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REVIEW

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# Decoying the enemy: soluble receptor for advanced glycation end products and cognitive impairment in neurodegenerative diseases—a systematic review and meta-analysis

Ngakan Putu Krishna Mahayana[1], Ni Putu Wulandari Putri Yadmika[2], Made Dhiyo Wiweka Aryaweda[1], Made Dwinanda Prabawa Mahardana[1], Christo Timothy Mamangdean[1], Ni Nyoman Ayu Dewi[3], Chandra Wirawan[4] and Anak Agung Ayu Putri Laksmidewi[4*]

## Abstract

**Background** Accumulation of advanced glycation end products (AGEs) has contribution in development of Alzheimer's disease (AD), vascular dementia (VAD), and mild cognitive impairment (MCI). AGEs activate several signaling pathways that have roles in development of those diseases via receptor for advanced glycation end product (RAGE), this receptor has its soluble form called sRAGE which has ability to bind AGEs but could not induce molecular signaling. Based on this property, sRAGE could work as RAGE decoy and prevent pathological effect of AGEs accumulation. This meta-analysis is aimed to evaluate correlation between sRAGE plasma level and risk of AD, VAD, and MCI.

**Methods** Standardized mean difference with 95% coincidence interval was used as effect size. Inverse variance was used as analysis method with random effect model. Egger test and funnel plot were used to assess publication bias.

**Results** We found 424 articles through database searching. Among those articles, 15 articles that fulfilled our eligibility criteria. After selection based on inclusion and exclusion criteria, only 5 articles were included in this meta-analysis. Our analysis found that AD and VAD patients have lower levels of plasma sRAGE when compared to healthy control. Significant correlation between low sRAGE plasma level and MCI was not found. However, publication bias is found in MCI group. Publication bias of VAD group could not be assessed due to limited number of studies.

**Conclusions** Here, we show inverse relationship between sRAGE and the incidence of AD alongside VAD suggests that lower sRAGE plasma levels may be associated with a higher incidence of AD and VAD. However, some limitations in sample size and minimal studies may introduce bias into our results.

**Keywords** Advanced glycation end products, Dementia, Alzheimer disease, Vascular dementia, Mild cognitive impairment, Amyloid plaque, Neurology, Neurosciences, Aging, Degenerative disease, Cognition, Molecular biology, Biochemical marker, Age related memory disorders

*Correspondence:
Anak Agung Ayu Putri Laksmidewi
putri_laksmidewi@unud.ac.id
Full list of author information is available at the end of the article

## Introduction

The world is facing an increasing number of aging population and demographic shifting [1]. This phenomenon increases the global health concern on degenerative disease including neurodegenerative disease [2, 3]. Neurodegenerative disease affects the neurons or nervous system due to aging-related pathological process [4]. Those type of diseases will affect the ability of elderly on performing basic daily activities and even lead to disability [5].

One example of neurodegenerative diseases that can be classified as a disability for the elderly is dementia. Dementia is the degeneration of one's neuronal condition which leads to further progressive deterioration of cognitive abilities. These cognitive abilities that is affected by dementia consist of thinking capability, memory, communication skill, and orientation [6]. Due to significant cognitive decline, dementia patient loss their capability in performing basic activities. Certainly, this condition gives significant impact on patient social life, their caregiver, and social environment around the patient [7, 8].

Dementia can be classified into several types based on its etiology such as Alzheimer's disease (AD), vascular dementia (VAD), frontotemporal dementia, and Lewy body dementia. Two of the most popular type of dementia are Alzheimer's disease and vascular dementia [9]. Alzheimer's disease occurred when there is an accumulation of tangled tau protein strands outside of neurons and beta-amyloid plaques inside of neurons. The accumulation of these proteins will lead to neuronal death. This condition will impair communication, judgement, and behavior over time [10]. Vascular dementia is another major cause for dementia besides AD. In contrast to AD, VAD happened when a cerebrovascular disease caused a person's cognitive abilities to deteriorate over time. Decreased blood flow to the brain due to vascular problem leads to brain performance decline. There are a few subtypes to this category, such as multi-infarct dementia, strategic infarct dementia, small vessel dementia, hemorrhagic dementia, hypoperfusion dementia, hereditary vascular dementia, and AD with cardiovascular disease [11].

Based on epidemiology data, the incidence of dementia is increasing alongside of global aging population growth. In 2016, it is estimated that there were 43.8 million people with dementia globally [12]. These number is projected to grow every year (4.6 million new cases/year) and will eventually reach 81.1 million people by the year of 2040. Developing countries, especially China and it's neighboring West-Pacific countries is expected to have a dementia patient population explosion, rising from 60.1% of all dementia patients in 2001 to 64.5% in 2020 and 71.2% in 2040 [13]. For AD, it is stated that the global prevalence in 2006 was 27 million in which this number increases to 32 million in 2023 [14]. VAD is often considered as the second most frequent type of dementia which prevalence varies in each continent. This type of dementia constitutes of about 15–20% of dementia cases in Europe and North America. In Asia and developing countries itself, VAD is estimated to jumps around 30% of dementia cases [15].

Mild cognitive impairment (MCI) is the transitional stage between a normal, healthy brain and dementia in which a person suffers from cognitive function decline outside of their normal age. The difference between MCI and dementia lies on its effect to the patient. While dementia disrupt patient daily activities, MCI patient remains relatively stable to perform basic daily activities. There are several types of MCI such as amnestic MCI, multiple domain MCI, and single domain non-amnestic MCI. Although its effect on patient quality of life is not as significant as dementia, people with amnestic MCI prone to develop AD at a later age [16].

Based on previous explanation, dementia and MCI should be a concern for clinicians and researchers. Therefore, the development of therapeutic strategy and prevention method are highly required. Many therapeutic strategies have been studied in clinical trials for several decades, but the current available treatments primarily only target the disease symptoms instead of being the curative therapies [17]. As a result, most research attention has shifted towards early prevention or minimizing the risk of Alzheimer's disease (AD) and other neurodegenerative diseases. Research on neurodegenerative molecular markers is an increasingly relevant area of study. Monitoring this group of molecular markers could provide additional tools in clinical practice for the early diagnosis of neurodegenerative and tracking the effectiveness of subsequent therapies. One of the most promising molecular markers in relation to this field is advanced glycation end products (AGEs) [18–20].

Advanced glycation end products (AGEs) are the results of glycation reaction of protein or lipid by glucose or other saccharides [19]. AGEs level tends to increase through aging. Accumulation of AGEs during aging is responsible for many degenerative diseases [20]. AGEs have receptor named receptor for advanced glycation end products (RAGE) [21]. AGEs–RAGE signaling pathway could activate several signaling that have roles in several degenerative diseases including age-related cognitive impairment [22]. For AD, studies have discovered that AGEs–RAGE signaling is able to induce beta-amyloid plaque formation and deposition [23, 24]. This signaling also plays an important role in the development of cerebrovascular impairment in VAD [22]. Based on

its roles in development of cognitive impairment in neurodegenerative disease, developing methods that can inhibit AGEs–RAGE signaling pathway has promising prospect for AD, VAD, and MCI treatment and prevention. Therefore, further understanding of AGEs–RAGE signaling pathway role in AD, VAD, and MCI is required.

RAGE has its soluble form called soluble receptor for advanced glycation end products (sRAGE). This form has binding affinity with AGEs but has no ability to induce any molecular signaling. Based on this capability, sRAGE could potentially work as a RAGE decoy and inhibit the AGEs–RAGE signaling pathway [25].

The neuro-protective effect of sRAGE in humans needs to be clarified. Several studies have shown that individuals with lower sRAGE level have higher risk of developing AD, VAD, and MCI [26, 27]. Meanwhile another study discovers conflicting result for MCI [28]. Another study also did not find significant association between low sRAGE plasma level and risk of AD and MCI [29]. The high variety results of difference studies indicates that a systematic review and meta-analysis is required. Thus, current systematic review and meta-analysis is conducted to clarify correlation between sRAGE plasma level and risk of AD, VAD, and MCI.

## Materials and methods

The process of conducting this systematic review and meta-analysis consists of study searching and selection based on the eligibility criteria, assessing study quality, data extraction, and analysis. NPKM was responsible for concepting the idea and method. NPKM, NPWPY, MDPM, and MDWA contributed to study screening, selection, and data extraction. MDWA and NPKM contributed to data analysis. NPKM, NPWPY, MDPM, and CTM contributed in writing the manuscript. NAD, CW, and AAAPL contributed to study manuscript inspection and results evaluation. All conflicts were resolved through discussion.

### Eligibility criteria

Studies included in this meta-analysis were qualified based on these criteria: (i) Studies on correlation between sRAGE plasma level and AD, VAD, and MCI; (ii) studies were cross-sectional and peer-reviewed; (iii) AD and VAD diagnosis was previously established by neurologist or biomarker examination and/or radiography examination; (iv) MCI must be diagnosed using mini mental state examination (MMSE); (v) both patients and healthy control must be older than 55 years; and (vi) study provides sufficient data to evaluate standardized mean difference (SMD) and 95% Confidence interval (95% CI). Studies with participants with other major diseases, animal studies, in vitro studies, and reviews were excluded. No restriction was applied in the study location. For studies that use the same participant, the most recently published study was selected.

### Search strategy

The studies were obtained from online databases, including PubMed, Cochrane Library, and ScienceDirect, a methodology commonly employed in similar research. The search was confined to studies published up until March 2023. The used search terms were Alzheimer, dementia, vascular dementia, and soluble receptor for advanced glycation end products. Boolean operators such as "and" and "or" were utilized to combine these keywords. The following keyword combination was used: ((Alzheimer) OR (Dementia) OR (vascular dementia)) AND ((soluble receptor for advanced glycation end products) OR (sRAGE)). This approach aligns with the search strategies used in comparable studies. Three reviewers were involved in this process.

### Study quality assessment

The modified New-Castle Ottawa scale (NOS) for cross-sectional study was used to assess the quality of studies pooled from our initial database search. This scoring system consists of seven parameters, which includes: representativeness of the sample, sample size, non-exposed (control) selection, ascertain of the exposure, comparability, outcome assessment, and statistical test [30]. Studies that achieved a score of 6 or higher were classified as high-quality studies and were consequently incorporated into this meta-analysis. This evaluation process was meticulously conducted by a team of four independent reviewers. Any disagreements between reviewers are concluded through discussion.

### Data extraction

Data used was independently extracted by 2 different reviewers. All disagreements between the two reviewers are resolved through discussion. The information that extracted from the studies include: author, year of publication, country, total number of patient and control, sRAGE plasma level and standard deviation.

### Statistical analysis

The statistical analysis was executed utilizing the R Studio software, specifically employing the "meta" package (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria), a method commonly used in similar studies [31]. The Standard Mean Difference (SMD) and the 95% Confidence Interval (CI) were employed to ascertain the correlation between sRAGE levels and the incidence of AD, VAD, and MCI. The inverse-variance

method was utilized as the statistical approach, with the choice between a random or fixed effect model being contingent on the degree of heterogeneity. In instances of high heterogeneity ($I^2 > 50\%$), the random effect model was preferred [32]. The risk of bias was evaluated and quantified using the funnel plot and Egger test, a technique frequently referenced in the literature [33].

## Results

### Study selection and characteristic

From searching using keyword combination, we found 424 potential articles. After duplicate elimination, abstract and title screening, we found 15 relevant studies. Then after comprehensive selection based on eligibility, inclusion and exclusion criteria, we finally found 5 relevant studies. Figure 1 shows the selection process. Study characteristic data is presented in Tables 1, 2 and 3.

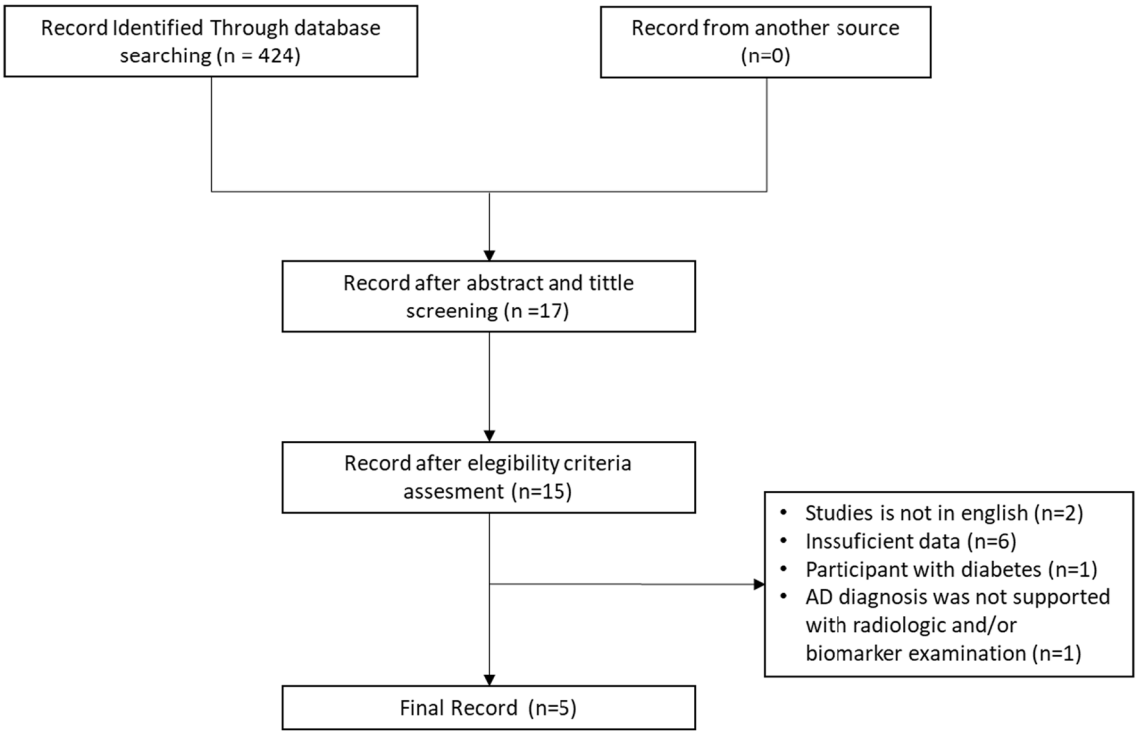


**Fig. 1** Study selection PRISMA flowchart

**Table 1** Study characteristics for studies invloved patient with AD, MCI, and control

| Author | | Country | Type | Age (SD) * (years) | Population (male/female) | NOS |
|---|---|---|---|---|---|---|
| Hernanz et al. [29] | AD | Spain | *3-centre cross-sectional* | 73.2 ± 7.1 | 25 (10/15) | 7 |
| | MCI | | | 75.9 ± 6.9 | 26 (14/12) | |
| | Control | | | 73.5 ± 3.2 | 44 (22/22) | |
| Ghidoni et al. [26] | AD | Italy | *3-centre cross-sectional* | 76.88 ± 8.0 | 100 (20/80) | 9 |
| | MCI | | | 72.43 ± 5.9 | 66 (26/40) | |
| | Control | | | 72.28 ± 3.8 | 161 (51/110) | |
| Atac et al. [28] | AD | Turkey | *3-centre cross-sectional* | 77.7 ± 6.1 | 79 (27/52) | 8 |
| | MCI | | | 75.2 ± 7.2 | 41 (16/25) | |
| | Control | | | 70.0 ± 4.2 | 40 (22/18) | |

*NOS* Newcastle–Ottawa Scale, *AD* Alzheimer disease, *MCI* mild cognitive impairment

* Data is expressed as mean ± standard deviation (SD)

### Studies quality assessment

We found all the studies included in this review have more than 6 score. Two studies have 9 score [26, 34]. Three studies have 8 score [27–29]. Scoring result is presented in Table 4 and Fig. 2. In general, high concerns have been found on sample size and control aspect of the studies.

### Quantitative analysis

The data from the studies are delineated in Table 5 for Alzheimer's, Table 6 for VAD, and Table 7 for MCI. It was observed that patients with Alzheimer's disease exhibited lower plasma levels of sRAGE compared to the healthy control group. Similarly, patients with vascular dementia also demonstrated lower sRAGE levels in comparison to the healthy control group. However, no significant correlation was found between low plasma levels of sRAGE and the incidence of MCI. The results of the Forrest plot are depicted in Fig. 3. These findings align with the methodologies and results reported in similar studies. Since all groups have high heterogeneity, random effect model was used for all groups.

### Publication bias assessment

The quantitative calculations from the Egger test revealed that the meta-analysis results for Alzheimer's

**Table 2** Study characteristics for studies invloved patient with AD, VD, and Control

| Author | | Country | Type | Age (SD) (years) | Population (male/female) | NOS |
|---|---|---|---|---|---|---|
| Emanuelle et al. [34] | AD | Spain | *3-centre cross-sectional* | 73.11 ± 10.45 | 152 (46/106) | 9 |
| | VD | | | 80.10 ± 6.58 | 91 (39/52) | |
| | Control | | | 72.28 ± 3.82 | 161 (51/110) | |

*NOS* Newcastle–Ottawa Scale, *AD* Alzheimer disease, *MCI* mild cognitive impairment

* Data is expressed as mean ± standard deviation (SD)

**Table 3** Study characteristics for studies involved patient with AD, VD, MD, OD, and Control

| Studies | | Negara | Type | Umur (SD) (tahun) | Jumlah (pria/wanita) | NOS |
|---|---|---|---|---|---|---|
| Xu et al. [27] | AD | China | *5-centre cross-sectional* | 77.0 ± 11.0 | 36 (17/19) | 8 |
| | VD | | | 79.0 ± 9.0 | 12 (7/5) | |
| | MD | | | 82.0 ± 8.0 | 14 (9/5) | |
| | OD | | | 78.0 ± 13.0 | 24 (17/7) | |
| | Control | | | 65.0 ± 9.0 | 35 (12/23) | |

*NOS* Newcastle–Ottawa Scale, *AD* Alzheimer disease, *MCI* mild cognitive impairment

* Data is expressed as mean ± standard deviation (SD)

**Table 4** Study quality assessment

| Author | | Hernanz et al. [29] | Ghidoni et al. [26] | Emanuelle et al. [34] | Xu et al. [27] | Atac et al. [28] |
|---|---|---|---|---|---|---|
| Selection (Max. 5 stars) | Representativeness of the sample | * | * | * | * | * |
| | Sample size | – | * | * | – | – |
| | Non-exposed (control) | – | * | * | * | – |
| | Ascertaint of the exposure | ** | ** | ** | ** | ** |
| Comparibility (Max. 2 stars) | The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled | ** | * | * | * | ** |
| Outcome (Max. 3 stars) | Assessment outcome | ** | ** | ** | ** | ** |
| | Statistical test | * | * | * | * | * |
| Total score | | 8 | 9 | 9 | 8 | 8 |

*indicate that the parameters have 1 point of score for contribution of total score, **indicate the parameters have 2 point of score for contribution of total score. The score is based on NOScriteria

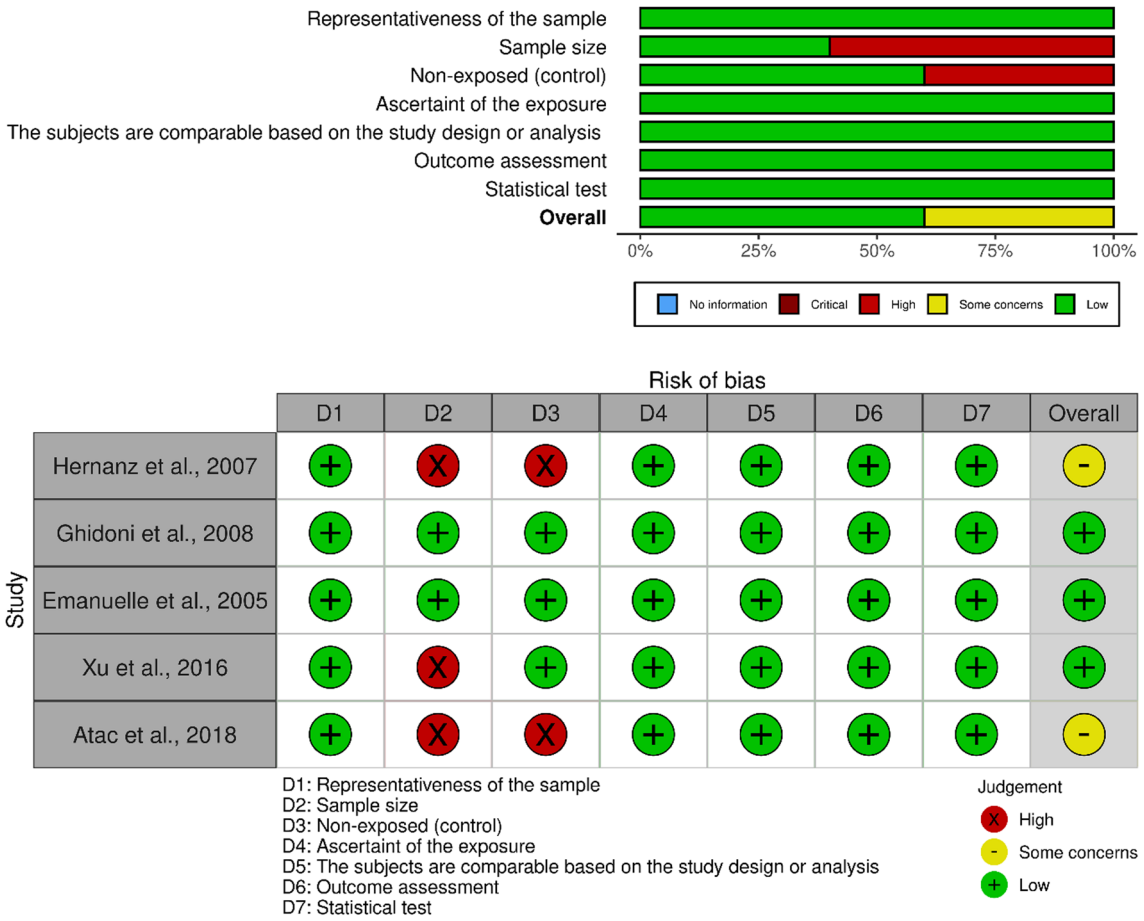


**Fig. 2** Study quality assessment result

**Table 5** Studies data for AD group

| Reference | AD/Normal | AD sRAGE (SD) | HC sRAGE (SD) | sRAGE measurement method |
|---|---|---|---|---|
| Ghidoni et al. [26] | 100/161 | 576 (521) | 1395 (658) | ELISA (Quantikine; R&D Systems) |
| Xu et al. [27] | 36/35 | 1700(1400) | 2700(2500) | ELISA (Quantikine; R&D Systems) |
| Hernanz et al. [29] | 25/44 | 1820 (640) | 2040 (771) | ELISA (Quantikine; R&D Systems) |

*AD* Alzheimer disease, *sRAGE* soluble receptor for advanced glycation end products, *HC* healthy control, *ELISA* enzyme-linked immunosorbent assay

**Table 6** Studies data for VAD group

| Reference | VD/Normal | VD sRAGE (SD) | HC sRAGE (SD) | sRAGE measurement method |
|---|---|---|---|---|
| Emanuella et al. [34] | 91/161 | 792 (555) | 1395 (658) | ELISA (Quantikine; R&D Systems) |
| Xu et al. [27] | 12/35 | 1700 (1000) | 2700 (2500) | ELISA (Quantikine; R&D Systems) |

*VAD/VD* vascular dementia, *sRAGE* soluble receptor for advanced glycation end products, *HC* healthy control, *ELISA* enzyme-linked immunosorbent assay

**Table 7** Studies data for MCI group

| Reference | MCI/Normal | MCI sRAGE (SD) | HC sRAGE (SD) | sRAGE measurement method |
|---|---|---|---|---|
| Atac et al. [28] | 41/40 | 1492.51 (929.29) | 1381.63 (703.75) | ELISA (Quantikine; R&D Systems) |
| Ghidoni et al. [26] | 66/161 | 928 (521) | 1395 (658) | ELISA (Quantikine; R&D Systems) |
| Hernanz et al. [29] | 26/44 | 1810 (618) | 2040 (771) | ELISA (Quantikine; R&D Systems) |

*MCI* mild cognitive impairment, *sRAGE* soluble receptor for advanced glycation end products, *HC* healthy control, *ELISA* enzyme-linked immunosorbent assay

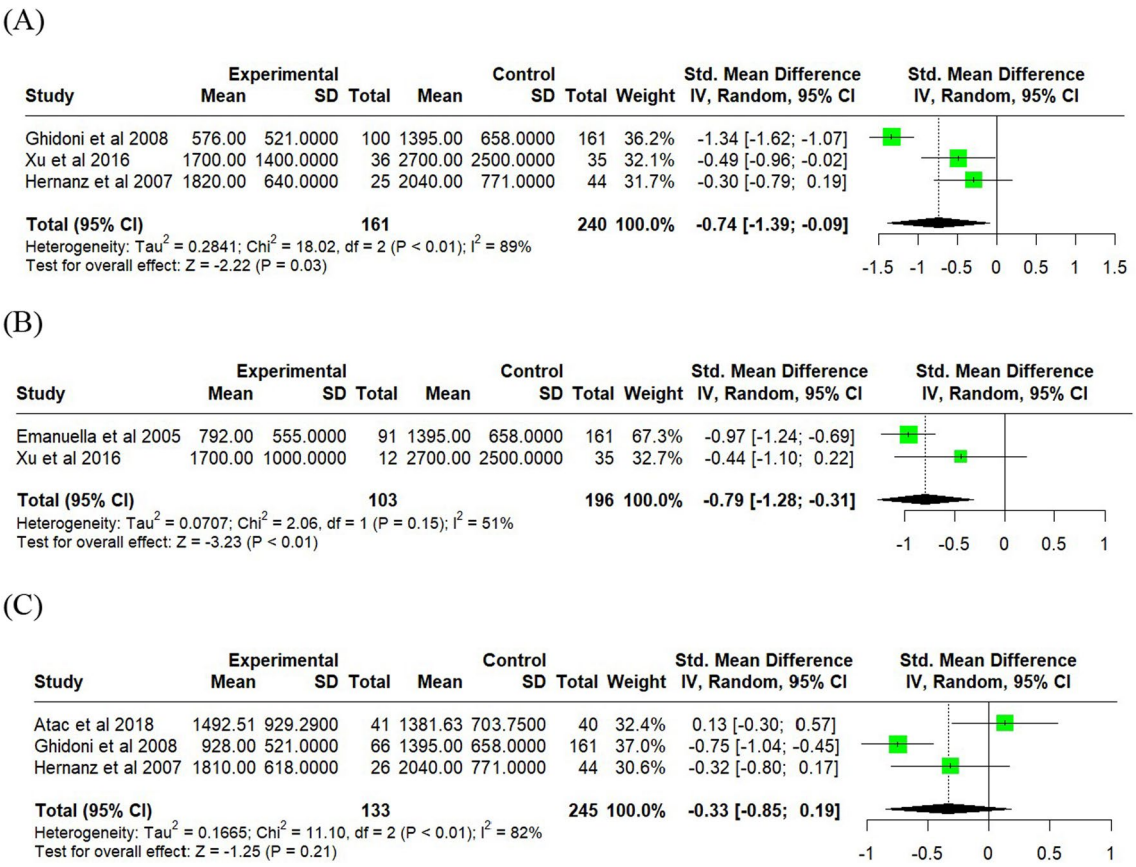


**Fig. 3** Forest plots shows correlation between sRAGE plasma level and incident of AD (**A**), VAD (**B**), and MCI (**C**)

disease were not influenced by publication bias. However, the Egger test calculations for MCI indicated the presence of publication bias affecting the meta-analysis for MCI. The Egger test of VAD group could not be performed due to insufficient numbers of studies. All funnel plots are illustrated in Fig. 4.

### Result summary

Overall, we found that low sRAGE plasma level is associated with incidence of AD and VAD but not with MCI. The risk of publication bias could affect the results of VAD and MCI analysis group.

## Discussion

Due to limited studies regarding this topic, only 5 studies were included within our meta-analysis. Using NOS as a screening tool for bias detection indicated that the studies included met the requirement to be deemed as decent in quality. The studies were shown to have decent representation of samples, were ascertain of the exposures, used comparable subjects based on the study design, and did a thorough assessment of the study outcome. However, there are some concerns regarding the sample size used in the study done by Hernanz et al. Xu et al. and Atac et al. which were much lower compared to the rest of the studies. Other than that,

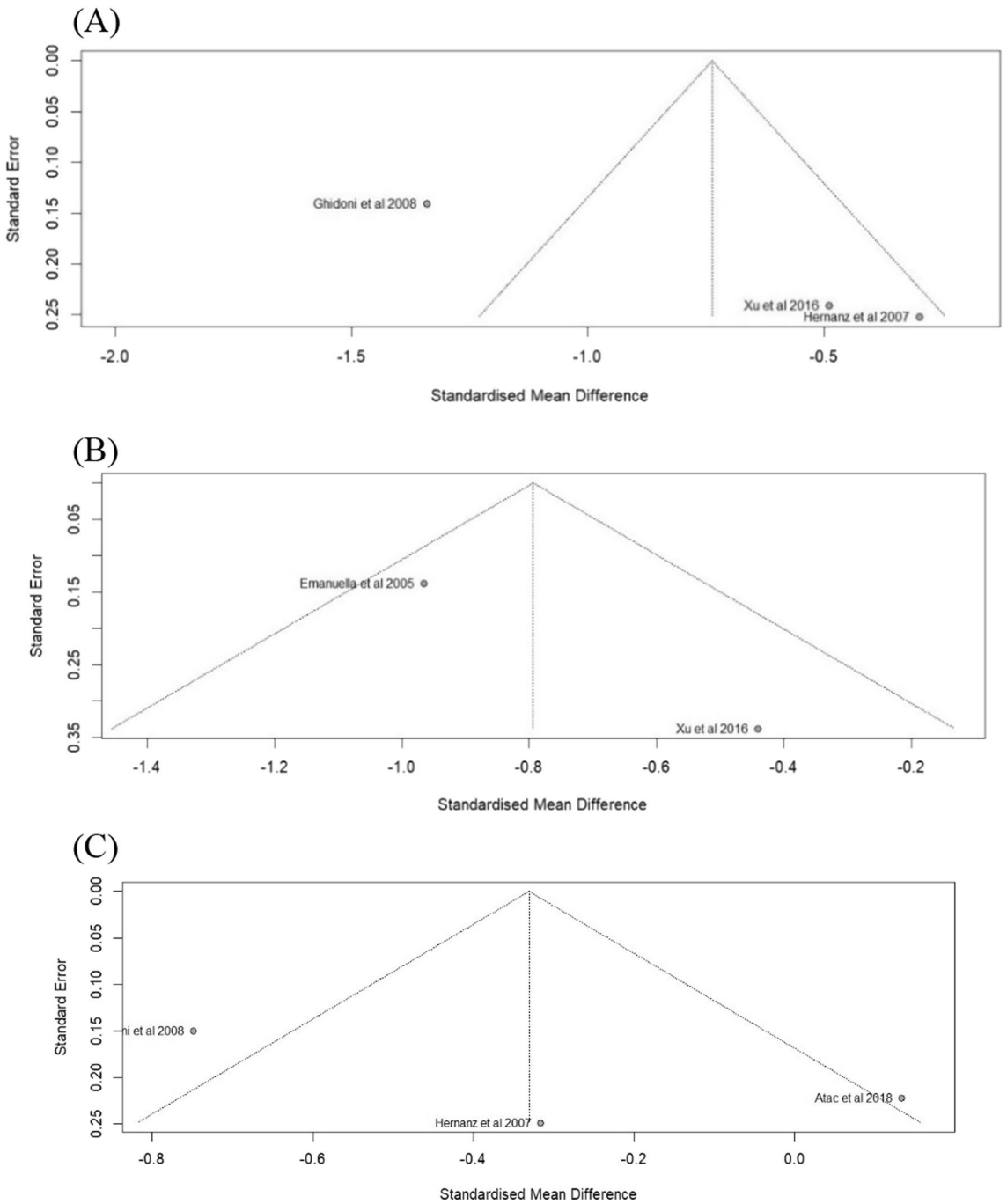


**Fig. 4** Funnel plot for AD (**A**), VAD (**B**), and MCI (**C**) meta-analysis

2 studies, Hernanz et al. and Atac et al. have some bias regarding the selection of the control groups within their study. Overall, 3 studies showed little overall risk of bias while 2 studies showed some concerns.

Within this meta-analysis, we found that AD, VAD, and MCI groups, the exposed groups, had lower mean levels of plasma sRAGE concentration compared to the healthy control group. This finding indicates that the presence of higher levels of plasma sRAGE content might have some association with lower incidence of being diagnosed with AD, VAD, and MCI. This was found to be true in the case of AD ($p=0.03$) and VAD ($p\leq0.01$) but not in MCI, this is due to the unsignificant overall effect between the exposed and the control groups of

MCI ($p=0.21$). To further assess if there is any small study bias, we did a funnel plot analysis using the egger test. This test, however, was only done on AD and MCI studies, because the limited number of studies attributed to the VAD analysis. Egger test was no longer a reliable way of discerning if there is small study bias or not. According to the egger test, there was no asymmetry in the funnel plots of AD analysis, meaning there was no small study bias detected. Studies attributed to the MCI analysis, however, did show funnel plot asymmetry which indicated that small study bias was present. The presence of small study bias may exaggerate or decrease the actual overall effect or in this case the difference in plasma sRAGE levels between the exposed and control groups.

The role of sRAGE in preventing neurodegenerative diseases can partly be explained by in-vivo studies done on rats with AD. These studies found that injection of sRAGE secreting mesenchymal stem cells (sRAGE–MSC) into the rats prevented beta-amyloid plaque deposition, inflammation, and neuron apoptosis in the rat's brain [35, 36]. Study by Oh et al. found that injection of sRAGE–MSC can prevent neuronal cell death in mice with AD. The reduced inflammation produced by injections of sRAGE–MSC were indicated by the number of M1 microglia, which were decreased. The other effects produced by this intervention might have been the result of lowered RAGE levels along with the suppression of RAGE ligand expressions. These effects produced by the injections were impactful enough to affect the overall survival of sRAGE–MSC intervention group, which were observed to be longer than MSC control group [35].

Other than apoptosis and inflammation, development of macrovascular and microvascular complications are also risk factors to the development of VAD and AD. A meta-analysis regarding endogenous secretory RAGE (esRAGE) and sRAGE in the incidence of carotid atherosclerosis found that esRAGE, a precursor of sRAGE, was found to be inversely correlated with carotid intima–media thickness, which is an indicator of atherosclerosis [37–39]. Although these findings were observed in diabetic patients, it gives us an insight of how sRAGE could lead to lower incidence of vascular disease. Another way sRAGE could lower vascular related disease is by binding with AGEs. Due to AGEs's induction of RAGE activation, endothelial cells undergo oxidative reactions and nuclear factor kappa-B is activated, which in turn results in proinflammatory and proangiogenic responses, damaging endothelial function alongside enabling plaque formation. Since RAGE requires AGEs to be activated, the presence of sRAGE introduces competitive binding of AGEs between RAGE and sRAGE, this effectively lowers the available AGEs that are freely available to bind with RAGE [40, 41].

The role of AGE–RAGE, however, is not only limited to the incidence of AD, VAD, or MCI since the same signaling pathway could be found in other neurodegenerative diseases such as Parkinson and cerebrovascular disease [42, 43]. It is also known that these diseases corelate linearly with age, the physiological process of aging itself is contributed by the accumulation of AGE–RAGE pathways which in this case further supports the important role of sRAGE and AGEs in the incidence of previously mentioned neurodegenerative diseases [21, 44]. The specific AGE–RAGE signaling pathway have been reported to induce several aging related signaling, which consists of NF-kB and NADPH oxidase signaling [45–47]. Studies also reported that this signaling is associated with telomere shortening but the exact molecular mechanism remains unclear [48, 49]. Moreover, variants of the RAGE protein through polymorphism are also associated with the risk of AD and other neurodegenerative diseases [50–52].

Previous studies showed that modulating sRAGE could prevent progression of several neurodegenerative diseases, which includes AD [35, 36]. These findings regarding sRAGE modulation seem to be a promising candidate to be used upon some neurodegenerative diseases such as AD, VAD, and MCI. Consensus between past studies and our current findings on this subject seems to arrive at the same conclusion that sRAGE is associated with the incidence of AD and VAD and therefore its modulation could prove useful in preventing neurodegenerative incidences. Nonetheless, due to the limited number of studies alongside high heterogeneity and low number of samples currently included on sRAGE and neurodegenerative within humans, these results are to be taken with a grain of salt. Furthermore, usage of cross-sectional studies within our meta-analysis hinders us to further analyze to what extent does sRAGE contributes to the progression of AD, VAD, and MCI. This is due to the nature of cross-sectional designs not having time to event analysis, which is crucial to conclude AD, VAD, and MCI incidence and progression in regard to the presence of sRAGE along with its plasma concentrations.

Despite its promising prospects in prevention and treatment of neurodegenerative diseases, previously proposed methods of modulating sRAGE levels are currently very difficult and expensive to execute. Current studies on modulating sRAGE level used sRAGE secreting stem cells that are injected into animal subject [35, 36]. Stem cell injection also has high risk of adverse effects [53]. Therefore, future studies on finding more viable and clinically practical methods that can modulate sRAGE level are highly warranted.

Developing sRAGE-modulating drugs could be an alternative method to injections of sRAGE secreting-stem cell. A literature review by Lanati et al. have listed several sRAGE and RAGE expression modulator drugs that can be used in development of sRAGE-modulating drug [54]. In order to enhance sRAGE levels, understanding molecular mechanism of sRAGE expression is essential. One of the ways to achieve sRAGE modulation is by alteration of the RAGE splicing process. sRAGE itself is created from proteolytic cleavage of RAGE by a disintegrin and metalloproteinase10 (ADAM10) [55]. Therefore, enhancing ADAM10 activity could theoretically be used to increase sRAGE levels in patients with neurodegenerative disease [56]. This is further supported by a study showing that enhanced ADAM10 overexpression in mouse with AD could reduce beta-amyloid level and beta-amyloid-associated pathologies [57, 58]. However, ADAM10 overactivity is associated with pathogenesis of others degenerative diseases including Huntington's disease and atherosclerosis [59, 60]. Hence, further investigation on understanding the molecular mechanism that can upregulate sRAGE level is still warranted for the development of sRAGE-modulating drugs.

It is important to note that there are some limitations to this meta-analysis. As previously mentioned, there is a scarcity of studies providing necessary data on the relationship between sRAGE levels and AD, VAD, and MCI. The low number of studies may include outliers that could skew our summary effect regarding sRAGE levels on AD, VAD, and MCI. With further increase in studies and number of samples used, it could prove useful in giving a more accurate representation of the real summary effect of sRAGE on neurodegenerative disease. Other than that, patients included within those studies also present varying baseline patient characteristics along with their location of origin. This can be explained by the origin of studies included within our analysis, one study is conducted in Asia while the other four studies were conducted in Europe; hence the result of this meta-analysis is yet to represent the bigger global population. Furthermore, differing protocols on how sRAGE was quantified and detected also heavily impact the results of each respective studies. All these concerns are reflected within the heterogeneity presented in our forest plots, the heterogeneity of all neurodegenerative diseases, which include AD ($I^2 = 81\%$), VAD ($I^2 = 51\%$), and MCI ($I^2 = 82\%$), present with very high heterogeneity. Therefore, Further studies regarding this topic needs to be performed on larger samples with more diverse ethnicities and baseline characteristics while using similar protocols in between studies is warranted.

## Conclusion

The observed inverse relationship between plasma level of sRAGE and the incidence of AD alongside VAD suggests that lower sRAGE plasma levels may be associated with a higher incidence of AD and VAD. Meanwhile there is no significant correlation between sRAGE plasma level and incidence of MCI. The significant risk of publication bias in the outcomes across different studies for AD group could not be found. However, the risk of publication bias is found in the MCI group. Meanwhile, the publication bias of VAD could not be assessed. Some limitations in sample size, minimal studies, and varying patient baseline characteristics may also introduce bias into our results. Therefore, larger studies surrounding this topic are essential in order to validate our findings. Aligned with previous in-vivo studies, our findings strengthened the role of sRAGE in neurodegenerative diseases treatment and prevention. However, further study is required to implement our findings in clinical practice. The development of a method that can modulate the sRAGE level is the main challenge of this topic.

#### Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| AGE | Advanced glycation end product |
| ELISA | Enzyme-linked immunosorbent assay |
| HC | Healthy control |
| MD | Mixed dementia |
| MCI | Mild cognitive impairment |
| NOS | Newcastle–Ottawa Scale |
| OD | Others dementia |
| RAGE | Receptor for advanced glycation end product |
| sRAGE | Soluble receptor for advanced glycation end product |
| VAD | Vascular dementia |

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*Cogito ergo sum* (I think, therefore I am), a famous quote by René Descartes has inspired the first author to make this small contribution in the field of cognitive neurosciences through this paper. The ability to think is essential part of the sense of self existence and memories are precious part of our self. We would also like to thank Department of Neurology and Department of Biochemistry, Faculty of Medicine, Udayana University, Bali, Indonesia.

#### Author contributions

NPKM contributed in the conception and design of the study. NPKM, NPWPY, MDPM, and MDWA contributed in study screening, selection, and data extraction. MDWA and NPKM contributed in data analysis. NPKM, NPWPY, MDPM, and CTM wrote the manuscript. NAD, CW, and AAAPL contributed in manuscript inspection.

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#### Data availability

The data that supporting the result are already available within the article. And data is directly extracted from included studies (available on included study articles).

## Declarations

#### Ethics approval and consent to participate

Not applicable.

**Consent for publication**
All the authors from this study have given their consent for publication.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]School of Medicine, Faculty of Medicine, Udayana University, Bali, Indonesia. [2]School of Medicine, Faculty of Medicine and Health Science, Warmadewa University, Bali, Indonesia. [3]Department of Biochemistry, Faculty of Medicine, Udayana University, Bali, Indonesia. [4]Department of Neurology, Faculty of Medicine, Udayana University, Bali, Indonesia.

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