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Effects of methionine intake on cognitive function in mild cognitive impairment patients and APP/PS1 Alzheimer's Disease model mice: Role of the cystathionine-β-synthase/H_2S pathway

Yujia Xi [a,1], Yuyu Zhang [a,1], Yiwen Zhou [b,1], Qing Liu [a], Xuhui Chen [c], Xuebo Liu [a], Tilman Grune [d], Lin Shi [e,***], Min Hou [b,**], Zhigang Liu [a,d,f,*]

[a] Laboratory of Functional Chemistry and Nutrition of Food, College of Food Science and Engineering, Northwest A&F University, Yangling, Shaanxi, 712100, China
[b] School of Public Health, College of Medicine, Shanghai Jiaotong University, Shanghai, 200025, China
[c] Department of Neurology, Peking University Shenzhen Hospital, Shenzhen, 518000, China
[d] German Institute of Human Nutrition (DIfE) Potsdam-Rehbruecke, Department of Molecular Toxicology, Arthur-Scheunert-Allee 114-116, 14558, Nuthetal, Germany
[e] College of Food Engineering and Nutritional Science, Shaanxi Normal University, Shaanxi, 710119, China
[f] Northwest A&F University, Shenzhen Research Institute, Shenzen, Guangdong, 518000, China

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ABSTRACT

As a dietary intervention, methionine restriction (MR) has been reported to increase longevity and improve metabolism disorders. However, the effects of MR on alleviating neurodegenerative diseases such as Alzheimer's disease (AD) are largely unexplored. Here we sought to investigate the neuroprotective effects of low methionine intake in mild cognitive impairment (MCI) patients and APP/PS1 AD model mice, and to uncover the underlying mechanisms. In a cohort composed of 45 individuals diagnosed with MCI and 61 healthy controls without cognitive impairment, methionine intake was found to be positively associated with the increased risk of MCI, where no sex differences were observed. We further conducted a 16-week MR intervention (0.17% methionine, *w/w*) on APP/PS1 AD model mice. Although MR reduced Aβ accumulation in the brain of both male and female APP/PS1 mice, MR improved cognitive function only in male mice, as assessed by the Morris water maze test. Consistently, MR restored synapse ultrastructure and alleviated mitochondrial dysfunction by enhancing mitochondrial biogenesis in the brain of male APP/PS1 mice. Importantly, MR effectively balanced the redox status and activated cystathionine-β-synthase (CBS)/H_2S pathway in the brain of male APP/PS1 mice. Together, our study indicated that lower dietary methionine intake is associated with improved cognitive function, in which CBS/H_2S pathway plays an essential role. MR could be a promising nutritional intervention for preventing AD development.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia, emerging as a global threat to human health [1]. The neuropathological changes of AD are characterized by the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles composed of aggregated amyloid β (Aβ) and hyperphosphorylated tau protein, respectively, leading to progressive cognitive impairment and dementia [2]. The disturbance of various intracellular signaling systems caused by Aβ will induce a decrease in the density of dendritic spines in the CA1 region of the hippocampus, abnormal postsynaptic density structure, and synaptic dysfunction [3,4]. Aβ further promotes oxidative stress and disrupts mitochondrial function [5]. Although the triggers, underlying mechanisms, and effective treatments of AD are still unclear, accumulating evidence has proved strong links of an unhealthy diet and lifestyle with

* Corresponding author. Laboratory of Functional Chemistry and Nutrition of Food, College of Food Science and Engineering, Northwest A&F University, Yangling, Shaanxi, 712100, China.
** Corresponding author.
*** Corresponding author.
E-mail addresses: linshi198808@snnu.edu.cn (L. Shi), minhou@sjtu.edu.cn (M. Hou), zhigangliu@nwsuaf.edu.cn (Z. Liu).
[1] These authors contributed equally.

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AD development [6]. Mediterranean diet has been associated with a lower risk of AD [7]. Dietary interventions are potential nutritional strategies to protect against cognitive decline [8].

Caloric restriction (CR) is a non-genetic intervention known to extend lifespan and delay age-related cognitive deficits among yeast, *D. melanogaster*, and mammals [9,10]. However, it is difficult for humans to stick to CR for decades. Restriction of specific macronutrient intakes, such as total protein or specific amino acid, has similar physiological effects to CR [11,12]. In particular, methionine restriction (MR) has been found to reverse the disturbing metabolic status and improve longevity in both animal models [13,14] and human studies [15,16]. Our recent research has demonstrated the neuroprotective effects of MR in rodent models, possibly due to its mediating effects on the redox status [17,18]. MR could enhance mitochondrial function and alleviate endogenous oxidative damage in the frontal cortex, including fatty acid peroxidation, protein oxidation, and mitochondrial DNA damage [19,20]. MR has also been reported to activate cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CGL) in the transsulfuration pathway to produce hydrogen sulfide (H_2S) [21], which is partly involved in cellular redox balance regulation.

H_2S exhibits potential neuroprotective effects [22,23], including reversing aging-associated amygdala synaptic plasticity and fear memory deficits and improving cognitive function in AD transgenic models [24]. The impaired locomotor activity and cognitive function in 3xTg-AD mice were ameliorated by the H_2S donor [25]. H_2S could stimulate mitochondrial biogenesis and function [26], and it has also been found that H_2S could protect neurons from oxidative stress by increasing glutathione (GSH), redistributing it to mitochondria [27], and lowering H_2O_2 level caused by $A\beta_{1\text{-}42}$ [28]. In addition, H_2S downregulated beta-secretase 1 (*BACE1*) mRNA in APP/PS1 transgenic mice, leading to the lower production of Aβ [29]. However, whether MR affects AD pathogenesis through H_2S is still unclear.

In the present study, we first investigated associations between dietary methionine intake and cognitive function in a case-control design human study. We then comprehensively investigated whether MR could improve cognitive impairment in APP/PS1 AD model mice, as reflected by the impacts of MR on cognitive behaviors, brain Aβ accumulation, and synapse ultrastructure. The effects of MR treatment on brain mitochondrial dysfunction and mitochondrial biogenesis, as well as oxidative stress and CBS/H_2S pathway, have also been determined. Our study reveals the positive association between methionine intake and increased risk of mild cognitive impairment (MCI). MR sex-specifically prevents the cognitive dysfunction, mitochondrial dysfunction, and oxidative stress of male APP/PS1 AD model mice, which could be partly explained by the activated CBS/H_2S pathway in the brain.

2. Materials and methods

2.1. Study population

The Cognitive Health Study recruited 658 participants aged between 60 and 89 years between 2018 and 2019, 55.4% of whom were female. Study participants were recruited from Xinjin, Chengdu, China. Cases of mild cognitive impairment (MCI) were identified by neurologists experienced in neurodegenerative disorders, according to international criteria for MCI [30]. MCI was diagnosed if there was any complaint of a decline in cognitive function, obtained from the individual or an informant who knows; the deterioration of at least one cognitive domain of memory, executive functioning, attention, language, or visuospatial skills at a higher level than expected at the given age and education of the patient on objective testing; absence of dementia [31]; and normal function or minimal impairment in activities of the daily living test [30,32]. As the effect of age and sex on cognitive function is well-documented [33,34], these factors were used as matching variables for this study. Controls were matched on age (within 5 years) and sex. If we were not able to find suitable controls for all cases using the matching criteria, so did two more matching cycles. Criteria were relaxed in each cycle to obtain more matches. If there were not enough controls, stratified random sampling based on age and sex was used to maintain overall similarities between cases and controls. All participants or family caregivers provided written informed consent before involving in this study. Sociodemographic data, including sex, age, education, and family income, as well as medical history involving diabetes, hypertension, and coronary heart disease, were collected from each participant using a questionnaire. Lifestyle was assessed by questions: "Do you currently smoke?" and "Do you currently drink beer, wine, or alcohol?". Height was measured by using a Stadiometer (SECA) in a standing position with shoes removed. Weight was measured with a body composition analyzer (Tanita). BMI was calculated by dividing weight (in kg) by height (in meters squared). The Ethics Committee of the School of Public Health at Shanghai Jiao Tong University for Human Subject Research approved all study procedures, and all experiments were performed in accordance with relevant guidelines and regulations.

For the present study, we excluded from the analysis participants who were missing information on clinical information or dietary intake. Subjects were also excluded if they had not received a cognitive function assessment. Additionally, participants in the fifth and 95th percentile of the sex-specific energy intake distributions were excluded, as they may represent aberrant reporting of dietary intakes. Dietary information was obtained from a 107-item food frequency questionnaire (FFQ), which ascertained the most commonly consumed foods in this region. In brief, participants were asked about their eating habits during the previous 12 months, and how often, on average, subjects had consumed a food item with never, the number of weeks in a month, the number of days in a week, and the number of times in a day as well as the portion sizes. The nutrient composition of foods was taken from the Chinese Food Composition Table [35]. Mean daily intakes of energy, protein, and methionine were estimated by multiplying the daily frequency of each food item by the nutrient composition. FFQ has been validated in 141 individuals aged between 60 and 89 years old, randomly chosen from this Cognitive Health study population conducted by trained interviewers. The Spearman correlation coefficients between the FFQ and the mean of four 3-day diet records collected at approximately three months intervals was 0.58 for total daily energy and 0.51 for protein.

2.2. Animal experiments

Double transgenic APPswe/PSEN1dE9 mice (APP/PS1) on B6C3-Tg background and wildtype (WT) littermates were purchased from Nanjing University (Nanjing, China). The APP/PS1 mice carry human amyloid precursor protein (*APP*) and human presenilin 1 (*PSEN1*) genes. To obtain test mice, we crossed heterozygote APP/PS1 mice with WT mice [36]. Genotyping 4-month-old offsprings by PCR using the following primers: *APP*: 5′-AGGACTGACCACTCGACCAG-3' (forward) and 5′-CGGGGGTCTAGTTCTGCAT-3' (reverse); *PS1*: 5′-AATAGAGAACGGC AGGAGCA-3' (forward) and 5′-GTAGGTGGAAATTCTAGCATCATCC-3' (reverse); reference gene: 5′-CTAGGCCACAGAATTGAAAGATCT-3' (forward) and 5′-GTAGGTGGAAATTCTAGCATCATCC-3' (reverse). Finally, we obtained APP/PS1 (23 males and 22 females) and WT mice (22 males and 22 females). Under standard conditions, all animals are allowed standard diet/methionine restriction mouse chow and water at will and maintained in a temperature of 22 ± 2 °C and humidity of 50 ± 15% under a 12:12 h light:dark cycle in Northwest A&F University animal facility.

The WT mice and APP/PS1 mice were randomly divided into 2 groups (n = 11–12/group), fed with standard diet (SD, 0.86% methionine, *w/w*) and methionine restriction diet (MR, 0.17% methionine, *w/w*) for 16 weeks respectively: (1) WT + SD: WT mice treated with a standard diet, (2) WT + MR: WT mice treated with methionine restriction diet, (3) AD + SD: APP/PS1 mice treated with a standard diet, and (4) AD + MR: APP/PS1 mice treated with methionine restriction diet. The methionine dose used in this study is based on previous studies [17].

The feed formula is shown in Table 1. The body weight, food intake, and water consumption of the mice were measured every week. The behavior tests were performed in week 16 (Fig. 2A). The sacrifice was performed under anesthesia, and every effort was made to reduce pain during all experiments. The serum samples were isolated from orbital bleeding after anesthesia. Remove the brain to separate the cortex and hippocampus and collect other tissues. The animal test protocol follows the guidelines for the care and use of laboratory animals (eighth edition, ISBN-10: 0-309-15, 396-4), and was approved by the Animal Ethics Committee of Northwest A&F University.

2.3. Morris water maze (MWM) tests

As previously described [37], the Morris water maze test was performed to assess spatial learning and memory abilities. The device consists of a circular pool with a diameter of 150 cm and a height of 35 cm and a video analysis system (SuperMaze software, Shanghai Xinruan Information Technology Co., Ltd, China). The pool is equally divided into 4 quadrants (quadrants 1–4), and the walls of each quadrant are marked with different colors and shapes. Then, a transparent escape platform with a diameter of 4.5 cm and a height of 15 cm was placed in one of the quadrants, and warm water (23–25 °C) was poured into the circular pool. During the adaptive training of the water maze on day 0, the escape platform was 2 cm above the water's surface. Initial spatial training was performed on days 1, 3, and 5. The escape platform was placed 1 cm below the water's surface to conceal the escape platform. The mouse was allowed to start from the opposite quadrant where the platform is located (target quadrant). The time spent to find the platform and swimming tracks were recorded by SuperMaze software. If the mouse did not find the escape platform within 60 s, it would be manually guided to find the escape platform, and make the mouse stand on the platform for 30 s. On the 6th day, the escape platform was evacuated, and a probe trial was performed to record the time of the mouse in the target quadrant within 60 s.

2.4. Thioflavin S staining

Thioflavin S staining can detect amyloid deposits, and the operation is as described before [38]. After the mice were sacrificed, brain tissue was separated, and half of the brain was cut and placed in a vial filled with paraformaldehyde (4% (*v/v*), pH 7.4) for 24 h. Then, it was embedded in paraffin and cut into 5 μm slices. The xylene, 100%, 90%, 80%, and 70% ethanol were used for washing for 5 min, followed by 5 min × 3 times PBS (pH 7.4) washing. The sections were permeated in permeate for 15 min and boiled for 20 min, followed by 5 min × 3 times PBS washing. The 0.5% Thioflavin S (CAS#1326-12-1; Shanghai Yuanye Bio-Technology Co., Ltd) was added to the sections for 8 min. After that, the sections were rinsed with 5 min × 3 times PBS, 50% ethanol, and PBS again, respectively. Finally, the sections were mounted with DAPI anti-fluorescence. The sections were observed, and images were acquired by an inverted fluorescent microscope (Olympus, Tokyo, Japan). Image J analysis software (National Institutes of Health, Scion Corporation, USA) was used for measuring the amyloid plaque area ratio in the cortex and CA1 regions of the hippocampus.

Table 1
Feed formula.

	Methionine restriction diet (0.17% methionine, *w/w*)/g	Standard diet (0.86% methionine, *w/w*)/g
Amino acid premix (no methionine, cystine)	131.9	131.9
Methionine	1.7	8.6
Glutamate	6.9	0
Carbohydrates (starch, dextrin, sucrose)	682.5	682.5
Cellulose	50	50
Minerals, vitamins (including choline)	47	47
Corn oil	80	80
Total	1000	1000
Additional volume density, kcal/g	3.7	3.7
Protein	15%	15%
Fat	19%	19%
CHO	65%	65%
Total	100%	100%

2.5. Analysis of hippocampal postsynaptic density and mitochondria structure

After the hippocampal tissues were separated on the ice and were cut into 1 mm^3 (1 mm × 1 mm × 1 mm) small pieces, which were fixed in 2.5% glutaraldehyde (pH 7.4) for 24 h, then the tissues were rinsed in PBS (0.1 M, pH 7.2). After that, samples were fixed in 1% OsO_4 for 1 h with PBS washing again and 30%, 50%, 70%, 80%, 90%, and 100% ethanol dehydrating for 15 min, respectively. Samples were permeated in LR-white gum (gum alcohol ratio 1:1) overnight and dried at 60 °C. The postsynaptic density (length and width) and mitochondria (number and morphology) were observed by JEM-1230 transmission electron microscope (TEM, JEOL, Tokyo, Japan) after sectioning. Image J analysis software (National Institutes of Health, Scion Corporation, USA) was used for measuring the postsynaptic density (length and width) and mitochondria (mitochondrial number and damage ratio).

2.6. Immunofluorescence staining

After dewaxing, the sections were incubated with CBS primary antibody (ab96252, 1:200, Abcam) overnight at 4 °C. On the second day, after PBS washing, the tissue slices were incubated with a secondary antibody (Goat anti-Mouse IgG (H + L)-Dylight 594, Jingcai Biotechnology, Xi'an, China) for 20 min. Rinse in PBS for 5 × 3 min, and histologic sections were sealed on the tablet with sealant containing DAPI. The sections were observed under a fluorescence microscope and photographed (Olympus, Tokyo, Japan). Image J analysis software (National Institutes of Health, Scion Corporation, USA) was used for measuring mean fluorescence intensity (AU).

2.7. Measurement of endogenous H_2S

The endogenous hydrogen sulfide assay kit (XL-SH036; Shanghai Xinle Biotechnology Co., Ltd.) was used to measure the H_2S content in the cortex and serum according to the manufacturer's instructions and previously described [39,40]. Briefly, H_2S reacts with zinc acetate, N, *N*-dimethyl-p-phenylenediamine, and ferric ammonium sulfate to form methylene blue. Methylene blue has a maximum absorption peak at 665 nm. The H_2S content can be calculated by measuring its absorbance value. The results are calculated based on standard NaHS (40 μmol/L). The content of H_2S in tissues is expressed as μmol H_2S/g tissue protein level, and the content of H_2S in serum is expressed as μmol H_2S/L serum.

2.8. Measurements of MDA, GSH, and GSSG

The levels of MDA (A003-1-2) in the cortex were measured with kits (Jiancheng Technology Co., Ltd., Nanjing, China) by using thiobarbituric acid (TBA) method as previously described [41]. The levels of total GSH and GSSG (A061-1-2) in the cortex were measured with kits (Jiancheng Technology Co., Ltd., Nanjing, China) by using the 5, 5-dithio-bis (2-nitrobenzoic) acid (DTNB) method as previously described [42].

2.9. Real Time-qPCR (qRT-PCR)

The total RNA in the cortex was extracted by TRIzol (Jingcai Bio., Xi'an, China), and its purity was detected by using a nucleic acid quantifier. Followed the instructions of the PrimeScript RT Master Mix Reverse Transcription Kit (TaKaRa PrimeScript RT Master Mix, Dalian, China), and used the 9600 Gene Amplifier to reverse 1 mg RNA into cDNA. After that, the CFX96TM real-time system quantitative PCR was used to detect gene mRNA levels. The relative changes in gene expression were calculated by $2^{-\triangle\triangle Ct}$. The primer sequences are shown in Table 2.

2.10. Western blots

The protein of cortex tissue was extracted using a protein extraction reagent. The total tissue proteins (n = 6) were separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred onto a polyvinylidene fluoride (PVDF) membrane by using a wet transfer apparatus. The membranes were incubated with primary antibodies anti-CBS-antibody (ab96252, 1:1000, Abcam), and anti-GAPDH-antibody (#5174, 1:1000, Cell Signaling Technology) at 4 °C overnight, and then blots were incubated for 2 h with secondary antibodies (anti Rabbit IgG (H&L), Jingcai Biotechnology, Xi'an, China). The immunoreactive bands were visualized with an enhanced chemiluminescence reagent and scanned by a ChemiDoc XRS imaging system (ChemiDoc™ XRS+, Bio-Rad). Quantification of the results of the western blot was analyzed by Image J analysis software (National Institutes of Health, Scion Corporation, USA).

2.11. Statistical analysis

For the human study, the total sample size of 86 subjects for this study is suitable to estimate the effect of methionine intake on the MCI with an odds ratio (OR) of 2.3 at 90% statistical power and 5% significance level using G-power software, version 3.1. The continuous variables of baseline characteristics presented in this study were expressed as the means ± SD. And the categorical variables were expressed as frequencies and percentages. The normal distribution of variables, including age, BMI, weight, and height, were assessed using the Shapiro-Wilk test. Baseline characteristics between cases and controls were compared using χ^2 test or Mann-Whitney *U* test, where appropriate. Intake of dietary methionine, the percentage of dietary methionine relative to total energy, and the percentage of dietary methionine relative to total protein between cases and controls were assessed by using the Mann-Whitney *U* test. Subjects were classified into quarters according to their daily methionine intake. The difference in quartiles of methionine intake between cases and controls was evaluated using $\chi 2$ test. The gender difference between cases and controls in quartiles of methionine intake was analyzed using Fisher's exact test. Biliary regression models were performed to estimate ORs and 95% confidence intervals (CIs) for MCI risk associated with methionine intake while controlling for confounding variables. Variables considered as confounding factors in the models had been previously associated with cognitive function. Model 1 adjusted for the main potential confounders: age, sex, education attainment, family income, smoking status, and alcohol status. Model 2 additionally adjusted for BMI, daily energy intake, and the number of chronic diseases. The trend across quartiles for methionine intake was tested by entering the median raw value in each quartile as a continuous variable in the linear regression model. *p* values < 0.05 were considered statistically significant. Analyses were completed using the IBM SPSS program, version 22 (IBM, Chicago, IL, USA).

For the animal study, Graphpad Prism 7.0 (GraphPad Software Inc, San Diego, CA, USA) was used for the data analysis. All data are reported as mean ± SEM. Two-way ANOVA analysis was used to compare differences between groups with Tukey's test for multiple comparisons. $p < 0.05$ means there is a significant difference between the data.

3. Results

3.1. The association between methionine intake and the risk of mild cognitive impairment

Of the 658 subjects in the cohort, 36 subjects were excluded from the current analysis due to the lack of information on clinical information (n = 18) or dietary information (n = 18). An additional 33 subjects diagnosed with AD and 42 subjects with incomplete cognitive function assessment were excluded. We also excluded 35 subjects whose total caloric intake was >3368.37 kcal/day (women) or >4026.11 kcal/day (men), or <531.69 kcal/day (women) or <699.34 kcal/day (men). Finally, a total of 106 individuals remained in this study, including 45 patients diagnosed with MCI and 61 controls without cognitive impairment.

As shown in Table 3, the mean ages were respectively 74.36 (±0.81 SD) years and 72.57 (±0.72 SD) years, and 57.8% and 57.4% of participants were female in MCI group and control group, respectively. There were no differences between age, sex, education attachment, family income, BMI, diabetes, hypertension, coronary heart disease, smoking status, or alcohol status in subjects with MCI and controls. Daily consumption of methionine was significantly higher in MCI participants compared to those with healthy cognitive functions ($p = 0.05$). We observed an increased association between methionine intake quartile and risk of MCI (quartile 1: Median = 285.99; quartile 2: Median = 444.30; quartile 3: Median = 721.52; quartile 4: Median = 1088.55, *p* for trends = 0.035, Table 3). The biliary regression analysis presents a relationship between methionine intake quartiles and MCI risk ($p = 0.047$, Fig. 1D). Adjusted analysis in model 2 also found that moderate methionine intake appeared to reduce the risk compared to the highest intake (quartile 2 vs. quartile 4: OR = 0.08 [0.01–0.47], $p = 0.005$, Table 3). Furthermore, results show that compared to the non-cases control group, the MCI cases group has higher levels of dietary methionine intake, the percentage of dietary methionine relative to total energy, and the percentage of dietary methionine relative to total protein (all using the Mann-Whitney U tests, $p \leq 0.05$, Fig. 1A–C). However, no sex difference within methionine intake quartiles was observed between cases and controls (Table S1).

Table 2
Primers Sequences Used for qRT-PCR Analysis.

	Forward primers 5′–3′	Reverse primers 5′–3′
Gapdh	TGGAGAAACCTGCCAAGTATGA	TGGAAGAATGGGAGTTGCTGT
APP	GCTGCCCAGCTTGGCACTGC	GGCAACGGTAAGGAATCACGATGTGGGTG
BACE1	CCGGCGGGAGTGGTATTATGAAGT	GATGGTGATGCGGAAGGACTGATT
CBS	GCGGCTGAAGAACGAAATCC	TGTCCAGCTTCCCATCACAC
PSD-95	TCTGTGCGAGAGGTAGCAGA	AAGCACTCCGTGAACTCCTG
COX5b	GCTGCATCTGTGAAGAGGACAAC	CAGCTTGTAATGGGTTCCACAGT
COX2	GCCGACTAAATCAAGCAACA	CAATGGGCATAAAGCTATGG
b-globin	GAAGCGATTCTAGGGAGCAG	GGAGCAGCGATTCTGAGTAGA

Table 3
Participants' characteristics at baseline and associations between methionine intake with risk of MCI.

	All	Cases	Non-cases	*p*-value[a]	Model 1[b]			Model 2[c]		
	(n = 106)	(n = 45)	(n = 61)		OR	95%CI	*p*	OR	95%CI	*p*
Age	73.31 ± 0.55	74.36 ± 0.81	72.57 ± 0.72	0.059	–	–	–	–	–	–
Sex, n (%)				0.967	–	–	–	–	–	–
Male	45(42.5)	19(42.2)	26(42.6)							
Female	61(57.5)	26(57.8)	35(57.4)							
Education, n (%)				0.313	–	–	–	–	–	–
No	24(22.9)	11(25.0)	13(21.3)							
Less than high school	78(74.3)	33(75.0)	45(73.8)							
High school or more	3(2.9)	0(0)	3(4.9)							
Family income (RMB/month), n (%)				0.757	–	–	–	–	–	–
<1000	53(50.0)	21(46.7)	32(52.5)							
1000-3000	37(34.9)	16(35.6)	21(34.4)							
>3000	16(15.1)	8(17.8)	8(13.1)							
Weight (kg)	59.03 ± 1.23	58.37 ± 1.91	59.49 ± 1.62	0.723	–	–	–	–	–	–
Height (cm)	155.61 ± 0.84	155.52 ± 1.04	155.52 ± 1.23	0.883	–	–	–	–	–	–
BMI	24.28 ± 0.41	23.97 ± 0.67	24.50 ± 0.53	9.586	–	–	–	–	–	–
No. of chronic diseases	0.82 ± 0.08	0.80 ± 0.13	0.84 ± 0.10	0.693	–	–	–	–	–	–
Diabetes, n (%)	20(18.9)	7(15.6)	13(21.3)	0.616	–	–	–	–	–	–
Hypertensions, n (%)	40(37.7)	14(31.1)	26(42.6)	0.311	–	–	–	–	–	–
Coronary heart disease, n (%)	7(6.6)	5(11.1)	2(3.3)	0.132	–	–	–	–	–	–
Currently Smoking	7(6.6)	9(20.0)	9(14.8)	0.602	–	–	–	–	–	–
Currently drinking	18(17.0)	11(24.4)	7(11.5)	0.115	–	–	–	–	–	–
Energy (kcal/d)	1648.76 ± 68.32	1774.50 ± 123.89	1560.75 ± 76.16	0.352	–	–	–	–	–	–
Methionine (in mg/d)	696.65 ± 56.03	889.04 ± 119.86	561.98 ± 37.45	**0.050**			0.087			**0.047**
Q1[54.43–365.31]	259.36 ± 16.94	276.23 ± 19.80	247.00 ± 25.64		0.35	0.09–1.31	0.119	0.24	0.04–1.36	0.107
Q2[365.31–534.31]	446.44 ± 10.16	451.03 ± 28.27	445.12 ± 10.73		**0.15**	**0.03–0.65**	**0.011**	**0.08**	**0.01–0.47**	**0.005**
Q3[534.31–841.96]	706.00 ± 17.76	699.69 ± 28.09	711.04 ± 23.55		0.38	0.10–1.26	0.109	0.26	0.06–1.09	0.065
Q4[841.96–4007.88]	1356.82 ± 147.61	1547.77 ± 228.08	1051.31 ± 42.24			Ref			Ref	
Test for trend [d]						0.051			**0.035**	

Data are represented as n (%) or mean ± SD. *p*-value <0.05 are in bold type. –, not applicable; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4.
[a] χ^2 test was used for categorical variables, the Mann-Whitney*U* test or Kruskal-Wallis one way ANOVA test was used for continuous variables.
[b] Model 1: Adjusting for age, sex, education level, family income, smoking status and alcohol status.
[c] Model 2: Adjusting for model 1 variables, BMI, daily energy intake and numbers of chronic diseases.
[d] To estimate the trend in quartiles, methionine intake was fitted as pseudo-continuous using the median raw value.

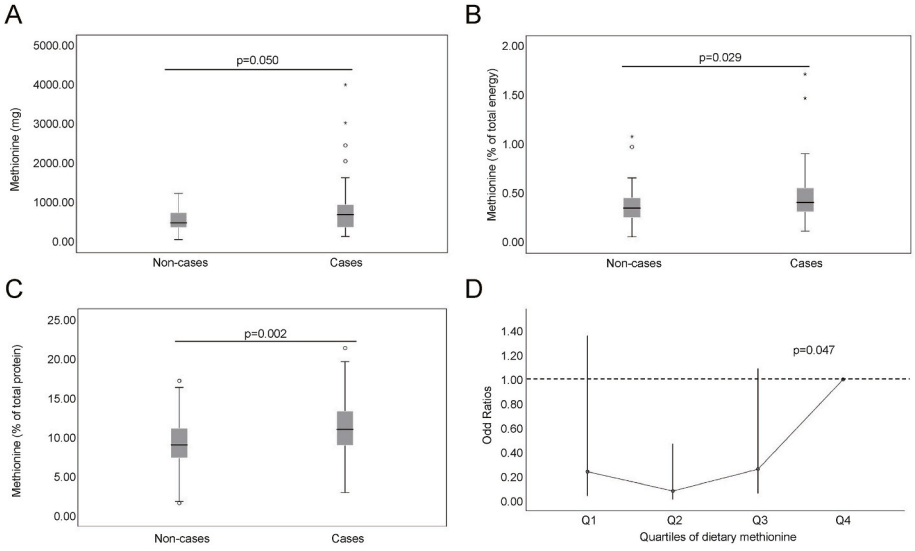

Fig. 1. Differences in methionine intake between MCI group and control group and the risk for the MCI
(**A**) Differences in daily methionine intake; (**B**) The percentage of dietary methionine relative to total energy; (**C**) The percentage of dietary methionine relative to total protein; (**D**) Methionine intake risk for MCI. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4.

3.2. Effects of MR on cognitive function in APP/PS1 AD model mice

Four-month-old male and female wildtype and AD mice were treated with standard diet or MR diet for 4 months (Fig. 2A). MR significantly decreased the body weight change in both male and female mice compared with the standard diet ($p < 0.01$) (Fig. S1A). MR reduced the body weight of male wildtype and AD mice and female wildtype mice ($p < 0.01$) (Fig. 2B&C). Female mice had lower food intake compared with the males under both the standard diet and MR diet ($p < 0.01$) (Fig. S1B). MR increased the food intake of male wildtype ($p < 0.05$) and AD mice ($p < 0.01$) compared with wildtype and AD fed with standard diet mice, respectively, but not in females (Fig. 2D). Also, female mice had lower water intake compared with the males under both the standard diet and MR diet ($p < 0.01$) (Fig. S1C). MR significantly increased

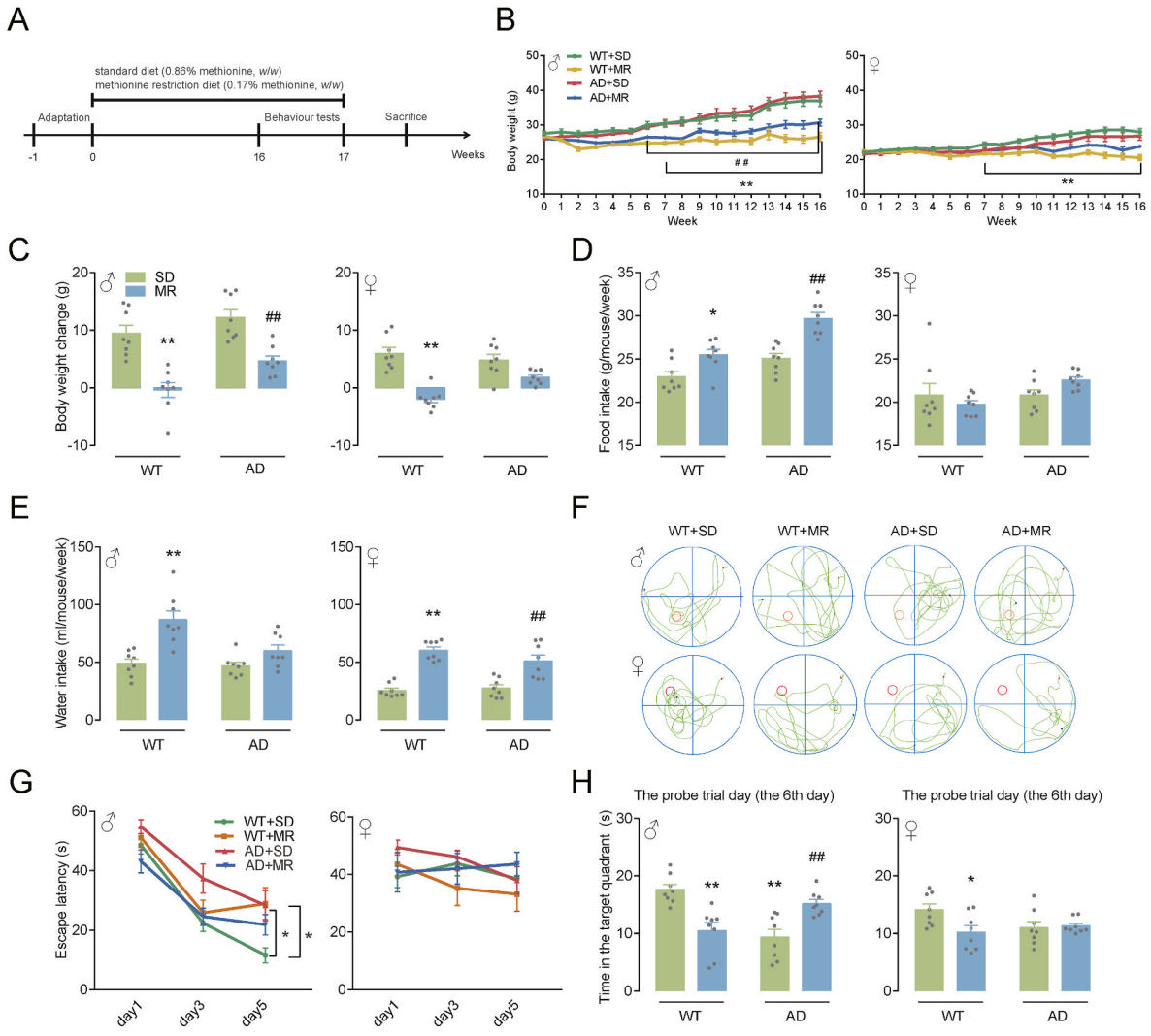

Fig. 2. Effects of MR on cognitive function behavior in male and female APP/PS1 AD model mice
(**A**) Schematic diagram of a phased protocol for animal experiments; (**B**) Body weight; (**C**) Body weight change; (**D**) Food intake; (**E**) Water intake; The cognitive function and spatial memory were evaluated by the Morris water-maze test (MWM), (**F**) Swimming paths of mice from each group; (**G**) Escape latency; (**H**) The time in the target quadrant on the probe trial day (the 6th day). Data were presented as mean ± SEM (n = 8). *$p < 0.05$, **$p < 0.01$, compared with the WT + SD group, #$p < 0.05$, ##$p < 0.01$ compared with the AD + SD group. Significant differences between mean values were determined by two-way ANOVA with Tukey multiple comparisons test.

the water intake in both male mice and female mice compared with the standard diet ($p < 0.01$) (Fig. S1C). In addition, MR substantially increased the water intake of male and female wildtype and female AD mice ($p < 0.01$) (Fig. 2E).

To evaluate the effects of MR on cognitive function in the AD mice, the Morris water maze test was performed. MR increased the escape latency of male wildtype mice in the 5-day navigation test ($p < 0.05$), while there were no effects on females ($p > 0.05$) (Fig. 2G). On the probe trial day (the 6th day), MR elevated the time spent in the target quadrants ($p < 0.01$) in male AD mice but not females. In contrast, MR degraded the time in the target quadrant spent by male ($p < 0.01$) and female wildtype mice ($p < 0.05$) (Fig. 2H). The tracks of mice in the maze were recorded in Fig. 2F. These results indicated that MR could sex-specifically improve cognitive function in male AD mice but not females. Notably, correlations between body weight change, food and water intake, and time in the target quadrants in males and females (Table S2, Fig. S2) showed that the observed sex-different neuroprotective effects of MR were not due to the differences in body weight, food intake or water intake.

3.3. Effects of MR on Aβ accumulation and synapse ultrastructure in APP/PS1 AD model mice brain

As shown in Fig. 3A, the accumulation of Aβ was significantly higher in the male and female AD mice brains than in the wildtype mice, while MR treatment significantly reduced the Aβ accumulation in the cortex and hippocampal CA1 region of both sexes ($p < 0.05$) (Fig. 3A&B). There is no detection of Aβ in both WT + SD or WT + MR groups mice (Fig. 3A). The mRNA expressions of Aβ precursor *APP* and cleaving enzyme *BACE1* were also examined. The mRNA expressions of *APP* ($p < 0.01$) and *BACE1* ($p < 0.05$) in male and female AD mice brains were higher than that of the wildtype ones (Fig. 3C&D), and MR treatment significantly inhibited *APP* mRNA expression in males ($p < 0.05$) and females ($p < 0.01$) AD mice brain (Fig. 3C). Additionally, MR significantly reduced *BACE1* mRNA levels in the brains of male AD mice ($p < 0.05$), but not in female AD mice ($p > 0.05$) (Fig. 3D).

The ultrastructure of hippocampal synapses is primarily involved in cognition and memory. Over-accumulation of Aβ leads to synaptic ultrastructure damage [4]. The results indicated that MR increased the length and width of the postsynaptic density (PSD) in male AD mice ($p <$

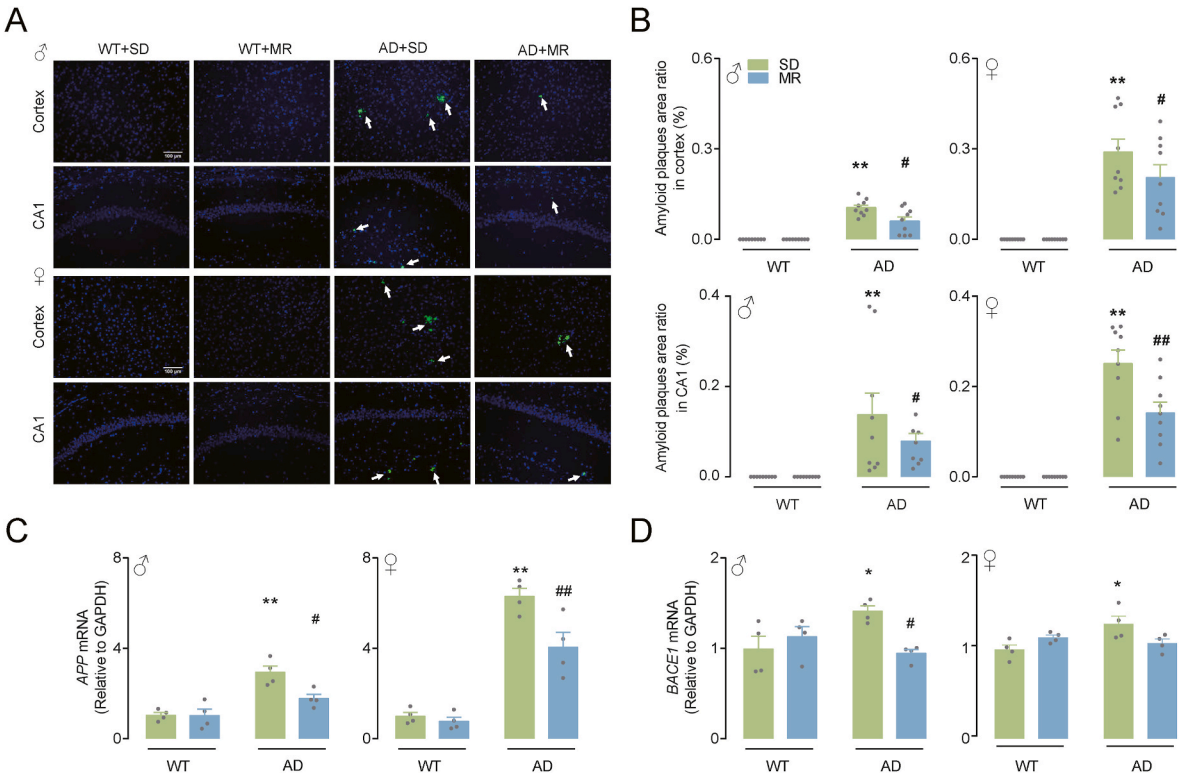

Fig. 3. Effects of MR on Aβ accumulation in the brain of male and female APP/PS1 AD model mice
(**A**) Representative images of Thioflavin S staining of different regions in the hippocampus (n = 3 slices per group); (**B**) Quantification of amyloid accumulation area based on Thioflavin S staining sections by ImageJ software (n = 9 slices from 3 mice per group); (**C, D**) mRNA levels of *APP* and *BACE1* in the cortex (n = 4). Data were presented as mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with the WT + SD group, $\#p < 0.05$, $\#\#p < 0.01$ compared with the AD + SD group. Significant differences between mean values were determined by two-way ANOVA with Tukey multiple comparisons test.

0.05) but not in female AD mice ($p > 0.05$) (Fig. 4A&B). Similarly, mRNA levels of *PSD-95* (a critical synaptic protein) were also increased in MR-treated male AD mice brains ($p < 0.05$) but not in female AD mice ($p > 0.05$) (Fig. 4C), which was consistent with PSD ultrastructural alterations. Therefore, these data demonstrated that MR reduced brain Aβ accumulation in both male and female AD mice brains, and MR restored synaptic ultrastructure in male AD mice but not females.

3.4. Effects of MR on mitochondrial damages and mitochondrial biogenesis in APP/PS1 AD model mice brain

Normal mitochondrial function plays a pivotal role in maintaining synaptic plasticity [43]. Abnormal mitochondrial morphology is observed in AD patients [44]. Here, the mitochondrial morphology was severely damaged in hippocampus neuronal cells of male and female AD mice compared with wildtype mice, as evidenced by an increase in vacuoles and loss of mitochondrial cristae (Fig. 5A). MR could reverse the damaged mitochondrial morphology in male AD mice but not in female AD mice (Fig. 5A). The number of neuronal mitochondria was significantly reduced, and the damage ratio was significantly increased in male AD mice ($p < 0.01$) (Fig. 5B). MR treatment significantly increased the number of mitochondria in the hippocampus ($p < 0.01$) and alleviated mitochondrial damage ($p < 0.05$) in male AD mice but not in female AD mice ($p > 0.05$) (Fig. 5B).

Decreased mtDNA/nDNA ratio indicates reduced mitochondrial biogenesis [45]. The mtDNA/nDNA ratio in the cortex was lower in female and male AD than that of wildtype mice ($p < 0.05$) (Fig. 5C). However, the mtDNA/nDNA ratio was significantly elevated in male AD mice cortex after 4-month MR treatment ($p < 0.01$) (Fig. 5C). Similarly, MR increased *COX5b* mRNA level (a gene related to mitochondrial function) in the cortex of male AD mice ($p < 0.05$) but not in females ($p > 0.05$) (Fig. 5D). These data indicated that MR improved brain mitochondrial function and enhanced mitochondrial biogenesis in male AD mice but not females.

3.5. Effects of MR on oxidative stress and H_2S in APP/PS1 AD model mice brain

Mitochondria are one of the major producers of ROS [46]. The GSSG/GSH ratio, indicative of cellular redox status, significantly increased in the cortex of male AD mice compared with the wildtype fed with standard diet mice ($p < 0.01$). However, MR significantly reduced the GSSG/GSH ratio in male AD mice ($p < 0.01$), but not in females ($p > 0.05$) (Fig. 6A, Fig. S3A). The GSH level was elevated, and GSSG level was reduced respectively by MR in male AD mice cortex compared with the standard diet AD mice ($p < 0.01$), but not in females ($p > 0.05$) (Fig. 6B&C, Fig. S3B&C). Surprisingly, MR remarkably decreased GSH levels and increased GSSG levels in the cortex of male wildtype mice ($p < 0.01$) (Fig. 6B&C). Furthermore, MR substantially reduced the MDA (a biomarker of oxidative damage) in the male AD mice cortex ($p < 0.05$) but not in female AD mice ($p > 0.05$) (Fig. 6D, Fig. S3D).

Homocysteine is a metabolite with biological functions in the transsulfuration pathway. The increased level of serum homocysteine is associated with cognitive impairment [47]. The serum level of homocysteine was measured. As shown in Fig. S4, there were no significant differences between the AD and WT groups, and MR had no effects on the serum level of homocysteine in both male and female mice as well ($p > 0.05$). Endogenous H_2S related to AD is considered a redox-active molecule that is produced by a key catalytic enzyme, CBS [48]. Male AD mice had significantly lower H_2S levels in serum and cortex than male wildtype mice ($p < 0.01$) (Fig. 6E, Fig. S5A). MR significantly increased serum ($p < 0.01$) and cortex ($p < 0.05$) H_2S levels in male AD

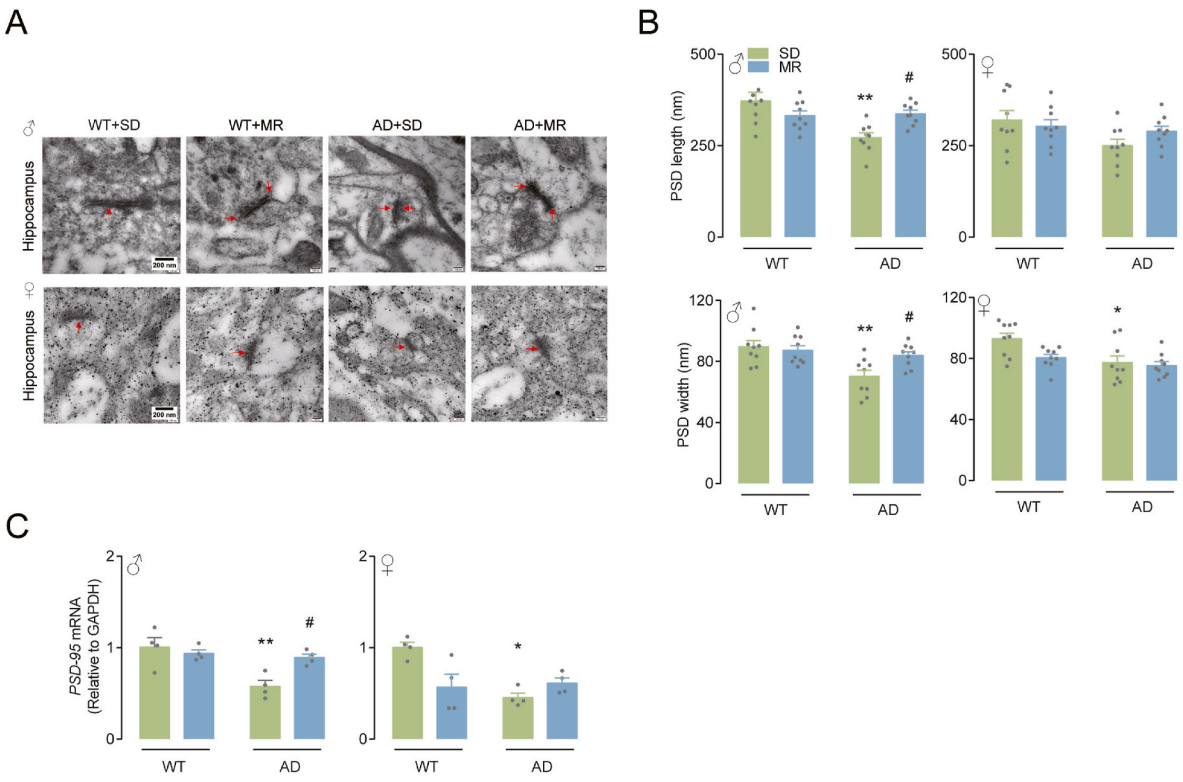

Fig. 4. Effects of MR on synapse ultrastructure and morphology in the brain of male and female APP/PS1 AD model mice
(**A**) Representative images of the ultrastructure of synapse in the hippocampus (n = 3 slices per group); (**B**) The length and width of PSD (n = 9 slices from 3 mice per group). (**C**) mRNA levels of *PSD-95* in the cortex (n = 4). Data were presented as mean ± SEM. *$p < 0.05$, **$p < 0.01$, compared with the WT + SD group, #$p < 0.05$, ##$p < 0.01$ compared with the AD + SD group. Significant differences between mean values were determined by two-way ANOVA with Tukey multiple comparisons test.

mice, but not in females (Fig. 6E, Fig. S3E, Fig. S5A), while the cortex H_2S levels in male wildtype mice were decreased by MR treatment ($p < 0.05$) (Fig. 6E). Similarly, MR treatment increased the mRNA and protein expression of *CBS* in the brain of male AD mice ($p < 0.05$), but not in females ($p > 0.05$) (Fig. 6F–J, Figs. S3F–J). These results indicated that MR might sex-specifically alleviate oxidative stress and activate CBS/H_2S pathway in the brain of male AD mice, but not females.

4. Discussion

In this study, we found that lower methionine intake was associated with increased cognitive function in MCI patients without sex differences. However, MR attenuated the cognitive declines in the male AD mice model but not in the females. MR significantly reduced the Aβ accumulation in both cortex and CA1, accompanied by decreased *APP* expression in both male and female AD mice. Whereas MR only restored the abnormal ultrastructure of synapses and mitochondria, possibly because of the enhanced *PSD-95* expression and mitochondrial biogenesis in male AD mice but not in females. More importantly, we found that MR significantly inhibited oxidative stress in the brain of male AD mice but not in females, which is partially dependent on the activated CBS/H_2S pathway.

Lower methionine intake diet may be achieved by using a predominately plant-based diet in humans [49]. Although the evidence for the effects of strictly plant-based diets on cognitive function is very limited, it seems that a plant-based diet might be able to influence brain function by still unclear underlying mechanisms [50]. Here we investigated the methionine intake of 45 subjects with MCI and 61 subjects without cognitive impairment. The results indicated that the MCI group had higher levels in the intake of dietary methionine compared with those who were healthy cognitive function (Fig. 1). There was no sex difference found in the association between methionine intake and cognitive function in the human study (Table S1). However, there was a significant sex difference observed during the treatment of MR on AD model mice, i.e., the beneficial effects of MR in males were much more significant than in the females, including cognitive function, Aβ accumulation, mitochondrial dysfunction, and oxidative stress in the brain. The different outcomes may be explained by the different impacts of MR across species. In addition, it has been reported that MR might be sexually dimorphic with different downstream nutrient-sensing signals and energy metabolism. Methionine deprivation induced the fibroblast growth factor (Fgf)-21-uncoupling protein (Ucp)-1 axis only in male high-fat-sucrose-fed mice to promote increased energy expenditure but not in females [51]. MR significantly changed the metabolic health and body composition in male wildtype and obese mice, whereas females showed moderate to minimal changes in most measured variables [52,53]. Another possible explanation is that the pathological development of MCI is weaker than AD, that MR could improve the cognitive impairment in both sexes. MCI is regarded as a transitional stage from the cognitive changes of normal aging to very early dementia [30,54]. Moreover, clinical and preclinical studies have shown that females have a higher risk of developing AD compared to males [55,56] for genetic risks [57], sex hormones [58], age-dependent development [59], etc. The sex differences in cognitive function of MR-treated AD model mice could be partly interpreted as more Aβ accumulation of AD in females than that in male ones (Fig. 3), which limited the beneficial effects of MR treatment. Nevertheless, the sexually dimorphic effects of MR treatment on cognitive decline and its underlying mechanism need further exploration in animal experiments and human clinical trials. These results indicated that the differences in sex, age, and health status might influence the beneficial effects of MR on individuals. Besides, we also observed that there was a cognitive function decline in both male and

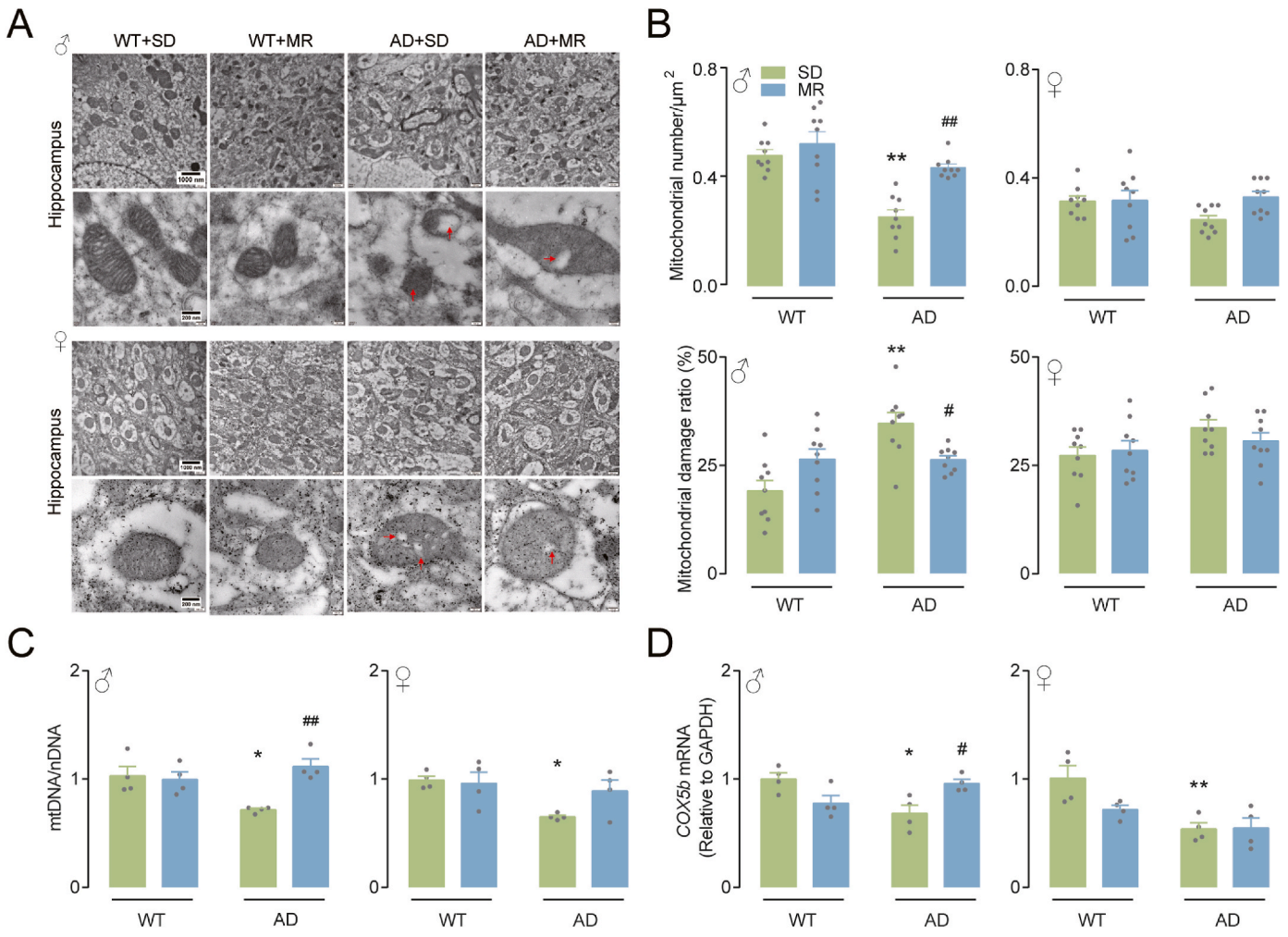

Fig. 5. Effects of MR on mitochondrial morphology and biogenesis in the brain of male and female APP/PS1 AD model mice
(**A**) Representative images of mitochondrial shape and number (n = 3 slices per group); (**B**) Quantification of mitochondrial number per μm^2 and mitochondrial damage ratio (n = 9 slices from 3 mice per group); (**C**) Mitochondrial DNA levels in brain tissue (n = 4); (**D**) mRNA levels of *COX5b* in the cortex (n = 4). Data were presented as mean ± SEM. *$p < 0.05$, **$p < 0.01$, compared with the WT + SD group, #$p < 0.05$, ##$p < 0.01$ compared with the AD + SD group. Significant differences between mean values were determined by two-way ANOVA with Tukey multiple comparisons test.

female MR-treated WT mice, which might be explained by the decreased GSH and H_2S levels or elevated MDA levels in the cortex. The other side effects of MR on cognitive function and other parameters in healthy subjects and the possible mechanisms need further investigation.

The neuroprotective effects of MR might be associated with the production of H_2S. A previous report demonstrated that MR activated the transsulfuration pathway and enhanced the production of H_2S by stimulating expressions and activities of two key enzymes, CBS and CGL [60]. MR treatment could elevate the cardiac and hepatic H_2S production in middle-aged obese mice and high-fat diet-fed mice, respectively [21,61]. Importantly, a recent study found that H_2S was also enhanced by MR in the hippocampus of high-fat-fed mice [62]. Moreover, H_2S exhibits neuroprotective effects, including suppressing Aβ formation and toxicity, inhibiting inflammatory responses, and enhancing mitochondrial function [63–65]. It has also been indicated that H_2S could reduce APP maturation and *BACE1* expression via activating the PI3K pathway [65]. Here, we found that MR significantly enhanced the H_2S levels in the serum and brain in the male AD mice but not in the females (Fig. 6, Fig. S3, Fig. S5). There were significant upregulations of the cortex CBS and H_2S in the male AD mice after MR treatment but not in the females (Fig. 6, Fig. S3), which was consistent with the sex differences in the results of cognitive function data mentioned ahead. It has been demonstrated that the serum level of H_2S in males is significantly higher than in females [66]. The sex differences could partly be explained by the L-cysteine/CSE/H_2S pathway may be preferentially activated in males leading to sex-specific H_2S biosynthesis, as testosterone plays a pivotal role in regulating H_2S biosynthesis [66]. Importantly, previous research found that the serum H_2S level tends to be lower in AD patients, and the decreased H_2S may be correlated with the severity of AD [67]. Consistently, in the current research, the serum and cortex levels of H_2S were lower in AD mice than in WT ones (Fig. S5B&C). In addition, there is emerging evidence that plasma H_2S can be elevated in AD and related dementias [68]. Notably, either lower or higher H_2S levels might be detrimental to brain health and may represent a neuroprotective system that breaks down under pathological conditions and induces cognitive dysfunction [69]. As a biomarker of cognitive function related-diseases, the normal concentration range of H_2S in the plasma and brain needs to be studied in the future. Moreover, the expressions of *APP* and *BACE1* were also down-regulated in the MR-treated male AD mice brain, which was consistent with the reduced Aβ accumulation in the cortex and hippocampus (Fig. 3).

The activated CBS/H_2S pathway by MR might partly balance redox status and enhance mitochondria biogenesis. Studies have reported that MR reduced the GSH level in hepatocytes [70,71]. The GSH level in the brain did not change under MR treatment [72]. However, the GSH and GSSG concentrations in the cortex were increased and decreased,

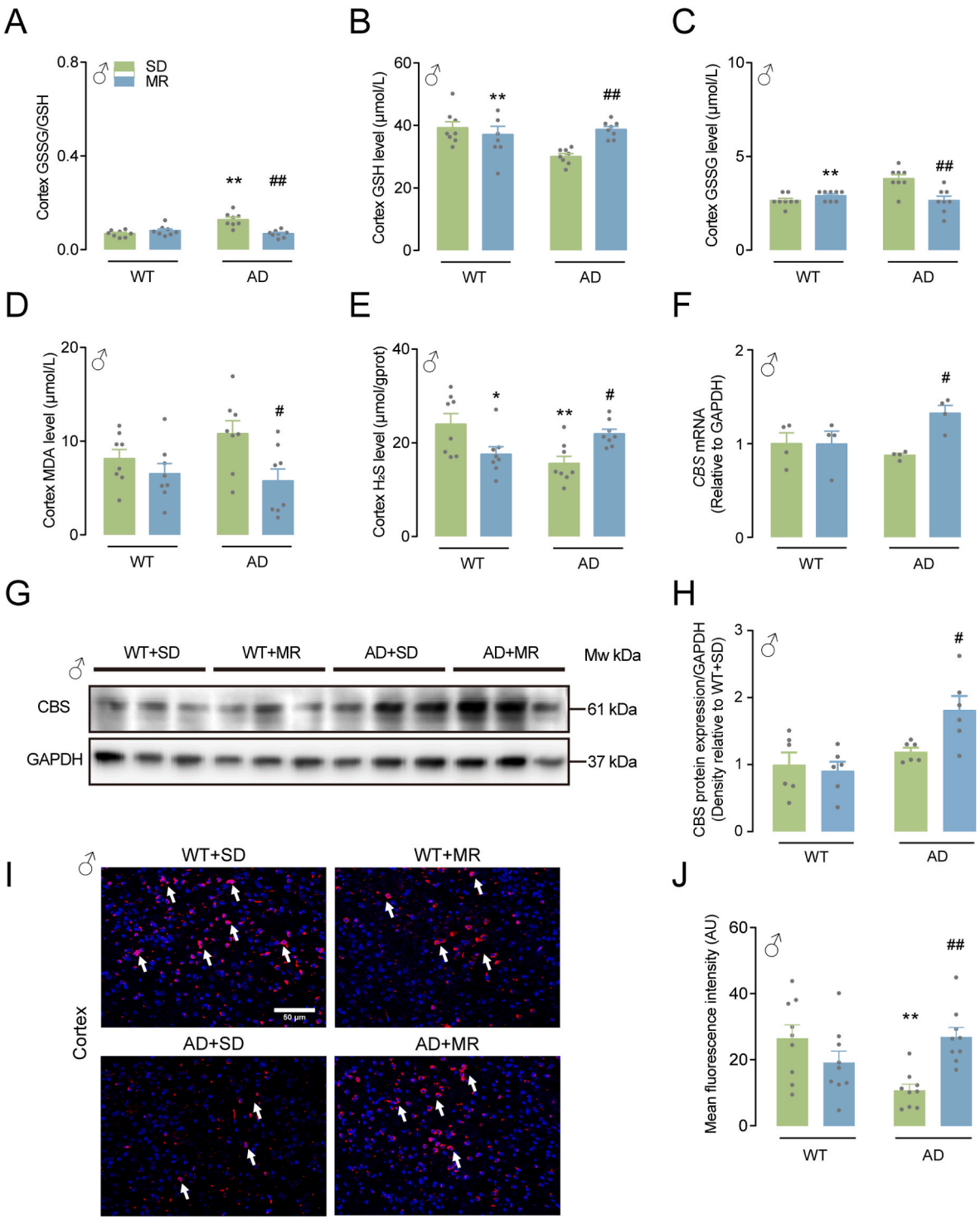

Fig. 6. Effects of MR on redox status and CBS/H_2S pathway in the brain of male APP/PS1 AD model mice
(**A**) The GSSG/GSH ratio in the cortex (n = 8); (**B**) The levels of GSH in the cortex (n = 8); (**C**) The levels of GSSG in the cortex (n = 8); (**D**) The levels of MDA in the cortex (n = 8); (**E**) The levels of H_2S in the cortex (n = 8); (**F**) mRNA levels of *CBS* in the cortex (n = 4); (**G**) Representative western blots of CBS protein levels in cortex (n = 3); (**H**) Quantification of the western blots of CBS protein levels in cortex (n = 6); (**I**) Representative images of immunofluorescence staining of CBS in the cortex (n = 3 slices per group); (**J**) Mean fluorescence intensity (AU) of CBS protein levels in cortex (n = 9 slices from 3 mice per group). Data were presented as mean ± SEM. $*p < 0.05$, $**p < 0.01$, compared with the WT + SD group, $\#p < 0.05$, $\#\#p < 0.01$ compared with the AD + SD group. Significant differences between mean values were determined by two-way ANOVA with Tukey multiple comparisons test.

respectively, resulting in the reduction of the GSSG/GSH ratio (Fig. 6), which is associated with decreased intracellular oxidative stress [73]. The activated CBS/H_2S pathway may increase the intracellular levels of GSH by enhancing the activity of cystine/glutamate transporter xCT as well as glutamate cysteine ligase, a rate-limiting enzyme for GSH production [74]. Additionally, previous studies indicated that MR decreased the mtROS generation and oxidative stress in the liver [75] and induced mitochondrial DNA copy numbers in the adipose tissue [76]. Moreover, H_2S derived by CBS could balance the mitochondrial reactive oxygen species (mtROS) and nitric oxide in glia [77] and

redistribute the localization of GSH to mitochondria [27]. A sufficient level of H_2S could maintain mtDNA copies, which is critical for mitochondrial biogenesis [78]. Normal mitochondrial function and quality play pivotal roles in maintaining synaptic plasticity [43]. Here, we found that MR reversed the alteration of synapse ultrastructure, further maintained the mitochondrial structure, and enhanced mitochondrial biogenesis in male mice hippocampus but not in the females (Figs. 4 and 5), which was consistent with the results of cognitive function and Aβ accumulation. MR protected brain mitochondria from imbalanced redox status to improve mitochondrial structure and biogenesis in male AD mice but not in females, which could be partly explained by the activation of the CBS/H_2S. However, the limitation of this study is that we lack sophistication for measuring in *vivo* H_2S. Although methylene blue has been reported to be used to measure H_2S levels in mice cortex and plasma [39,40], it may also have limitations, including its insensitive nature, harsh chemical treatments, and inability to obey Beer's law, leading to exceedingly high measurements of biological sulfide [79]. Separation techniques such as gas or liquid chromatography with mass spectrometry could be employed in detecting the H_2S in specific brain regions in future research. Besides, the effects of MR on mitochondrial bioenergetics and other mitochondrial function are not investigated in the current research, which is valuable to be further illustrated in the future.

In conclusion, we found that in the human study, lower dietary methionine intake was associated with improved cognitive function. Although dietary methionine intake was correlated with MCI in humans without sex differences, MR could sex-specifically attenuate the cognitive decline and oxidative stress in AD mice, which could be partly explained by the activated CBS/H_2S pathway. Our findings demonstrated that MR might be an effective nutritional intervention for cognitive decline and agree across species. The dietary methionine intake and cognitive function of AD patients should be further investigated, and preclinical trials of MR on AD patients can be appropriately conducted without protein malnutrition. Since low protein intake in the elderly might be associated with unpredictable outcomes, especially in muscle mass loss and heart failure [80–82], it might be more appropriate to maintain or even increase the protein intake in the elderly along with maintaining a low methionine intake. This might be achieved by using plant protein sources, which are generally lower in methionine content compared to animal proteins, and may, therefore, have beneficial effects [83].

Author contribution

Z. L., M. H., L. S., and T. G. designed the experiments; Y. X., Y. Z., Y. Z., and Q. L. performed and analyzed the experiments; M. H., L. S., and Y. X. interpreted the data; Z. L., X. L., T. G., Y. X., Y. Z., Y. Z., and X. C. wrote the manuscript; Z. L., M. H., L. S., and T. G. supervised the work. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare no competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2022.102595.

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