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Review article

Magnetic resonance spectroscopy as a non-invasive tool for assessing brain and muscle adaptation to exercise training in older age: a scoping review into existing research

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ABSTRACT

Background: Exercise training has attracted increasing attention as a non-pharmacological intervention approach to counteract age-related deterioration of brain and muscle function, yet objective biomarkers are needed to understand mechanisms and optimize interventions. Magnetic resonance spectroscopy (MRS) provides non-invasive, in vivo assessment of metabolic profiles altered by aging and exercise. However, MRS-based exercise research in older populations remains limited. This scoping review aims to identify brain and muscle metabolites detectable by MRS that can serve as markers of exercise training effects in aging.

Methods: We conducted a literature search from inception to October 2024 in PubMed, Embase, Web of Science, and Scopus. Inclusion criteria comprised randomized control trials (RCT) and observational studies including older adults (≥60 years) who underwent exercise training interventions which were preceded/followed by brain/muscle MRS scanning.

Results: Fourteen studies were included. Exercise intervention characteristics varied from low or moderate aerobic type of exercise to high intensity training, with the interventions placing variable emphasis on the strength-endurance continuum. Scanning methods were ^{1}H brain MRS ($n = 6$), ^{31}P brain MRS ($n = 1$), ^{31}P muscle MRS (n

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= 8) and ^{1}H muscle MRS (n = 1). Main ^{1}H-MRS brain neurometabolic outcomes were the ratios to creatine of total *N*-acetyl-aspartate (tNAA/tCr) and total choline (tCho/tCr) in the right/left hippocampus. However, findings regarding the effect of exercise training interventions on these neurometabolic outcomes were inconclusive. ^{31}P muscle MRS demonstrated an increase in phosphocreatine (PCr) recovery rate from pre-to-post exercise suggesting an improvement of mitochondrial function following exercise when applying exercise interventions with an emphasis on improving cardiometabolic functions.

Conclusions: Despite limited guidance on methods and biomarkers, this scoping review supports MRS as a promising tool for monitoring exercise-induced metabolic changes in muscle and brain of older adults. However, standardized methodologies and larger number of studies are required to determine which metabolites reliably reflect exercise benefits in aging brain and muscle.

1. Introduction

Magnetic resonance spectroscopy (MRS) enables non-invasive assessment of physiological, biochemical, and functional properties in living brain and muscle tissue (Cichocka and Bereś, 2018; Kršňák et al., 2021). In the brain, ^{1}H-MRS can be used for monitoring dynamic changes in cortical neurochemicals, including gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter (Coxon et al., 2018; Maddock et al., 2016); the glutamate-glutamine complex (Glx), which is central to excitatory neurotransmission (Maddock et al., 2011, 2016); and lactate, a metabolic activity marker (Coxon et al., 2018; Maddock et al., 2011). Standard ^{1}H-MRS protocols can be used for quantifying key metabolites of aging and neurodegenerative disorders (Aboul-Enein et al., 2010; Chang et al., 2013; Cleeland et al., 2019; Kantarci, 2013; Liu et al., 2021; Oz et al., 2014; Vints et al., 2022a; Weerasekera et al., 2019; Zhang et al., 2015), including: total *N*-acetylaspartate (tNAA) which reflect neuronal viability, total choline (tCho) which associated with membrane turnover, total creatine (tCr) which serves as a marker of energy metabolism; and myo-inositol (mIns) which is a marker of glial activation and neuroinflammation (Chang et al., 2013; Vints et al., 2022a; Weerasekera et al., 2019); for a review see Oz et al. (2014). Multi-nuclear MRS approaches, including carbon-13 (^{13}C-MRS) and phosphorus-31 (^{31}P-MRS), provide insights into specific metabolic pathways in both brain and muscle tissue (Gruetter et al., 2003; Rothman et al., 2011, 2019). In muscle, ^{31}P-MRS is routinely used to quantify mitochondrial function by assessing phosphocreatine (PCr) recovery rate (Forbes et al., 2008; Layec et al., 2013), while ^{1}H-MRS is commonly employed to evaluate muscle lipid metabolism (Brechtel et al., 2001; Boesch et al., 2006; Kršňák et al., 2021). Collectively, these capabilities make MRS a powerful tool for monitoring intervention-induced changes in the biochemical, morphological, and physiological properties of brain and muscle in both healthy and pathological populations. Incorporating MRS into healthy aging research can therefore enhance our understanding of the mechanisms and molecular signaling pathways underlying muscle-brain crosstalk (Vints et al., 2022b) and help address existing knowledge gaps regarding how muscle and brain adapt to exercise (Sanford et al., 2020).

The beneficial effects of maintaining high levels of physical activity and engaging in well-planned exercise-based lifestyle interventions on brain health, cognition, and psychological well-being and cognition are well known (Berryman et al., 2014; Biazus-Sehn et al., 2020; Colcombe and Kramer, 2003; Gallardo-Gómez et al., 2022; Iso-Markku et al., 2022; Levin et al., 2017; Liu-Ambrose et al., 2010; Northey et al., 2018). From an anatomical point of view, exercise training interventions have been shown successful in preserving or increasing brain volume in healthy older adults (e.g., Colcombe et al., 2006; Erickson et al., 2011) and in older adults at risk of Alzheimer's disease (Andrade-Guerrero et al., 2023; Xu et al., 2024; Zhang et al., 2020). However, findings regarding the efficacy of such interventions in both clinical and healthy aging populations at risk for cognitive decline or neurodegenerative disorders remain somewhat inconclusive (e.g., Hvid et al., 2021). From a functional point of view, engaging in regular physical activity has been shown to enhance brain function in middle-aged and older adults (Berryman et al., 2014; Coelho-Júnior et al., 2020; Liu-Ambrose et al., 2010; Northey et al., 2018; Vints et al., 2024a; Voelcker-Rehage et al., 2011), and to slow the progression of cognitive decline in individuals with mild cognitive impairment (MCI) and dementia (Enette et al., 2020; Huang et al., 2022; Sofi et al., 2011; Vints et al., 2024a, 2024b; Xu et al., 2017; Zhang et al., 2020). Furthermore, physical activity is beneficial for immune system resilience (Chastin et al., 2021; Chow et al., 2022; Salimans et al., 2024; Zhou et al., 2024) or can be used as a non-pharmaceutical intervention in the management of various metabolic diseases such as type 2 diabetes (Cannata et al., 2020; Kanaley et al., 2022; Sabag et al., 2017). These functional and anatomical adaptations are likely to be complemented by biochemical and physiological changes that can be detected using MRS. However, the current literature still lacks a comprehensive synthesis and systematic analysis of findings from MRS studies on brain and muscle adaptation to exercise in the older population.

With respect to the type of exercise, resistance training has been found to be effective for prevention of age-related decline in muscle mass and lipid infiltration (Sabag et al., 2017; Stokie et al., 2023) and decrease the prevalence of sarcopenia and frailty (Beckwée et al., 2019; Lopez et al., 2018; Navarrete-Villanueva et al., 2021; Talar et al., 2021; Valenzuela et al., 2023; Yang et al., 2024). Cardiovascular training has been demonstrated to enhance overall cardiovascular health (Albinet et al., 2010; Perini et al., 2002; Varas-Diaz et al., 2021) and improve mitochondrial efficiency (De Strijcker et al., 2018; Hey-Mogensen et al., 2010; Jeppesen et al., 2006). In this regards, ^{1}H-MRS and ^{31}P-MRS can be employed to assess the effects of exercise training on structural, functional, and energy metabolism of the skeletal muscle system (Argov et al., 1996; Baguet et al., 2011a; Kršňák et al., 2021; Krumpolec et al., 2020; Layec et al., 2013; Stokie et al., 2023; Yoshida and Watari, 1992). For example, skeletal muscle ^{31}P-MRS can be used to estimate muscular oxidative capacity by monitoring the rate of recovery of phosphocreatine (PCr) (e.g., Argov et al., 1996; Krumpolec et al., 2020; Meyerspeer et al., 2005). Other metabolites that can be monitored with ^{31}P-MRS are inorganic-phosphate (Pi) and adenosine triphosphate (ATP) which can be used for modeling muscle force production capacity and mitochondrial functioning (Sassani et al., 2020; Zane et al., 2017). Skeletal muscle ^{1}H-MRS can be implemented to feature the effects of both acute and chronic exercise interventions on lactate, intramyocellular lipids, acetylcarnitine, creatine/phosphocreatine (Boesch et al., 2006; Just Kukurová et al., 2016; Kršňák et al., 2021; Krumpolec et al., 2020; Stokie et al., 2023) and carnosine (Baguet et al., 2011b; Bex et al., 2017; Derave et al., 2010); the latter may be used as an indicator for muscle-fiber type (Baguet et al., 2011b; Derave et al., 2010; Kršňák et al., 2021).

The overarching goal of the present scoping review was to examine and synthesize studies that have investigated the effects of exercise training on muscle and brain metabolism in older adults. The literature search focused primarily on datasets from proton (^{1}H) and Phosphorus-31 (^{31}P) and/or multi-nuclei MRS where the effects of acute exercise training (a single bout of exercise) and chronic exercise training (repeated bouts of exercise) on brain and muscle metabolites were studied. From this body of literature, it was aimed to identify neurochemical and metabolic changes in the period following acute or chronic exercise training in older adults aged 60 years or older. The focus was specifically on brain and muscle biochemical properties with the

potential to serve as biomarkers of exercise-induced cognitive and brain/muscle functional gains (or losses) in older adults. Secondary outcomes from cognitive tests, motor tests, neuromuscular tests, blood tests, and/or functional or structural imaging of brain and muscle will be examined whenever possible. The review's specific questions are summarized in Box 1. The study was pre-registered on OSF: https://osf.io/mjda4/resources.

2. Methods

2.1. Literature search strategy and inclusion/exclusion criteria

Database consisted of literature that were published between January 1988 and November 2023. The search was conducted by using a keyword search of the following terms: ("magnetic resonance spectroscopy" OR spectroscopy OR MRS OR "single voxel MRS" OR "sv MRS" OR "magnetic resonance spectroscopy imaging" OR "MRS imaging" OR MRSI OR "multivoxel MRS" OR "edited MRS") AND (muscle OR brain) AND (physical activity OR training OR aerobic OR cardiorespiratory OR resistance OR strength OR "blood-flow restriction" OR dance OR yoga OR "tai chi" OR "martial art" OR qigong OR endurance OR balance OR cycling OR swimming OR running OR jogging OR walking OR "cross country" OR "high-intensity interval training" OR "mind-body"). All available records retrieved from the databases were uploaded to the Rayyan QCRI website to remove duplicates. Eligible datasets for inclusion were studies reporting quantitative measures of metabolite concentrations or ratios from in-vivo single voxel (SVS) MRS or multivoxel MRS imaging (MRSI) datasets.

Eligible study designs for inclusion in this scoping review included: (1) randomized controlled trials (RCTs) or non-RCTs where single bout or chronic exercise training interventions were applied; (2) longitudinal studies where assessment of MRS outcome measures and physical activity were reported at multiple time points; (3) case reports or case-series studies reporting the effects of exercise training intervention. Non-eligible study designs were: (1) studies without pre-to-post exercise comparisons; (2) cross-sectional studies where assessment was conducted at one time point; (3) cross-sectional studies where acute exercise challenges (either fatiguing or submaximal) were applied without pre- and post-exercise testing, and (4) exercise challenging protocol using ^{31}P MR-spectra for exploring the effect of aging or age-related pathologies on muscle mitochondrial function (e.g., Varadhan et al., 2019). We focused on older adult cohorts with a mean age of 60 years and older with no restrictions on health conditions and exercise type. The 60-year age threshold was determined based on a preliminary review of the exercise and cognitive aging literature, which revealed that seminal studies commonly employ age inclusion criteria ranging from 55 to 65 years (Colcombe and Kramer, 2003; Erickson et al., 2011), with 60 years being the most frequently used threshold. This approach aligns with World Health Organization operational definitions for aging research (WHO, 2015) and American College of Sports Medicine guidelines for older adult exercise (Chodzko-Zajko et al., 2009) and ensured comprehensive coverage of relevant MRS-based exercise studies in aging populations. Cross-sectional studies comparing active and sedentary older adults were excluded because: (1) they cannot establish temporal or causal relationships between exercise and metabolic changes; (2) "active lifestyle" classifications are heterogeneous and poorly quantified, introducing confounding variables that limit exercise-specific inference; and (3) controlled interventions with standardized exercise regimens provide superior evidence for informing exercise prescription recommendations and identifying key exercise-related biomarkers. Finally, animal studies or studies exploring tissue samples from human subjects or animals (e.g., biopsies) were excluded. Review screening instructions describing eligibility criteria and the definitions of inclusion and exclusion criteria are provided in the Supplemental materials (Supplementary Table S1).

2.2. Study selection

All available records retrieved from the databases ($n = 5653$) were uploaded to the Rayyan QCRI website to remove duplicates. The remaining 3694 articles were screened for title and abstract by the principal investigator (co-author OL) and seven reviewers (co-authors IJ, RK, SH, AFS, AL, SBS and CK) who independently screened 67% of the potential studies. The agreement between the principal investigator and the seven reviewers was 97.6%. Of the 3694 articles, 3538 (95.8%) were excluded at the title/abstract screening level after the first screening session and 43 articles for which no full-text document was available were excluded after a second screening session. The remaining 113 articles were screened at the full-text level, leading to the exclusion of an additional 100 studies (88 conflicts). Conflicts were resolved by the principal investigator (OL) and one of the two senior co-authors (UH and MK) served as a tiebreaker when consensus was not met. A second search was conducted on PubMed in November 2024, yielding another 44 articles that were published between January 2024 and October 2024 and were screened for title and abstract by OL. This search yielded one additional study. In total, 14 studies were included in the final analysis of this scoping review. A final search was conducted in January 2026 for literature published in 2025, which yielded no additional studies. A flowchart summarizing the literature search and step-by-step screening process is illustrated in Fig. 1. Spectra acquisition protocol, spectra quality, spectra processing pipelines/toolbox and quality of quantification are reported in Supplementary Table S2 (brain MRS) and Supplementary Table S3 (muscle MRS). Protocols were reported according to the experts' consensus recommendations for minimum reporting standards for in-vivo magnetic resonance spectroscopy (MRSinMRS); see https://doi.org/10.1002/nbm.4484 (Lin et al., 2021).

2.3. Data extraction

In line with the specific research questions, findings from the included studies were grouped into four key factors including type of MRS method, site and size of the MRS voxel from which spectra were extracted, metabolites that were quantified, and the effect of intervention on each of the quantified metabolites. The following variables were extracted from the eligible articles: (1) reference information including first author's name and year of publication; (2) sample characteristics (number of participants, age, gender and health status); (3) intervention protocol (type of exercise, exercise intensity, exercise volume, intervention duration); (4) MRS voxel locations; (5) reported metabolic outcomes; and (6) exercise-induced effects on MRS metabolic outcomes. The extracted information was controlled by co-authors SH and UH for articles reporting findings from the six studies of brain MRS (Table 1) (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016; Zhou et al., 2018) and by co-authors IJ, RK and MK for articles reporting findings from the nine studies of muscle MRS (Table 2) (Back et al., 2000; Berg et al., 2020; Broskey et al., 2014; Bucci

Box 1
Relevant research questions addressed by this scoping review.

- Which brain and muscle metabolites detectable by MRS have been examined as potential biomarkers of exercise effects in aging populations?
- What MRS metabolites and biochemical properties have been most frequently reported, and what patterns of findings have emerged regarding exercise-induced outcomes in brain and muscle tissue of older adults?
- Is there a sufficient body of experimental data coming from MRS studies to guide evidence-based recommendations on exercise characteristics to maximize its beneficial effects and what are the current methodological and research gaps in the field?

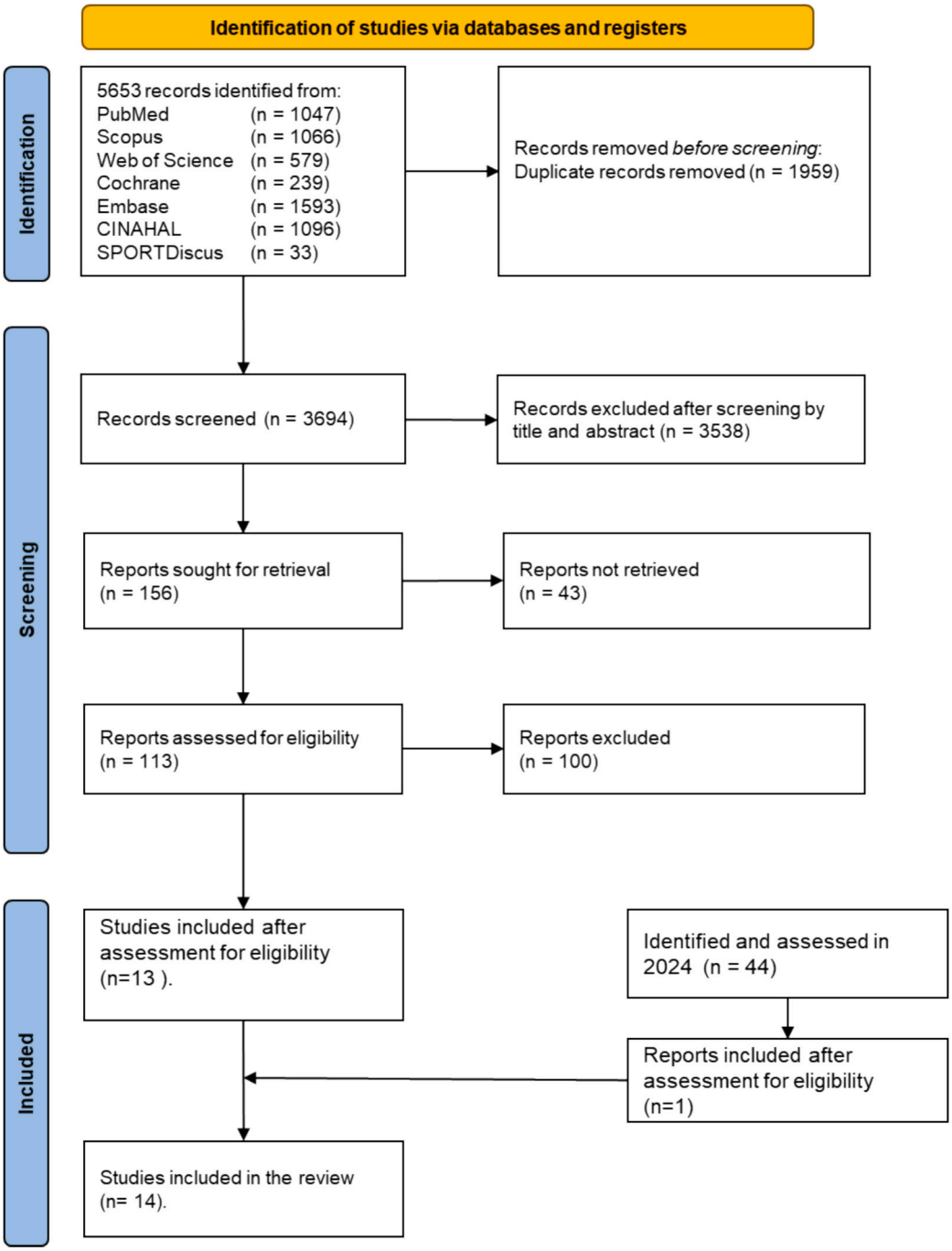

Fig. 1. PRISMA flow chart.

et al., 2016; Hurley et al., 2019; McKeough et al., 2006; Slade et al., 2021; van Tienen et al., 2012; Zhou et al., 2018).

3. Results

3.1. General study characteristics

Fourteen full text articles were included in this scoping review. Thirteen articles (Back et al., 2000; Berg et al., 2020; Broskey et al., 2014; Bucci et al., 2016; Hurley et al., 2019; Matura et al., 2017; McKeough et al., 2006; Reitlo et al., 2023; Sheoran et al., 2023; Slade et al., 2021; van Tienen et al., 2012; Yang et al., 2016; Zhou et al., 2018) were extracted from the original search and one full text article (Vints et al., 2024b) was included after the second search. Of the 14 included studies, one study (Zhou et al., 2018) included data of brain ^{1}H and muscle ^{31}P MRS and two studies included data of both ^{1}H and ^{31}P MRS from brain (Matura et al., 2017) or muscle (van Tienen et al., 2012). The remaining studies used single-nuclei MRS. Number of participants ranged from 6 (Zhou et al., 2018) to 63 (Reitlo et al., 2023). Nine studies (64.3%) (Berg et al., 2020; Broskey et al., 2014; Bucci et al., 2016; Hurley et al., 2019; Matura et al., 2017; Reitlo et al., 2023; Slade et al., 2021; Sheoran et al., 2023; Vints et al., 2024b) included cohorts of apparently healthy older adults (minimum age $\geq$ 60 years). Two studies (14.3%) (Yang et al., 2016; Zhou et al., 2018) included mixed samples of apparently healthy middle-aged and older adults with a minimum $\geq$51 years and a mean age $\geq$ 63.7 years and three studies (21.4%; all muscle MRS) included participants with specific health conditions such as COPD (n = 1, mean age = 68 years) (McKeough et al., 2006), type 2

Table 1
Summary of included studies with brain MRS ($n = 6$).

Reference	Sample	Intervention	MRS method & voxel location	Reported MRS metabolites	Effect
Matura et al., 2017†[A]	$n = 53$, Mean age: 75.5 ± 7.2 y, 28 Male, 25 Female Cognitive healthy participants	EG ($n = 29$): 40 min of moderate cardiovascular training. 3 sessions/ week CG ($n = 24$): Passive controls (no exercise) 12 weeks	^{1}H-MRS 2D MRSI & SVS of hippocampus contralateral to the dominant hemisphere ^{31}P-MRS 3D MRSI	tNAA/tCr, tNAA/tCho, tCho/tCr tCho/tCr, PCr/Pi, ATP/Pi, GPC/Pr, PCho/PCr	The exercise group did not improve their max aerobic capacity (VO2max) or ventilatory threshold (VT1) but maintained them. Overall a trend for positive training effects on NAA/tCr and NAA/tCho: contrast analysis showed significant effect for NAA/tCho for the training group as compared to the control group ($p = 0.04$, $\eta p^2 = 0.083$), showing a decrease in NAA/tCho in CG while the EG group maintained their levels. Significant increase in tCho/Cr in CG ($p = 0.017$, paired *t*-test) but no changes in EG. No significant effect of training on NAA/tCr ($p = 0.4$, $\eta p^2 = 0.004$). Significant moderate positive association of VT1 changes and NAA/tCho changes was evident only in EG. No significant Group × time interaction for any of the ^{31}P brain metabolites ($p \geq 0.49$).
Reitlo 2023†[B]	$n = 63$, Mean age: 75.3 ± 1.9 y, 32 Male, 31 Female No info available for initial cognitive status	EG ($n = 32$): Supervised exercise group (SEG) contained a subgroup performing 4 × 4 min HIIT at 90% peak HR twice a week, or 50 min MICT at 70% peak HR. 2 sessions/ week CG ($n = 31$): active controls -followed the national physical activity guidelines of ≥30 min moderate activity ≥ 5 sessions/week 3 years No diet monitoring.	^{1}H-MRS 2D MRSI of hippocampal (HPC) body and head. MRS spectra were acquired at 3 years follow-up. MRI volumes recorded but not explicitly reported. MRS data were corrected for age, gender and HPC volumes in body or head respectively. .	tNAA/Cr tCho/Cr	Both group participants had similar aerobic fitness levels (which they maintained over the 3-year period). The exercise intensities of both group participants overlapped (ranging from 70 to 90% peak heart rate). Both group participants showed high exercise adherence, >80%. At 3 years follow -up, participants who exercised 5xweek (CG) showed significantly higher levels of NAA/Cr in HPC body as compared to those exercising 2xweek (SEG). No differences in Cho/Cr between groups. Higher exercise intensity, irrespective of group, was associated with lower Cho/Cr level in the HPC body
Sheoran et al., 2023†	$n = 41$ Mean age: 69.6 ± 5.57 y 18 Male 23 Female MoCa score levels were used to stratify the allocation to experimental and control groups.	EG ($n = 20$): 50 min of progressive RT (70–85% 1-RM). 2 sessions/ week. CG ($n = 21$): Passive controls (no added exercise) 12 weeks All participants were novices to resistance training but according to IPAQ were moderately to highly active individuals. No diet monitoring.	^{1}H-MRS Hippocampus (HPC), left sensorimotor cortex (SM1), right dorsolateral prefrontal cortex (dlPFC)	tNAA/tCr tCho/tCr mIns/tCr Glx/tCr	No baseline fitness or neurometabolite ratio differences between groups. The EG increased its strength performance overall (despite including non-responders to RT*). Participants in the CG showed a significant decrease of tNAA/tCr and Glx/tCr. The EG maintained similar levels of pre and post neurometabolites (all metabolites). Delta changes in strength indices were positively associated with delta changes in SM1tNAA/tCr, SM1Glx/tCr, and dlPFC Glx/tCr * Non-responders to RT had better levels of weekly PA, MoCa and strength at baseline as well as overall better neurometabolite levels vs responders to RT.
Vints et al., 2024b†	$n = 35$ Mean age: 69.9 y Cognitive status: High MCI risk ($n = 16$) Low MCI risk ($n = 19$).	EG ($n = 22$): 50 min of progressive RT (70–85% 1-RM). 11/11 high/low MCI risk 2 sessions/ week. CG ($n = 13$): Passive controls (no exercise). 5/8 high/low MCI risk 12 weeks	^{1}H-MRS left hippocampus	tNAA/tCr mIns/tCr tNAA/mIns	No significant group differences after 12 weeks. Marginal Group × Cognitive status effect with moderate effect size ($\eta p^2 = 0.11$, $p = 0.07$) for tNAA/tCr.

(*continued on next page*)

Table 1 (*continued*)

Reference	Sample	Intervention	MRS method & voxel location	Reported MRS metabolites	Effect
Yang et al., 2016†	$n = 25$ Mean age: 67.4 y 13 Male 12 Female Subjects had mild cognitive impairment	EG ($n = 14$): Low intensity activity, based on breathing exercises, combination of Kirtan Kriya (KK) meditation and Kundalini Yoga (KY) One 60-min (KY + KK) session/week. Plus, 12 min of daily homework-not specified CG ($n = 11$): Memory Enhancement Training (MET)-mnemonic based. On the other hand if one divides One 60-min session/week Plus, 12 min of daily homework-not specified 12 weeks	^{1}H-MRS Bilateral hippocampus and dorsal anterior cingulate cortex (dACC)	Bilateral HPC: tNAA/tCr Cho/tCr Glx/tCr dACC: tNAA/tCr, Cho/tCr Glx/tCr GABA/tNAA	No information is provided on whether fitness changed due to the interventions. Significant decrease in levels of Cho/Cr for MET in bilateral hippocampus ($p = 0.01$) but not for the KK + KY ($p = 0.8$). A trend towards a decrease of NAA/Cr in the bilateral hippocampus for the KK + KY but not for MET No significant effect of intervention on the remaining neurometabolites. No significant interactions or main effects identified for any metabolite in the dACC.
Zhou et al., 2018#	n = 6 Mean age: 63.7 ± 9.9 y 1 Male 5 Female	EG (n = 6): 60 min Tai Chi training. ≥2 sessions/ week. No control group 12 weeks	^{1}H-MRS posterior cingulate gyrus (PCG)	NAA/Cr	Metabolic fitness improved with the Tai Chi intervention (see Table 2). A significant within-subject increase in NAA/Cr from baseline to posttraining scans ($p < 0.05$).

† Reported as a randomized controlled trial (RCT). [A]Trial registration NCT02343029; [B]Trial registration NCT01666340.
*Acronyms.
EG: exercise group.
CG: control group.
HIIT: high intensity interval training.
MICT: moderate intensity continous training.
HPC: hippocampus.
PCG: posterior cingulate gyrus.
dACC: dorsal anterior cingulate cortex.
SM1: sensorimotor cortex.
dlPFC: dorsolateral prefrontal cortex.
study that also reporte don muscle metabolites (see Table 2).

diabetes (n = 1, mean age = 60.5 years) (van Tienen et al., 2012), and intermittent claudication (n = 1, mean age = 71.2 years) (Back et al., 2000). Finally, one study (Bucci et al., 2016) included a cohort of frail women (muscle MRS, mean age = 71.9 years) and two studies (both brain MRS) (Sheoran et al., 2023; Vints et al., 2024b) included subgroups of older adults with high risk of MCI but otherwise in good general health. Among the 14 included studies, seven (50%) were reported as randomized or described the method of randomization trials (Hurley et al., 2019; Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Slade et al., 2021; Vints et al., 2024b; Yang et al., 2016). However, only two studies (14.3%) were registered as clinical trials online (Matura et al., 2017; Reitlo et al., 2023) and in seven (50%) of the studies (Bucci et al., 2016; Berg et al., 2020; Broskey et al., 2014; McKeough et al., 2006; Reitlo et al., 2023; van Tienen et al., 2012; Zhou et al., 2018) no non-active control group was included. Five types of interventions were identified: (1) light to moderate walking or aerobic exercise (42.9%, $n = 6$) (Back et al., 2000; Broskey et al., 2014; Hurley et al., 2019; Matura et al., 2017; Reitlo et al., 2023; Slade et al., 2021), (2) moderate to vigorous resistance training (35.7%, $n = 5$) (Berg et al., 2020; Bucci et al., 2016; Sheoran et al., 2023; Vints et al., 2024b; van Tienen et al., 2012), (3) high-intensity interval training (7.1%, n = 1) (Reitlo et al., 2023), (4) combined resistance and aerobic training (7.1%, n = 1) (McKeough et al., 2006), (5) mind-body exercises (14.3%, $n = 2$) including yoga (Yang et al., 2016) and Tai-Chi (Zhou et al., 2018). Control groups included inactive controls (42.9%, n = 6) (Back et al., 2000; Hurley et al., 2019; Matura et al., 2017; Sheoran et al., 2023; Slade et al., 2021; Vints et al., 2024b) and active controls (14.3%, n = 2) (Reitlo et al., 2023; Yang et al., 2016). Finally, in one 3-year follow up study (Reitlo et al., 2023) brain data were reported in a pooled fashion despite heterogeneity in exercise modality and intensity implementation in the supervised exercise group where one subgroup implemented continuous exercise at about 70% of peak heart rate and another subgroup implemented HIIT at about 90% of peak heart rate. Pooled data from this 'exercise group' was contrasted with a 'control' unsupervised exercise group which was calculated to exercise at an intermediate intensity. Considering that both intervention and active control group exercised for about 150 min per week, it is interesting to note that data from that study indicated that whether exercising intensely for couple of times per week or moderately for up to 5 times per week, participants maintained a good lipidemic and a similar aerobic profile (withstanding the expected detrimental aging effects). Our systematic search revealed no acute exercise studies examining metabolite responses in brain or muscle of older adults. A recent systematic review by Ryberg et al. (2023) summarized the effects of acute exercise on brain metabolites measured by ^{1}H-MRS, including data from 9 studies on young adults. The review found that GABA and lactate tended to increase following acute cardiovascular training, while findings for other ^{1}H-MRS metabolites were either inconclusive (Glx) or insignificant (tCho, tNAA, tCr).

3.2. MR spectra acquisition methods

3.2.1. Brain MRS

Spectral acquisition methods included proton (^{1}H) MRS and phosphorus (^{31}P) MRS. The main ^{1}H MRS spectral acquisition method from the brain was the single-voxel (SVS) point-resolved spectroscopy (PRESS) pulse sequence with an echo time (TE) of 30 milliseconds and repetition time (TR) ranging from 2000 to 3000 milliseconds (Matura et al., 2017; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016;

Table 2
Summary of included studies with muscle MRS ($n = 9$).

Reference	Sample	Intervention	MRS method & voxel location & testing exercise regimen	Reported MRS metabolites	Effects
Calf Muscles					
Back et al., 2000	n = 17 Mean age: 71.2 y 15 Male 2 Female Patients with Intermittent Claudication	EG (n = 13): 30–40 min of walking exercise. 2 sessions/ week CG (n = 4): Passive control 10 weeks	^{31}P-MRS Medial gastrocnemius (plus possibly soleus – slightly flexed knee) Well controlled test-retest analysis dynamic contraction $f_{EXE} = 0.25\ s^{-1}$ 25% MVC 10 min, 15–20 min rest and 85% MVC until fatigue	PCr Pi, β-ATP	No statistically significant differences in peak Pi, Pcr, or Pi/Pcr values or Pcr recovery characteristics
Bucci et al., 2016	$n = 37$ Mean age: 71.9 y Frail women offspring of obese/ overweight (OOM, $n = 17$) or lean/ normal weight (OLM, n = 20) mothers.	EG (n = 37): 60 min of resistance training (RT) upper/lower body at 50–80% 1-RM 3 sessions/ week No Control group. 16 weeks	^{1}H-MRS Tibialis anterior No testing exercise, resting muscle acquisition. Information on quality in previous publication	Intramyocellular lipid content (IMLC)	Significant decrease of IMLC from pretest to posttest in the OOM group ($p < 0.05$).
Hurley et al., 2019†	$n = 23$ Mean age: 67.0 y 4 Male 19 Female	EG (n = 13): 40 min of uphill walking at 70% HR reserve. CG(n = 10): Passive control 12 weeks.	^{31}P-MRS Calf muscle Controlled dynamic plantar flexion 100% MVC repetitions for 30 s at $f_{EXE} = 0.66\ s^{-1}$. 5 min recovery	PCr Pi	Significant increase in PCr recovery rate from baseline to posttest for EG ($p < 0.05$).
Slade et al., 2021	$n = 30$ Mean Age: 67.4 y 5 Male 25 Female Apparently healthy with a subset ($n = 14$) on chronic low-moderate Statin therapy	EG ($n = 15$): 40 min walking on a graded treadmill at 70% HR reserve CG (n = 15): Passive control 12 weeks	^{31}P-MRS Plantar flexors Dynamic plantar flexion for 30 s of 25% MVC at $f_{EXE} = 0.66\ s^{-1}$. 25% PCr drop.	PCr Pi	Significant Exercise group × Time interaction ($p < 0.05$) Increased in PCr recovery rate from baseline to posttest in the EG without Statin
Quadriceps muscles					
Berg et al., 2020	$n = 10$ Mean age: 75.0 y	EG (n = 10): Maximal strength training (MST) at 85%–90% 1-RM (knee extensors) 3 sessions/ week. No control group 8 weeks	^{31}P-MRS Quadriceps Well controlled, Isometric knee extension for 24 s at 100% MVC isotonic followed by 5 min recovery	PCr Pi	No statistically significant differences in resting levels of PCr, Pi, or pH. Slower PCr recovery time at post-MST compared to baseline ($p < 0.05$, $d = 0.55$)
Broskey et al., 2014	$n = 12$ Mean age: 65.6 y 7 Male 5 Female	EG ($n = 80$): 30–60 min of moderate-intensity aerobic training. 3 sessions/ week No control group. 16 weeks	^{31}P-MRS Quadriceps Well controlled Dynamic knee extension against adjusted rubber band at $f_{EXE} = 1\ s^{-1}$ for 22, 28, 36, 44 s Adjusted to 25–40% PCr drop	PCr Pi	Significant increase in PCr recovery rate ($p < 0.001$) and ATPmax, $p < 0.01$) from baseline to posttest.
McKeough et al., 2006	n = 10 Mean age: 68.0 y 6 Male 4 Female Patients with COPD	EG (n = 10) Combined leg cycling (20–30 min, 80% peak load), walking (20–30 min, 80% walking speed) and leg strength training (70% 1-RM). 2 sessions/ week No Control group 8 weeks	^{31}P-MRS Quadriceps Well controlled Dynamic knee extension 3 min of 60% MVC. 3 s extension/1 s relaxation 7 min recovery	PCr Pi ATP ADP	Significant increase in initial PCr resynthesis rate and significant improvement in PCr recovery half-time from baseline to posttest.

(*continued on next page*)

Table 2 (*continued*)

Reference	Sample	Intervention	MRS method & voxel location & testing exercise regimen	Reported MRS metabolites	Effects
van Tienen et al., 2012	n = 8 Mean age: 60.5 y All male with Type 2 Diabetes on EI treatment	EG (n = 8): Resistance training (weeks 0–22) and endurance + resistance training (weeks 22–52) No control group 52 weeks	^{31}P-MRS Vastus lateralis Dynamic incremental knee extension Up to 8 min to achieve 50% PCr drop at $f_{EXE} = 0.66\ s^{-1}$. May include fatigue if achieved before 8 min. At least 5 min recovery measured ^{1}H-MRS Vastus lateralis Resting muscle	PCr Intramyocellular lipid (IMCL) content	Significant increase in PCr recovery rate from baseline to posttest. No exercise-induced changes in IMCL content
Zhou et al., 2018	n = 6 Mean age: 63.7 y 1 Male 5 Female	EG (n = 6): 60 min of Tai Chi training, ≥2 sessions/ week. No control group 12 weeks	^{31}P-MRS Vastus medialis Well controlled Dynamic knee extension. Up to 3 min or until fatigue of 30% MVC repetition at $f_{EXE} = 0.5\ s^{-1}$ Or until fatigue	PCr	Significant decrease in PCr recovery time from baseline to post training scans ($p < 0.05$) indicative an enhanced oxidative capacity

† Reported as a randomized controlled trial (RCT).
*Acronyms:
EG: exercise group.
CG: control group.
RM: repetition maximum.

Zhou et al., 2018). All spectra were acquired on 3 Tesla MRI systems and neurometabolite concentrations were quantified with the LCModel software package (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016; Zhou et al., 2018). The quantified neurometabolites in all six studies using brain ^{1}H-MRS (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016; Zhou et al., 2018) were the ratios of total NAA to total creatine (tNAA/tCr) and in four studies (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Yang et al., 2016) pre-to-post changes in ratios of tCho to tCr (tCho/tCr) were reported. Regions of interest were the hippocampus (HPC) (Matura et al., 2017; Reitlo et al., 2023; Vints et al., 2024b; Yang et al., 2016), the sensorimotor cortex (SM1) (Sheoran et al., 2023), the dorsolateral prefrontal cortex (dlPFC) (Sheoran et al., 2023), dorsal anterior cingulate cortex (dACC) (Yang et al., 2016), and the posterior cingulate gyrus (PCG) (Zhou et al., 2018). Pooled data from the above-mentioned studies were analyzed post hoc to further characterize the effect of the different exercise interventions on these two principal neurometabolic ratios. Note that in Reitlo et al. (2023), MRS data were pooled from a mixed supervised exercise group (SEG) that underwent either high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT) and were then contracted to a control group that performed unsupervised moderate-intensity physical activity for ≥5 days/week. Because the MRS data could not be separated for HIIT versus MICT in the SEG group, a dose–response analysis could not be performed for these data.

Other reported ^{1}H brain metabolic ratios were the ratio of glutamate-glutamine to total creatine (Glx/tCr) (Sheoran et al., 2023; Yang et al., 2016), myo-inositol (mIns) to tCr (Sheoran et al., 2023; Vints et al., 2024b), tNAA to mIns (Sheoran et al., 2023; Vints et al., 2024b), and tNAA to tCho (Matura et al., 2017). Finally, in one study (Matura et al., 2017) ^{31}P MRSI acquisition was performed (in addition to ^{1}H MRSI and SVS ^{1}H MRS) to explore exercise-induced changes in brain energy metabolites (ATP, PCr, and Pi). One study (Yang et al., 2016) reported observation from edited MRS (using the MEGA-PRESS sequence) to examine exercise-induced changes in concentration of gamma-aminobutyric acid (GABA). One study (Matura et al., 2017) did not provide measures of spectral quality. For the remaining five studies, assessment of spectral quality was based on the evaluation of signal to noise ratio (SNR), Cramer-Rao lower bounds (CRLB), and/or water signal linewidths (see Supplementary Table S2 for details). For all five studies, the spectral quality and/or the quality of quantification were within the acceptable boundaries as outlined in the consensus paper by Lin et al. (2021).

3.2.2. *Muscle MRS*

Eight studies (Back et al., 2000; Berg et al., 2020; Broskey et al., 2014; Hurley et al., 2019; McKeough et al., 2006; Slade et al., 2021; van Tienen et al., 2012; Zhou et al., 2018) implemented dynamic ^{31}P MRS acquisition protocols for quantification of exercise-induced changes in muscle energy metabolites (ATP, PCr, Pi) and two studies (Bucci et al., 2016; van Tienen et al., 2012) used SVS ^{1}H-MRS acquisition protocols for quantification of changes in intramyocellular lipid (IMCL) content. Of the eight ^{31}P MRS studies, three focused on calf muscles (Back et al., 2000; Hurley et al., 2019; Slade et al., 2021) and five focused on the quadriceps muscles (Berg et al., 2020; Broskey et al., 2014; McKeough et al., 2006; van Tienen et al., 2012; Zhou et al., 2018). Notably, quadriceps and calf muscles exhibit distinct rates of intramuscular lipid infiltration across the lifespan, with differential susceptibility to age-related changes and metabolic perturbations in obesity and diabetes mellitus (Addison et al., 2014; Hilton et al., 2008; Yoshida et al., 2012). These compositional differences can substantially influence the dynamic characteristics of PCr recovery observed in both ^{31}P-MRS and ^{1}H-MRS acquisitions (Klepochová et al., 2025; Prompers et al., 2006; Sleigh et al., 2011). Consequently, data from these anatomically distinct muscle groups are presented separately in Table 2 to account for their inherent biochemical and metabolic heterogeneity.

The tested exercise regime during the dynamic ^{31}P MRS in all studies was a fatiguing exercise followed by a rest period that was conducted in the scanner. However, the protocols were diverse with respect to intensity and duration of the fatiguing exercise and the duration of the

recovery period. Specifically, of the eight studies implementing dynamic ^{31}P MRS protocols, three (Broskey et al., 2014; Slade et al., 2021; van Tienen et al., 2012) utilized exercise protocols designed to induce 20–50% depletion in PCr levels, whereas the remaining five (Back et al., 2000; Berg et al., 2020; Hurley et al., 2019; McKeough et al., 2006; Zhou et al., 2018) employed protocols with relatively high load (60–100% MVC) or targeting either complete force exhaustion or repeated fatigue-recovery cycles. Furthermore, there was diversity in the outcome measures used. Four studies reported pre-to-post exercise changes in PCr recovery rate (Broskey et al., 2014; Hurley et al., 2019; Slade et al., 2021; van Tienen et al., 2012), two reported PCr recovery time (Berg et al., 2020; Zhou et al., 2018), and two reported PCr recovery half-time (Berg et al., 2020; McKeough et al., 2006). The heterogeneous exercise testing regimens likely engaged different metabolic pathways, generating distinct intramuscular metabolic environments that differentially influenced phosphocreatine (PCr) recovery kinetics. This methodological heterogeneity fundamentally undermines quantitative data synthesis through pooling of PCr recovery kinetics profiles from the eight included studies, as the diverse experimental conditions produce non-comparable metabolic responses that confound interpretation of exercise-induced changes in mitochondrial capacity. Consequently, cross-study comparisons of PCr recovery kinetics in this review remain qualitative rather than quantitative in nature.

All ^{31}P MR spectra were acquired using either commercial (Berg et al., 2020; Broskey et al., 2014; Hurley et al., 2019; McKeough et al., 2006; Slade et al., 2021; van Tienen et al., 2012; Zhou et al., 2018) or custom built (Back et al., 2000) surface coils. In five of the nine studies (Berg et al., 2020; Broskey et al., 2014; Hurley et al., 2019; Slade et al., 2021; Zhou et al., 2018), spectra were acquired on a 3.0 Tesla MR system and in four studies a 1.5 Tesla MR scanner was used (Back et al., 2000; Bucci et al., 2016; McKeough et al., 2006; van Tienen et al., 2012). For the study of van Tienen et al. (2012) ^{31}P and ^{1}H MRS measurements and subsequent data analysis protocols were reported in a separate study (De Feyter et al., 2008). Quantified outcome measures were dynamic changes in PCr and Pi spectral peaks and the chemical shift between the Pi and PCr from which the pH response in the fatigue/recovery cycle was estimated using the Henderson-Hasselbach equation (Arnold et al., 1984). No quality control measures have been documented or reported for the muscle MRS. However, recent findings from meta-analysis (Singh et al., 2025) and a research study (Naëgel et al., 2023) combining findings from both health and patient groups showed that estimates of PCr recovery time in lower limb muscle are robust and provide an accurate assessment of PCr recovery kinetics.

3.3. *Effect of exercise training on brain MRS characteristics*

Observations from the six studies with brain MRS data are summarized in Table 1. The pooled effect estimates and confidence intervals for the effect of exercise for tNAA/tCr, tCho/tCr, Glx/tCr and mIns/tCr are illustrated in Figs. 2–5. In general, we found no consistent evidence that the exercise training interventions investigated had a significant beneficial effect on brain neurometabolic status, and this can be due to the fact that in some studies the participants receiving an exercise intervention had similar fitness levels to the participants considered as controls (e.g. Reitlo et al., 2023). Moreover, not all studies reported HPC volumes, another factor impeding data interpretation. Nevertheless, some trends were found that will be reported below.

3.3.1. *Total N-acetyl-aspartate*

The pooled effect estimates and confidence intervals for the ratio of tNAA to tCr are illustrated in Fig. 2, revealing mixed effects. Regarding the effect of the exercise on hippocampus, one study (Vints et al., 2024b) reported an increase of hippocampal tNAA/tCr (d = 0.48) from baseline to post-test, one study (Yang et al., 2016) reported a decrease of hippocampal tNAA/Cr (d = −0.58) and one study (Matura et al., 2017) reported no effect of exercise (d = 0.00). For the other cortical regions,

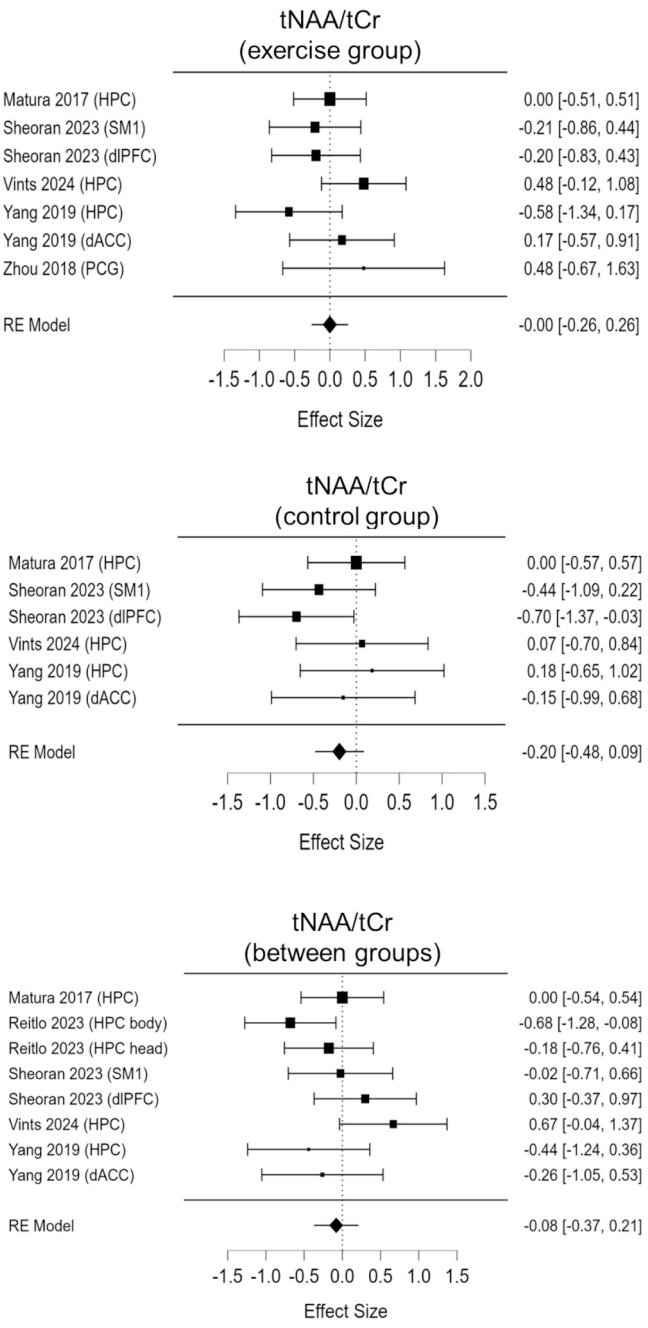

Fig. 2. Forest plots for brain total *N*-acetyl-aspartate (tNAA) to total creatine (tCr) ratio (tNAA/tCr). Effect sizes (Cohen's d) are presented separately for exercise group, control group and differences between group. Note: in the study of Reitlo et al. (2023) a supervised exercise group (SEG) of two subgroups implementing either a continuous exercise at about 70% of peak heart rate or HIIT at about 90% of peak heart rate was contrasted with a 'control' unsupervised exercise group that exercises at an intermediate intensity.

one study (Zhou et al., 2018) reported an increase of tNAA/tCr in the posterior cingulate cortex (d = 0.48) and two studies (Sheoran et al., 2023; Yang et al., 2016) showed no apparent changes in levels of tNAA/tCr (| d | ≤ 0.21). The mean effect size suggested no significant effect (d = −0.00, p = 0.997). Further, in five of the six studies (Matura et al., 2017; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016; Zhou et al., 2018) we analyzed the pre- to post-test changes of tNAA/tCr in the controls. Regarding the pre-to-post changes of tNAA/tCr in controls, one study revealed a decrease of tNAA/tCr (Sheoran et al., 2023), but there were no apparent changes in levels of tNAA/tCr otherwise (| d | ≤ 0.18),

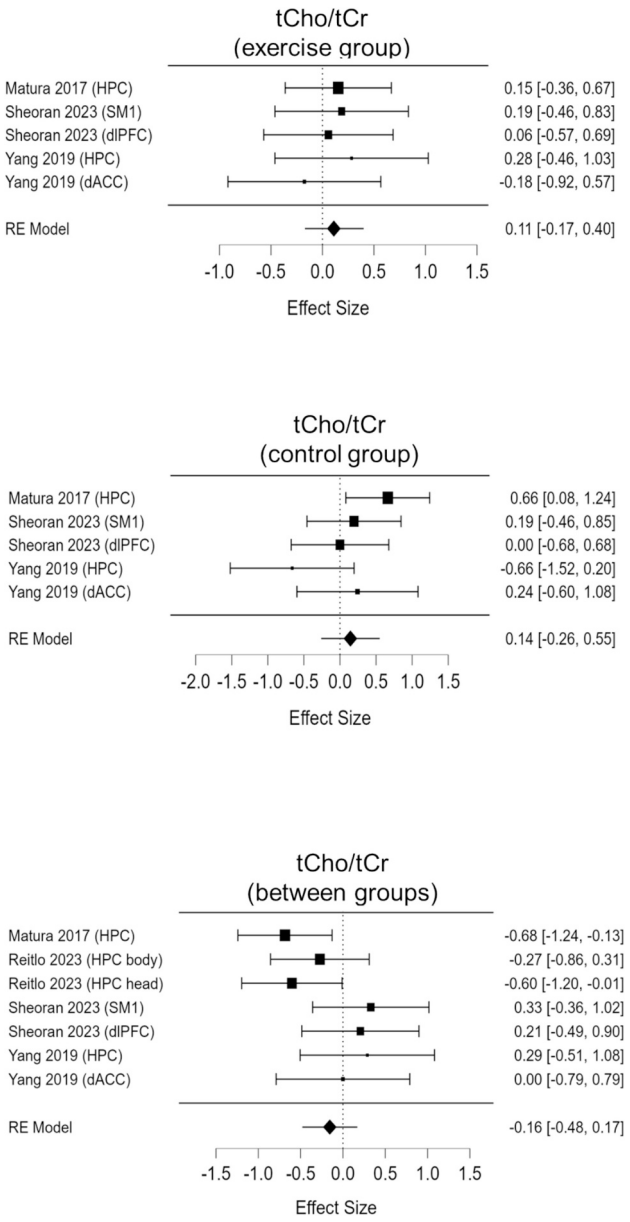

Fig. 3. Forest plots for brain total choline (tCho) to total creatine (tCr) ratio (Cho/Cr) (tCho/tCr). Effect sizes (Cohen's d) are presented separately for exercise group, control group and differences between group.

yielding an overall decrease with a small pooled effect size ($d = -0.20$, $p = 0.178$). Finally, we observed no significant group differences at post-test ($d = -0.08$, $p = 0.587$).

3.3.2. *Total choline*

The pooled effect estimates and confidence intervals for the ratio of total choline to total creatine (tCho/tCr) are illustrated in Fig. 3. The pooled effect showed no significant change in levels of tCho/tCr neither between nor within exercise and controls ($|d| \leq 0.16$, $p \geq 0.351$). A close inspection of the data showed large effects ($|d| \geq 0.60$) for lower hippocampal tCho/tCr levels in the intervention group compared to the control group at post-test (Matura et al., 2017; Reitlo et al., 2023). This effect may be attributed to an increase in hippocampal tCho/tCr ratio in passive control participants, as reported in Matura et al. (2017) (Fig. 3). In that study of cognitive healthy participants, the exercise stimulus was not sufficient to improve the peak aerobic capacity but improved cardiopulmonary efficiency (reflected in the significant improvement of the ventilatory threshold) while the lack of changes in tCho/Cr for the exercise participants was interpreted as a neuroprotective effect of exercise. Of note, the study of Reitlo et al. (2023) did not report within group effects while controls were as active as experimental participants, and in the study of Sheoran et al. (2023) MR spectra were extracted from cortical regions (SM1 and dlPFC). Finally, in the study of Yang et al. (2016), investigators used a mind-body intervention that appeared to combine low intensity movements with breathing exercises and posture maintenance in participants with mild cognitive impairment. In that latter study no information regarding fitness benefits of the "exercise" intervention perhaps due to the overall low intensity. In view of this heterogeneity of outcomes, and the lack of nutritional control in the above studies (given that exercise engagement increases choline demands), any interpretation of the pooled effect should be made with caution.

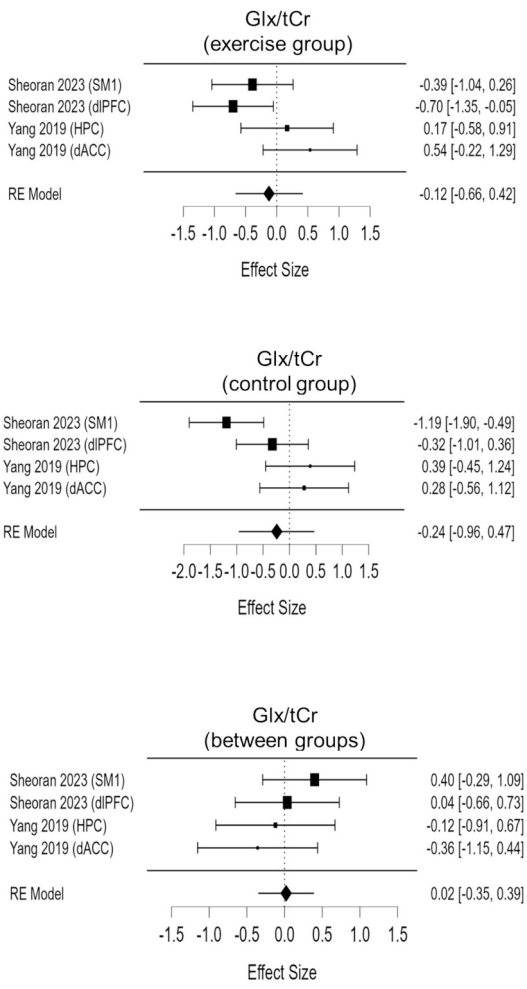

Fig. 4. Forest plots for brain glutamate-glutamine (Glx) to total creatine (tCr) ratio (Glx/tCr). Effect sizes (Cohen's d) are presented separately for exercise group, control group and differences between group.

3.3.3. *Glutamate-glutamine*

The pooled effect estimates and confidence intervals for the ratio of glutamate-glutamine complex to total creatine (Glx/tCr) are illustrated in Fig. 4. A significant decrease in dlPFC Glx/tCr ratio with a large effect size ($d = -0.70$) was found in a study where effects of progressive resistance training intervention was studied (Sheoran et al., 2023) (see Fig. 4). However, findings from the same study reported a similar decrease in SM1 Glx/tCr in the control group ($d = -1.09$) and no between-group effect, neither for dlPFC Glx/tCr nor for SM1 Glx/tCr ratios. Finally, findings from a second study (Yang et al., 2016) reported

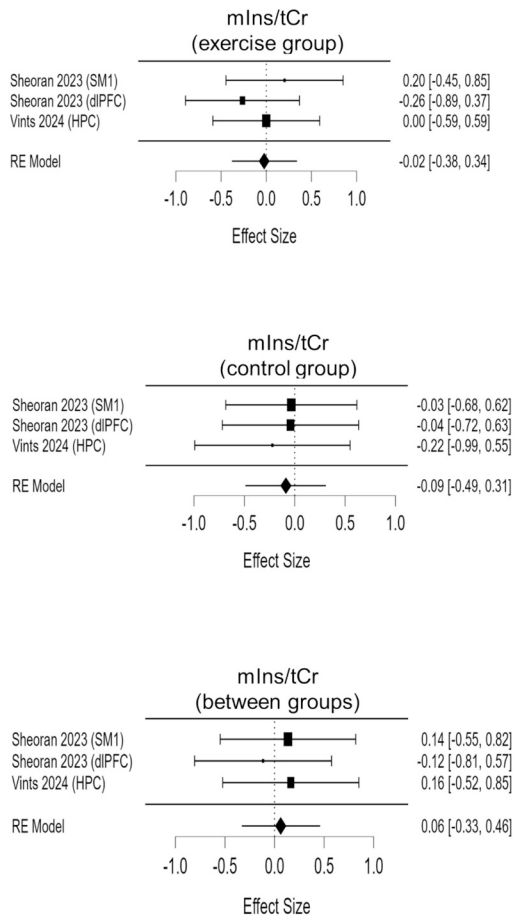

Fig. 5. Forest plots for brain myoinositol (mIns) to total creatine (tCr) ratio (mIns/tCr). Effect sizes (Cohen's d) are presented separately for exercise group, control group and differences between group.

no exercise-related changes in Glx/tCr.

3.3.4. Myo-inositol

The effects of chronic physical activity interventions on the myo-inositol to total creatine (mIns/tCr) ratio were reported in the study by Vints et al. (2024b) for the left hippocampus, and by Sheoran et al. (2023) for the left SM1 and right dlPFC (see Fig. 5). The combined findings from these two studies, which involved the same cohort of participants, showed no exercise-related changes or between group effects (all $|ds| < 0.22$). However, a closer examination of the findings from Vints et al. (2024b) indicated that, while the overall pre-to-post changes in mIns/tCr in the exercise group were negligible, subdividing the group into low and high MCI risk revealed an average 3.7% decrease in hippocampal mIns/tCr among participants with high MCI risk, with no measurable changes observed in the low MCI risk subgroup. Interestingly, a similar decrease in mIns/tCr was observed in the control group, with the high MCI risk subgroup showing a 5.8% reduction and the low MCI risk subgroup a 2.7% reduction. Importantly, none of these changes reached statistical significance.

3.3.5. Other neurometabolites

Effects of chronic physical activity interventions on the expression of other ^{1}H-MRS brain neurometabolites were reported, including: hippocampal tNAA/Cho (Matura et al., 2017), hippocampal tNAA/mIns (Vints et al., 2024b) and GABA/tNAA (Yang et al., 2016) in the dACC. Findings from these three studies revealed a significant group effect for hippocampal tNAA/Cho (Matura et al., 2017) but no evidence for any exercise-related changes in the other neurometabolite ratios (i.e., tNAA/mIns and GABA/tNAA). Finally, in one study 2D ^{31}P-MRS imaging was used to examine exercise-related changes in the concentrations or ratios of phosphorus-containing metabolites (e.g., PCr, ADP, ATP, Pi) (Matura et al., 2017). Again, no significant effects or trends were observed.

3.4. Effect of exercise training on muscle MRS characteristics

Our observations included data extracted from eight studies where phosphorus-containing metabolites in calf (Back et al., 2000; Hurley et al., 2019; Slade et al., 2021; van Tienen et al., 2012) or quadriceps muscles (Berg et al., 2020; Broskey et al., 2014; McKeough et al., 2006; Zhou et al., 2018) were evaluated with ^{31}P-MRS and two studies where the content of intramyocellular lipid (IMCL) was evaluated with ^{1}H-MRS (Bucci et al., 2016; van Tienen et al., 2012). The reviewed studies used different exercise interventions, with variable intensities and differing emphasis on the strength-endurance continuum. For details see Table 2.

3.4.1. Phosphorus-containing metabolites

Overall, observations supported the expectation that chronic exercise improves the metabolic proficiency of muscles. Specifically, seven of eight studies with ^{31}P muscle MRS reported improvements in PCr recovery kinetics from baseline to post-intervention time (Berg et al., 2020; Broskey et al., 2014; Hurley et al., 2019; McKeough et al., 2006; Slade et al., 2021; van Tienen et al., 2012; Zhou et al., 2018). These improvements were expressed by an increase in post-exercise PCr recovery rate from baseline to post-test (Broskey et al., 2014; Hurley et al., 2019; Slade et al., 2021; van Tienen et al., 2012), an increase in initial PCr resynthesis rate (McKeough et al., 2006) or decrease in post-exercise PCr recovery time (Berg et al., 2020; Zhou et al., 2018), irrespective to whether baseline phosphorus metabolite levels were affected. In addition to improvement of PCr recovery, findings from one included study (Broskey et al., 2014) reported an improvement in the maximal rate of oxidative ATP synthesis, which was calculated as ATPmax using the rate constant of PCr recovery multiplied by the baseline [PCr] concentration. Finally, one study (Back et al., 2000) reported no significant finding in any of the examined ^{31}P-MRS properties. Taken together, these observations pointed at the improvement of muscle oxidative metabolism.

3.4.2. IMCL

Two studies (Bucci et al., 2016; van Tienen et al., 2012) used ^{1}H-MRS to examine the effect of chronic exercise interventions on the content of IMLC. The findings from these studies gave inconclusive results. On the one hand, a significant reduction of IMCL ($p = 0.043$) was observed in offspring of obese/overweight mothers but not in offspring of lean/normal weight mothers after the two groups underwent a training protocol where moderate to vigorous resistance training exercise was applied for 16 weeks (Bucci et al., 2016). On the other hand, van Tienen et al. (2012) reported no significant effect of exercise on the content of IMCL in a group of 8 participants with type 2 diabetes mellitus who underwent a training program combining 22 weeks of moderate resistance training and 30 weeks of combined moderate endurance and resistance training.

3.5. Associations between MRS markers and behavioral/physiological outcomes

In six of the 14 included studies (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; McKeough et al., 2006; van Tienen et al., 2012), observations were reported regarding the effect of exercise on the associations between MRS markers and behavioral or physiological markers. Overall, observations from these studies showed that exercise-induced changes in levels of metabolites or metabolic ratios in the brain or muscle were accompanied by changes in cognitive status (Reitlo et al., 2023), behavioral outcomes (Sheoran et al., 2023; McKeough et al., 2006), blood circulation properties (Matura et al., 2017; Vints et al., 2024b), and structural/histological properties of brain

and muscles (Vints et al., 2024b; van Tienen et al., 2012). Regarding the brain, associations were found between: (1) high tNAA/tCr ratio and better scoring on the Montreal Cognitive Assessment (MoCA) and Hospital Anxiety and Depression Scale (HADS) assessments (Reitlo et al., 2023), (2) increase in Glx/tCr and mIns/tCr and increase of muscle strength in responders to a 12-weeks progressive resistance training program (Sheoran et al., 2023), (3) decrease of hippocampal tNAA/mIns with increase of hippocampus CA1 subfield volume (Vints et al., 2024b), (4) increase in PCr recovery rate and muscle force production capacity (McKeough et al., 2006) and mitochondrial density (van Tienen et al., 2012).

4. Discussion

The objective of this scoping review was to provide a preliminary evaluation of the existing research on the effects of exercise training on muscle and brain metabolism in older adults assessed by MRS. Specifically, we aimed to summarize which MRS methods are used, which metabolites can be measured, and is there sufficient evidence to recommend exercise based on MRS findings. Our systematic search identified only 14 published studies that investigated the effects of exercise on brain and muscle metabolites using magnetic resonance spectroscopy. The reviewed literature focused only on chronic exercise effects. This is because (1) ^{1}H-MRS studies on the immediate impact of acute exercise on GABA, glutamate, and lactate levels primarily involved young adults (e.g., Coxon et al., 2018; Maddock et al., 2011, 2016; Ryberg et al., 2023) or middle-aged cohorts (Gonzales et al., 2013). (2) ^{31}P-MRS studies that assessed phosphocreatine depletion and recovery during exercise were conducted without any intervention and did not directly address metabolic changes related to exercise. Therefore, we included only data that were collected from muscle and/or brain before and after chronic exercise training interventions, whether those interventions were deemed successful or not from an exercise physiology point of view.

All brain-related studies employed ^{1}H-MRS. However, due to inadequate and inconsistent reporting, we were unable to create a framework to guide evidence-based recommendations for exercise characteristics intended to improve brain health. For muscle-related studies, the technique used included ^{31}P-MRS before, during and after the execution of an exercise challenging protocol. Most of these studies observed a significant increase in the phosphocreatine (PCr) resynthesis rate following the intervention, suggesting that chronic exercise interventions improved metabolic efficiency and oxidative capacity. However, the diversity of protocols employed in implementing the exercise challenge restricted our ability to develop a dose-response model based on the PCr findings. A summary of the findings from this scoping review is presented in Box 2.

4.1. Effect of exercise training on brain metabolite profile

Neurometabolites that are potentially affected by exercise are tNAA (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016; Zhou et al., 2018) and tCho (Matura et al., 2017; Reitlo et al., 2023; Sheoran et al., 2023; Vints et al., 2024b; Yang et al., 2016). However, significant variability in training and testing protocols, along with inconsistent effects of exercise on these metabolites, hinder definitive conclusions about exercise's impact on brain neurometabolic status. Additionally, not all 'exercise' interventions adhered to exercise physiology design principles, and in some cases exercise activities were of too low an intensity to be expected to confer physical fitness benefits (e.g., Yang et al., 2016). Likewise, not all 'control' conditions included non-exercising people, and in one study the controls were as active, and thus as fit, as the supervised exercise participants (Reitlo et al., 2023). Other confounding factors may include variations in participants' health status (e.g., mild cognitive impairment versus apparently healthy older adults), which can influence baseline neurometabolic levels, as well as changes related to the specific locations and functions of the scanned brain regions.

Our findings also highlight the importance of exercise intensity in overall prescription of exercise. To illustrate this, we refer to two studies that examined exercise-induced changes in brain neurometabolites following 12 weeks of body-mind protocols (kundalini yoga + meditation or tai chi) (Yang et al., 2016; Zhou et al., 2018). These studies found no significant exercise-induced changes in tNAA/tCr levels, contrasting with 12-week strength training studies (Sheoran et al., 2023; Vints et al., 2024b) that demonstrated pre-to-post exercise increases in hippocampal tNAA/tCr levels. Notably, control group participants in these resistance training studies experienced significant tNAA/tCr declines across multiple regions, highlighting exercise's protective role against age-related neuronal decline. Collectively, these findings suggest that lack of exercise exerts widespread negative effects on brain health in older adults. These observations are further supported by MRI evidence from the same participant cohorts (or subsets). For example, Vints et al. (2024b) identified a significant positive correlation between resistance exercise-induced increases in hippocampal tNAA/tCr and volumetric expansion in the CA1 subregion. Similar associations between hippocampal volume and tNAA/tCr increases were reported in studies of middle-aged adults (Den Ouden et al., 2018) and adults with schizophrenia (Pajonk et al., 2010), both following 12-weeks of aerobic training. Overall, these findings suggest that pre-to-post increases in tNAA/tCr can serve as a marker for exercise-induced improvements in neuronal integrity and brain health. Notably, the tNAA peak includes *N*-acetylaspartylglutamate (NAAG), which cannot be distinguished separately at 3 T or lower-field scanners. As NAAG participates in neurotransmission and serves as a potential neuroplasticity biomarker (Tyson and Sutherland, 1998; Zuo et al., 2012), investigating how exercise modulates NAAG independently of NAA could yield valuable insights into exercise-induced neuroplastic changes. To date, however, no studies have examined the effects of physical activity or exercise on brain NAAG levels.

Concerning the observations related to tCho, we found no explicit exercise-induced effects on the levels of this neurometabolite or its ratios to tCr in any of the intervention groups across the six studies. However, two studies (Matura et al., 2017; Reitlo et al., 2023) found that the group undergoing the exercise intervention exhibited lower tCho/tCr ratios compared to the control group at the end of the intervention. In a healthy older adult population, elevated levels of choline or an increased

Box 2
Summary of findings.

- Our findings highlighted two MRS techniques: ^{1}H-MRS, primarily utilized to evaluate the impact of physical activity interventions on brain metabolic status, and ^{31}P-MRS, mainly used to assess the effects of these interventions on muscle metabolic status.
- Key brain biomarkers assessed with ^{1}H-MRS were tNAA a marker for neuronal health and density and tCho which is often taken as a marker of neuroinflammation or cell damage in aging population.
- Findings from brain ^{1}H-MRS studies suggest that physical activity interventions may offer protective benefits for brain health. However, the limited number of studies prevented us from drawing final conclusions about the specific effects of exercise on the studied brain neurometabolites.
- ^{31}P-MRS was applied primarily to examine the effects of chronic exercise training interventions on the muscle. Key muscle biomarkers assessed included the levels of adenosine triphosphate (ATP), inorganic phosphate (Pi), creatine phosphate (PCr), and PCr resynthesis rate. Two studies utilized ^{1}H-MRS to investigate exercise-induced changes in the intramyocellular lipid (IMCL) content of the muscle.
- Most studies using muscle ^{31}P-MRS indicated a significant improvement in PCr resynthesis. However, there are insufficient data sets to establish a dose-response relationship for this metabolite. Findings regarding exercise-induced changes in IMCL remained inconclusive.

ratio of choline to creatine may reflect increased cell membrane synthesis and turnover which often occur during inflammatory processes as cells respond to injury or stress (e.g., Chang et al., 2013; Vints et al., 2022a). Furthermore, elevated tCho/tCr may suggest ongoing neuroinflammation which can be associated age-related neurodegenerative disorders such as Alzheimer's diseases (e.g., Kantarci, 2013; Marjańska et al., 2019; Song et al., 2021). Therefore, a lower tCho/tCr ratio in the experimental group compared to the controls at the end of the intervention can be interpreted as a marker of the neuroprotective effects of exercise on brain health.

Similar to tCho, elevated levels of mIns or mIns/tCr are considered as indicatives of neuroinflammation and compromised brain health (Chang et al., 2013; Kantarci, 2013; Marjańska et al., 2019; Song et al., 2021; Valatkevičienė et al., 2023; Vints et al., 2022a; Vints et al., 2023). Additionally, studies have shown that elevated mIns levels in various brain regions are associated with higher concentrations of pro-inflammatory markers, including interleukin-6 (IL-6) (Vints et al., 2022a), C-reactive protein (CRP) (Lind et al., 2021), and kynurenine (Vints et al., 2022a). Findings from one of the studies included in this scoping review (Vints et al., 2024b) partially supported the existence of associations between brain neurometabolites and blood-based biomarkers of inflammation (e.g., Lind et al., 2021; Vints et al., 2022a). However, the findings did not support the hypothesis of exercise-induced decreases in mIns levels. Specifically, the study revealed a general decline in hippocampal mIns/tCr levels in the control group, whereas mIns/tCr levels in the exercise group remained unchanged. Additionally, Vints et al. (2024b) provided evidence suggesting a potential role for mIns (and glial cells) in hippocampal volume increases (e.g., Ekdahl et al., 2009). Their findings also indicated a triad relationship between lower kynurenine levels, higher mIns/tCr levels, and larger total hippocampal volume. While these trends were not statistically significant, they highlight the need to reconsider the interplay between exercise and neuroinflammation. It is important to note that, to date, only the cohorts studied by Vints et al. (2024b) and Sheoran et al. (2023) have specifically examined pre-to-post changes in mIns levels following chronic exercise interventions. As a result, current evidence remains insufficient to conclusively determine how exercise affects mIns levels or whether exercise-induced changes in mIns are indicative of improvements in brain health. It is important to note that the consistency of mIns measurements across repeated assessments is generally lower than that of other metabolites such as tNAA, tCho, and tCr (e.g., Vints et al., 2022a), This variability may contribute to the inconclusive findings regarding the effects of exercise on mIns levels.

GABA and glutamate are two major neurotransmitters that play critical roles in exercise-induced neuroplasticity. Due to their low concentration and spectral overlap with other metabolites, their levels are typically quantified using edited MRS techniques, such as MEGA-PRESS (Mescher-Garwood Point Resolved Spectroscopy) (Mescher et al., 1998), which allow for robust quantification of these neurotransmitters. Studies using ^{1}H-MRS have previously investigated the effect of a single bout of high-intensity cardiovascular exercise on cortical levels of GABA and glutamate in young healthy adults (e.g., Coxon et al., 2018). Overall, these studies showed rapid regional modulations of GABA levels that were located primarily in the sensorimotor cortex. However, these studies were performed only on young adults and therefore were not included in this scoping review.

Finally, two studies (Sheoran et al., 2023; Yang et al., 2016) investigated the effect of exercise training interventions on Glx/tCr. Despite implementing different types of interventions, both studies reported no exercise-induced changes in Glx/tCr within the exercise groups or any significant differences between groups. These findings contrast with the hypothesis that exercise-related improvements in cognitive functioning are at least partly mediated by increases in regional glutamate. A closer examination of the study by Sheoran et al. (2023) revealed that Glx/tCr remained stable in the exercise group after 12 weeks of resistance training, while controls showed a significant decline in Glx/tCr over the same period. This observation suggests once more that certain types of exercise interventions may have a protective effect on brain health. It is important to acknowledge that precise quantification of glutamate-glutamine complex remains challenging, primarily due to spectral overlaps with other metabolites and the inherent limitations associated with short echo time magnetic resonance spectroscopy protocols (e.g., Bednařík et al., 2015; Geurts et al., 2004). Finally, the quantification of Glx has been shown to be least robust among post-processing tools (e.g., Vints et al., 2022a). These methodological constraints may contribute to the inconsistent and inconclusive findings observed in the studies examining the effects of exercise on Glx.

4.2. *Effect of exercise training on muscle metabolite profile*

Regarding studies involving muscle MRS, most of the research conducted used ^{31}P-MRS to quantify the effect of chronic exercise on the recovery (resynthesis) of phosphocreatine (PCr) (Back et al., 2000; Berg et al., 2020; Broskey et al., 2014; Hurley et al., 2019; McKeough et al., 2006; Slade et al., 2021; van Tienen et al., 2012; Zhou et al., 2018). In a minority of studies, ^{1}H-MRS was implemented to quantify the effect of chronic exercise on content of intramyocellular lipid (Bucci et al., 2016; van Tienen et al., 2012). The studies included in this review encompassed diverse participant cohorts, ranging from apparently healthy older adults (e.g., Vints et al., 2024b) to those with chronic conditions such as COPD (McKeough et al., 2006) and diabetes (van Tienen et al., 2012). Additionally, the studies examined various types of exercise training regimes. Despite this diversity, the outcome measures assessed using ^{31}P-MRS consistently demonstrated robust findings, indicating that the interventions effectively improved mitochondrial function. These findings align with observations from other systematic reviews highlighting the beneficial effects of exercise training in enhancing mitochondrial function and modulating muscle fiber energetic capacity in athletes (e.g., Hug et al., 2006; Pesta et al., 2013) and health young adults (e.g., Forbes et al., 2008; Hoff et al., 2013). The exercise intensity among the included studies ranged from light (e.g., Zhou et al., 2018) to moderate (e.g., Broskey et al., 2014; Bucci et al., 2016), and from moderate to vigorous (e.g., Berg et al., 2020; McKeough et al., 2006). However, due to the limited number of studies and the variability in duration, intensity, and types of interventions, as well as the variability of the testing exercise challenge for the dynamic ^{31}P MRS measurement, it was not possible to establish a dose-response relationship between exercise volume and the observed exercise-induced gains.

Finally, two studies (Bucci et al., 2016; van Tienen et al., 2012) used 1H-MRS to examine the effect of chronic exercise interventions on IMLC content. However, findings were inconsistent and cannot be generalized, due to considerable heterogeneity in subject populations (type 2 diabetes versus apparently healthy older adults), exercise regimens (16 weeks of resistance training versus 22 weeks of resistance training followed by combined endurance-resistance training), and muscle groups (tibialis anterior versus vastus lateralis). Moreover, technical challenges inherent to ^{1}H-MRS may have further contributed to these discrepancies, including difficulty in achieving adequate spectral resolution to separate overlapping IMCL and extramyocellular lipid (EMCL) peaks (Boesch and Kreis, 2000), variability in the orientation of muscle fibers relative to the static magnetic field (B_0) and shimming quality across measurements (Kršňák et al., 2021). These technical factors can substantially influence quantification accuracy and reproducibility, thereby compounding interpretation of intervention effects. The same challenges can also affect the quantification of other ^{1}H MRS muscle biomarkers, such as carnosine (Baguet et al., 2011a; Bex et al., 2017; Derave et al., 2010; Just Kukurová et al., 2016; Lievens et al., 2021; Ozdemir et al., 2007) and acetylcarnitine (Lindeboom et al., 2014). Carnosine, a dipeptide concentrated in fast-twitch fibers and higher in men (Just Kukurová et al., 2016; Posa et al., 2023), serves as a non-invasive marker for exercise-induced fiber-type changes (Derave et al., 2010; Ozdemir et al., 2007) and potential sarcopenia indicator, as its levels decline with age

alongside muscle mass/function (Gasmi et al., 2025; Posa et al., 2023). Acetylcarnitine, detected at long echo times (Lindeboom et al., 2014, 2017), correlates with insulin sensitivity and phosphocreatine metabolism (Klepochová et al., 2024; Lindeboom et al., 2014), making it valuable for studying exercise benefits in obese/diabetic patients. Despite their promise, no studies have yet used ^{1}H-MRS to assess exercise-induced effects on these two muscle metabolites in the aging population.

4.3. Limitations, knowledge gaps, and further directions

While MRS studies have indicated that it is a useful method to assess exercise-induced changes in aging brain and muscle metabolic profiles, the evidence included in this scoping review regarding the use of MRS to assess exercise-induced changes in brain and muscle metabolic profiles is limited by the small number of studies and significant variability in technical approaches, exercise intensity, exercise type, modality and duration of interventions. In many cases there is no clarity whether the physical activity or exercise intervention was successful or not in conferring fitness benefits, which is counterintuitive in any effort to establish neuroprotective lifestyle approaches. Another limitation of the present work was the reliance on a limited number of image acquisition methods, primarily involving proton (^{1}H) and phosphorus (^{31}P) MRS spectra acquired at 3 T. While these methods are considered standard and reliable for measuring key metabolites such as tNAA, tCho and tCr in the brain and PCr in muscle, they are limited in their ability to detect other metabolites and neurotransmitters due to their low concentrations (e.g., carnosine) or overlapping spectral peaks (e.g., GABA and NAAG). This limitation can be addressed by employing edited MRS techniques for the detection of specific low-level metabolites like GABA and glutathione (e.g., DeMayo et al., 2025; Michels et al., 2024), by using high-field MRS scanners, such as 7 T, to improve the separation of glutamate and glutamine peaks (e.g., Brandt et al., 2016; Hone-Blanchet et al., 2023; Oeltzschner et al., 2019) or novel tracer techniques such as DMI (Bednarik et al., 2023; De Feyter et al., 2018). Furthermore, most of the included studies utilizing brain MRS reported only the hippocampal tNAA/tCr and tCho/tCr ratios as primary outcome measures. Focusing solely on these two metabolite ratios limits the interpretability of the findings, as other metabolites and ratios—such as mIns, Glx, and tNAA/mIns—also appeared to be affected by the intervention (Sheoran et al., 2023; Vints et al., 2024b).

Most studies included in this scoping review comprised mixed-sex populations of male and female participants. Potential sex differences in outcomes were not examined or reported. Given established sex differences in brain structure, hormonal influences, and neurodegenerative disease susceptibility (Cosgrove et al., 2007; Ritchie et al., 2018), this represents an important gap in the literature. However, the limited number of available studies included in this review makes it difficult to systematically analyze sex-specific patterns. This highlights a critical direction for future MRS aging research, as recent evidence suggests that sex may modulate age-related brain metabolite trajectories (Gao et al., 2013). Similarly, the scarcity of studies specifically examining sex-stratified patterns of exercise-induced effects on intramuscular fat accumulation represents an important gap in the muscle MRS literature. For instance, Goodpaster et al. (2001) demonstrated significant sex differences in thigh muscle composition in the Health ABC Study, with older women showing greater intramuscular fat infiltration than men, even after adjusting for total body fat percentage. This underscores the need for sex-specific analyses in future metabolic muscle MRS studies of aging populations.

Another challenge is forcing the assumption that any changes may be uniform, and thus detectable, over the whole brain and not controlling for a diffuse infiltrative component as indicated in studies examining contralateral hemisphere variations of tNAA/tCr and tCho/tCr (e.g., Davitz et al., 2017, 2019). Apparently, certain neurometabolites demonstrated region-specific responsiveness to intervention, indicating that exercise may exert differential effects on neurometabolic processes across various brain areas. Standardizing exercise protocols and expanding the scope of neurometabolite monitoring would facilitate more meaningful comparisons between studies and contribute to a more comprehensive understanding of how exercise influences neurochemical and metabolic functioning in both the brain and muscle. In this regard, we wish to highlight the substantial heterogeneity in exercise testing protocols as a major limitation, which hindered our ability to quantitatively assess exercise-induced effects on PCr recovery kinetics through data pooling. Another challenge in evaluating the role of MRS for quantifying exercise-induced changes in muscle metabolic and structural characteristics was the insufficient number of studies employing muscle ^{1}H-MRS included in this review (Bucci et al., 2016; van Tienen et al., 2012). The use of muscle ^{1}H-MRS techniques in future studies could eliminate the need for muscle biopsies to estimate the long-term effects of exercise on lipid content and muscle fiber-type populations. This would make future assessments of muscle properties more adequate for research involving older adults, as this population may be more vulnerable and less willing to participate in studies requiring biopsy collection.

Finally, future research should consider adopting a multimodal neuroimaging approach to better understand and describe relationships between neurometabolic changes and other neuroadaptive processes. For example, using direct ^{13}C-MRS and indirect ^{1}H-[^{13}C] MRS can be employed to investigate cerebral metabolic pathways involved in the synthesis of glutamate and GABA which are principal neurotransmitters in the mammalian brain (An et al., 2022; de Graaf et al., 2003; Rothman et al., 2019). The scarcity of multimodal neuroimaging studies using MRS in healthy aging research limits our understanding of the mechanisms underlying exercise-induced cognitive and motor improvements, as well as the potential adverse effects. This knowledge gap also hinders the ability to establish dose-response relationships and to comprehend the complex interplay among various mechanisms involved in neuroadaptation to exercise, such as neurotrophic, anti-inflammatory, and pro-inflammatory processes (Vints et al., 2022b). Some recent studies have begun to integrate blood biomarkers with multimodal neuroimaging, revealing interactions between gray matter alterations, neuroinflammation, and cognitive function (Vints et al., 2024b). Expanding this multidisciplinary approach in future research will be crucial for advancing our understanding of the underlying neurobiological mechanisms and optimizing exercise interventions for healthy aging. Fig. 6 presents a proposed structured framework for developing study designs to systematically address these knowledge gaps.

5. Conclusion

This scoping review offers an initial overview of the literature examining studies that utilized MRS to investigate neurochemical changes in brain and muscle tissue following chronic exercise in aging populations. In terms of brain adaptations, findings underscoring the neuroprotective effect of physical activity/exercise on brain health appear to be promising. However, the variable, and often poor, design of exercise interventions, the lack of clear fitness indicators and a lack of sufficient experimental data from MRS studies make it difficult to support evidence-based recommendations on the specific exercise characteristics that optimize brain health. In terms of muscle adaptations, the findings from this review indicate that both aerobic and resistance training approaches can significantly enhance mitochondrial function in muscle tissue and provide some benefits to muscle metabolic profiles and function; findings that corroborate the other available literature on muscle metabolism. Future prospective studies should be designed with rigorous methodological planning that specifies (1) the intervention type and appropriate control conditions, (2) intervention volume, (3) standardized MRS acquisition and processing protocols, and (4) the inclusion of physiological and behavioral outcomes. This design standardization will enable reliable dose–response assessments for muscle

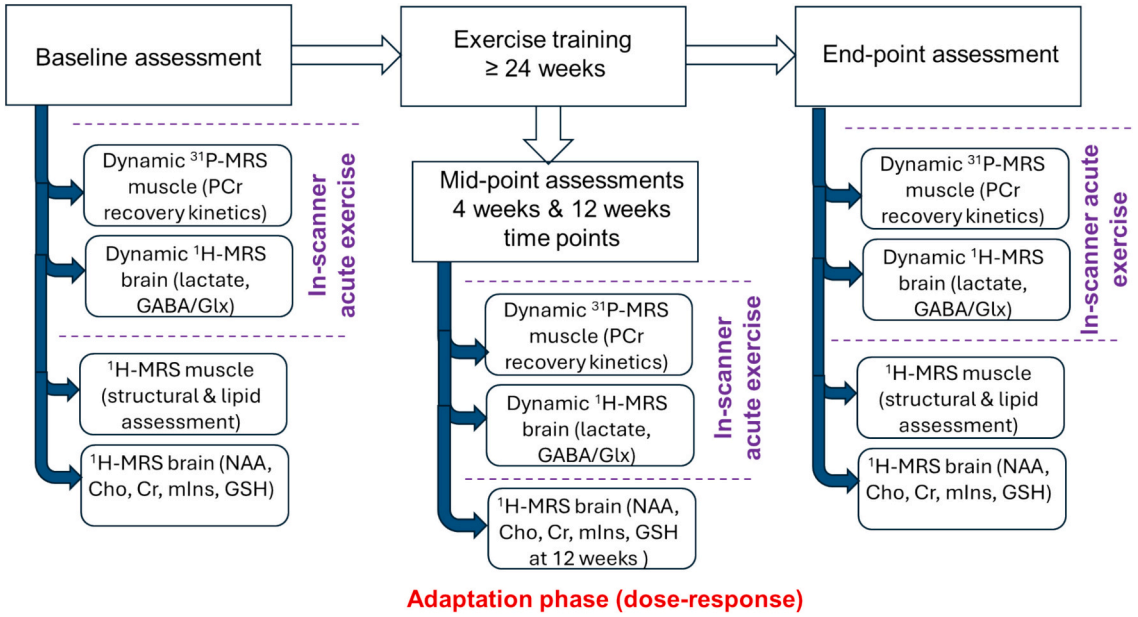

Fig. 6. Schematic framework that proposes a comprehensive study design for evaluating exercise training effects on metabolic and structural properties in brain and skeletal muscle through advanced magnetic resonance spectroscopy techniques. Methodology: (i) Phosphorus-31 MRS (^{31}P-MRS) for in-scanner assessment of phosphocreatine (PCr) recovery kinetics in skeletal muscle. (ii) Edited Proton MRS (^{1}H-MRS) for quantification of brain metabolites including lactate, γ-aminobutyric acid (GABA), and glutamate/glutamine complex (Glx) using spectral editing sequences (e.g., MEGA-PRESS; Coxon et al., 2018). (iii) Single voxel ^{1}H-MRS for assessment of longitudinal changes in brain and muscle metabolites. Assessment Timepoints: Baseline, 4 weeks (early adaptation), 12 weeks (late adaptation), and end-of-intervention (chronic adaptations).

and brain metabolites and clarify their roles as markers of exercise effects in aging and age-related disease conditions.

CRediT authorship contribution statement

Oron Levin: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ivica Just:** Writing – original draft, Investigation, Data curation. **Radka Klepochova:** Writing – original draft, Investigation, Formal analysis, Data curation. **Shannon Helsper:** Writing – original draft, Investigation, Data curation. **Wouter Vints:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ana Filipa Silva:** Writing – original draft, Investigation, Data curation. **Antoine Langeard:** Writing – original draft, Investigation, Data curation. **Salit Bar Shalom:** Writing – original draft, Investigation, Data curation. **Christina Karatzaferi:** Writing – original draft, Investigation, Data curation. **Maryam Ziaei:** Writing – original draft, Investigation, Data curation. **Michel Audiffren:** Writing – original draft, Investigation, Data curation. **Claudia Voelcker-Rehage:** Writing – original draft, Investigation, Data curation. **Yael Netz:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Nerijus Masiulis:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Uwe Himmelreich:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Martin Krššák:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2026.113082.

Data availability

Data will be made available on request.

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