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Predictors for survival in patients with Alzheimer's disease: a large comprehensive meta-analysis

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The prevalence of Alzheimer's disease (AD) is increasing as the population ages, and patients with AD have a poor prognosis. However, knowledge on factors for predicting the survival of AD remains sparse. Here, we aimed to systematically explore predictors of AD survival. We searched the PubMed, Embase and Cochrane databases for relevant literature from inception to December 2022. Cohort and case-control studies were selected, and multivariable adjusted relative risks (RRs) were pooled by random-effects models. A total of 40,784 reports were identified, among which 64 studies involving 297,279 AD patients were included in the meta-analysis after filtering based on predetermined criteria. Four aspects, including demographic features ($n = 7$), clinical features or comorbidities ($n = 13$), rating scales ($n = 3$) and biomarkers ($n = 3$), were explored and 26 probable prognostic factors were finally investigated for AD survival. We observed that AD patients who had hyperlipidaemia (RR: 0.69) were at a lower risk of death. In contrast, male sex (RR: 1.53), movement disorders (including extrapyramidal signs) (RR: 1.60) and cancer (RR: 2.07) were detrimental to AD patient survival. However, our results did not support the involvement of education, hypertension, APOE genotype, $A\beta_{42}$ and t-tau in AD survival. Our study comprehensively summarized risk factors affecting survival in patients with AD, provided a better understanding on the role of different factors in the survival of AD from four dimensions, and paved the way for further research.

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INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder with progressive cognitive impairment and is the predominant form of dementia [1, 2]. As of 2020, approximately 55 million people worldwide are living with dementia, and that number is predicted to reach 78 million by 2030 [3]. The mortality of AD increased by 29.28% from 1990 to 2019 with the increase in the aging population [4, 5]. Moreover, AD and other dementias were the fourth cause of disability-adjusted life-years (DALYs) for those aged 75 years and older [5], leading to a tremendous burden on society and caregivers.

In the context of emerging treatments for preclinical AD, despite intensive research and development efforts to identify therapeutic drugs, there is still no effective strategy to stop progression due to insufficient knowledge of the etiology of AD [6]. Under these circumstances, focusing on influential factors potentiating AD progression since diagnosis is critical for neurologists and patients' families. Great efforts have been made [7–10] to determine predictive factors for survival of AD, and a number of predictors that may worsen the disease prognosis have been identified. Prognostic factors such as age at diagnosis, underweight, extrapyramidal signs (EPS) and psychosis, and history of vascular or heart disease appear to be key players in the progression of AD [7, 8, 10–14]. Nutritional status was found to be the exact predictor of an unfavorable course, which was suggested to therefore form part of the clinical evaluation [15]. One study proposed that combination therapies targeting AD pathophysiology and vascular risk factors might enhance therapeutic effects [16]. Patients could benefit similarly from remedies that target modifiable factors. However, previous studies which tried to sum up the predictors only kept eyes on a limited dimension of factors, and on account of the research inconsistencies and limited number of studies, the conclusions were inauthentic and the supportive reasons were inadequate [7, 17, 18]. Therefore, an extensive summary is urgently needed, and we performed this meta-analysis to fill this research gap.

With the aim of further understanding the prognostic factors of AD and guiding clinical work from specifically modifiable issues, we designed a systematic meta-analysis to summarize predictive factors for the survival and quality of life of AD patients from various dimensions.

METHODS

Search strategy

The PubMed, Embase and Cochrane databases were systematically searched from inception to December 2022 by terms "Alzheimer disease OR dementia OR Alzheimer* OR AD OR Dement*" AND "prognosis* OR progress* OR survival OR outcome OR mortality OR death OR hazard" by two independent researchers (XZ and SW). Furthermore, we refined the search scope for case-control or cohort studies by limiting "prospective

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OR retrospective OR cohort OR case-control OR case control OR consecutive" in the title or abstract. The comprehensive meta-analysis was performed following the Preferred Reporting Item for Systematic Review and Meta-analysis (2020) guidelines [19] (Supplementary Table S1). The titles and abstracts of all retrieved articles were reviewed. We also considered other publications in the full-read reports reference lists as supplementary papers. There were no restrictions applied in the literature search. The protocol for the study was registered with PROSPERO (registration number: CRD42022365357).

Selection criteria

The inclusion criteria were as follows: 1) the diagnostic criteria for AD patients were clearly stated; 2) case-control or cohort studies published in English; 3) the literature reported risk factors for the survival outcome of AD; and 4) the study provided adjusted effect sizes, relative risks (RRs), or hazard ratios (HRs) with 95% confidence intervals (CIs) through multivariate analysis. The exclusion criteria were as follows: 1) duplicate literature without new data; 2) incomplete data or odds ratios (ORs) as effect variables; 3) case reports, conference abstracts, reviews, comments, author replies and editorial materials; 4) studies on animals, cells and genes; and 5) patients diagnosed with any other type of dementia, including but not limited to vascular dementia, frontotemporal dementia, Parkinson's disease dementia, and dementia with Lewy bodies. Further, considering the search scope of observational studies, we excluded predictors involving only treatment or nursing care to avoid inadequate aggregation.

Data extraction and quality assessment

Data extraction was performed by two independent researchers (XZ and SW). If a study had multiple estimates for the same factor, we only selected the estimates with the most adjusted variables and the longest follow-up time. According to previous survival research, survival was defined as the time when instruments were needed to sustain vital signs or mortality data retrieved from the registration system. For several causes of death, all-cause mortality was chosen to avoid underestimating the real death toll. Only when there were enough studies to conduct meta-analysis (≥3 studies concerning a potential variable) could the adjusted results be extracted. In addition, different studies might use different models or classifications of factors concerning survival and report various estimates in terms of one reference. Given that, we combined the poly-values into an overall value by a random-effects model. For variable inclusion, only categorical data providing the same classification criteria and continuous variables (per year/point increase) were included. The author, publication year, sample size, country, AD diagnostic criteria, included factors, endpoints, mean age, sex ratio, follow-up period, mean disease duration and median survival time were listed.

In addition, we exhibited the Newcastle-Ottawa Scale (NOS) and confounding factors of each eligible study. The endpoints included death, institutionalization, nursing home place (NHP) and cognitive decline (especially rapid decline). For possible factors and endpoints, the combined estimates of items were extracted from four aspects, and the details are described in the Supplementary Materials (Supplementary Table S2). All the variables of rating scales, clinical features or comorbidities were considered at diagnosis or at enrollment. Quality assessment was performed by two independent researchers (XZ and SW) using NOS scores. When there was divergence between the other two researchers, a third researcher was consulted to help reach a consensus.

Statistical analysis

To assess the potential impact on survival, the RR with a 95% CI was used as the estimate to be pooled for quantitative synthesis. Due to the adjusted survival time, the HR was considered equal to the RR for analysis, while studies that reported ORs were excluded for their tendency to overestimate the effect size. Four aspects were investigated to probe factors influencing the survival of AD. The primary outcome was the combined adjusted RR and 95% CI for mortality. Additionally, we consolidated the remaining endpoints, including institutionalization, NHP and cognitive decline, into "poor prognosis" as the secondary outcome to represent quality of life.

The multivariable-adjusted estimates and 95% CIs were transformed into log relative risks to calculate combined values using the random-effects model. As a result, those whose effect value was the same as the lower and upper CIs were eliminated to obtain a calculable standard error (SE). For those that provided values with opposite reference objects, we converted them into a unified one to achieve consistency [20].

Heterogeneity was assessed using the Q test and quantified by the I^2 metric. $I^2 < 25\%$ indicated no evidence of heterogeneity; $25\% < I^2 < 50\%$ indicated acceptable heterogeneity, and in such cases, the fixed-effects model was adopted for pooled analysis; $50\% < I^2 < 75\%$ indicated possible heterogeneity; and $I^2 > 75\%$ indicated considerable heterogeneity, for which the random-effects model was chosen and further analysis was performed. To explain and reduce heterogeneity, subgroup analysis was applied if necessary. In addition, for heterogeneity that could not be explained, a multivariate sensitivity analysis was performed to examine if the pooled effect size was influenced by sequentially omitting individual studies and to detect the stability of results as well. Meanwhile, a meta-regression ($n \geq 10$) was performed to explore the potential source of heterogeneity using the conservative Hartung–Knapp method [21, 22] and to assess the underlying interaction of study characteristics, with the terms age, sex, geographic region, sample size, NOS scores and follow-up period. The Egger test was used to detect potential publication bias, and the trim-and-fill method was constructed for adjustment when significant bias was found.

All of the above statistical analyses were performed using Stata 15.1, with a two-tailed $p < 0.05$ considered indicative of statistical significance.

RESULTS

Literature retrieval and characteristics

According to the preset retrieval strategy, a total of 40,784 articles were considered from the outset. By excluding 13,876 duplicates and 24,949 records not associated with survival in AD, 1959 potential articles and an additional 12 from reference lists were fully reviewed. A further re-evaluation of each article led to the inclusion of 64 studies [11, 23–85] concerning 26 probable prognostic factors, which were categorized into four groups, namely, demographic features ($n = 7$), clinical features or comorbidities ($n = 13$), rating scales ($n = 3$) and biomarkers ($n = 3$). The detailed search flow diagram is shown in Fig. 1, and the statistically significant predictors are listed in Table 1. Moreover, the characteristics of the 64 eligible studies involving 297,279 AD patients are summarized in Supplementary Table S3. Confounding factors for the included studies are shown in Supplementary Table S4. The total results are shown in Supplementary Table S5 and the specific forest plots are listed in Supplementary Figs. S1–5.

Primary outcomes

Demographic features. Six factors (age, sex, race, years of education, marital status and smoking) for which there was prior evidence for an association with AD survival were included in the primary analysis (Supplementary Fig. S1). We found that there was a poor prognosis for older patients (RR 1.05, 95% CI 1.04–1.07 for baseline age; RR 1.03, 95% CI 1.01–1.05 for age of onset), males (RR 1.58, 95% CI 1.49–1.68) and white patients (RR 1.36, 95% CI 1.21–1.53) (Fig. 2). However, years of education (RR 1.00, 95% CI

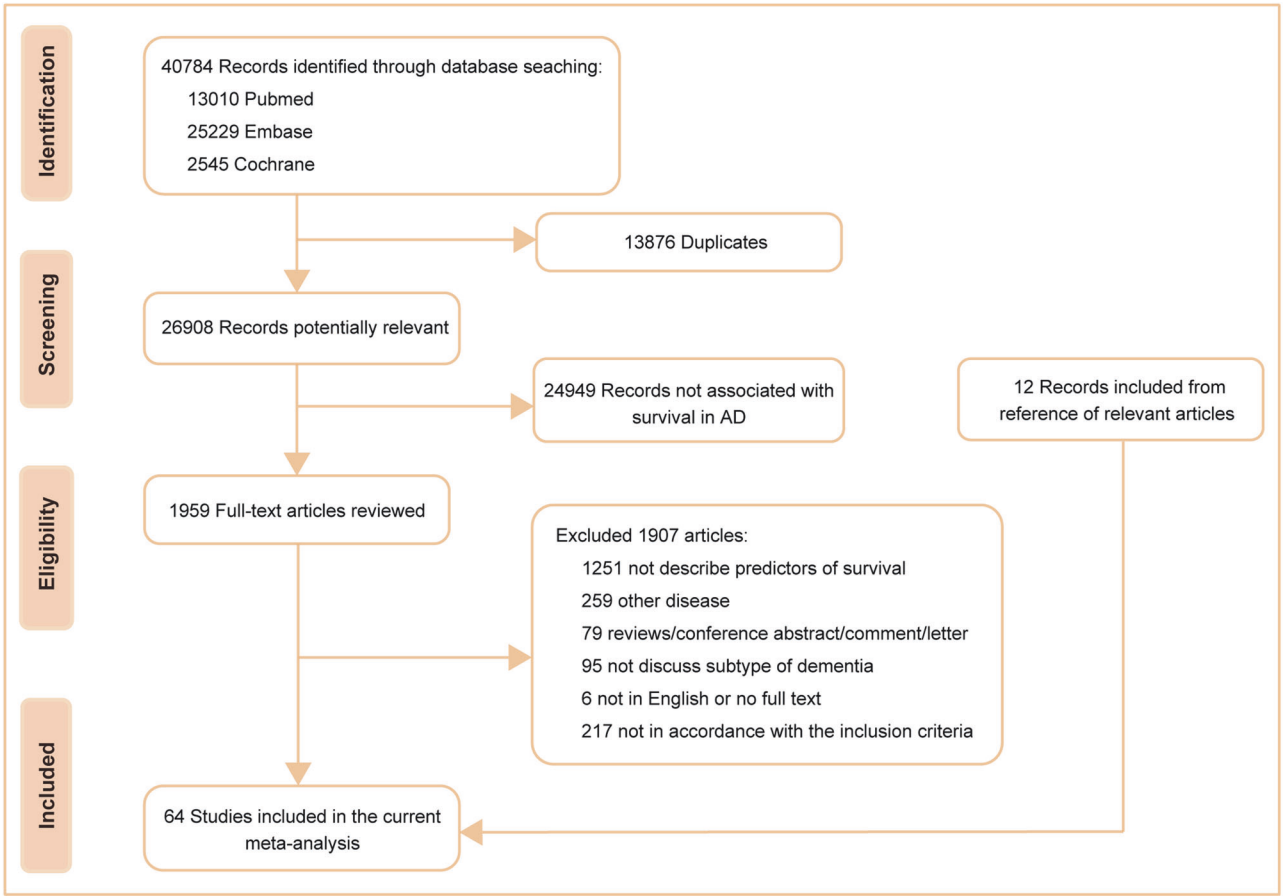

Fig. 1 PRISMA flowchart for systematic review and meta-analysis. Flowchart of the literature search according to Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA).

0.98–1.02), living alone (RR 1.07, 95% CI 0.97–1.19), and smoking (RR 1.00, 95% CI 1.00–1.01) did not show a significant association.

Clinical features or comorbidities. Clinical features or comorbidities also play an important role in the prognosis of AD (Supplementary Fig. S2). In our analysis, those who had hyperlipidaemia (RR 0.69, 95% CI 0.59–0.80) had a lower risk of death (Fig. 2). In contrast, we found that manifestations of movement disorders (including EPS) (RR 1.60, 95% CI 1.32–1.93) and cancer (RR 2.07, 95% CI 1.17–3.67) were more detrimental to AD patient survival. Moreover, other features, such as neuropsychiatric symptoms (NPS) (RR 1.16, 95% CI 1.08–1.24), depression (RR 1.12, 95% CI 1.03–1.22), heart disease (RR 1.24, 95% CI 1.11–1.37), cerebrovascular disease (RR 1.30, 95% CI 1.20–1.41), respiratory disease (RR 1.23, 95% CI 1.19–1.27), diabetes mellitus (RR 1.30, 95% CI 1.15–1.48) and a higher somatic comorbidity score (RR 1.24, 95% CI 1.06–1.44), were associated with poor prognosis (Fig. 2). Beyond that, the pooled analysis failed to exhibit a significant outcome in patients with a history of hypertension (RR 1.19, 95% CI 1.00–1.41), wandering or falling (RR 1.39, 95% CI 0.95–2.06) and vascular risk factors (VRF) (RR 1.02, 95% CI 0.93–1.13).

Rating scales. For rating scales (Supplementary Fig. S3), patients with higher activity of daily living (ADL) scores (RR 1.11, 95% CI 1.07–1.16) and physical self-maintenance scale (PSMS) scores (RR 1.09, 95% CI 1.07–1.10), which indicated a lack of self-care ability, had an increased risk of death (Fig. 2). Similarly, higher Mini-Mental State Examination (MMSE) scores, which indicated relatively good cognitive function, decreased the risk for shorter survival (RR 0.93, 95% CI 0.91–0.95) (Fig. 2).

Biomarkers. An increasing number of studies have been devoted to elucidating the impact of biomarkers in developing AD rather than survival since diagnosis. However, due to the various cut-off values among different researches, it is not easy to perform quantitative analysis for all biomarkers. Therefore, only three biomarkers were analyzed in the current study (Supplementary Fig. S4). We found that neither apolipoprotein E (APOE) ε4 carriers (RR 0.94, 95% CI 0.78–1.14), the level of cerebrospinal fluid (CSF) β-amyloid ($A\beta_{42}$) (RR 1.09, 95% CI 0.91–1.32) nor total tau protein (t-tau) (RR 1.00, 95% CI 1.00–1.01) had a significant impact on AD patient survival.

Secondary outcome

In the secondary analysis, nine potential factors were calculated (Supplementary Fig. S5). We found that movement disorders (including EPS) (RR 1.76, 95% CI 1.11–2.79) and NPS (RR 1.35, 95% CI 1.25–1.46) had a detrimental influence on the prognosis of AD. Same as before, higher MMSE scores (RR 0.93, 95% CI 0.90–0.96) were associated with longer survival (Fig. 2). However, age (RR 1.02, 95% CI 0.98–1.06 for baseline age; RR 0.98, 95% CI 0.92–1.05 for age of onset), male sex (RR 0.92, 95% CI 0.81–1.04), living alone (RR 1.67, 95% CI 0.66–4.26), increased ADL scores (RR 1.05, 95% CI 0.96–1.16) and APOE ε4 carrier (RR 0.93, 95% CI 0.72–1.19) had no evident effect on living quality (institutionalization, NHP and cognitive decline) in patients with AD.

Heterogeneity and sensitivity analysis

Heterogeneity exists in some combination of this meta-analysis. In the primary outcome, depression ($I^2 = 26.4\%$), respiratory disease ($I^2 = 11.5\%$), hyperlipidaemia ($I^2 < 0.001$) and PSMS scores

Table 1. Meta-analysis of prognostic factors for mortality in patients with AD.

Prognostic factors	Number of studies	Pooled RR and 95% CI	*P* value	I^2
Demographic features (4)				
Age (per year increase)	27	1.05 (1.04–1.07)	<0.001	92.2%
Age of onset (per year increase)	6	1.03 (1.01–1.05)	0.003	73.9%
Sex (ref: female)	37	1.58 (1.49–1.68)	<0.001	84.8%
Race (ref: none-white)	8	1.36 (1.21–1.53)	<0.001	75.8%
clinical features or comorbidities (10)				
Hyperlipidaemia	4	0.69 (0.59–0.80)	<0.001	0.0%
Cancer	3	2.07 (1.17–3.67)	0.013	92.9%
Movement disorders (including EPS)	7	1.60 (1.32–1.93)	<0.001	58.4%
NPS	14	1.16 (1.08–1.24)	<0.001	94.2%
Depression	7	1.12 (1.03–1.22)	0.011	26.4%
Heart disease	12	1.24 (1.11–1.37)	<0.001	76.7%
Cerebrovascular disease	12	1.30 (1.20–1.41)	<0.001	61.6%
Respiratory disease	5	1.23 (1.19–1.27)	<0.001	11.5%
Somatic comorbidity score	4	1.24 (1.06–1.44)	0.007	99.6%
Diabetes mellitus	12	1.30 (1.15–1.48)	<0.001	75.1%
Rating scales (3)				
MMSE scores (per point increase)	15	0.93 (0.91–0.95)	<0.001	85.6%
ADL scores (per point increase)	10	1.11 (1.07–1.16)	<0.001	93.4%
PSMS scores (per point increase)	4	1.09 (1.07–1.10)	<0.001	36.1%

AD Alzheimer's disease, *RR* relative risk, *CI* confidence intervals, *MMSE* The Mini Mental State Examination, *ADL* Activity of Daily Living, *PSMS* Physical Self-Maintenance Scale, *EPS* extrapyramidal signs, *NPS* neuropsychiatric symptoms.

($I^2 = 36.1\%$) demonstrated unobvious or acceptable heterogeneity. We found that the heterogeneity of movement disorders was reduced by removing the study performed by Stern et al. [37]. Meanwhile, subgroup analysis was performed to reveal possible heterogeneity among studies, and the heterogeneity for age of onset, sex, cancer, NPS (subdivided into four types: behavioral problems, specific hallucinations or delusions, psychosis, mood disorder, any of the above symptoms), cerebrovascular disease, heart disease (cardiovascular disease), somatic comorbidity score, diabetes mellitus, and ADL scores was reduced to varying degrees (Supplementary Fig. S6). Hence, multiple sensitivity analyses for age, race and MMSE scores were performed by removing each study, but there was no change. Furthermore, we carried out meta-regression concerning items of age, sex, geographic region, sample size, NOS scores and follow-up time but failed to explain the source of heterogeneity. For the sensitivity analysis to test the robustness of the overall outcome, there appeared to be no significant difference in the results with any study removed except for depression and cancer (Supplementary Fig. S7).

In the secondary outcome, subgroup analysis based on age and NOS scores led to reduced heterogeneity for MMSE scores (Supplementary Fig. S6), and the outcome of the combination was stable in the sensitivity analysis (Supplementary Fig. S8).

Assessment of publication bias

For the primary analysis, no influences of publication bias on the combined results were identified and the specific items are demonstrated in the Supplementary Materials. Whereas for MMSE scores ($P = 0.040$), there exists latent publication bias. Hence, the further trim-and-fill method was used and showed the authenticity and stability of the result (unchanged adjusted RR 0.934, 95% CI 0.917–0.950 for MMSE scores).

For the secondary outcome, the multiple sensitivity analysis exhibited no difference by eliminating any single study (Supplementary Materials). However, for MMSE scores, a bias was observed ($P = 0.001$). After the application of the trim-and-fill method, the combined estimate did not change (adjusted RR 0.930, 95% CI 0.915–0.946), which meant that the impact of publication bias was acceptable.

DISCUSSION

To the best of our knowledge, there has been no meta-analysis summarizing prognostic factors for predicting the survival of AD patients from multiple dimensions. In this study, predictors, including demographic features, clinical features or comorbidities, rating scales and biomarkers, were investigated. In total, 26 probable prognostic factors were finally explored for AD survival, and 17 factors were identified as possibly related to the survival of AD (Fig. 3). Among them, hyperlipidaemia and higher MMSE scores were predictors of longer survival. However, males, features of movement disorders (including EPS) and cancer showed a worse prognosis. Moreover, older age, white race, a history of NPS, depression, heart disease, cerebrovascular disease, respiratory disease, higher somatic comorbidity score, diabetes mellitus, higher ADL scores and PSMS scores in patients also impaired AD survival. However, our results did not support the involvement of education, marital status, hypertension, wandering or falling, VRF, APOE genotype, $A\beta_{42}$ or t-tau in AD survival. In the secondary analysis, we found that only movement disorders (including EPS), NPS and lower MMSE scores played a meaningful role in the deterioration of progress in AD patients, which was in accordance with our primary analysis. For intervenable symptoms such as NPS and diabetes mellitus, patients may benefit from regular treatments.

Less is known about the clinical value of various factors in AD progression or survival in the past, and many studies have attempted to spell out their associations [7–11, 86–92]. Compared with the results of former studies, either accordance or difference was observed in our analysis.

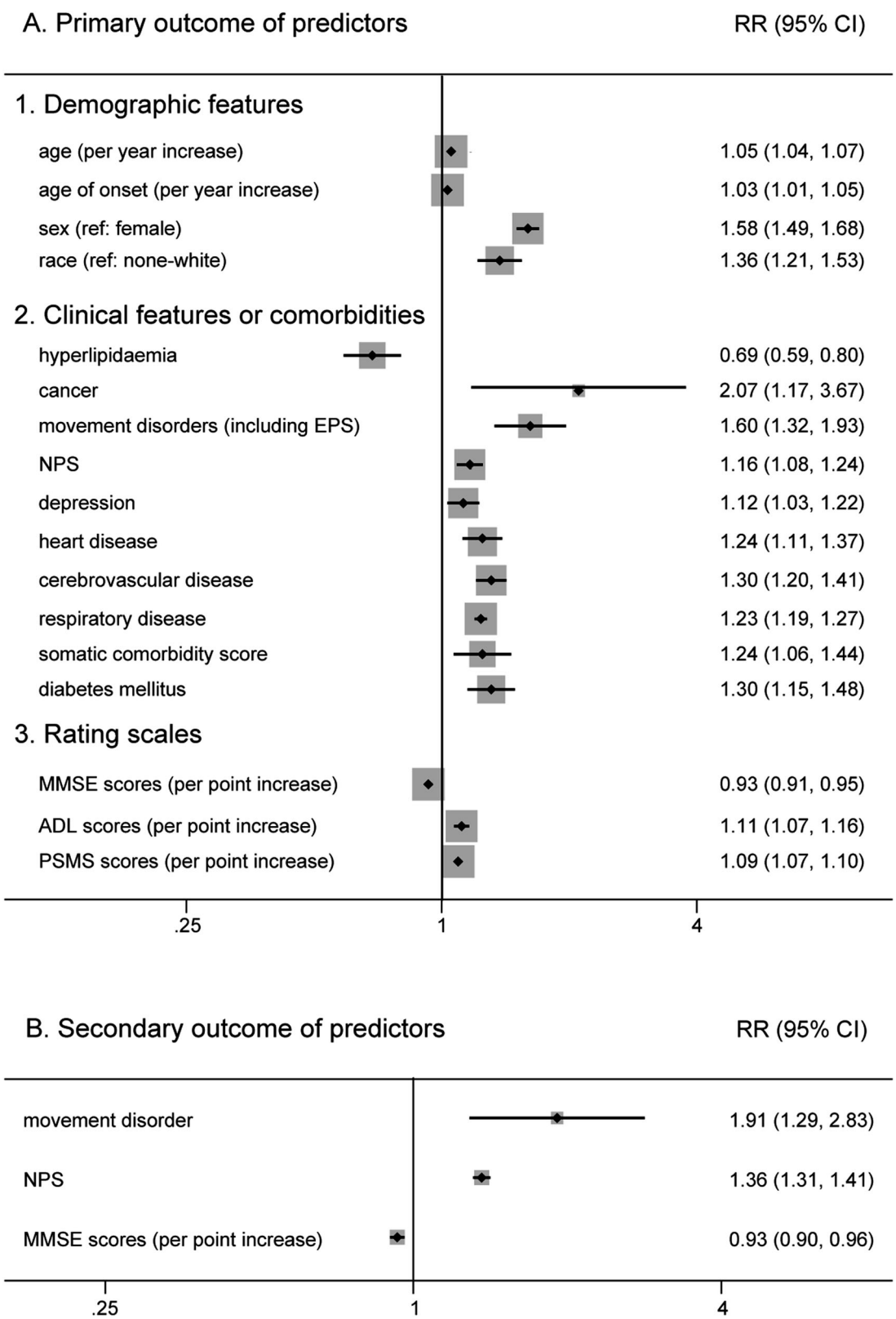

Fig. 2 Forest plot of the prognostic factors in AD. The forest plot displays meta-analysis results of the prognostic factors in AD. AD Alzheimer's disease, RR relative risk, CI confidence intervals.

Our findings indicated that hyperlipidaemia was related to longer survival of AD, and yet other VRF, including overall VRF and some separate diseases such as smoking and hypertension, did not show a similar significant association. Earlier research stated that there was no difference in the rate of deterioration between people with and without VRF and assumed that VRF may contribute to the expression of AD initially but was not part of the underlying etiologic process [93, 94]. What amazed us was the

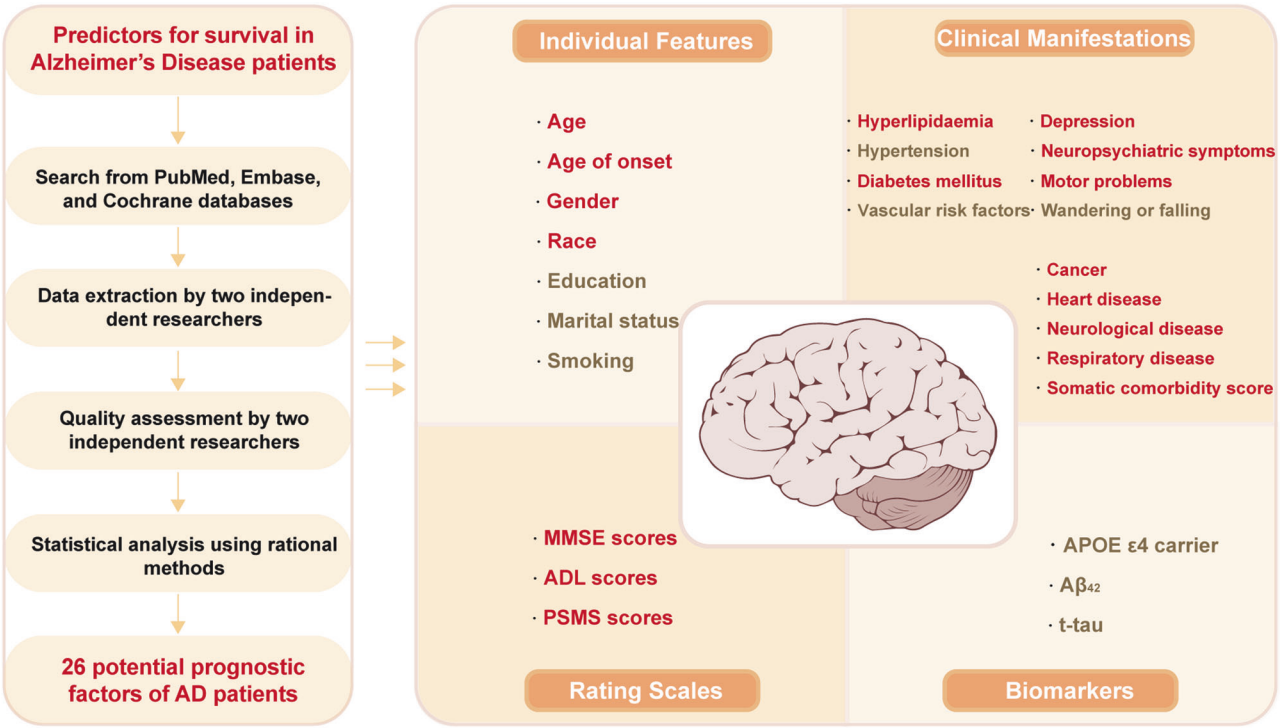

Fig. 3 Workflow and main findings of the meta-analysis. AD Alzheimer's disease, MMSE The Mini Mental State Examination, ADL Activity of Daily Living, PSMS Physical Self-Maintenance Scale, APOE Apolipoprotein E, CSF cerebrospinal fluid, Aβ β-amyloid, t-tau total tau protein.

negative link between hyperlipidaemia and mortality. It should be noted that elevations in blood lipids prolonged the survival of AD patients compared with those without hyperlipidaemia. Hyperlipidaemia has been identified as a risk factor for developing dementia. However, our analysis, which aggregated previous research findings, yielded conflicting results. These findings underscore the complexity of the role of hyperlipidaemia in the occurrence and progression of AD.

Other diseases, such as heart disease and cerebrovascular disease, which have been identified as driving forces in the process of dementia progression, were significantly associated with AD survival. Diabetes mellitus, one of the most prevalent comorbidities, plays an expediting role in disease progression [92, 95, 96], which might originate from an identical source as AD. This is not difficult to accept, as some researchers refer to AD as "diabetes of the brain" or "type-3 diabetes" [97]. In addition, movement disorders, often accompanied by functional defects, were discovered as a strong predictor of mortality and were associated with adverse outcomes [10, 98–100]. In our work, EPS influenced not only the survival of AD patients but also the quality of life since diagnosis, which is not hard to interpret because EPS, such as rigidity, tremor, and postural instability, means a loss of self-care to a certain extent. Similar to most of the following factors, cancer also significantly increased the risk of death in AD. One hypothesis was that the poor prognosis of patients with cancer shortened life expectancy, let alone those before the onset of AD. In terms of other clinical features, behavioral and psychological symptoms are common nonmotor symptoms during the natural history of AD, leading to distress for patients and their caregivers [101]. NPS and behavioral problems were proven to be detrimental to survival [10, 102], and similar results were found for depression, as in our work. In fact, how these manifestations interact remains unknown, and there is still controversy in some studies that disagree with the findings [93].

For demographic features, some items emerged as significant predictors of mortality. Older age and white race increased the risk of death in our study, which was in accordance with previous studies [7, 103, 104]. Meanwhile, a Framingham study suggested that due to "survival bias", men appeared to have a lower risk for dementia, in which the included male participants who survived to 65 years old possessed a better physical condition [105]. The fact remains that once diagnosed with AD or other dementias, having male sex resulted in a worse prognosis compared to having female sex. Similarly, previous studies and our findings showed that a higher education level was not associated with decreased survival in AD [87, 106], in contrast to the evidence that a lower level of education was a risk factor for dementia [107]. The role of marital status should not be ignored, although we did not obtain a meaningful outcome because a former study reported that younger patients living alone exhibited a nearly threefold risk of death than those living with a family [108]. One explanation was that patients living alone were likely to be diagnosed at a later time than those who lived together with a spouse, which can influence the intervention measures to be taken.

Additionally, we found that cognitive decline and deterioration of personal self-care ability (such as ADL and PSMS scores) were associated with mortality risk in individuals with AD. Previous studies drew the same conclusion as well [109–112]. A result from a real-world cohort indicated that poorer baseline cognitive ability and short-term decline in functional ability independently predicted the transition from mild to more severe AD dementia [110]. Additionally, Aβ42 and tau are generally recognized as diagnostic biomarkers, but few studies have examined whether AD biomarkers are associated with mortality. In our analysis, no difference was observed for APOE ε4 carriers and different levels of CSF biomarkers in disease progression, similar to previous studies [113–115]. The possible reason was that growing evidence of shared molecular mechanisms between AD and atherosclerosis, showed an association with more cardiovascular mortality [34]. Notably, it was also reported that AD patients with extreme levels of CSF biomarkers exhibited worse clinical outcomes over time [114], which might be explained by more advanced disease that contributed to the risk of death. In addition, baseline plasma neurofilament light (NFL) chain was regarded as a predictor of

cognitive decline, along with plasma tau in the late mild cognitive impairment (MCI) population [116].

The primary strength of our meta-analysis lies in its comprehensive and large-scale summary of prognostic factors for predicting survival in patients with AD from four dimensions. Another strength is that more high-quality prospective studies with nearly 300,000 AD patients were included, and stricter inclusion and exclusion criteria were used, which exhibited substantial power in drawing a conclusion. Moreover, we chose the most adjusted variables to decrease the impact of confounding factors that might influence the outcome. Last, a single type of dementia (Alzheimer's disease) rather than multiple types of dementia was focused on to understand the course of the disease pertinently [9, 92, 113, 117]. Although some predictors that affected AD survival were identified, these results should be considered with caution due to several limitations. First, we excluded studies that reported different classifications of categorical data or reported ORs as estimate variables to avoid bias. Second, heterogeneity still existed in the analysis of age, race and MMSE scores after the application of multifarious methods, and the generated estimates of clinical type, depression and cancer were not robust in the sensitivity analysis on account of the restricted number of studies. Third, publication bias could not be ignored in that some studies only reported significant results, and the personal characteristics, follow-up time, and sample size varied among studies, although efforts have been made to take that into account. Fourth, the potential relationship between hyperlipidaemia and AD survival could not be interpreted clearly, indicating a need for more research on this topic. Finally, we did not discuss the influence of therapeutic measures on survival in AD patients since observational studies were the major study type within the scope of the search strategy and randomized control studies were incomplete. Similarly, genetic factors were not taken into consideration due to the complicated pathogenesis.

This meta-analysis comprehensively identified intervenable and unmodifiable risk factors for predicting survival in patients with AD from the dimensions of demographic features, clinical features or comorbidities, rating scales and biomarkers.

DATA AVAILABILITY

All data analyzed during this study are included in the Supplementary Materials.

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AUTHOR CONTRIBUTIONS

XZ and CL conceived and designed the study. XZ and SW selected studies and collected data and quality assessment. JH and CL cross-checked the data and quality assessment. XZ, SW and JH contributed to the statistical analysis. XZ wrote the first draft of the manuscript. XZ, SW, JL and HS revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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