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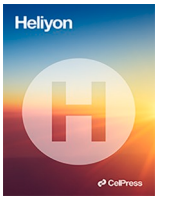

Research article

The association between methylmalonic acid, a biomarker of mitochondrial dysfunction, and cause-specific mortality in Alzheimer's disease and Parkinson's disease

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ABSTRACT

Background: Alzheimer's disease (AD) and Parkinson's disease (PD) are the leading causes of death among the elderly. Recent research has demonstrated that mitochondrial dysfunction, which is hallmark of neurodegenerative diseases, is a contributor to the development of these diseases.

Methods and materials: Methylmalonic acid (MMA), AD, PD, inflammatory markers and covariates were extracted from the National Health and Nutrition Examination Survey (NHANES). The classification of the inflammatory markers was done through quartile conversion. A restricted cubic spike function was performed to study their dose-response relationship. MMA subgroups from published studies were used to explore the correlation between different subgroups and cause-specific mortality. Multivariable weighted Cox regression was carried out to investigate MMA and cause-specific mortality in patients with AD and PD. Weighted survival analysis was used to study the survival differences among MMA subgroups.

Results: A non-linear correlation was observed between MMA and AD-specific death and PD-specific mortality. The presence of MMA Q4 was linked to increased death rates among AD patients (HR = 6.39, 95%CI: 1.19–35.24, P = 0.03) after controlling for potential confounders in a multivariable weighted Cox regression model. In PD patients, the MMA Q4 (Q4: HR: 5.51, 95 % CI: 1.26–24, P = 0.02) was also related to increased mortality. The results of survival analysis indicated that the poorer prognoses were observed in AD and PD patients with MMA Q4.

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Conclusion: The higher level of mitochondria-derived circulating MMA was associated with a higher mortality rate in AD and PD patients. MMA has the potential to be a valuable indicator for evaluating AD and PD patients' prognosis in the clinic.

Abbreviations

NHANES	the National Health and Nutrition Examination Survey
MMA	Methylmalonic acid
AD	Alzheimer's disease
PD	Parkinson's disease
SII	systemic immune-inflammation index
NLR	neutrophil-to-lymphocyte ratio
PLR	platelet-to-lymphocyte ratio
PPN	product of platelet count and neutrophil count
LC	lymphocyte
NC	neutrophil cells
MC	monocyte
PC	platelet count

1. Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are now the leading causes of death in the elderly, affecting approximately 50 million people worldwide [1]. AD is categorized as a cognitive impairment, whereas PD is labeled as a form of dyskinesia. In 2021, AD was the seventh leading cause of death in the United States [2]. PD is the second most prevalent neurodegenerative disease globally, with an estimated 6.1 million people affected [3,4]. The role of mitochondrial dysfunction, a hallmark of neurodegenerative diseases, in their development has been confirmed. This is one of the primary pathological features of neurodegeneration [5]. By interfering with the mitochondrial respiratory chain and producing reactive oxygen species (ROS), mitochondrial dysfunction can impact the metabolism of methylmalonic acid (MMA) and lead to the accumulation of MMA [6]. Wang et al. [7] have identified that mitochondrial-derived methylmalonic acid (MMA) can be a surrogate marker for mitochondrial dysfunction. Therefore, mitochondrial function may be objectively evaluated. Some studies have shown that an increase in MMA levels can be found in AD, PD, renal insufficiency, heart failure, and so on [6,8,9]. A study has shown that the expression of cell-cycle exit and neuronal differentiation 1 (END1) in the presynaptic mitochondria was significantly decreased in the brain of AD mice [10]. END1 exhaustion leads to an increase in mitochondrial division mediated by up-regulation of dynamin-related protein 1 (Drp1), resulting in mitochondrial dysfunction. The voltage-dependent anion channel 1 (VDAC1), expressed in the mitochondrial and plasma membrane, was involved in AD pathogenesis by interacting with over 150 other proteins including phosphorylated tau, Aβ, and γ-secretase [11]. VDAC1 was associated with neuronal cell destruction due to over-expression of VDAC1, causing cell death. Targeting VDAC1 to prevent mitochondrial dysfunction could slow the progression of AD. Short-chain dehydrogenase reductase family member ABAD, which is found in mitochondria, is responsible for triggering cell apoptosis and ROS production in neurons [12]. It can bind to Aβ to disrupt mitochondrial function, aggravating AD pathogenesis. Pan et al. [13] confirmed that tau promotes the aggregation and proliferation of α -synuclein in PD. α-synuclein can interact with PD-linked mutations, such as A53T, E46K and H50Q, which are responsible for mitochondrial fragmentation and ROS production [14]. Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) were the main cause of familial PD. LRRK2 overexpression resulted in an increased vulnerability to mitochondrial toxins, along with defects in mitochondrial dynamics and increased ROS production. Furthermore, it can bind with other proteins to have pathological effects on mitochondria, which can result in mitochondrial fragmentation and exacerbate PD pathogenesis.

Neuroinflammation has been demonstrated to play a crucial role in the pathogenesis of AD and PD in recent studies [15–17]. Chronically activated microglia are a source of pro-inflammatory and toxic products that neuroinflammation releases, and it also mediates amyloid precursor protein (APP) γ-secretase and β-secretase, which causes an aggravating effect on Aβ accumulation [17]. In a mouse model, the expression of interleukin-10 (IL-10) mediated by adeno-associated virus (AAV2/1) in the brain induced Aβ accumulation and APOE expression, which led to the deterioration in cognitive behavior and decline of Aβ phagocytosis of microglia [18]. Interferon (IFN)-γ was found to regulate the expression of β-site APP lyase 1 protein in astrocytes by activating the JAK2-ERK1/2 signaling pathway [19]. Bottigliengo et al. [20] found that higher IL-6 production may be the decisive factor in prodromal PD. TRPV4 is involved in the endoplasmic reticulum stress and inflammation pathways, triggering the loss of dopamine (DA) neurons in the substantia nigra of mice and affecting PD mice's movements [21]. An animal experiment has shown that the accumulation of MMA in body fluids will increase the levels of IL-1β and tumor necrosis factor (TNF)-α in cerebral cortex, and enhance the expression of proinflammatory markers such as inducible nitric oxide synthase (iNOS) and neurotrophin-3 (3-NT), thus promoting the progress of cognitive dysfunction [22]. Sbai et al. [23] confirmed that microglial activation and cytokine secretion were related to glial fibrillary

acidic protein and TXNIP. The RAGE-TXNIP axis activation resulted in the transport of Aβ from the cell surface to mitochondria, resulting in Drp1 activation and mitochondrial dysfunction aggrandizement, leading to the release of IL-1β and activation of Gasdermin D. In addition to relying on molecular basis for diagnosis and classification, gait analysis was proposed to objectively measure mobility performance and enhance our understanding of neurological conditions [24,25]. In brief, it works based on the differences in the gait characteristics among different diseases, using detection and analysis systems, contributing to improve dementia diagnosis and distinguishing between different dementia subtypes [26]. In the study, we aim to investigate the association between serum MMA levels and cause-specific mortality in AD and PD patients.

2. Methods and materials

2.1. Study population

Participants who had neurodegenerative diseases (primarily AD and PD) were gathered for the study during five cycles of the National Health and Nutrition Examination Survey (NHANES 1999–2014). Participants with detectable methylmalonic acid were included in our analysis. After deleting missing values in each variable, the study included 19457 participants who had complete data.

2.2. Methylmalonic acid (a surrogate marker of mitochondrial dysfunction)

In mobile examination centers (MEC) administered by NHANES, venipuncture was performed on participants to collect blood samples and determine the concentration of MMA in plasma. In the 1999–2004 cycles, gas chromatography-mass spectrometry was used to measure MMA, while in the 2011–2014 cycles, liquid chromatography-tandem mass spectrometry was used. The calculations done by these two methods are almost identical in comparison. The total coefficient of variation of MMA concentrations was 4–10 %, and the average recovery rate was 96.0 ± 1.9 % [7]. All the detection protocols and data conversion details are available on the NHANES.

2.3. Assertation of Alzheimer's disease

Medications were classified by their role in the NHANES database. AD patients were identified as participants who were taking AD medications. These drugs that we used to identify AD patients included Rivastigmine, Galantamine, Donepezil, and Memantine [27].

2.4. Identification of Parkinson's disease

Identifying patients with PD was done by using the PD drugs listed below, which include Benztropine, Carbidopa, Levodopa, Ropinirole, Methyldopa, Entacapone, Amantadine, trihexyphenidyl, selegiline, pramipexole and bromocriptine [27].

2.5. Inflammatory markers

A detailed laboratory methodology for the complete blood count test was provided by the NHANES website []. The inflammatory markers that play an important role in other diseases were included in our study [28]. Combining inflammatory markers in the NHANES database, systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), the product of platelet count and neutrophil count (PPN), lymphocyte (LC), neutrophil cells (NC), monocyte (MC) and platelet (PC) were included to investigate the potential inflammatory markers that were associated with the cause-specific mortality in AD and PD patients. LC, NC, MC and PC were measured in 1000 cells/μL. SII was calculated using the following formula: SII═(NC*PC)/LC [29]. The inflammatory markers were categorized by quartile conversion to examine the potential risk partition.

2.6. Incorporated covariates

In our analysis, we accounted for several potential confounding factors that could impact the progression of neurodegenerative diseases. The crucial variables included age (<65 and ≥ 65 years), gender, ethnicity (Mexican American, Non-Hispanic White, Non-Hispanic Black, and other race), education (less than high school level, high school graduate or college graduate or above), body mass index (BMI), alcohol consumption, coffee consumption, total fat intake, total cholesterol intake, smoking, walking and bicycling among physical activity, hypertension, diabetes, coronary heart disease, and stroke. BMI was regarded as a continuous variable and was split into normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), and obesity (>30 kg/m^2). Alcohol consumption was categorized into two categories, one being alcohol consumption and the other being non-alcohol consumption. The classification of coffee consumption matched that of alcohol consumption. Total fat intake was treated as a continuous variable and was grouped into low-fat intake groups and high-fat intake groups according to the mean value. The classification of total cholesterol intake was identical to that of total fat intake. Smoking status was divided into never (smoking less than 100 cigarettes in their lifetime), former (smoking more than 100 cigarettes in their lifetime but did not smoke during the survey), and current (smoking more than 100 cigarettes in their lifetime and still smoking during the survey) [29]. Walking and bicycling were considered to be representative of physical activity. Participants' disease histories were based on medical arguments.

2.7. Statistical analysis

The weight of the sample in NHANES 1999–2002 cycles was calculated as 2/5 *WTMEC4YR, while in NHANES 2003–2004, 2011–2014, it was calculated as 1/5* WTMEC2YR. The continuous MMA was log-transformed. The dose-response relationship between MMA and cause-specific mortality was elucidated by utilizing restricted cubic spline function. A non-linear trend between MMA and cause-specific mortality was investigated using the Wald test in R software with access to the "nhanesR" package. The association between MMA and cause-specific mortality was evaluated through Univariable and Multivariable weighted Cox regression. Univariable weighted Cox regression was used to create the crude model. The model 1 was built on multivariable weighted Cox regression adjusting for age, gender, ethnicity, education, BMI, alcohol consumption, coffee consumption, total fat intake, total cholesterol intake, smoking, walking and bicycling, hypertension, diabetes, cardiovascular disease, and stroke. To evaluate the relation between inflammatory markers and cause-specific mortality, weighted Cox regression was employed with MMA concentration as a stratification factor. The model was tested using the Wald test. Using a weighted survival analysis, it was evaluated how the survival probabilities of different MMA subgroups differed. All analyses were performed in R software (version: 4.2.2) by using the "nhanesR" package. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Data extraction and baseline characteristics

33916 participants with measurable MMA were identified in the five cycles. The samples for each variable can be seen in the flow chart (Fig. 1). All variables did not contain the missing values. The integration of AD (PD) data, MMA, covariates, and inflammatory markers by their common serial number resulted in the preparation of 19457 participants with complete data for further analysis. 70 AD patients and 140 PD patients were included in the study. The baseline characteristics of variables was showed in Supplementary Table 1. The categorical variables were displayed by frequency (percentage), while the continuous variables were displayed by median (IQR).

3.2. Association of MMA and cause-specific mortality in AD and PD patients

In order to investigate the dose-response relationship between MMA and cause-specific mortality in AD and PD patients, restricted cubic spline (RCS) was first performed and its number of knots was set at 3. In Fig. 2A, it was observed that MMA had a non-linear correlation with AD-specific death (P for non-linear <0.001). It was observed that the mortality of AD patients went up with the increase of logMMA to 5.88 nmol/L. Then, the mortality began to decrease. The association between MMA and PD-specific death was also non-linear (P for non-line <0.001) (Fig. 2B). The result showed that an increase in logMMA led to an increase in the mortality rate of PD patients.

According to the crude model conducted using univariable weighted Cox regression, logMMA was linked to greater mortality rates in AD patients (HR = 1.77, 95%CI: 1.13–2.78, P = 0.01) (Table 1). However, the correlation between logMMA and AD mortality was not significant after adjusting for confounding factors (HR: 1.73, 95%CI: 0.5–5.93, P = 0.38) (Table 1). Published studies [7] used MMA subgroups to examine the correlation between different subgroups and cause-specific mortality. The AD samples for MMA Q1 (<120 nmol/L), MMA Q2 (120–175 nmol/L), MMA Q3 (175–250 nmol/L), MMA Q4 (>250 nmol/L) were 7281, 6944, 3140, and

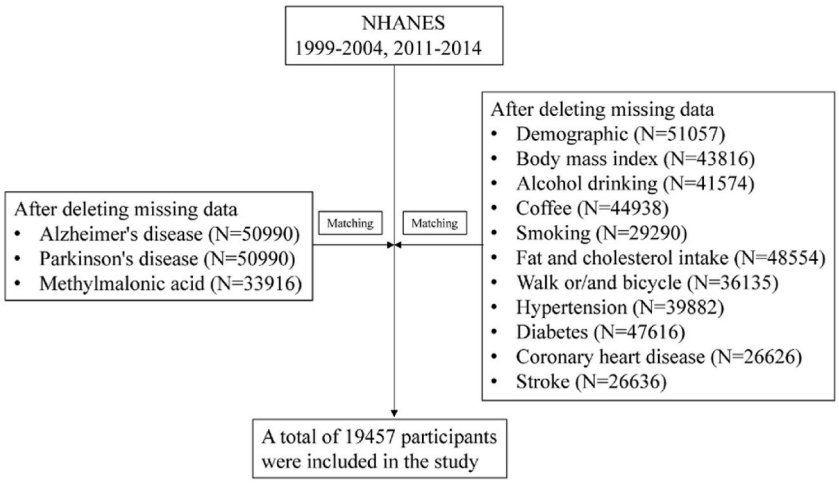

Fig. 1. The flow chart of gaining each variable. No variable had the missing values. The integration of AD (PD) data, MMA, covariates, and inflammatory markers by their common serial number resulted in the acquisition of complete data for 19457 participants.

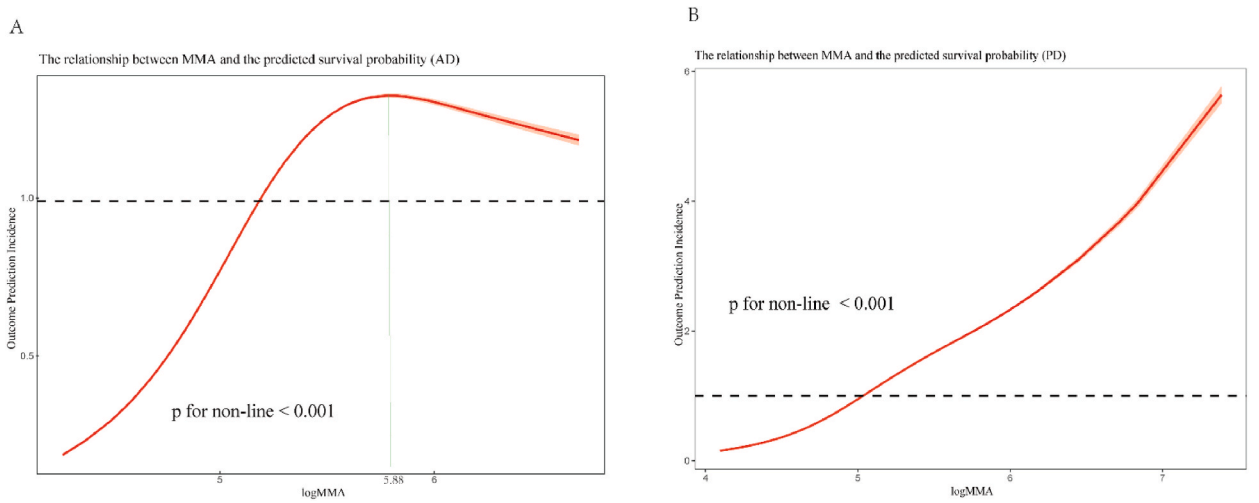

Fig. 2. A restricted cubic spline analysis for methylmalonic acid. (A) Response variable for AD. MMA had a non-linear correlation with AD-specific mortality. The X axis represents the log MMA level, while the Y axis refers to the predicted mortality rate. The mortality rate for AD patients increased when logMMA was raised to 5.88 nmol/L. Then, the mortality began to decrease. (B) Response variable for PD. MMA and PD had a correlation that was not linear. PD patients have a higher mortality rate with an increase in logMMA.

Table 1
The association between MMA and AD-specific mortality.

	Cutoff	Crude	P value	Model 1	P value
MMA (log)		1.77 (1.13,2.78)	0.01	1.73 (0.5–5.93)	0.38
MMA					
Q1	<120	ref		ref	
Q2	120_175	3.88 (1.48,10.15)	0.01	3.06 (0.59–16)	0.18
Q3	175_250	2.53 (1.01, 6.31)	0.05	0.68 (0.11–4.14)	0.68
Q4	>250	6.10 (2.58,14.40)	<0.0001	6.39 (1.19–35.24)	0.03

MMA: methylmalonic acid; AD: Alzheimer's disease; 95%CI: 95 % confidence intervals.
P < 0.05 was considered statistically significant.

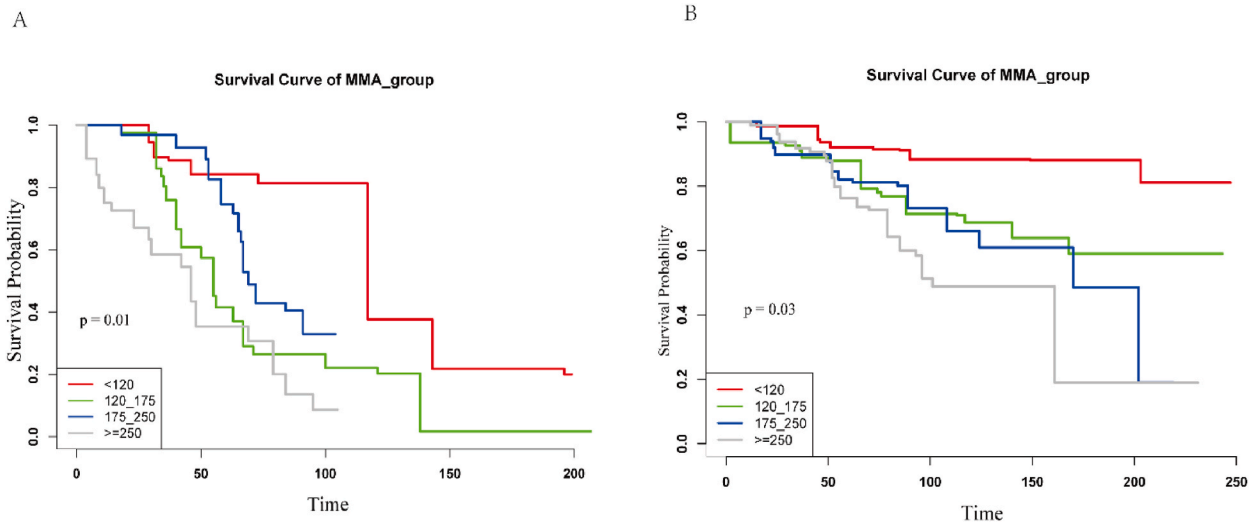

Fig. 3. Survival analysis for MMA subgroups in AD and PD patients. (A) Survival analysis for MMA subgroups in AD patients. Taking the red line (MMA <120 nmol/L) as a reference, the farther away the other lines were, the worse the prognosis was. (B) Survival analysis for MMA subgroups in PD patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2092, respectively. As displayed in Table 1, the result of crude model demonstrated that MMA (Q2: 120–175 nmol/L, Q4: >250 nmol/L) was associated with incremental mortality in AD patients (Q2: HR: 3.88, 95%CI: 1.41–10.45, P = 0.01; Q4: HR: 6.10, 95%CI: 2.58–14.4, P < 0.001) as compare to MMA Q1 (<120 nmol/L) (Table 1). The association between MMA Q4 and increased death among AD patients persists even after controlling for confounding factors (HR: 6.39, 95%CI: 1.19–35.24, P = 0.03). The weighted survival analysis revealed a statistically significant difference in survival rate between MMA subgroups. The survival probability of AD patients with a higher MMA level was lower than that of the lowest MMA group (Q1) (Fig. 3A). The findings suggested that higher levels of MMA were associated with a higher cause-specific mortality in AD patients.

In PD patients, logMMA was linked to a higher mortality of PD patients based on the result of univariable weighted Cox regression (HR: 2.94, 95%CI: 1.61–5.36, P < 0.01) and the result of multivariable weighted Cox regression after adjusting for confounding factors (HR: 2.63, 95%CI: 1.19–5.82, P = 0.02) (Table 2). MMA Q4 was still linked to the poor prognosis of PD patients even after adjusting for covariates (Q4: HR: 5.51, 95%CI: 1.26–24, P = 0.02). The survival rate of MMA subgroups was found to be significantly different by the weighted survival analysis result. In PD patients with higher MMA, the survival probability was less likely (Fig. 3B). The results revealed that a rise in MMA was linked to a higher rate of cause-specific mortality in PD patients.

3.3. The profiles of inflammatory markers related to cause-specific mortality under MMA subgroups

The profiles of inflammatory markers related to cause-specific mortality under MMA subgroups were investigated due to the significant role of mitochondrial dysfunction in the hallmark features of the AD brain [30,31]. The above discovery demonstrated that MMA Q4 was connected to specific mortality in AD and PD patients. Our analysis was directed towards the profiles of inflammatory markers that relate to cause-specific mortality when MMA >250 nmol/L.

In AD patients, after adjusting for age, gender, smoke, BMI, hypertension and diabetes, we found that PLR Q3 (HR: 0, 95%CI: 0–0.45, P = 0.02), PPN Q4 (HR: 0.11, 95%CI: 0.02–0.61, P = 0.01), and WBC Q2 (HR: 0, 95%CI: 0–0.2, P < 0.001) were connected to a decrease in mortality when MMA >250 nmol/L (Fig. 4A). Platelet Q2 (HR: 9.12, 95%CI: 1.62–51.4, P = 0.03) was linked to a negative outcome. These inflammatory markers may be involved in regulating the progression of the disease when MMA >250 nmol/L.

In PD patients, after controlling for confounding factors including age, gender, smoke, BMI, hypertension, and diabetes, we discovered that PLR Q3-Q4 (HR: 23.7, 95%CI: 1.47–38.4, P = 0.03; HR: 39.9, 95%CI: 4.93–79.3, P < 0.001), SII Q2-Q4 (HR: 13.2, 95% CI: 2.73–64.6, P = 0.001; HR: 15.4, 95%CI: 3.03–78.5, P < 0.001; HR: 16.5, 95%CI: 3.62–85.6, P < 0.0001), NC Q4 (HR: 18.4, 95%CI: 4.03–32.7, P < 0.001), PPN Q3-Q4 (HR: 3.2, 95%CI: 2.1–5.9, P = 0.002; HR: 20.7, 95%CI: 16.0–26.7, P = 0.02), and WBC Q4 (HR: 9.7, 95%CI: 1.06–18.6, P = 0.04) were linked with the increase in mortality (Fig. 4B). Hemoglobin Q4 (HR: 0.03, 95%CI: 0–0.85 P = 0.04) and lymphocyte Q2-Q4 (HR: 0.03, 95%CI: 0.01–0.14, P < 0.001; HR: 0.07, 95%CI: 0.01–0.84, P = 0.04; HR: 0.04, 95%CI: 0–0.41, P = 0.01) were correlated to retard the death of PD patients. The progression of the disease may be modulated by these inflammatory markers when MMA >250 mmol/L. Based on our analysis, it can be concluded that inflammatory factors were linked to cause-specific mortality when MMA levels >250 nmol/L in AD and PD patients.

4. Discussion

We investigated the connection between MMA and cause-specific mortality in AD and PD patients in our study. The correlation between MMA and cause-specific mortality in AD and PD was found to be non-linear by RCS analysis. We observed that a rise in logMMA was associated with an increase in mortality rates among individuals suffering from AD and PD. MMA Q4 was linked to the poor prognosis of AD and PD patients even after adjusting for covariates among MMA subgroups. We also discovered when MMA >250 nmol/L, in AD and PD patients, certain inflammatory factors were linked to cause-specific mortality. Our research is the first to comprehensively investigate the relationship between MMA and cause-specific mortality in AD and PD patients. It may be considered as a good indicator for assessing the prognosis of Alzheimer's disease and Parkinson's disease patients in the clinic.

The evidence suggests that the trend of higher MMA values in the elderly is linked to cognitive decline [32]. It has been suggested that MMA triggers oxidative stress in the brain of rats and leads to prolonged behavioral impairments [33]. MMA has the potential to induce neuronal apoptosis in different cell culture systems. The United Kingdom longitudinal study has identified that MMA is a significant indicator of cognitive impairment [34]. In addition, wang et al. [7] have come to the conclusion that mitochondrial-derived methylmalonic acid (MMA) can be used as a marker of mitochondrial dysfunction. It has the ability to evaluate cardiovascular adverse events (risk and prognosis). Our findings supported that higher circulating MAA can be considered a biomarker of mitochondrial

Table 2
The association between MMA and PD-specific mortality.

	Cutoff	Crude	P value	Model 1	P value
MMA (log)		2.94 (1.61,5.36)	<0.01	2.63 (1.19–5.82)	0.02
MMA					
Q1	<120	ref		ref	
Q2	120_175	2.94 (0.93, 9.30)	0.07	2.55 (0.65–9.99)	0.18
Q3	175_250	3.80 (1.21,11.90)	0.02	1.4 (0.31–6.31)	0.66
Q4	>250	5.77 (1.67,19.99)	0.01	5.51 (1.26–24.0)	0.02

MMA: methylmalonic acid; PD: Parkinson's disease; 95%CI: 95 % confidence intervals.
P < 0.05 was considered statistically significant.

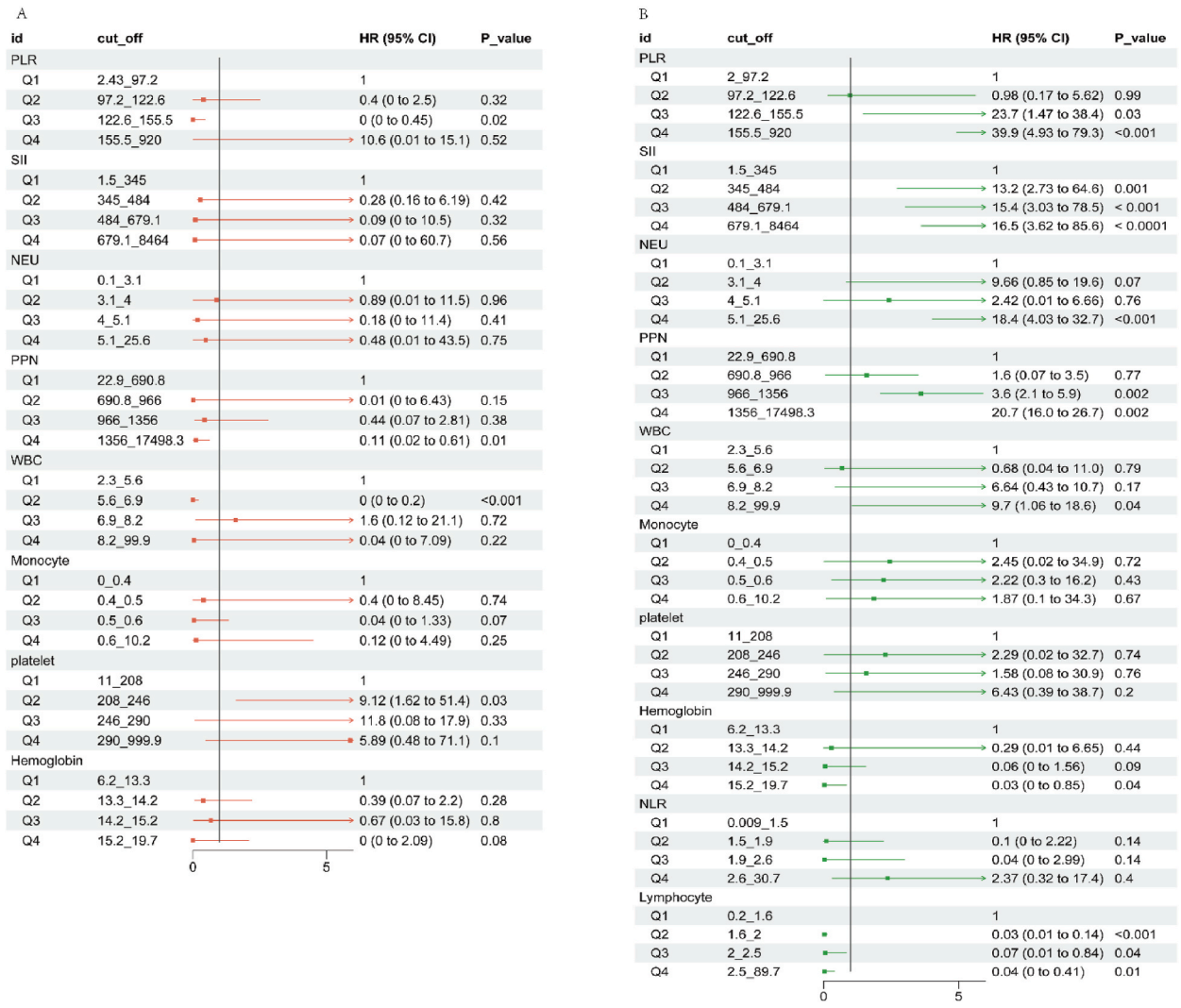

Fig. 4. Results of inflammatory markers associated with cause-specific mortality after adjusting confounding factors. The solid black line represents a HR value of 1. (A) The results of inflammatory markers were associated with cause-specific mortality in AD patients. (B) The results of inflammatory markers are associated with cause-specific mortality in PD patients.

dysfunction and can be used to evaluate the cause-specific mortality in AD and PD patients. Mitochondrial dysfunction in the pathogenesis of AD includes decreased metabolism, interruption of Ca^{2+} homeostasis, increased production of reactive oxygen species (ROS), decreased mitochondrial DNA (mtDNA), morphological changes of mitochondrial, decreased axon transport of mitochondrial and so on [35], which may trigger more apoptotic cell death in neurons, resulting in mortality in AD patients. P53 was involved in the regulation of dopaminergic neuron degeneration due to mitochondrial dysfunction in the pathogenesis of PD. The activation of p53 led to mitochondrial dysfunction through dynamic changes such as transmembrane permeability, ROS production, Ca^{2+} overload, electron transfer chain defects, etc., causing dopaminergic neurons degeneration, which becomes an important cause of death in PD patients.

Proinflammatory cytokines are activated by the continuous accumulation of Aβ plaques in AD patients, which stimulates the release of more proinflammatory cytokines in plaques. The damage caused to nerve cells was made worse by the positive feedback [36]. Our study revealed that WBC Q2 was a protective factor that was associated with a lower mortality rate of AD. It is important to further explore the role of WBC in AD's development and progression. Platelet count was related to higher mortality rates in AD. Inyushin et al. [37] have found that the activation of platelets may lead to Aβ releasing from the blood to nearby tissue, aggravating the severity of the disease until death. Our analysis revealed that PLR Q3 and PPN Q4 were protective factors that contributed to a decrease in AD mortality. Farah et al. [38] have concluded that PLR increased as the severity of Helicobacter pylori symptoms increased in a randomized controlled trial. It exhibited a strong predictive capacity in assessing the severity of Helicobacter pylori symptoms. The calculation of PLR was based on PC and LC. PPN was based on platelet count and neutrophil counts. Therefore, their interpretation should depend on the particular context.

This study found that neutrophils were linked to a poor prognosis for PD patients. Fan et al. [39,40] have elucidated that neutrophils were a valuable resource for research into LRRK2 kinase pathway activity in vivo, and have revealed that R1441G but not G2019S mutation triggers LRRK2 mediated Rab10 phosphorylation in human peripheral blood neutrophils. LRRK2 was well-known as the cause of PD. Targeting LRRK2 may be a feasible strategy for PD. In Parkinson's disease tissues, hemoglobin (Hb) has been localized to the mitochondria. In PD patients, Hb levels may decrease. α-synuclein, a key protein involved in PD pathology, interacts directly with Hb protein and forms complexes in erythrocytes and brains of monkeys and humans [41,42]. Thus, Hb may be a protective factor for PD, which was consistent with our result.

We found that LC was related to a decreased mortality of PD. In the Swedish apolipoprotein-related mortality risk cohort, higher lymphocytes were inversely proportional to the occurrence and development of PD (HR = 0.74, 95%CI = 0.59–0.94) [43], which was consistent with our finding. The specific meanings of PLR, SII and PPN should be integrated with the specific context.

The strength of the article is that our research is the first comprehensive retrospective study to investigate the association between MMA, a biomarker of mitochondrial dysfunction, and cause-specific mortality in AD and PD patients in an NHANES cohort. MMA can be used to investigate the association between mitochondrial dysfunction and the risk and prognosis of cardiovascular adverse events [7]. Thus, it may be possible to explore the association between mitochondrial dysfunction and cause-specific mortality in AD and PD patients using MMA. Although previous studies based on molecular mechanisms have shown that mitochondrial dysfunction was involved in the progression of AD and PD, the relationship has not been studied in a cohort study. Quantifying mitochondrial dysfunction allowed us to study this relationship. The findings suggested that mitochondrial dysfunction could be a valuable indicator for evaluating the prognosis of AD and PD patients. Moreover, we encouraged the investigation of the mechanism for MMA that regulates pathologies of AD and PD, as well as for MMA that promotes dementia through certain signal pathways, providing a potential strategy for diagnosis and prognostic analysis.

It is necessary to clarify some limitations in our study. It was difficult to carry out casual inference. Longitudinal studies and animal experiments were promoted to clarify the association. Secondly, clinical practice necessitates a larger number of cohorts to validate the relationship. Thirdly, the lack of other metabolite measurements prevented us from investigating the association between MMA and other potential metabolites that influence MMA levels. Finally, our analysis included certain inflammatory markers and the analysis can be expanded to incorporate new markers that are discovered in the future. The interaction between mitochondrial dysfunction and inflammatory factors needs further exploration, either based on clinical studies or basic experiments.

5. Conclusion

The progression of neurodegenerative diseases is influenced by mitochondrial dysfunction, which provides a strategy for diagnosis and treatment. Our study found a non-linear association between mitochondria-derived circulating MMA and cause-specific mortality in Alzheimer's Disease and Parkinson's Disease. The presence of higher MMA levels (>250 nmol/L) was associated with an increase in mortality in AD and PD patients. MMA has the potential to be a useful indicator for assessing the prognosis of AD and PD patients in clinic.

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Data availability statement

The data used and analyzed during the present study are available from NHANES (https://www.cdc.gov/nchs/nhanes/).

Ethics approval

The study protocols were approved by the Ethical Committee Review Board of the First Affiliated Hospital of Fujian Medical University (Fuzhou, Fujian, China) (No: 202304T003).

CRediT authorship contribution statement

Fangfang Zhan: Writing – review & editing, Writing – original draft, Validation, Software, Data curation, Conceptualization. **Gaoteng Lin:** Software, Methodology, Data curation. **Lifang Su:** Software, Investigation, Data curation. **Lihong Xue:** Methodology, Data curation. **Kefei Duan:** Supervision, Software, Data curation. **Longfei Chen:** Visualization, Validation, Supervision, Conceptualization. **Jun Ni:** Supervision, Data curation, Conceptualization.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29357.

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