RESEARCH PAPER

Associations of cytokine genes with Alzheimer’s disease and depression in an elderly Korean population

Hee-Ju Kang,1 Jae-Min Kim,1 Sung-Wan Kim,1 Il-Seon Shin,1 Sung-Woo Park,2 Young-Hoon Kim,2 Jin-Sang Yoon1

ABSTRACT

Background Inflammatory processes regulated by cytokines are important in the aetiology of Alzheimer’s disease (AD) and depression. Differences in transcriptional activities associated with several genetic polymorphisms affect cytokine production. We investigated the involvement of alleles associated with higher production of proinflammatory and lower production of anti-inflammatory cytokines in AD and depression in a community-dwelling sample of elderly individuals.

Method A total of 732 community-dwelling elders were clinically evaluated for AD applying the NINCDS-ADRDA criteria and for depression applying the Geriatric Mental State Schedule. Genotyping was performed for six proinflammatory (interleukin (IL)-1β −511C/T and +3953C/T, IL-6 −174G/C, IL-8 −251T/A, tumour necrosis factor (TNF)-α −850C/T) and two anti-inflammatory (IL-4 +33T/C, IL-10 −1082G/A) cytokines. The sums of risk alleles of proinflammatory and anti-inflammatory cytokine genes were estimated. Age, gender, education and apolipoprotein E genotype were considered covariates.

Results TNF-α −308G/A and IL-8 −251T/A were significantly associated with AD and IL-1β +3953C/T with late-life depression, while the significance of these associations was lost after Bonferroni correction. A greater number of risk alleles producing proinflammatory cytokines was significantly associated with AD, but not with depression, after adjustment for the covariates. No association was found between the increased number of risk alleles for anti-inflammatory cytokine production and either AD or depression.

Conclusions The present findings support the inflammatory hypothesis in the aetiology of AD as measured by several cytokine genes associated with increased proinflammatory cytokine production.

INTRODUCTION

Alzheimer’s disease (AD) and late-life depression are common and represent a large burden on the health of the elderly. With increasing life spans globally, the number of patients with dementia and depression and the related negative consequences are expected to increase considerably. Therefore, understanding the aetiology of dementia and depression in older population is an important step towards early detection and effective treatment. Both AD and late-life depression have complex and heterogeneous aetiologies. Hypothalamic-pituitary-adrenal axis dysfunction, chronic inflammation and a loss of neurotrophin may all play a role in the pathogenesis of AD and depression. The inflammatory process is of great interest in the pathophysiology of AD and depression, because numerous studies have suggested that inflammation is related to the development of AD as well as depression.

Cytokines are believed to be responsible for regulating both the type and degree of an inflammatory response, and may therefore be important in AD and depression. The involvement of cytokines is supported by previous studies on dementia and depression, in which the amounts of proinflammatory cytokines such as interleukin (IL)-1, IL-8 and tumour necrosis factor α (TNF-α) are increased and those of anti-inflammatory cytokines such as IL-4 and IL-10 are decreased. Individual differences in the plasma level and/or functional activity of these cytokines may be strongly influenced by single nucleotide polymorphisms (SNPs) in the corresponding genes. Recently, variations in cytokine genes have been investigated in terms of their role in dementia and depression. Polymorphisms of cytokines, such as TNF-α −850C/T, IL-1β +3953C/T and IL-1α −889 C/T, are correlated with a heightened risk of AD, although conflicting findings have also been reported. With respect to depression, significant associations were found with polymorphisms of cytokine genes, such as TNF-α −308G/A, IL-1β −511C/T and IL-1α −1082G/A, which are correlated with a heightened risk of AD and depression. Therefore, we suspected that a single polymorphism would be insufficient to foretell the risk of AD and depression. The conflicting results of previous studies may be explained by the heterogeneity of the population and the small sample sizes. Additionally, the effects of cytokines have been shown to be synergistic and therefore, investigation of a larger set of cytokine polymorphisms may enhance understanding of the pathophysiology of AD and depression. However, few studies have investigated whether combinations of different cytokine polymorphisms can determine the risk of AD and depression. In a previous study of AD, proinflammatory polymorphisms, such as those in the genes encoding IL-6, IL-1β, matrix metalloproteinase 3 and 9, and intracellular adhesion molecule 1, were related to different levels of AD risk, depending on the number of high-risk genotypes...
carried concomitantly by a given individual. This study was limited by the investigation of polymorphisms in proinflammatory cytokines without consideration of those in anti-inflammatory cytokines. No studies have examined the associations between sets of cytokine polymorphisms and either depression or late-life depression. Thus, we investigated the association of cytokine gene polymorphisms with AD and depression in community-dwelling older participants.

METHODS

Participants

The present analysis was conducted as a component of a larger prospective community study of psychiatric morbidity in late-life, in Kwangju, South Korea, from 2001 to 2003 in collaboration with the 10/66 Dementia in Developing Countries Research Program. The study protocol has been delineated precisely in previous publications. In brief, all community-dwelling elders aged 65 years or over within two geographic catchment areas (one urban and one rural) were drawn from national registers and asked to participate, at baseline. Examinations included clinical screening for AD, blood samples for genotyping to identify cytokine polymorphisms and apolipoprotein E (APOE) genotype, and demographic characteristics on age, gender and education. Written informed consent was formally acquired from all participants. The Chonnam National University Hospital Institutional Review Board approved this study.

Assessment of dementia and depression

Interviews to assess dementia and AD featured use of the Korean versions of the Mini-Mental State Examination,16 the Instrumental Activities of Daily Living Scale17 and the Clinical Dementia Rating Scale.18 Participants and their family members offered information on medical records, present diseases and family histories of dementia. Physical evaluations included blood pressure assessment and a neurological examination. Using such integrated information, three psychiatrists and a neurologist finalised consensus diagnoses. Dementia was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria.19 AD was diagnosed applying the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria,20 and vascular dementia (VaD) employing the NINDS-the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria.21 A third class, ‘other’ dementia, was assigned to the remaining dementia diagnoses. Owing to the very low prevalence of VaD (13 of 732 participants) and other dementia (8 of 732 participants), and the insufficiency of statistical power to allow estimation of associations within these groups, subsequent analyses were confined to older participants with AD (n=86) compared with those without dementia (n=625).

Depression was ascertained applying the community version of the Geriatric Mental State diagnostic schedule (GMS B3); a structured diagnostic instrument running an accompanying computerised algorithm, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), which is used widely in international epidemiological research. The GMS B3 has been formally standardised in the Korean language. In line with previous studies, we used a ‘stage 1’ (non-hierarchical) confidence level of 3 or above in the AGECAT algorithm. As a result, current depression was defined at a level of severity requiring clinical intervention, at 1 month before the interview.

Determination of cytokine polymorphisms and genotyping

The selected polymorphisms and methods used for allele detection are shown in columns 1–5 of the online supplementary table. With stored DNA, six cytokine gene polymorphisms were examined, which encoded four proinflammatory (TNF-α, IL-1β, IL-6 and IL-8) and two anti-inflammatory cytokines (IL-4 and IL-10). All polymorphisms examined have been characterised as promoter-region regulatory variants according to allele-specific disparities in nuclear-factor binding activity and/or in transcriptional activity measured in functional assays. Proinflammatory cytokines activate and stimulate the immune response and therefore increase the risks of AD and depression, whereas anti-inflammatory cytokines hamper the proinflammatory cytokines production. Thus, polymorphisms associated with elevated proinflammatory cytokine generation (TNF-α ~ 850T and ~ 308A, IL-1β ~ 511T and +3953T, IL-6 ~ 174C, and IL-8 ~ 251A) and reduced anti-inflammatory cytokine generation (IL-4 +33C, and IL-10 ~ 1082A) were conceived to be plausible risk alleles for AD and depression. Three types of genotypes were classified based on the combinations of each of the two types of alleles. IL-1β +3953T/T and IL-10 ~ 1082A/G genotypes were incorporated with the heterozygotes because they were extremely uncommon in our population. Regarding the IL-6 ~ 174G/C polymorphism, the G/G genotype was exclusively detected and was thus not considered in further analyses. The APOE genotype was determined by methods described previously with minor modifications and was based on the presence of the APOE ε4 allele.

Covariates

Covariates were deductively selected based on characteristics correlated with cytokine levels and/or AD and depression in earlier studies. Age, gender and education were considered to be covariates. APOE genotype was also considered a covariate in analyses of associations with AD.

Statistical analyses

AD and depression were considered to be two dependent variables for the purpose analysis. Initially, demographic factors and APOE genotype were compared between individuals with and without AD, and between those with and without depression employing t tests or χ2 tests, as appropriate. Testing for the Hardy-Weinberg equilibrium and linkage disequilibrium was conducted with the aid of Haplovie V4.2 software. Allelic frequencies of the eight polymorphisms were compared in AD and depression using χ2 tests. Bonferroni corrections were administered to set an overall type I error rate of 0.05 against the multiple comparisons. To investigate the combined effects of the various genotypes, the sums of potential risk alleles were separately estimated and then categorised as hypothesised proinflammatory (0–1, 2, 3, 4+) or anti-inflammatory (1, 2, 3, 4) cytokine genes. Correlations with AD and depression were initially sought with the aid of χ2 tests (tests for linear correlation), followed by logistic regression modelling with demographic characteristics and APOE genotype as covariates. Lastly, generalised multifactor dimensionality reduction (GMDR) methods26 were used to examine gene–gene interactions. GMDR reduces an n-dimensional space created by a given set of SNPs into a single dimension, to examine n-way interactions. Next, GMDR score-based statistics derived employing maximum-likelihood estimates were used to arrange multifactorial cells into high-risk and low-risk groups. All possible two-locus to seven-locus SNP combinations were explored in this analysis, and the
RESULTS

Patient characteristics according to AD and depression status

Of the 732 total participants, AD was present in 86 (12.1%) and depression was present in 101 (13.8%). Comparisons of baseline characteristics according to dementia and depression are shown in table 1. AD was profoundly associated with older age, female gender, lower educational level and the presence of the APOE e4 allele. Depression was significantly correlated with female gender.

Genotype distribution according to AD and depression status

All genotypes were in Hardy-Weinberg equilibrium (all p values >0.05). Genotype distributions were compared according to AD and depression status (table 2). Higher frequencies of TNF-α −308G/A and IL-8 −251T/A alleles were observed in participants with AD, compared with those without AD. Regarding depression, only the IL-1β +3953T allele was present significantly more frequently in elders with depression than those without. After applying the Bonferroni correction, all associations lost their significance.

Combined polymorphism genotypes in AD and depression

The effect of genotypes containing combinations of polymorphisms on AD status is summarised in table 3 and figure 1. In this analysis (figure 1 and table 3), an increase in the number of risk alleles producing proinflammatory cytokines was significantly correlated with AD, while an increased number of risk alleles generating anti-inflammatory cytokines was not. Depression was not correlated with the presence of increased numbers of risk alleles of either proinflammatory or anti-inflammatory cytokines.

Gene–gene interactions

Linkage disequilibrium was not found among any genotype. GMDR analyses using the two-locus to seven-locus model, with combination exhibiting the lowest misclassification error was chosen. Also, 1000 permutations were run to obtain an empirical p value of prediction accuracy. All gene–gene interaction analyses were performed using covariates. Statistical analyses were performed with the aid of SPSS V21.0 and GMDR software.

Table 1 Characteristics of participants by Alzheimer’s disease (AD) and depression status

<table>
<thead>
<tr>
<th></th>
<th>Dementia analysis</th>
<th></th>
<th>Depression analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AD (N=625)</td>
<td>AD (N=86)</td>
<td>p Value*</td>
<td>No depression (N=631)</td>
</tr>
<tr>
<td>Age, mean (SD) years</td>
<td>72.0 (5.3)</td>
<td>77.6 (6.8)</td>
<td>&lt;0.001</td>
<td>72.0 (5.3)</td>
</tr>
<tr>
<td>Gender, N (%) women</td>
<td>352 (56.3)</td>
<td>71 (82.6)</td>
<td>&lt;0.001</td>
<td>359 (56.9)</td>
</tr>
<tr>
<td>Education, median (IQR) years</td>
<td>3.8 (4.3)</td>
<td>1.0 (2.7)</td>
<td>&lt;0.001</td>
<td>3.8 (4.3)</td>
</tr>
<tr>
<td>Apolipoprotein e4, N (%) have</td>
<td>91 (14.6)</td>
<td>32 (37.2)</td>
<td>&lt;0.001</td>
<td>109 (17.3)</td>
</tr>
</tbody>
</table>

* t Test, χ² test or Mann–Whitney U test as appropriate.

Table 2 Genotype distribution by AD and depression status

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>Dementia analysis</th>
<th></th>
<th>Depression analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No AD (N=625)</td>
<td>AD (N=86)</td>
<td>p Value*</td>
<td>No depression (N=631)</td>
</tr>
<tr>
<td>TNF-α −850C/T</td>
<td>C/C</td>
<td>399 (63.8)</td>
<td>48 (55.8)</td>
<td>0.100</td>
<td>399 (63.2)</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>195 (31.2)</td>
<td>31 (36.0)</td>
<td>0.406</td>
<td>200 (31.7)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>31 (5.0)</td>
<td>7 (8.1)</td>
<td>0.839</td>
<td>32 (5.7)</td>
</tr>
<tr>
<td>TNF-α −308G/A</td>
<td>G/G</td>
<td>514 (82.2)</td>
<td>64 (74.4)</td>
<td>0.025</td>
<td>507 (80.3)</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>104 (16.6)</td>
<td>18 (20.9)</td>
<td>0.881</td>
<td>114 (18.1)</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>7 (1.1)</td>
<td>4 (4.7)</td>
<td>0.034</td>
<td>10 (1.6)</td>
</tr>
<tr>
<td>IL-1β −511C/T</td>
<td>C/C</td>
<td>207 (33.1)</td>
<td>27 (31.4)</td>
<td>0.741</td>
<td>208 (33.0)</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>320 (51.2)</td>
<td>46 (53.3)</td>
<td>0.429</td>
<td>319 (50.6)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>98 (15.7)</td>
<td>13 (15.1)</td>
<td>0.003</td>
<td>104 (16.5)</td>
</tr>
<tr>
<td>IL-1β +3953C/T</td>
<td>C/C</td>
<td>575 (92.0)</td>
<td>80 (93.0)</td>
<td>0.003</td>
<td>590 (93.5)</td>
</tr>
<tr>
<td></td>
<td>C/T or T/T</td>
<td>50 (8.0)</td>
<td>6 (7.0)</td>
<td>0.301</td>
<td>41 (6.5)</td>
</tr>
<tr>
<td>IL-8 −251T/A</td>
<td>T/T</td>
<td>264 (42.2)</td>
<td>27 (31.4)</td>
<td>0.034</td>
<td>252 (39.9)</td>
</tr>
<tr>
<td></td>
<td>T/A</td>
<td>270 (43.2)</td>
<td>41 (47.7)</td>
<td>0.429</td>
<td>283 (44.8)</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>91 (14.6)</td>
<td>18 (20.9)</td>
<td>0.034</td>
<td>96 (15.2)</td>
</tr>
<tr>
<td>IL-4 +33 T/C</td>
<td>T/T</td>
<td>378 (60.5)</td>
<td>51 (59.3)</td>
<td>0.232</td>
<td>390 (61.8)</td>
</tr>
<tr>
<td></td>
<td>T/C</td>
<td>228 (36.5)</td>
<td>29 (33.7)</td>
<td>0.034</td>
<td>221 (35.0)</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>19 (3.0)</td>
<td>6 (7.0)</td>
<td>0.839</td>
<td>20 (3.2)</td>
</tr>
<tr>
<td>IL-10 −1082G/A</td>
<td>G/G or G/A</td>
<td>55 (8.8)</td>
<td>7 (8.1)</td>
<td>0.839</td>
<td>56 (8.9)</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>570 (91.2)</td>
<td>79 (91.9)</td>
<td>0.839</td>
<td>575 (91.1)</td>
</tr>
</tbody>
</table>

* Data are N (%).

Alleles related to increased proinflammatory cytokine production (TNF-α −850T, TNF-α −308A, IL-1β −511T, IL-1β +3953C/T and IL-8 −251A) or decreased anti-inflammatory cytokine production (IL-4 +33C and IL-10 −1082A) were considered risks for AD and depression.

AD, Alzheimer’s disease; IL, interleukin; TNF, tumour necrosis factor.
covariates, were run to investigate the impacts of combinations of the seven genotypes on AD and depression status. No model indicated any significant interaction between any genotype combination, on the hand, and AD or depression, on the other (all p values >0.15).

DISCUSSION

This study is the first to examine the combined effects of genes affecting the production of proinflammatory and anti-inflammatory cytokines. Our principal finding is that a positive and linear relation existed between the risk allele numbers of proinflammatory cytokines and AD, but not late-life depression. TNF-α−308G/A and IL-8−251T/A were significantly associated with AD, and IL-1β+3953C/T with late-life depression; however, the significance of these associations was lost after Bonferroni correction. There was no significant association between anti-inflammatory cytokine gene polymorphisms and AD or late-life depression.

Our results suggest a possible synergistic effect of proinflammatory high-risk polymorphisms on the risk of AD, but not depression. Accumulating evidence indicates that cytokines have a major role in the pathophysiology of AD. One meta-analysis reported higher blood levels of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-12 and IL-18, in patients with AD.27 The transcriptional activities of cytokine gene polymorphisms largely determine cytokine production levels,28 and therefore probably modulate AD risk. Nonetheless, the findings of genetic association studies related to cytokine production have been controversial. For TNF-α−308G/A polymorphism, earlier work found an increased AD risk in elderly people with the AA compared with the AG or GG genotypes,29 while another study found no association.6 Although a meta-analysis reported no association with AD, the heterogeneity of these studies should be considered in the interpretation of results.30 Considering IL-1β+3953C/T, although the TT genotype increased the risk of AD in two previous reports,7 31 only one of these studies found a statistically significant difference.7 Another study found no association between IL-1β+3953C/T and AD.7 Several studies have investigated IL-8−251T/A, and despite a slight over-representation of the AA genotype in AD in one study, the results failed to reach statistical significance.32 Our finding that TNF-α−308G/A and IL-8−251T/A were

**Table 3** Combined effects of proinflammatory and anti-inflammatory cytokine risk alleles on Alzheimer’s disease (AD) in the adjusted* model

| Table 3 Combined effects of proinflammatory and anti-inflammatory cytokine risk alleles on Alzheimer’s disease (AD) in the adjusted* model |
|---|---|---|---|---|
| Number of risk alleles | Participants number | AD | OR (95% CI) | p Value |
| Proinflammatory cytokine | | | | |
| 0–1 | 161 | 12 (7.5) | Ref | 0.007 |
| 2 | 279 | 29 (10.4) | 1.37 (0.62 to 3.02) | |
| 3 | 167 | 27 (16.2) | 2.90 (1.29 to 6.50) | |
| 4+ | 104 | 18 (17.3) | 2.46 (1.01 to 6.00) | |
| Anti-inflammatory cytokine | | | | |
| 1 | 43 | 5 (11.6) | Ref | 0.915 |
| 2 | 404 | 47 (11.6) | 0.74 (0.25 to 2.22) | |
| 3 | 241 | 30 (12.4) | 0.70 (0.23 to 2.18) | |
| 4 | 23 | 4 (17.4) | 1.06 (0.22 to 5.11) | |

*Adjusted for age, gender, education and apolipoprotein e4.

**Figure 1** Combined effect of proinflammatory and anti-inflammatory risk alleles on Alzheimer’s disease (AD) and depression status. As risk alleles for depression, those related to higher proinflammatory cytokine production (tumour necrosis factor (TNF)-α−850T and −308A, interleukin (IL)-1β−511T and −3953T, and IL-8−251A) or lower anti-inflammatory cytokine production (IL-4−33C and IL-10−1082A) were considered. p Values were for the increasing numbers of proinflammatory or anti-inflammatory cytokine risk alleles (linear association).
significant association in our study despite the difference between our work and other studies. AD is a multifactorial and polygenic disorder, and several genes with small effects are apt to affect vulnerability conjointly rather than separately. Nevertheless, most prior findings on the associations of cytokine genes with AD have estimated the effects of only one or a limited number of polymorphisms and reported controversial conclusions. In a complex disease such as AD, combined effects may be derived from combinations of diverse polymorphisms affecting the same pathway. Although most individual correlations with proinflammatory polymorphisms did not attain statistical significance, analysis of pools of risk alleles showed a stronger influence in our study.

Proinflammatory genotypes were significantly over-represented; in contrast, anti-inflammatory genotypes were significantly under-represented. We expected that alleles associated with the decreases in anti-inflammatory cytokine production would be correlated with AD. However, we found no meaningful individual or combined effect of anti-inflammatory cytokine gene polymorphisms on AD status. Plausible explanations are as follows. First, we examined only two anti-inflammatory cytokine genes compared with four pro-inflammatory cytokine genes, and any underlying correlation might have been obscured. Second, an anti-inflammatory mechanism may not be a major risk factor for AD. A recent meta-analysis reported that the peripheral concentration of IL-4 and IL-10 did not differ significantly between patients with AD and controls, although this analysis had limitations of the small sample size and the heterogeneity of the included studies. Moreover, a meta-analysis of IL-10 polymorphisms in AD suggested that the available evidence is not sufficient to support a protective effect of IL-10 on the risk of AD. Also, chronic rather than acute inflammation may have a central influence on the pathogenesis of AD, as the lack of an anti-inflammatory response to prolonged pro-inflammatory stimuli represents a dysregulation of the immune system which may be part of AD pathogenesis, although this concept needs further examination in a large study population. Third, we did not measure the levels of other anti-inflammatory compounds including M2, T-helper 2 or T-regulatory cytokines; tumour growth factor-β; or IL-1RA. These compounds should be considered in future investigations. Finally, it is possible that expression of anti-inflammatory cytokine genes may depend on environmental conditions that are rare in Korea. An association might not have been observed because the SNPs have impacts only in particular situations that are relatively rare in our region.

With respect to depression, we found neither a significant individual nor combined effect of proinflammatory or anti-inflammatory cytokine gene polymorphisms. Many reports support the cytokine hypothesis, which states that cytokine production is increased in those with depressive disorders, including the elderly. A recent meta-analysis also found notably higher levels of the proinflammatory cytokines in depressed participants. However, cytokines-related genetic association studies have yielded controversial findings. In terms of the TNF-α −308G/A polymorphism, a prior Korean research suggested a significant correlation between possession of the A allele and the presence of depression, whereas an Italian study reported a profound correlation between the GG genotype and depression in older people. Another study of a Caucasian population reported no such associations. Significant associations have been found between the T allele of the IL-1β −511C/T polymorphism and an earlier onset of late-life depression, as well as depressive symptomatology in schizophrenia patients and those with AD, although no association was evident in another report. The IL-10 −1082G/A polymorphism was not associated with childhood depressive disorder. To the best of our knowledge, the other polymorphisms explored in the present study have not been examined in the context of depressive disorders. In our present work, only the IL-1β +3953T allele was shown to be a risk factor for depression, despite the loss of significance after Bonferroni correction. Several potential explanations may be advanced to explain the lack of significance noted in the present study, despite the fact that we combined the influences of cytokine polymorphisms in analysis. First, genetic influences on the stress response may be more robust in major depressive disorder. The GMS B3 used in the present study defines depression of ‘clinical significance’, in a rather broad manner, including those with moderate depressive symptoms. Second, late-life depression is a heterogeneous and complex disorder with multiple contributory factors, including oxidative and nitrosative stress, decreased concentrations of ω-3 fatty acids, and reduced concentrations of antioxidants like zinc and glutathione, which together with increased concentrations of M1 and Th1 cytokines, may cause neuroprogression. Therefore, the lack of significant associations may be due to the fact that cytokines are likely not the most important factors in these pathways. Third, cytokine production by expression of cytokine genes is dependent on particular environmental factors, such as physical disorders, which were not considered in this study.

Turning to allelic frequencies, the established ethnic discrepancies between East Asian and Caucasian races are described in columns 6–8 of the online supplemental table. Compared with Caucasians, in our population and those of East Asia in general, most of the conjectured risk alleles for AD and depression (TNF-α −850T, TNF-α −308A, IL-1β +3953T, IL-8 −251A and IL-4 +33C) were in general, comparatively rare. The low frequencies of such alleles in East Asian populations may have limited the ability of the present study to discover their modifying effects and suggests that previous results might be more readily replicated in Caucasian groups, which would have a higher frequency of risk alleles.

The strengths of our study are as follows. First, cytokines have been reported to have an additive or synergistic effect on depression. Thus, it may be beneficial to assay a broad set of cytokine genes in pathophysiological studies. In the present analysis, eight polymorphisms of six cytokine network genes encoding both proinflammatory and anti-inflammatory cytokines were investigated. Second, AD and depression were diagnosed using widely validated instruments and standardised assessment methods were used to obtain the information on a variety of crucial covariates.

Our study also had several limitations. First, the study sample was restricted to the elderly, and this age group tends to suffer chronic physical disorders. A crucial limitation of our study was that physical disorders were not considered to be covariates. Another limitation was that the statistical power of the regression analysis was relatively inadequate for estimating interactions, and non-significant results should be interpreted with caution.

Elderly Koreans with increased numbers of risk alleles encoding proinflammatory cytokines were more vulnerable to AD, but not late-life depression. Our results suggest that a combination
of polymorphisms in genes encoding multiple cytokines is a better predictor of AD than is an SNP. Considering the high disease burden of AD, more deliberate assessment and management might be required for those at higher vulnerability. However, further studies are needed to investigate the utility of genetic testing, and to develop individualised interventions for high-risk groups. Our results provide useful evidence, but should be replicated in larger and more ethnically diverse samples, as well as in cohorts with specifically defined dementia and depression.

Contributors H-JK and J-MK conducted data analysis and drafted the article. S-WK, I-S5, S-WP, Y-HK and J-SY helped to analyse the data and to draft the article. All authors approved the final version of the manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval Institutional Review Board of Chonnam National University Hospital.

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These include:

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- Drugs: CNS (not psychiatric) (1852)
- Drugs: musculoskeletal and joint diseases (248)
- Memory disorders (psychiatry) (1335)
- Psychiatry of old age (328)
- Mood disorders (including depression) (215)

**Notes**

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