domestic and foreign databases. The article assessed pooled data using a random-effects model.The I-square index (I^2) was used to assess inconsistency and publication bias was assessed by examining funnel plot asymmetry using the Begg and Egger test. Results: Among 1348 identified studies, the article selected 45 studies for analysis, 36 to investigate IL-6 levels in peripheral blood and 9 to investigate IL-6 levels in CSF of AD versus healthy controls (HCs). The analysis revealed that IL-6 content in peripheral blood of AD was significantly higher than that of HCs[SMD = 0.913, 95% CI (0.345, 1.481), P < 0.05], while the level of IL-6 in CSF showed no statistical significance [SMD = 0.132, 95% CI (-0.579, 0.843), P > 0.05] and could not be used as a marker in AD. CONCLUSIONS: In AD, the level of IL-6, a relevant marker, is increased, and spontaneous IL-6 production by peripheral blood mononuclear cells may be a marker of future AD risk in the elderly, and these data strengthen evidence of the pathophysiological role of inflammation in the development of clinical AD, but suggest that the mechanism of IL-6 action still needs more research and can be used as a potential target to address the problem of AD in the future.*

Keywords: *Alzheimer's disease; IL-6; plasma; CSF; meta-analysis*

1. Introduction

Alzheimer's disease (AD) is a common degenerative disease of the central nervous system in the elderly, and autopsy studies of the brains of AD have shown the presence of acute phase reactants (including C-reactive protein [CRP], pro-inflammatory cytokines, and activated complement cascade proteins) in senile plaques and neurofibrillary tangles[1]. Histopathologic changes in AD are mainly senile plaques, neurofibrillary tangles, and neuronal loss. At present, the specific pathogenesis of AD has not been fully clarified, of which the amyloid β-protein (Aβ) toxicity hypothesis is the dominant pathogenic mechanism theory, β has neurotoxicity, and can activate complement. In AD brains, the persistence of amyloid plaques may continuously activate microglia, which can trigger chronic inflammation of the central nervous system, and then accelerate cell death. Recently, several studies have elucidated the mechanisms of inflammatory effects. Among them, inflammatory factors and lymphocytes that enter the brain through the blood-brain barrier can cause pathological inflammatory responses in AD. Cytokines and chemokines are involved in the initiation, propagation, and regulation of immune and inflammatory responses, and these soluble mediators play an important role in a variety of neurological diseases such as multiple sclerosis, AIDS dementia, stroke, and AD[2]. Peng, Y[3]et al showed that non-psychotic older adults are characterized by increased levels of inflammatory markers in CSF.IL-6 released from PBMCs may be a useful marker of AD disease severity and NPS severity[4]. Therefore, further elucidation of the functional characteristics of relevant inflammatory factors capable of eliciting AD will provide new insights into understanding the pathogenesis of AD and provide new interventions for the treatment of AD.

Interleukin-6 (IL-6) is a pleiotropic cytokine with pro- and anti-inflammatory properties that has a broad spectrum of biological actions, including modulation of immune responses, hematopoiesis, and acute phase responses[5]. In addition, it has been shown that immune responses are disturbed in patients with Alzheimer 's dementia (DAT), which may be due to the fact that the cell surface interleukin 6

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receptor (IL-6R) is associated with T lymphocyte immune function[6]. Alternatively, the important role of IL-6 in innate, humoral, and cell-mediated immunity does provide an indication of immune system status, which in turn may influence pathways affecting vascular health and contribute to AD pathology. Therefore, we performed an updated population-based meta-analysis on the association between the inflammatory marker IL-6 and AD.

2. Materials and Methods

2.1 Search strategy

This meta-analysis was performed according to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) entries. The Chinese Academic Journals Full-text Database (CNKI), Chinese Science and Technology Journal Database, and Wanfang Database were searched by computer, and the English databases PubMed, Embase, Web of Science, and Cochrane Library were searched to search the proportion of IL-6 in AD, at the same time, to avoid omissions, references of relevant studies were manually searched. The search period was from database establishment to December 2022. MeSH medical subject headings combined with free words were used for the search. Chinese search terms included "Alzheimer's disease", "cytokine IL-6", etc. English search terms included "Alzheimer Disease", "Interleukin-6", etc.

2.2 Study Selection and Data Extraction

2.2.1 Inclusion Criteria

A. The subjects in the case group were AD who met the MMSE grading criteria of the Mini-Mental State Examination, and the controls were healthy individuals. Based on the MMSE grading criteria of the Mini-Mental State Examination, the MMSE scores of AD included were not higher than 26 points. **B.** The study type was a case-control study published at home and abroad on the IL-6 content of markers in AD. **C.** The article provided complete data to calculate the mean and standard deviation (SD) and 95% confidence interval (CI) of IL-6 proportion in the peripheral blood and CSF of AD and controls. **D.** The full text (web link or PDF) could be obtained on the Internet, and the age, gender, and ethnicity of the study subjects were not limited. The course of disease and disease activity of AD were still not limited.

2.2.2 Exclusion Criteria

A. Reviews, case reports, cohort studies, uncontrolled studies, and non-human studies. **B.** Studies for which valid raw data are not available. **C.** Non-Chinese and English literatures. **D.** Repeated publications using the same data.

2.2.3 Data Extraction and Quality Assessment

Studies were independently screened by two researchers applying the same inclusion and exclusion criteria and assessed in full text. Relevant data from each eligible article were extracted using a uniformly designed data collection form, including characteristics such as article author, article publication date and location, level of literature evidence, sample size, and sample age and sex.

Quality assessment of each study was performed independently by two investigators using the Newcastle − Ottawa Quality Assessment Scale (NOQAS) and summarized in tabular form.

2.3 Statistical Analysis

We calculated the standard deviation (SD) and 95% confidence interval (95% CI) of Treg-related cytokine (IL-6) in AD and control participants. We treated these results as continuous variables, calculated the mean standard deviation (SMD), and calculated summary estimates of standardized mean differences in serum IL-6 levels between patients and controls. Heterogeneity and risk of bias were statistically examined with the I-squared index (I^2). If there was significant heterogeneity among studies ($I^2 > 50\%$), the random effects model was used to compare the data in the set, otherwise, the fixed effects model was used. Egger 's test was used to assess potential publication bias. The test level of Meta analysis is $\alpha = 0.05$. All statistical analyses were performed using Stata (version 15.0).

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3. Results

3.1 Literature Search Results

A total of 1348 articles were initially screened, including 1211 articles in the English database PubMed, 16 articles in Web of Science, 19 articles in EMBASE, and 35 articles in Cochran library. There were 39 Chinese Academic Journals Full-text Database (CNKI), 4 VIP database and 46 Wanfang database. Forty-one duplicate articles were excluded using EndNoteX9 software. A total of 1307 studies were identified, of which 45 studies were included in the final meta-analysis after careful reading of the study title, abstract, and original text according to the inclusion and exclusion criteria. Including 2158 AD and 1959 HCs retrieved, initially screened, and included, the comprehensive process is detailed in Figure 1.

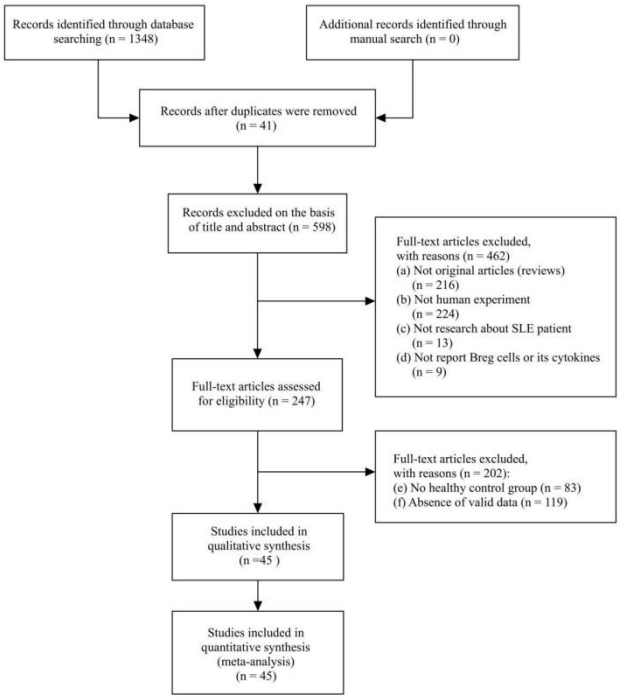

Figure 1: Literature screening flow chart

The databases searched and the articles retrieved were PubMed 1211, Web of Science 16, EMBASE 19, and Cochran library 35. There were 39 Chinese Academic Journals Full-text Database (CNKI), 4 VIP database and 46 Wanfang database.

3.2 Risk of bias assessment

Table 1: A summary table of basic characteristics and risk of bias evaluation from PBMC studies

Author	Evidence Level[a]	Year	Number of Cases		IL-6 level in peripheral blood ((mean(or median)±SD) pg/ml	Concentration units
			AD	HC		
Ruosong Yang	4	2010	26	23	AD：48.07±3.89 HC：34.21±10.54	pg/ml μg/ml
Li Ma	4	2017	82	74	AD：1287.6±140.32 HC：938.3±28.75	pg/ml pg/ml
Wennström, M.	4	2015	45	36	AD：1.37±1.09 HC：1.17±1.10	U/ml pg/ml
Wang, S. S.	4	2022	30	30	AD：7.81±3.42 HC：5.05±1.93	pg/ml pg/ml
van Duijn, C. M	4	1990	127	79	AD：8.60±7.35 HC：8.4±10.61	pg/ml pg/ml
Shen, H., Han, C	4	2021	60	50	AD：14.17±3.11 HC：2.26±0.88	pg/ml ng/ml

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O'Bryant, S. E.	4	2016	79	65	AD：13.6±10.5 HC：2.1±2.1	pg/ml pg/ml
Kim, Y. S.	4	2017	35	28	AD：26.04±50.62 HC：9.72±26.43	pg/ml pg/ml
Khemka, V. K	4	2014	55	37	AD：7.26±2.95 HC：4.2±0.26	pg/ml ng/ml
Yingman Wu	4	2010	16	19	AD：192.8±47.6 HC：80.1±46.1	pg/ml pg/ml
Westman, G.	4	2014	30	35	AD：6±3.77 HC：5.69±5.24	pg/ml pg/ml
Teunissen, C. E.	4	2003	34	61	AD：2.54±0.72 HC：2.51±0.87	pg/ml pg/ml
Johansson, P.	4	2017	52	18	AD：0.88±0.34 HC：1.04±0.24	pg/ml pg/ml
Hongwei Guo	4	2012	36	32	AD：43.12±14.73 HC：45.28±15.24	pg/ml ng/ml
Zhao, S. J.	4		150	150	AD：1.86±1.12 HC：1.72±1.11	pg/ml pg/ml
Savas, S.	4	2016	59	38	AD：2.82±4.3 HC：1.55±2.2	pg/l pg/ml
Chao, C. C	4	1994	22	22	AD：116±19 HC：102±17	pg/ml pg/ml
C.E. Teunissen	4	2003	34	61	AD：2.54±0.72 HC：2.51±0.87	pg/ml pg/ml
Dongming Huang	4	2018	70	70	AD：18.04±6.52 HC：3.63±1.24	pg/ml pg/ml
Xin, Y.	4	2021	80	71	AD：17.5±3.1 HC：10.6±2.3	pg/ml pg/ml
Wu, Y. Y.	4	2015	41	40	AD：2.3±1.4 HC：1.6±0.8	pg/ml pg/ml
O'Bryant, S. E.	4	2016	79	65	AD：4.8±5.9 HC：4.7±5.6	pg/ml pg/ml
Llano, D. A.	4	2012	15	7	AD：2.44±2.03 HC：2.15±0.4	pg/ml pg/ml
Gubandru, M	4	2013	21	10	AD：37.5±11.03 HC：10.8±1.08	pg/ml pg/ml
Bermejo, P.	4	2008	45	28	AD：0.32±0.18 HC：1.09±0.35	pg/ml pg/ml
Zhu, Y	4	2017	96	79	AD：11.9±0.78 HC：59.8±1.59	pg/ml pg/ml
Wang, T	4	2014	97	122	AD：20.07±4.71 HC：25.02±5.74	pg/ml pg/ml
Singh, V. K.	4	1994	6	6	AD：6.66±2.42 HC：2.08±0.81	pg/ml pg/ml
Licastro, F.	4	2000	145	51	AD：6.64±1.25 HC：1.18±0.36	pg/ml pg/ml
Kliushnik, T. P	4	2017	91	38	AD：4.9±0.55 HC：4.10±0.44	pg/ml pg/ml
King, E.	4	2019	21	20	AD：1.13±3.32 HC：1.71±0.99	pg/ml pg/ml
K, Yamada	4	1995	12	7	AD：17±0.26 HC：2.67±0.34	pg/ml pg/ml
Huang, C. W	4	2012	28	19	AD：3.11±1.99 HC：2.62±2.01	pg/ml pg/ml
Walker, K. A.	4	2020	26	150	AD：2.82±4.81 HC：1.83±2.44	pg/ml pg/ml
Carmen Vida1	4	2017	18	38	AD：10798±4432 HC：5791±3022	pg/ml pg/ml
Ciabattoni, G	4	2007	44	44	AD：0.54±0.58 HC：0.95±0.65	pg/ml pg/ml

Note: AD: Alzheimer 's disease, HC: Healthy controls, [a] Level of evidence for each study was based on 2011 Oxford Centre for Evidence-Based Medicine guidelines

Case-control studies targeting IL-6 levels in peripheral blood of AD included 45 studies with high overall quality and low risk of bias. The Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 guidelines showed that all studies were case-control studies or case series with poor quality evidence level 4. In addition, we scored all included studies using the Newcastle – Ottawa Quality Assessment

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Scale (NOQAS) with a score of 5 - 7. The basic characteristics and risk of bias evaluation of the included studies are shown in Table 1 and Table 2.

Table 2: A summary table of basic characteristics and risk of bias evaluation from CSF studies

Author	Evidence Level[a]	Year	Number of Cases		IL-6 level in CSF ((mean(or median)±SD) pg/ml	Concentration units
			AD	HC		
Llano, D. A.	4	2010	15	7	AD：2.46±2.14 HC：3.04±1.88	pg/ml pg/ml
Yingman Wu	4	2017	16	19	AD：216.6±46.4 HC：80.1±46.1	pg/ml pg/ml
Yamada, K.	4	2015	12	7	AD：1.17±0.26 HC：2.67±0.34	pg/ml pg/ml
Rösler, N.	4	2022	27	49	AD：3.52±1.63 HC：3.22±2.81	pg/ml pg/ml
Johansson, P.	4	1990	52	18	AD：1.14±0.17 HC：1.18±0.17	pg/ml pg/ml
Jia, J. P.	4	2021	39	35	AD：23.17±14.33 HC：12.06±9.89	pg/ml pg/ml
Hampel, H	4	2016	25	19	AD：2.93±1.64 HC：2.89±1.29	pg/ml pg/ml
Gómez-Tortosa, E	4	2017	33	46	AD：7.14±5.74 HC：4.96±4.72	pg/ml pg/ml
Fraga, V. G	4	2014	32	36	AD：1.75±1.25 HC：2.53±2.94	pg/ml pg/ml

Note: AD: Alzheimer 's disease, HC: Healthy controls, [a] Level of evidence for each study was based on 2011 Oxford Centre for Evidence-Based Medicine guidelines

3.3 Meta analysis results

3.3.1 IL-6 cytokine content in peripheral blood

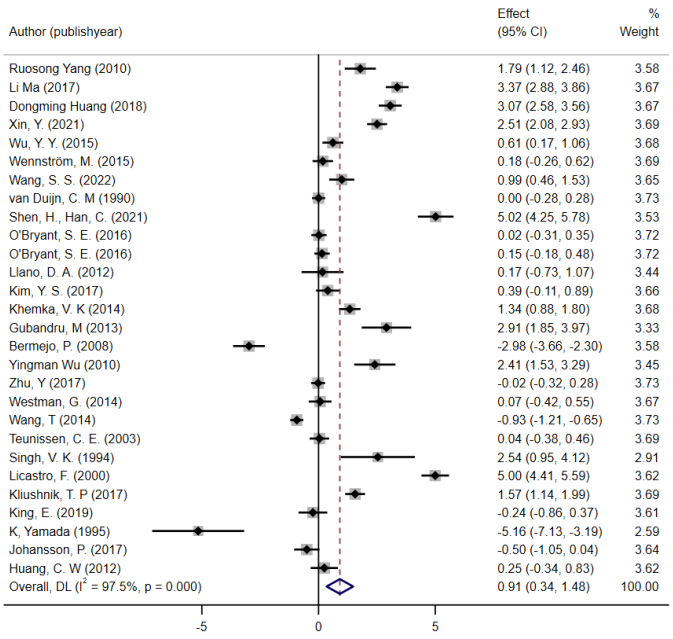

Figure 2: Forest plot of IL-6 content in peripheral blood of AD versus HCs

We performed a subgroup analysis based on IL-6, a different marker of cell surface derived from

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different tissues of AD, including 1,907 AD versus 1,723 HCs from 36 case-control studies in peripheral blood (Tab 1). The results of the analysis indicated that the proportion of IL-6 in peripheral blood was significantly higher in AD than in HCs [SMD = 0.913, 95% CI (0.345, 1.481), P < 0.05] (Figure 2). The results of Egger 's test showed no significant publication bias (t = 1.68, P = 0.104), and the funnel plot was basically symmetrical left and right, suggesting that IL-6 may play a role in the pathogenesis of AD.

3.3.2 IL-6 cytokine content in CSF

It has been reported that IL-6 levels in CSF of AD vary from unchanged to increased [7] or decreased[8], all of which are controversial. In this paper, 251 AD and 236 HCs from nine case-control studies of CSF were included (Tab 2). The results of the analysis indicated that there was no significant difference in the levels of IL-6 in CSF between AD and HCs [SMD = 0.132, 95% CI (-0.579, 0.843), P > 0.05] (Figure 3). Among them, differences in sample size, selection of AD and control subjects, or experimental procedures may be responsible for these different results.

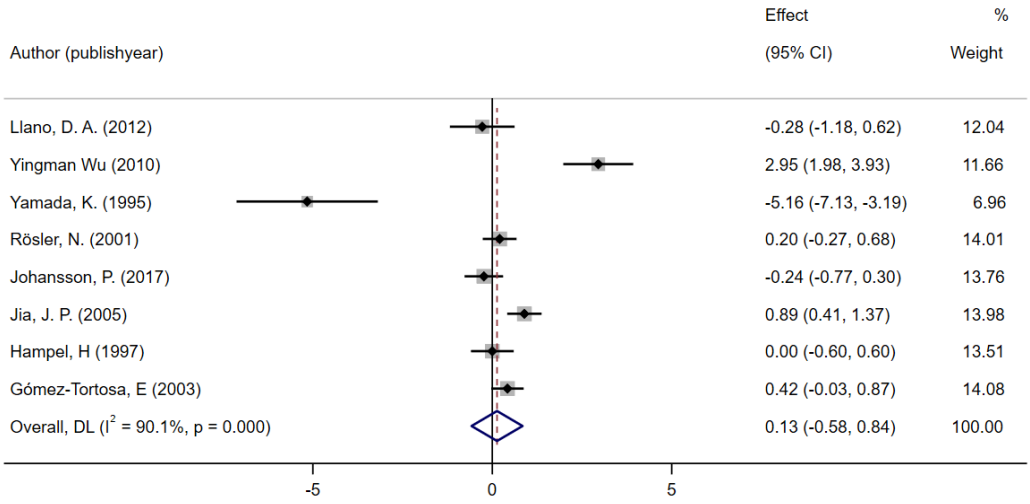

Figure 3: Forest plot of IL-6 content in CSF of AD versus HCs

4. Discussion

Interleukin-6 (IL-6), a cytokine with pro- and anti-inflammatory properties, was originally described by Hirano[9] as a B-cell differentiation factor, usually derived from T cells, and it can also be produced by astrocytes and microglia in the central nervous system[10], [11]. IL-6 is not only associated with innate immunity, vascular health and increased cardiac risk, blood-brain barrier permeability and microglial activation, but also with cognitive impairment.IL-6 is involved in the pathophysiology of AD with several statements. First, IL-6 is involved in remodeling of the microvascular system, leading to endothelial thickening and reduced lumen available for blood flow[12] , as well as defective angiogenesis. Second, the relationship between IL-6 and AD pathology is consistent with meta-analysis of cytokines showing that IL-6 is involved in AD and increases the risk of all-cause dementia[13]. Third, increases in IL-6 levels increase serum levels of amyloid A and negatively affect the transport mechanism of Aβ clearance. When we examine IL-6 levels in peripheral blood, it is necessary to understand whether these peripheral cytokines can cross the blood-brain barrier. Evidence suggests that circulating IL-6 in blood can influence tight junctions by up-regulating the adhesion molecule VCAM-1, allowing t cells to cross the endothelial layer along with IL-6.This allows IL-6 and t cells to cross the blood-brain barrier without being controlled by transporters, thereby activating astrocytes and microglia in the central nervous system, resulting in more IL-6 secreted by the brain[14]. Although Nation[15] did not find a direct relationship between IL-6 in CSF and AD pathology or disease stage, our present data suggests that IL-6 is associated with greater AD pathology in the context of possible emerging blood-brain barrier dysfunction. Taken together, IL-6 may act as a proxy for immune system up-regulation causing AD.

Prior to AD onset, the search for inflammatory molecules involved in AD (and related dementia disorders) is motivated by aetiology and predictive parameters. If an inflammatory process is identified with a causal role in AD, it could become a target for disease-modifying intervention trials. In the

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meantime, if elevated levels of inflammatory markers merely reflect a sustained inflammatory response to other pathological processes of AD, they can still be used to predict the onset of dementia. In this context, we conducted a comprehensive search of the literature to include all published population-based data on the association between inflammatory markers and incident dementia. Among them, IL-6 is a frequently assessed, relatively non-specific inflammatory marker, and it is a pro-inflammatory cytokine produced in a variety of tissues. In this study, the association with dementia was statistically analyzed, and each showed a moderate association with all-cause dementia. This is consistent with studies between IL-6 and cognitive decline[16].

Limitations of this meta-analysis were that age, sex, disease activity, disease duration, geographical location, and treatment effects on IL-6 level outcomes were not considered, which may be responsible for the high heterogeneity, and in addition, this study excluded articles that were not available in original text and unpublished, which may have contributed to publication bias.

In summary, IL-6 levels are significantly increased in the peripheral blood of AD, suggesting that the increase in IL-6 may play a role in the development of AD, but more research is still needed on the mechanism of IL-6 action in the peripheral blood and CSF of AD, which can be used as a potential target to solve the problem of AD in the future.

5. Conclusion

The analysis revealed that IL-6 content in peripheral blood of AD was significantly higher compared with controls [SMD = 0.913, 95% CI (0.345, 1.481), $P < 0.05$], while the level of IL-6 in CSF showed no statistical significance [SMD = 0.132, 95% CI (-0.579, 0.843), $P > 0.05$] and could not be used as a marker in AD. In conclusion, levels of the relevant marker IL-6 are elevated in AD, and spontaneous IL-6 production by peripheral blood mononuclear cells may be a marker of future AD risk in the elderly. These data strengthen the evidence for the pathophysiological role of inflammation in the development and progression of clinical AD, but suggest that the mechanism of action of IL-6 still needs more investigation. It can be used as a potential target to solve AD problems in the future.

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