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# A systematic review and meta-analysis of pteridines in mild cognitive impairment and Alzheimer's disease

Arduino A. Mangoni[1,2*] and Angelo Zinellu[3]

## Abstract

**Background** Alterations in specific pteridine metabolites, particularly neopterin, biopterin, and tetrahydrobiopterin have been reported in mild cognitive impairment, Alzheimer's disease, and other types of dementia. However, the available evidence regarding such alterations has not been comprehensively and critically appraised.

**Methods** We systematically reviewed studies reporting the concentrations of biopterin, tetrahydrobiopterin, and neopterin in different biological fluids in patients with mild cognitive impairment, Alzheimer's disease or other types of dementia, and healthy controls. Electronic databases were searched from inception to 29 February 2024.

**Results** Overall, there were no significant differences in plasma/serum concentrations of neopterin between patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, when grouped together, and healthy controls after adjusting for publication bias (11 studies, standard mean difference, SMD = 0.20, 95% CI -0.02 to 0.41, $p = 0.076$). In meta-regression and subgroup analysis, the effect size was significantly associated with age, number of participants, study continent, presence of mild cognitive impairment, presence of Alzheimer's disease, analytical method, and assessment of serum vs. plasma. One study reported higher urine neopterin in patients with Alzheimer's disease vs. controls whereas another study reported non-significant between-group differences in cerebrospinal neopterin. The cerebrospinal fluid concentrations of biopterin were significantly lower in patients with Alzheimer's disease vs. controls (two studies, SMD = -0.75, 95% CI -1.23 to -0.27, $p = 0.002$; $I^2 = 0.0\%$, $p = 0.46$). One study showed non-significant between-group differences in plasma biopterin whereas another study showed higher concentrations of urine biopterin in patients with Alzheimer's disease. Our search did not identify studies investigating tetrahydrobiopterin.

**Conclusion** Our study showed no significant differences in circulating neopterin between patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, when grouped together, and healthy controls. The significant associations observed between the effect size and mild cognitive impairment and Alzheimer's disease in subgroup analysis warrant further investigation. (PROSPERO registration number: CRD42024523478).

**Keywords** Pteridines, Neopterin, Biopterin, Mild cognitive impairment, Alzheimer's disease, Biomarkers, Inflammation, Oxidative stress

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## Introduction

Dementia, a condition primarily affecting the older population, is characterized by a decline in one or more cognitive domains, e.g., memory, executive function, language, learning, complex attention, and social cognition, which significantly impair daily function and overall independence [1]. Another condition, mild cognitive impairment, while involving objective cognitive impairment, is not associated with significant functional deficits [1]. With the current and projected trends in population ageing, the number of people suffering from dementia is expected to increase. An analysis for the Global Burden of Disease Study 2019 has estimated that 57.4 million people had dementia globally in 2019. This number is projected to increase to 152.8 million in 2050 [2]. The diagnosis of dementia and its different types is based on a range of assessments, including history, cognitive testing, screening for other conditions (e.g., depression), physical examination, and laboratory, genetic, and neuroimaging tests [3–6]. However, a definitive diagnosis of specific dementia subtypes can only be confirmed postmortem [7–9].

There have been significant advances in understanding the cellular, molecular, and biochemical mechanisms underpinning the pathophysiology of mild cognitive impairment and the most common form of dementia, Alzheimer's disease [10–15]. However, despite this knowledge, there is still a lack of treatments exerting tangible effects on disease progress and quality of life in those affected [16–20]. This has stimulated a significant amount of research investigating the role of alternative biochemical pathways to discover novel disease biomarkers and, potentially, new therapies.

A wide range of biomarkers reflecting neurodegeneration and extracellular abnormalities has been investigated in biological fluids in the context of mild cognitive impairment, Alzheimer's disease, and frontotemporal dementia. Examples of such biomarkers include neurofilaments, regulating cytoskeletal structure and synaptic function, the growth factor progranulin, and β-amyloid and tau, which reflect critical abnormalities in Alzheimer's disease, i.e., extracellular amyloid plaques and intraneural neurofibrillary tangles [21, 22]. Notably, these biomarkers have been shown to have significant associations with incident all-cause dementia in epidemiological studies [23].

Further findings in experimental and clinical studies of dementia are represented by a state of excessive local and systemic inflammation and alterations in the synthesis of the critical endogenous modulator, nitric oxide (NO), and various neurotransmitters [12, 24–31]. Such neurotransmitters, e.g., dopamine, norepinephrine, epinephrine, acetylcholine, and serotonin, are involved in the maintenance of higher cognitive function and the overall brain homeostasis [32–34]. Notably, different components within a specific group of endogenous compounds, i.e., pteridines, play an important role in regulating these processes. Pteridines are aromatic compounds that are generated by the fusion of pyrazine and pyrimidine rings in many living organisms, including humans. Pteridines normally act as pigments, enzymatic cofactors, and immune system activators. All natural pterins produced in prokaryotic and eukaryotic organisms are formed from guanosine triphosphate (GTP) with the involvement of GTP cyclohydrolase (Fig. 1). Although a significant amount of pteridines found in nature are pigments, other naturally synthesised pteridines play essential metabolic roles. As enzymatic cofactors, pteridines are involved in the synthesis of nucleic acids, amino acids, neurotransmitters, nitrogen monoxides as well as purine and aromatic amino acids [35]. 5,6,7,8-tetrahydrobiopterin ($BH_4$) and biopterin act as cofactors for several aromatic amino acid hydroxylases as well as NO synthase. $BH_4$ deficiency has been associated with several pathologies [36–38]. By contrast, neopterin is an established biomarker of interferon-γ production, macrophage activation, inflammation, and oxidative stress. When produced in excess, neopterin dysregulates the inflammatory and immune pathways [39–41]. Neopterin is synthesised from the oxidation of 7,8-dihydroneopterin, a potent radical scavenging and chain breaking antioxidant derived from the interferon-γ mediated conversion of GTP by GTP cyclohydrolase [42–45] (Fig. 1). One advantage of investigating the role of pteridines as biomarkers of mild cognitive impairment, Alzheimer's disease, and other types of dementia, is their detection and measurement in different biological fluids. This may theoretically allow assessing their pathophysiological role in fluids close to the progression of disease, e.g., cerebrospinal fluid, and their elimination kinetics in the urine.

However, there is a lack of a comprehensive assessment and critical appraisal of the available evidence regarding the possible diagnostic and pathophysiological role of neopterin, biopterin, and $BH_4$, in mild cognitive impairment, Alzheimer's disease, and other types of dementia. This does not allow establishing whether pteridines are worthy of further study as candidate biomarkers of such conditions, singly or in combination with existing biomarkers, and, potentially, chemical leads for the discovery of new therapies. We sought to address these issues by conducting a systematic review and meta-analysis of studies reporting pteridine concentrations in different biological fluids in patients with mild cognitive impairment, Alzheimer's disease or other types of dementia, and healthy controls. Where possible, we also conducted meta-regression and subgroup analysis to investigate

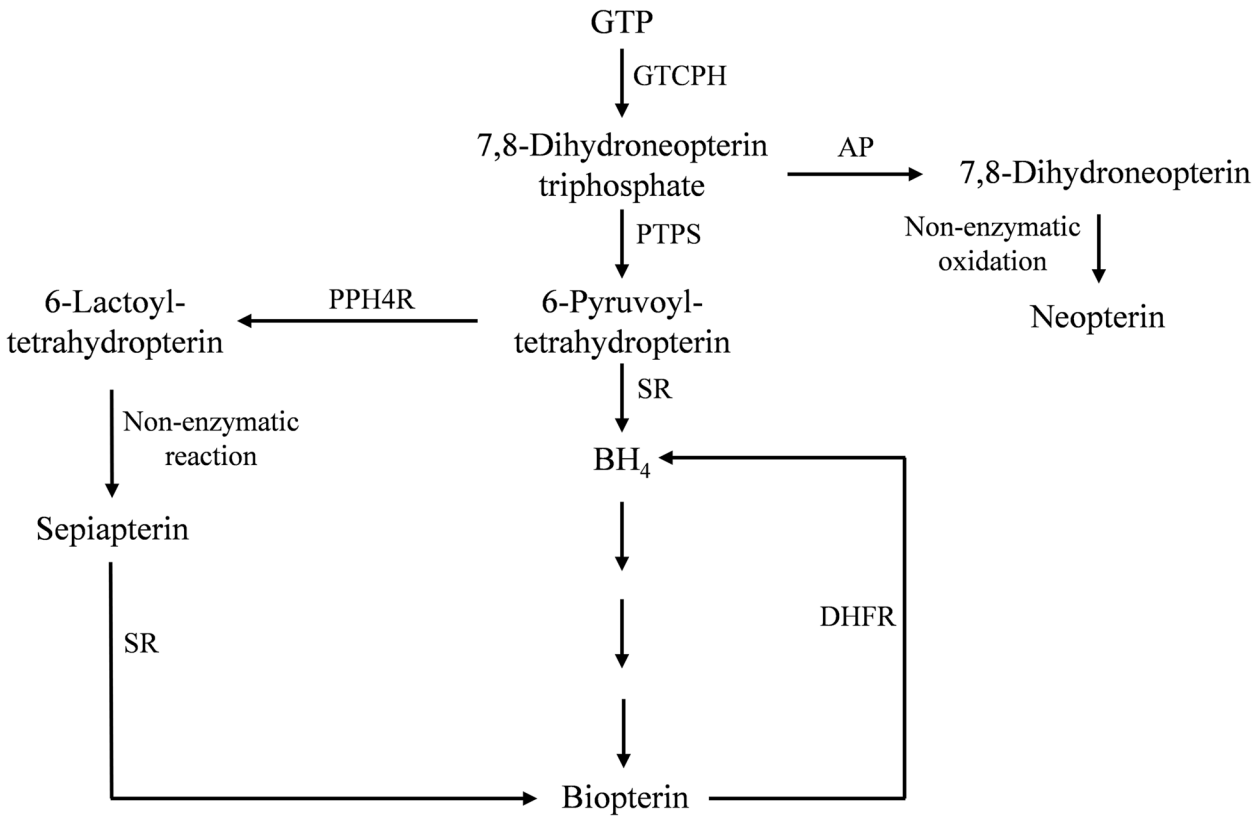


**Fig. 1** Schematic description of pteridine metabolism. AP, alkaline phosphatase; BH4, tetrahydrobiopterin; DHFR, dihydrofolate reductase; GTCPH, GTP cyclohydrolase I; GTP, guanosine triphosphate; PPH4R, 6-pyruvoyl-tetrahydropterin-2′-reductase; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase

possible associations between the effect size of the between-group differences and pre-defined study and patient characteristics.

## Materials and methods

### Search strategy and study selection

Web of Science, Scopus, and PubMed were searched from their inception to 29 February 2024 for relevant articles using the following terms: "neopterin" OR "biopterin" OR "tetrahydrobiopterin" OR "$BH_4$" AND "dementia" OR "Alzheimer's disease" OR "vascular dementia" OR "cognitive impairment" OR "mild cognitive impairment" OR "frontotemporal dementia" OR "Parkinson's disease dementia" OR "Lewy body dementia". Two independent investigators screened each abstract and the full-text of relevant articles according to the following inclusion criteria: (i) the assessment of neopterin, biopterin, or $BH_4$ in biological fluids in patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, with or without concomitant neurological and/or neuropsychiatric conditions, and healthy controls in case–control studies; (ii) the recruitment of adult participants; and (iii) the use of English language. The references of individual articles were hand searched for additional studies. Exclusion criteria were: (i) the study of pteridines specifically in neurological or neuropsychiatric conditions other than mild cognitive impairment, Alzheimer's disease, or other types of dementia; (ii) studies including participants aged < 18 years; and (iii) non-case–control studies (as the lack of a control group prevented the calculation of the SMD for that study).

The two investigators independently extracted the following data from each article: year of publication, first author, country where the study was conducted, type of dementia, sample size, age, male to female ratio, concentrations of individual analytes, sample matrix, and assay used for analyte measurement.

The risk of bias and certainty of evidence were assessed using validated tools [46–49]. The PRISMA 2020 statement was used as a reference (Supplementary Table 1) [50]. An international repository was used to register our study protocol (PROSPERO registration number: CRD42024523478).

### Statistical analysis

Forest plots were generated to assess standardized mean differences (SMDs) and 95% confidence intervals (CIs) of neopterin, biopterin and $BH_4$ concentrations between patients with mild cognitive impairment, Alzheimer's disease or other types of dementia, and healthy controls ($p < 0.05$ for statistical significance). If necessary, means and standard deviations were estimated using accepted methods [51]. The heterogeneity of the SMD was quantified using the $I^2$ statistic and the significance was assessed using the Q-statistic [52, 53]. A random-effect model based on the inverse-variance method was used if high heterogeneity was present. Conventional methods were used for sensitivity analysis (leave-one-out method) and assessment of publication bias (Egger's test, Begg's test, and "trim-and-fill" method) [54–57]. Associations between the effect size and year of publication, study continent, mild cognitive impairment, type of dementia, sample size, age, male to female ratio, sample matrix, and assay used for analyte measurement were investigated by means of meta-regression and subgroup analysis [58, 59]. All analyses were conducted using Stata 14 (Stata Corp., College Station, TX, USA).

## Results

### Systematic search

Figure 2 describes the flow chart of study selection. From a total of 788 articles initially identified, 764 were excluded because they were not relevant to the research question or presented redundant data. After a full-text review of the remaining 24 articles, five were excluded because they did not have a case–control design, three because they presented redundant data, and two because of missing data, leaving 14 studies for analysis [60–73] (Table 1). The risk of bias was ranked as low in ten studies [62–66, 68, 69, 71–73] and moderate in the remaining four [60, 61, 67, 70] (Table 2). The cross-sectional study design of the selected studies downgraded the initial level of the certainty of evidence to low.

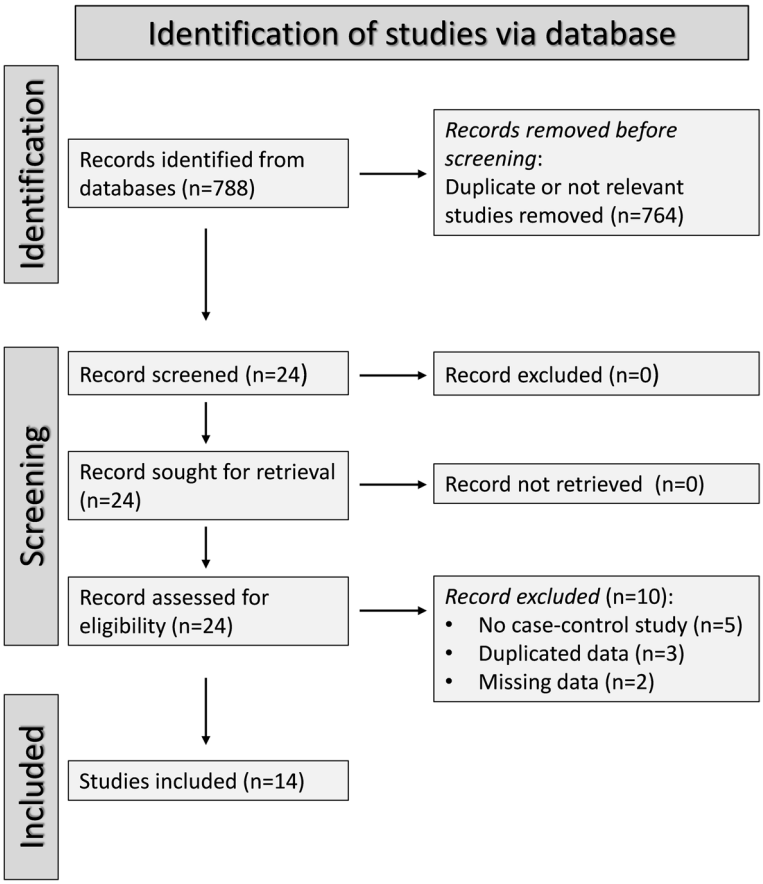


**Fig. 2** PRISMA 2020 flow diagram

**Table 1** Characteristics of studies included in the meta-analysis

| Study | Disease | Matrix | Method | Healthy controls | | | | Patients with dementia | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | Age (years) | M/F | Neopterin Biopterin Mean ± SD (nmol/L) | n | Age (years) | M/F | Neopterin Biopterin Mean ± SD (nmol/L) |
| Kay AD et al., USA (a), 1986 [60] | AD | P | LC | 14 | 64.7 ± 3.1[a] | 10/4 | NR<br>10.4 ± 34 | 30 | 66.8 ± 1.7[a] | 18/12 | NR<br>14.5 ± 8.2 |
| Kay AD et al., USA (b), 1986 [60] | AD | CSF | LC | 14 | 64.7 ± 3.1[a] | 10/4 | NR<br>18.9 ± 8.2 | 30 | 66.8 ± 1.7[a] | 18/12 | NR<br>13.5 ± 4.4 |
| Kaye JA et al., USA, 1988 [61] | AD | CSF | LC | 11 | NR | NR | NR<br>17.9 ± 5.6 | 29 | NR | NR | NR<br>14.5 ± 6.3 |
| Armstrong RA et al., UK, 1995 [62] | AD | U | LC | 10 | 82.0 ± 8.1[b] | NR | 0.09 ± 0.06*<br>0.09 ± 0.06* | 22 | 79.0 ± 7.7[b] | NR | 0.41 ± 0.35*<br>0.23 ± 0.09* |
| Lebhuber F et al., Austria, 1999 [63] | AD | S | ELISA | 14 | 69.7 ± 8.8[b] | 4/10 | 7.64 ± 2.7 | 24 | 73.1 ± 6.2[b] | 8/16 | 16.2 ± 10.3 |
| Hull M et al., USA, 2000 [64] | AD | P | ELISA | 38 | 70.0 ± 10.0[a] | 24/14 | 6.3 ± 2.6° | 51 | 73.0 ± 10.0[a] | 23/28° | 9.3 ± 5.9 |
| Licastro F et al., Italy, 2000 [65] | AD | P | ELISA | 51 | 78.0 ± 2.0[a] | 20/31 | 13.4 ± 10.7 | 145 | 75.0 ± 1.0[a] | 54/91 | 11.9 ± 7.2 |
| Casal JA et al., Spain (a), 2003 [66] | AD | S | ELISA | 24 | 80.7 ± 7.2[b] | 11/13 | 11.1 ± 4.1 | 30 | 78.6 ± 7.2[b] | 9/21 | 12.5 ± 5.0 |
| Casal JA et al., Spain (b), 2003 [66] | Dementia | S | ELISA | 24 | 80.7 ± 7.2[b] | 11/13 | 11.1 ± 4.1 | 19 | 73.9 ± 8.7[b] | 6/13 | 10.1 ± 3.8 |
| Frick B et al., Austria (a), 2003 [67] | AD | S | ELISA | 5 | 69.0 ± 8.7[b] | NR | 5.6 ± 2.5 | 27 | 81.0 ± 8.8[b] | NR | 14.3 ± 14.0 |
| Frick B et al., Austria (b), 2003 [67] | MCI | S | ELISA | 5 | 69.0 ± 8.7[b] | NR | 5.6 ± 2.5 | 13 | 78.0 ± 7.9[b] | NR | 11.2 ± 7.8 |
| Frick B et al., Austria (c), 2003 [67] | VD | S | ELISA | 5 | 69.0 ± 8.7[b] | NR | 5.6 ± 2.5 | 10 | 77.0 ± 6.7[b] | NR | 13.7 ± 7.1 |
| Greilberger J et al., Austria, 2008 [68] | MCI/AD | S | ELISA | 15 | 60.8 ± 4.7[b] | 4/11 | 6.8 ± 1.5 | 16 | 67.6 ± 5.2[b] | 7/9 | 7.6 ± 3.8 |
| Parker DC et al., USA (a), 2013 [69] | AD | P | ELISA | 30 | 72.6 ± 7.7[b] | 6/24 | 8.05 ± 1.66 | 34 | 73.2 ± 8.9[b] | 16/18 | 10.35 ± 4.33 |
| Parker DC et al., USA (b), 2013 [69] | MCI | P | ELISA | 30 | 72.6 ± 7.7[b] | 6/24 | 8.05 ± 1.66 | 27 | 78.2 ± 8.1[b] | 13/14 | 9.15 ± 2.35 |
| Rommer PS et al., Austria (a), 2016 [70] | MCI/AD | S | ELISA | 15 | 62.8 ± 3.6[b] | 4/11 | 6.76 ± 1.54 | 16 | 63.3 ± 13.7[b] | 7/9 | 7.28 ± 4.42 |
| Rommer PS et al., Austria (b), 2016 [70] | MCI/AD | S | ELISA | 15 | 62.8 ± 3.6[b] | 4/11 | 6.76 ± 1.54 | 17 | 76.4 ± 6.7[b] | 7/10 | 8.83 ± 4.63 |
| Savas S et al., Turkey, 2016 [71] | AD | S | ELISA | 38 | 72.0 ± 5.9[b] | 16/22 | 8.89 ± 4.5 | 59 | 75.0 ± 6.4[b] | 20/39 | 17.37 ± 22.3 |
| Giil LM et al., Norway, 2017 [72] | AD | P | LC | 65 | 81.6 (8.6)[c] | 14/51 | 18.9 ± 7.6 | 65 | 74.3 (15.1)[c] | 22/43 | 17.8 ± 5.6 |
| Jacobs KR et al., Australia (a), 2019 [73] | AD | P | LC | 18 | 73.1 ± 7.9[b] | 15/3 | 21.66 ± 8.84 | 20 | 77.9 ± 7.5[b] | 9/11 | 26.4 ± 5.0 |
| Jacobs KR et al., Australia (b), 2019 [73] | AD | CSF | LC | 18 | 73.1 ± 7.9[b] | 15/3 | 6.46 ± 2.90 | 20 | 77.9 ± 7.5[b] | 9/11 | 7.20 ± 4.24 |

Legend: *AD* Alzheimer disease, *CSF* cerebrospinal fluid, *ELISA* enzyme-linked immunosorbent assay, *LC* liquid chromatography, *MCI* mild cognitive impairment, *M/F* male to female ratio, *NR* not reported, *P* plasma, *S*, serum; U, urine; VD, vascular dementia

*, μmol/mmol creatinine; °, ng/mL

[a] mean±SEM

[b] mean±SD

[c] median (IQR)

## Neopterin

### *Plasma/serum neopterin*

Eleven studies including a total of 16 group comparators reported plasma/serum neopterin concentrations in 573 patients with dementia (mean age 75 years, 62% females) and 392 healthy controls (mean age 72 years, 63% females) [63–73] (Table 1). Four studies were conducted in Austria [63, 67, 68, 70], two in USA [64, 69], one in Italy [65], one in Spain [66], one in Turkey [71], one in Norway [72], and one in Australia [73]. Nine group comparators included subjects with Alzheimer's disease [63–67, 69, 71–73], two with mild cognitive impairment [67, 69], three with both Alzheimer's disease and mild cognitive impairment [68, 70], one with vascular dementia [67], and one with other forms of dementia [66]. An enzyme-linked immunosorbent assay (ELISA) was used in nine studies [63–71], and liquid chromatography in the remaining two [72, 73]. Serum was assessed in six studies [63, 66–68, 70, 71] and plasma in the remaining five [64, 65, 69, 72, 73]. The risk of bias was assessed as low in nine studies [63–66, 68, 69, 71–73] and moderate in the remaining two [67, 70] (Table 2).

The forest plot showed that the plasma/serum concentrations of neopterin were significantly higher in patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, when grouped together, compared to controls (SMD = 0.39, 95% CI 0.17 to 0.61, $p = 0.001$; $I^2 = 57.5\%$, $p = 0.002$; Fig. 3 and Table 3). The

**Table 2** Assessment of the risk of bias using the Joanna Briggs Institute critical appraisal checklist

| Study | Were the inclusion criteria clearly defined? | Were the subjects and the setting described in detail? | Was the exposure measured in a reliable way? | Were standard criteria used to assess the condition? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were the outcomes measured in a reliable way? | Was appropriate statistical analysis used? | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|
| Kay AD et al. [60] | Yes | No | Yes | Yes | No | No | Yes | Yes | Moderate |
| Kaye JA et al. [61] | No | Yes | Yes | Yes | No | No | Yes | Yes | Moderate |
| Armstrong RA et al. [62] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Lebhuber F et al. [63] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Hull M et al. [64] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Licastro F et al. [65] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Casal JA et al. [66] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Frick B et al. [67] | No | Yes | Yes | No | No | No | Yes | Yes | Moderate |
| Greilberger J et al. [68] | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low |
| Parker DC et al. [69] | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Rommer PS et al. [70] | Yes | No | Yes | Yes | No | No | Yes | Yes | Moderate |
| Savas S et al. [71] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Giil LM et al. [72] | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Jacobs KR et al. [73] | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Low |

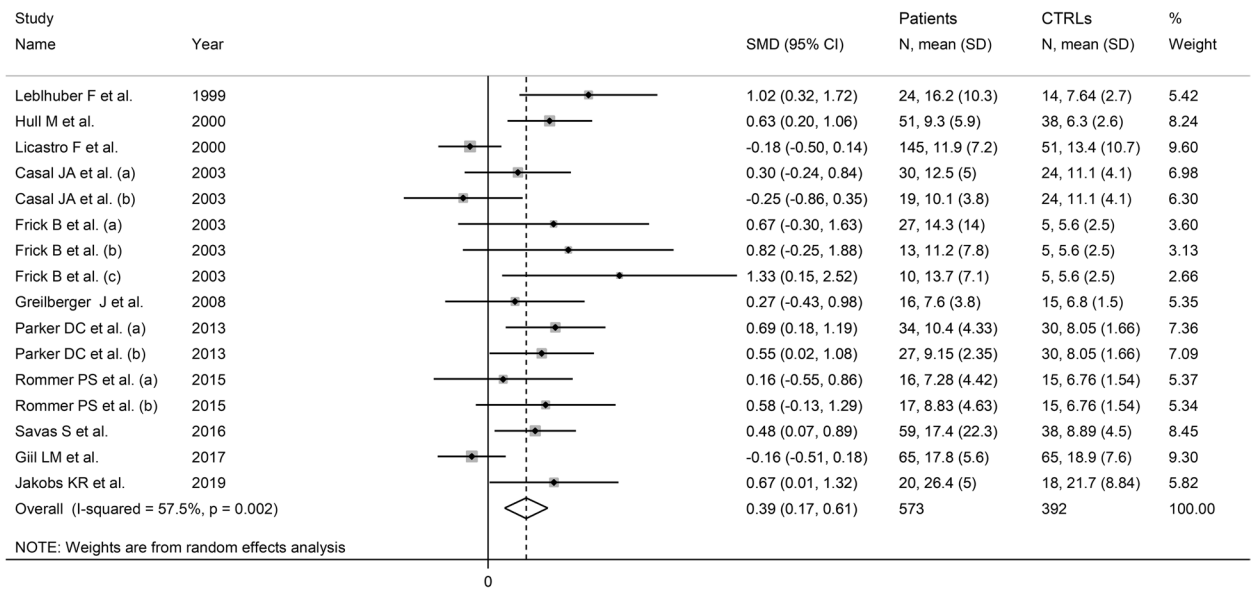


**Fig. 3** Forest plot of studies examining serum/plasma neopterin concentrations in patients with dementia and healthy controls

pooled SMD values were stable in sensitivity analysis, ranging between 0.35 and 0.44 (Fig. 4).

There was evidence of publication bias according to Egger's ($p=0.012$) but not Begg's ($p=0.26$) test (Table 4). The "trim-and-fill" method identified six missing studies ensuring symmetry (Fig. 5). However, the resulting effect size was no longer significant (SMD = 0.20, 95% CI −0.02 to 0.41, $p=0.076$).

There were no significant associations in univariate meta-regression analysis between the effect size and male to female ratio (t = 0.54, $p=0.60$) or publication year (t = −0.14, $p=0.89$). By contrast, significant associations were observed with age (t = 3.92, $p=0.002$, Fig. 6A) and number of participants (t = −2.94, $p=0.011$, Fig. 7A), as also confirmed in the cumulative meta-analysis using the metacum command (Fig. 6B and 7B).

In subgroup analysis, the pooled SMD was significant in studies conducted in non-European continents (SMD = 0.59, 95% CI 0.37 to 0.81, $p<0.001$; $I^2=56.4\%$, $p=0.011$), but not Europe (SMD = 0.27, 95% CI −0.01 to 0.56, $p=0.062$; $I^2=0.0\%$, $p=0.972$). Furthermore, there was a virtually absent between-study variance in the European subgroup (Fig. 8). Moreover, the pooled SMD was significant in studies of patients with Alzheimer's

**Table 3** Outcomes, number of patients and controls, and side of standardized mean difference (SMD) and 95% confidence intervals with respect to zero SMD

| Outcome | n study groups | Side of 95% confidence intervals | | | | Patients | Controls | Total participants |
|---|---|---|---|---|---|---|---|---|
| | | < 0 | Overlap 0 and SMD < 0 | Overlap 0 and SMD > 0 | > 0 | | | |
| Blood neopterin | 16 | 0 | 3 | 6 | 7 | 573 | 392 | 965 |
| CSF biopterin | 2 | 1 | 1 | 0 | 0 | 59 | 25 | 84 |

Legend: *CSF* cerebrospinal fluid, *SMD* standard mean difference

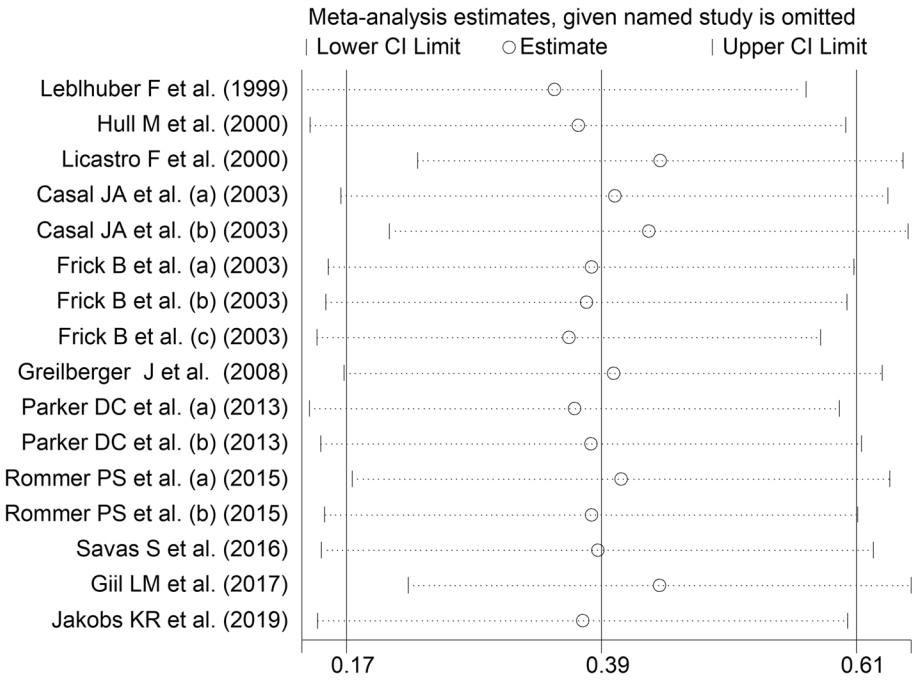


**Fig. 4** Sensitivity analysis of the association between serum/plasma neopterin and dementia

**Table 4** Results for publication bias

| Outcomes | Begg's z test | p-value | Egger's t test | p-value | Missing studies (side) | After adjusting |
|---|---|---|---|---|---|---|
| Blood neopterin | 1.13 | 0.26 | 2.89 | 0.012 | 6 (Left) | 0.20 (−0.02–0.41) |

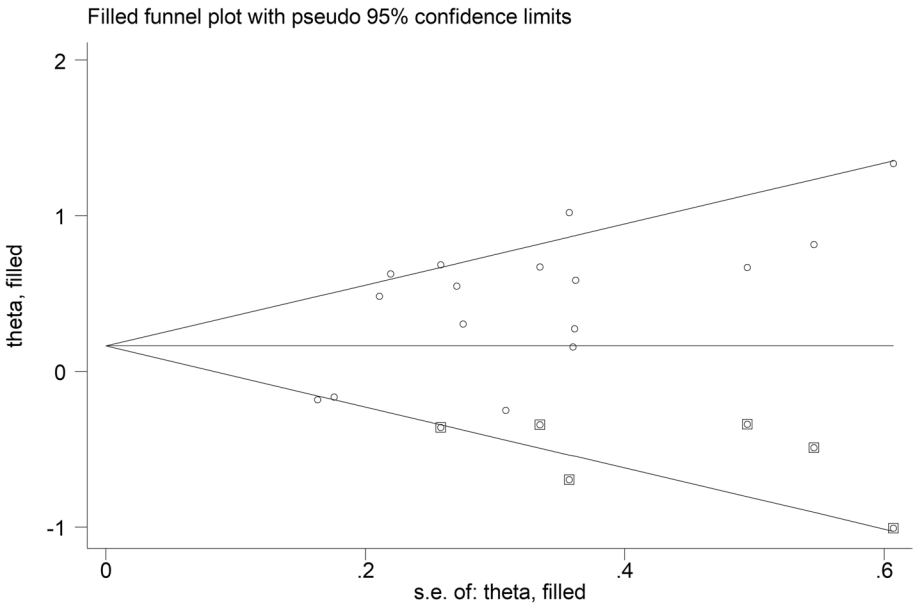


**Fig. 5** Funnel plot of studies investigating the association between serum/plasma neopterin and dementia after "trimming-and-filling". Dummy studies (those required to ensure symmetry) and genuine studies (those identified in the systematic review and meta-analysis) are represented by enclosed circles and free circles, respectively

disease (SMD = 0.40, 95% CI 0.10 to 0.69, $p = 0.009$; $I^2 = 69.8\%$, $p = 0.001$) and mild cognitive impairment (SMD = 0.60, 95% CI 0.12 to 1.07, $p = 0.013$; $I^2 = 0.0\%$, $p = 0.66$), but not in studies including both patients with Alzheimer's disease and mild cognitive impairment (SMD = 0.37, 95% CI −0.07 to 0.75, $p = 0.11$; $I^2 = 0.0\%$, $p = 0.69$), or other forms of dementia (SMD = 0.46, 95% CI −1.09 to 2.00, $p = 0.77$; $I^2 = 81.6\%$, $p = 0.020$). There was a virtually absent between-study heterogeneity in the Alzheimer's and mild cognitive impairment subgroups (Fig. 9). The pooled SMD was significant in studies using ELISA (SMD = 0.42, 95% CI 0.20 to 0.65, $p < 0.001$; $I^2 = 51.3\%$, $p = 0.014$), but not liquid chromatography (SMD = 0.20, 95% CI −0.61 to 1.02, $p = 0.62$; $I^2 = 79.5\%$, $p = 0.027$; Fig. 10). Finally, the pooled SMD was significant in studies assessing serum (SMD = 0.44, 95% CI 0.19 to 0.69, $p = 0.001$; $I^2 = 23.7\%$, $p = 0.23$) but not plasma (SMD = 0.32, 95% CI −0.04 to 0.69, $p = 0.084$; $I^2 = 75.9\%$, $p = 0.001$; Fig. 11), with a lower heterogeneity in the serum subgroup. However, there was no significant difference between the SMD in serum studies and that in plasma studies ($p = 0.51$).

The overall level of certainty was downgraded to very low because of the presence of significant publication bias.

#### *Urine neopterin*

One study with low risk of bias investigated the association between urine neopterin concentrations and Alzheimer's disease [62]. In this study, patients with Alzheimer's disease had significantly higher urine neopterin concentrations when compared to controls (0.41 ± 0.35 vs. 0.09 ± 0.06 μmol/mmol creatinine, $p < 0.01$).

#### *Cerebrospinal fluid neopterin*

One study with low risk of bias investigated the concentrations of neopterin in the cerebrospinal fluid [73]. In this study, non-significant differences were reported in cerebrospinal fluid neopterin between patients with Alzheimer's disease and controls (median 6.46, IQR 2.9, vs. 7.2 nM, IQR 4.24, $p = 0.54$).

### Biopterin

#### *Plasma biopterin*

One study with moderate risk of bias investigated plasma biopterin [60]. In this study, non-significant differences were reported between patients with Alzheimer's disease and controls (10.3 ± 0.9 vs. 14.5 ± 1.5 nM, p˃0.05).

#### *Urine biopterin*

One study with low risk of bias investigated urine biopterin [62]. In this study, urine biopterin concentrations were significantly higher in patients with Alzheimer's disease when compared to controls (0.23 ± 0.09 vs. 0.09 ± 0.06 μmol/mmol creatinine, $p < 0.05$).

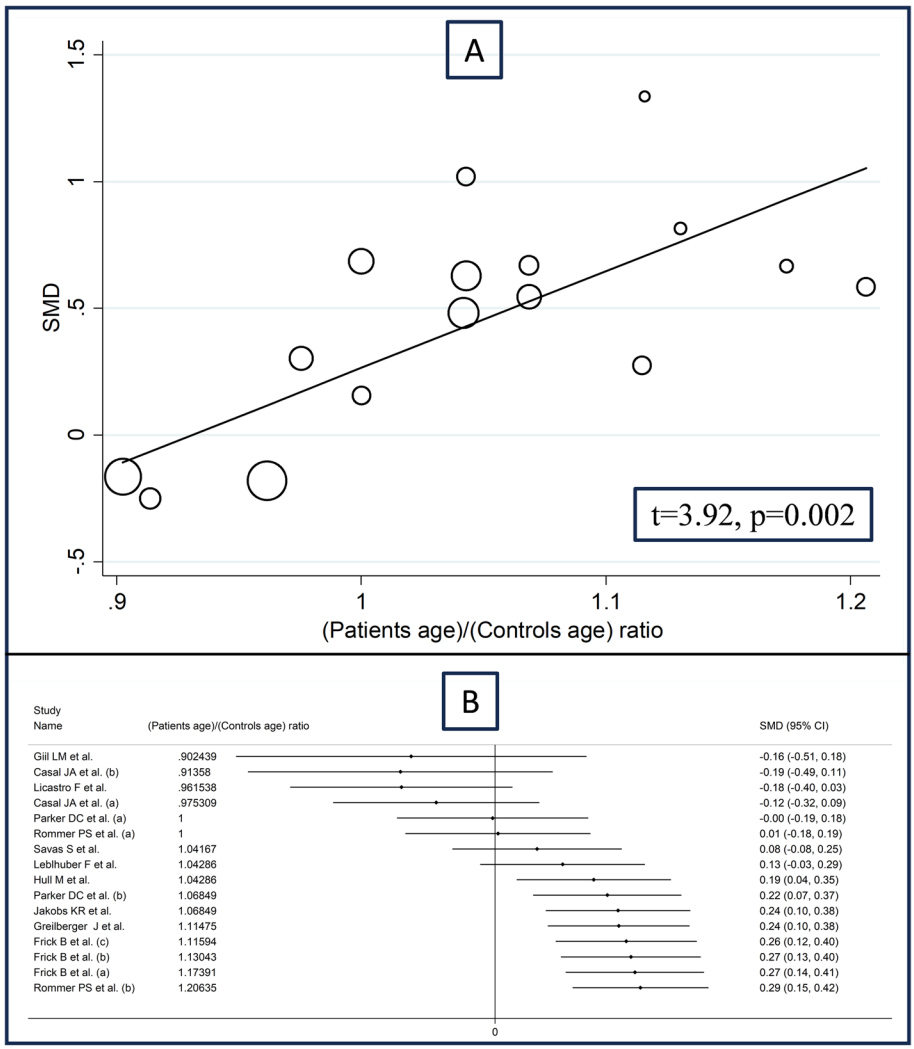


**Fig. 6** Bubble plot reporting univariate meta-regression analysis between the effect size and (patients age)/(controls age) ratio (**A**) and cumulative meta-analysis of total neopterin serum/plasma concentrations based on (patients age)/(controls age) ratio (**B**)

### *Cerebrospinal fluid biopterin*

Two studies with moderate risk of bias investigated biopterin in the cerebrospinal fluid in 59 patients with Alzheimer's disease and 25 controls [60, 61]. Both studies were conducted in USA and used liquid chromatography.

The forest plot showed that the cerebrospinal fluid concentrations of biopterin were significantly lower in patients with Alzheimer's disease when compared to controls (SMD = −0.75, 95% CI −1.23 to −0.27, $p = 0.002$; $I^2 = 0.0\%$, $p = 0.46$; Supplementary Fig. 1). Assessment of sensitivity, publication bias and meta-regression analysis could not be performed because of the small number of studies.

The overall level of certainty was downgraded to very low because of the lack of assessment of publication bias.

### Tetrahydrobiopterin

No study investigating the concentrations of tetrahydrobiopterin in patients with dementia and healthy controls was identified in our search.

## Discussion

Our study showed no significant differences in plasma/serum concentrations of neopterin between patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, when grouped together, and healthy controls after adjusting for publication bias. Meta-regression analysis did not show any significant associations between the effect size and male to female ratio or publication year. By contrast, significant associations were observed with age and number of participants. In subgroup analysis, the pooled SMD of neopterin was

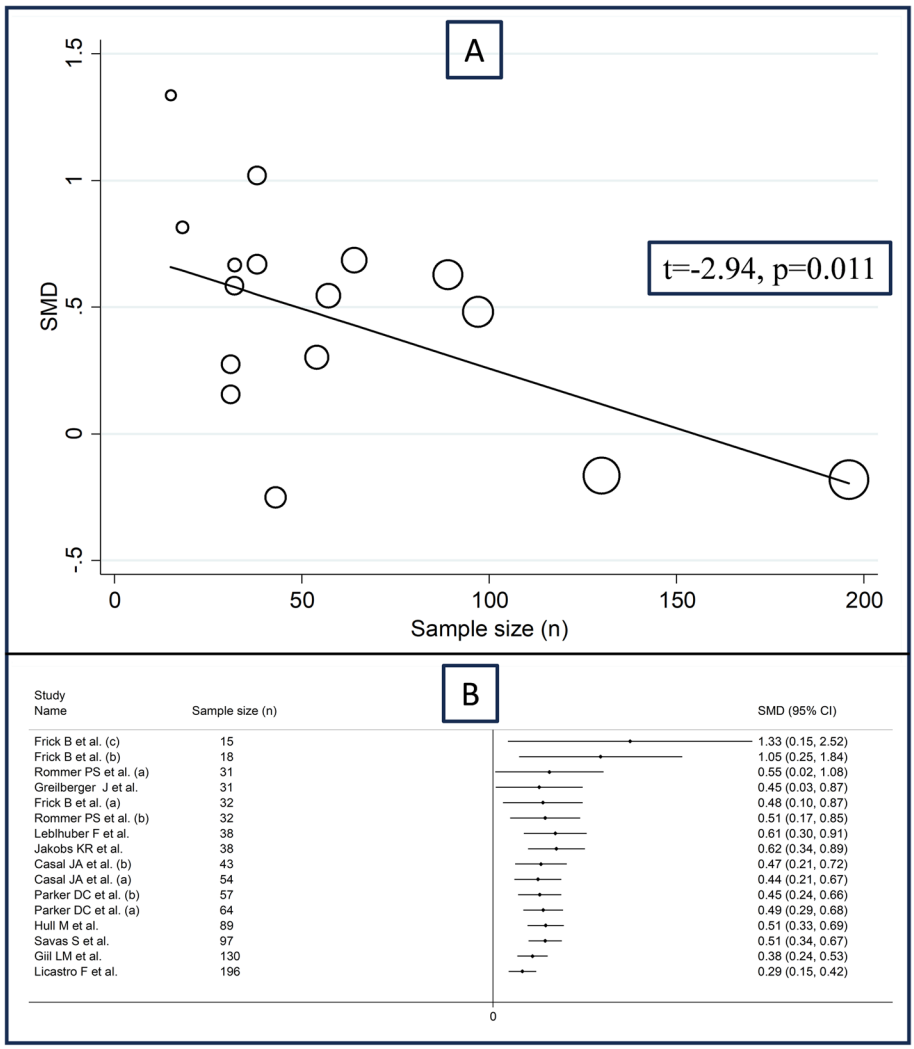


**Fig. 7** Bubble plot reporting univariate meta-regression analysis between the effect size and sample size (**A**) and cumulative meta-analysis of total neopterin serum/plasma concentrations based on sample size (**B**)

significantly higher in studies conducted in non-European continents, in studies of patients with mild cognitive impairment, in studies of patients with Alzheimer's disease, in studies using ELISA, and in studies investigating serum. Importantly, the subgroup analysis also allowed identifying sources of heterogeneity, particularly when investigating associations with study geographical location, presence of mild cognitive impairment or Alzheimer's disease, and biological matrix assessed. The only study identified in our search that investigated urine neopterin reported higher concentrations in patients with Alzheimer's when compared to controls [62]. By contrast, one study investigating neopterin in the cerebrospinal fluid reported similar concentrations between patients with Alzheimer's disease and controls [73]. We identified only one study investigating patients with vascular dementia [67], and no studies investigating patients with frontotemporal dementia, Parkinson's disease dementia, or Lewy body dementia.

Contrasting results were observed in isolated studies investigating plasma and urine biopterin in patients with Alzheimer's disease and healthy controls [60, 62]. However, in two studies investigating cerebrospinal fluid, the concentrations of biopterin were significantly lower in patients with Alzheimer's disease when compared to controls [60, 61]. Our search did not identify any relevant study investigating $BH_4$ concentrations in patients with dementia and healthy controls.

Taken together, the observed pteridine alterations are indicative of excessive interferon-γ production and inflammation, macrophage activation, and oxidative stress (neopterin increase) in mild cognitive impairment and Alzheimer's disease, and impaired synthesis of neurotransmitters (biopterin decrease) in Alzheimer's disease.

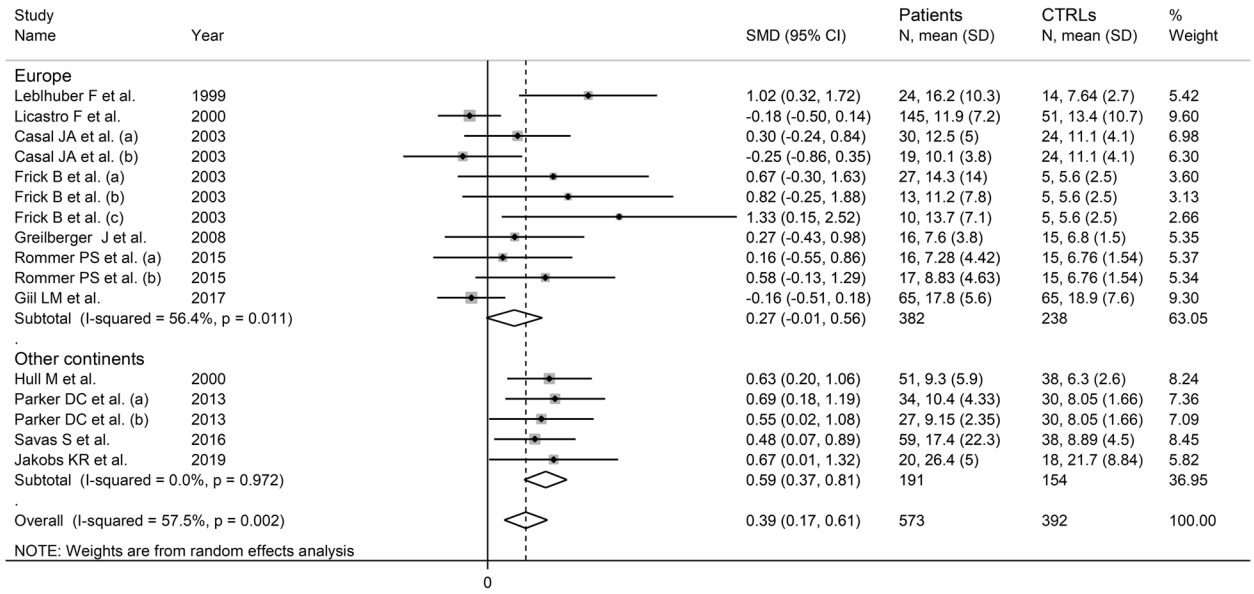


**Fig. 8** Forest plot of studies examining serum/plasma neopterin in patients with dementia and controls according to the continent where the study was conducted

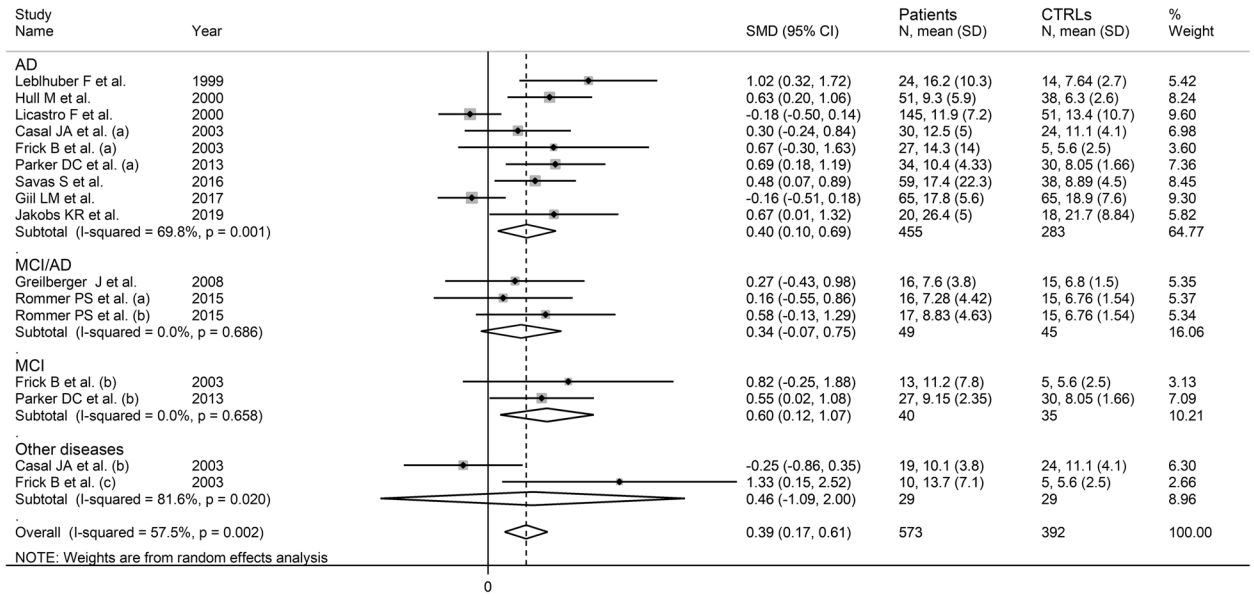


**Fig. 9** Forest plot of studies examining serum/plasma neopterin in patients with dementia and controls according to the type of dementia

Several observations support this proposition. Circulating concentrations of interferon-γ-induced protein 10 (IP-10), a chemokine secreted in response to interferon-γ, have been shown to be significantly elevated in patients with Alzheimer's disease compared to healthy controls in a systematic review and meta-analysis (SMD = 0.74, 95% CI 0.08 to 1.40) [74]. However, non-significant differences in cerebrospinal IP-10 concentrations between patients with mild cognitive impairment and healthy controls have been reported in another systematic review and meta-analysis (ratio of mean = 1.19, 95% CI 0.48 to 2.97) [75]. Macrophage activation, excess inflammation, and oxidative stress are well-recognized processes in mild cognitive impairment and Alzheimer's disease [76–80]. Therefore, alterations in neopterin concentrations could potentially reflect dysregulation of several different

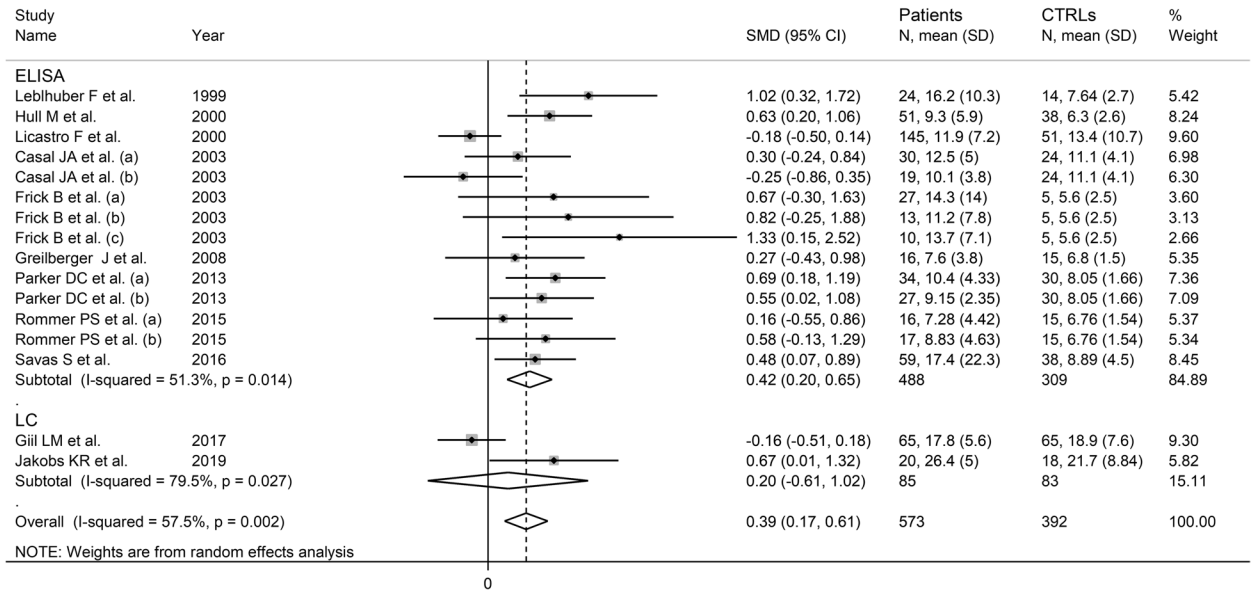


**Fig. 10** Forest plot of studies examining serum/plasma neopterin in patients with dementia and controls according to analytical method used

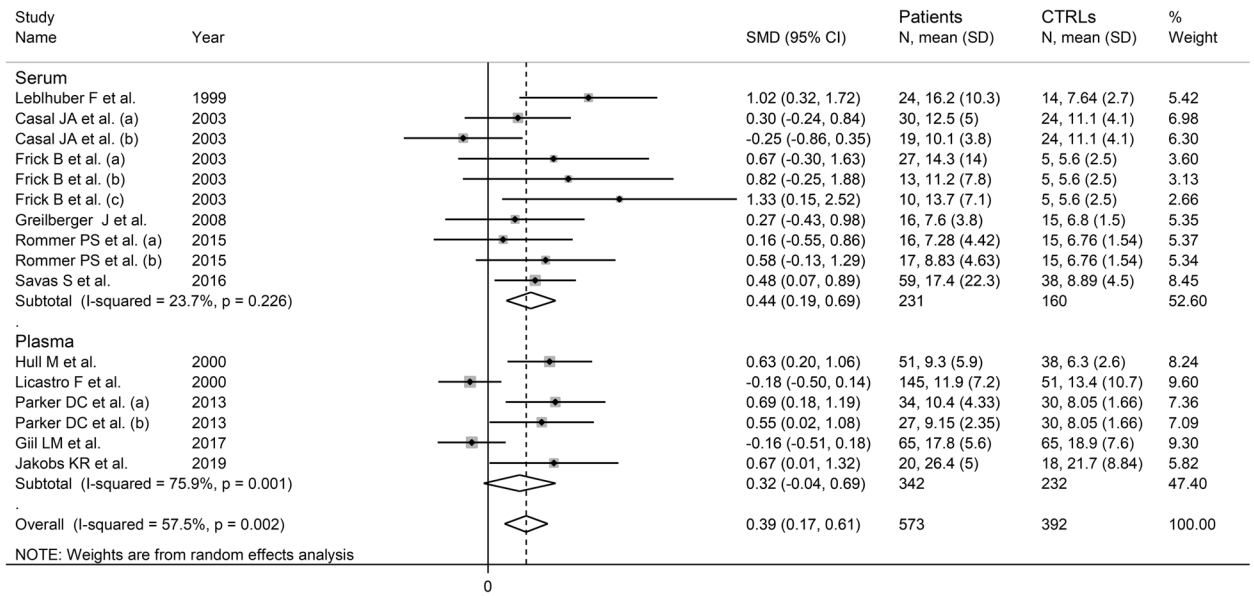


**Fig. 11** Forest plot of studies examining serum/plasma neopterin in patients with dementia and controls according to sample matrix

pathways associated with immunity, inflammation, and redox balance.

The elevations of plasma/serum neopterin reported in mild cognitive impairment and Alzheimer's disease have been observed in other neuropsychiatric conditions. For example, a systematic review and meta-analysis of 24 studies in subjects with depression reported significantly higher blood neopterin concentrations when compared to controls (SMD = 0.36, $p < 0.001$; $I^2 = 58.2$), with an effect size that was similar to that observed in our study [81]. It is possible that the increased concentrations of neopterin reflect alterations of similar inflammatory, immune, and redox pathways in mild cognitive impairment, Alzheimer's disease, and depression [82–87]. Treatments targeting these pathways, particularly inflammation, have shown promise in Alzheimer's disease and depression [88, 89]. Further studies are warranted to investigate whether the magnitude of anti-inflammatory

effects with different therapies is associated with improvements in depressive symptoms and/or cognitive domains and whether changes in neopterin are useful in quantifying such associations.

The lower cerebrospinal concentrations of biopterin in patients with Alzheimer's disease vs. controls suggest an impaired synthesis of specific amino acids, e.g., dopamine, norepinephrine, epinephrine, and serotonin. This hypothesis is supported by studies reporting lower concentrations of dopamine [90], norepinephrine [91], and serotonin [92] in Alzheimer's disease. Pending additional research, biopterin alterations could reflect alterations of specific amino acids in Alzheimer's disease and complement the information provided by other markers reflecting dysregulated inflammation and immunity, neuronal damage, and extracellular accumulation of toxic products.

The lack of relevant studies investigating $BH_4$ in patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia should stimulate further research given the important role played by this pteridine cofactor in the synthesis of specific amino acids as well as NO. The pathophysiological role of $BH_4$ is supported by the results of a study on a triple-transgenic mouse model of Alzheimer's disease. After receiving a control diet or a high-fat diet from 6 to 13 months, mice were treated with intraperitoneal $BH_4$ or vehicle for ten days. Notably, $BH_4$ treatment rescued memory impairment, assessed using the novel object recognition test, but did not affect the neuropathological features of the animals (tau and amyloid-β) [93]. Large, prospective studies should investigate alterations in pteridines in mild cognitive impairment and Alzheimer's disease, associations with other markers of inflammation, immune activation, and oxidative stress, and possible changes during treatment.

Strengths of our study include the assessment of different pteridines involved in inflammation, activation of immunity, oxidative stress, and the synthesis of specific neurotransmitters in patients with mild cognitive impairment, Alzheimer's disease, and other types of dementia. An additional strength is the investigation, when possible, of potential associations between the effect size of the between-group differences and various study and patient characteristics, and sources of heterogeneity using subgroup analysis. Significant limitations include the relatively small number of studies investigating biopterin, the absence of studies investigating $BH_4$, the inclusion of only one study investigating patients with vascular dementia or other types of dementia, and the potential for selection bias as we included only English-language publications. Furthermore, the previously described significant publication bias warrants additional research to confirm or refute the observed alterations in plasma/serum neopterin in mild cognitive impairment and Alzheimer's disease.

## Conclusion

Our study showed no significant differences in circulating neopterin between patients with mild cognitive impairment, Alzheimer's disease, or other types of dementia, when grouped together, and healthy controls. The significant associations observed between the effect size and mild cognitive impairment and Alzheimer's disease in subgroup analysis warrant further investigation to determine the role of neopterin as biomarker and, potentially, as lead for developing novel pharmacological interventions.

## Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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**Authors' contribution**
Study conception: AZ, AAM; Data collection and analysis: AZ; Data interpretation: AZ, AAM; Writing—first draft: AAM; Writing—Review & Editing, AZ, AAM.

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**Data availability**
The datasets generated during and/or analysed during the current study are available from AZ on reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable as this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Consent for publication**
Not applicable as this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Competing interests**
The authors declare no competing interests.

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