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Methionine restriction - Association with redox homeostasis and implications on aging and diseases

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ABSTRACT

Methionine is an essential amino acid, involved in the promotion of growth, immunity, and regulation of energy metabolism. Over the decades, research has long focused on the beneficial effects of methionine supplementation, while data on positive effects of methionine restriction (MR) were first published in 1993. MR is a low-methionine dietary intervention that has been reported to ameliorate aging and aging-related health concomitants and diseases, such as obesity, type 2 diabetes, and cognitive disorders. In addition, MR seems to be an approach to prolong lifespan which has been validated extensively in various animal models, such as *Caenorhabditis elegans*, Drosophila, yeast, and murine models. MR appears to be associated with a reduction in oxidative stress via so far mainly undiscovered mechanisms, and these changes in redox status appear to be one of the underlying mechanisms for lifespan extension and beneficial health effects. In the present review, the association of methionine metabolism pathways with redox homeostasis is described. In addition, the effects of MR on lifespan, age-related implications, comorbidities, and diseases are discussed.

1. Introduction

Disturbed redox homeostasis is closely related to aging and metabolic dysfunction and is influenced by diet and energy intake, with the organism adapting to changes in nutrients available in the environment. A network of nutrients and nutrient-sensing pathways regulates metabolism, growth, and aging. As a dietary intervention, caloric restriction (CR), without causing malnutrition, is recognized as an experimental method capable of prolonging lifespan and positively affecting metabolic health and various diseases of the organism, such as obesity, type 2 diabetes, and cardiovascular disease [1], partly by reducing cellular oxidative stress [2–5]. However, it is difficult for individuals to stick to CR for decades. With increasing evidence that protein restriction (PR) may extend lifespan and reduce the risk of age-related diseases, numerous studies have focused on investigating the role of amino acids in the diet [6–8]. Studies have shown that restriction of a specific amino acid, methionine restriction (MR), has similar physiological effects as CR and is related to longevity, metabolic health but also cognitive disorders.

The restriction of methionine seems to be related to a reduction of oxidative stress, through mechanisms not yet discovered, but these changes of the redox status seem to be one of the underlying mechanisms of life-span prolongation [9] and beneficial health effects [10,11]. Proposed mechanisms for reducing a pro-oxidative environment by methionine restriction are multifold and include (i) induction of autophagy in particular mitophagy and, therefore, the enhanced removal of reactive oxygen species (ROS)-producing, non-functional mitochondria [12], (ii) a reduction of ROS production within the mitochondria [13]

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Abbreviations

Acox1	acyl-coenzyme A oxidase 1
AD	Alzheimer's disease
ADF	alternate day fasting
AGE	advanced glycation endproduct
ATF4	activating transcription factor 4
Aβ	beta-amyloid
B2M	β2-microglobulin
BAT	brown adipose tissue
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BHMT	betaine homocysteine methyltransferase
C. elegans	*Caenorhabditis elegans*
CBS	cystathionine-β-synthase
CGL	cystathionine-γ-lyase
CNS	central nervous system
CO	carbon monoxide
Cpt1a	carnitine palmitoyltransferase
CVD	cardiovascular disease
DACD	diabetes-associated cognitive decline
dcSAM	decarboxylated SAM
E. coli	*Escherichia coli*
EOD	every-other-day
ER	endoplasmic reticulum
FGF	fibroblast growth factor
FGFRs	fibroblast growth factor receptors
GPx	glutathione peroxidases
GSH	glutathione
GSTP	glutathione S-transferase
H_2S	hydrogen sulfide
HDL-C	high-density lipoprotein cholesterol
HFD	high-fat diet
HO-1	hemoxygenase-1
HPA	hypothalamic-pituitary-adrenal
IBD	inflammatory bowel disease
IER	intermittent energy restriction
IR	insulin resistance
IUGR	intrauterine growth restriction
Keap1	Kelch-like ECH-associated protein 1
LDL-C	low-density lipoprotein cholesterol
LOVs	lacto-ovo vegetarians
LPD	low-protein diet
MAPK	mitogen-activated protein kinase
MAT	methionine andenosyltransferase
MCI	mild cognitive impairment
MCM	methionine cycle metabolites
MD	methionine deprivation
MDA	malondialdehyde
Met	methionine
MPO	myeloperoxidase
MR	methionine restriction
MTA	5′-methylthioadenosine
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
mtROS	mitochondrial ROS
Nfe2l2	hepatic Nrf2
$Nfe2l2^{fl/(Alb)}$	liver-specific deletion of Nfe2l2
NFκB	nuclear = factor 'kappa-light-chain-enhancer' of activated B-cells
NO	nitric oxide
Nrf2	nuclear factor erythroid 2-related factor 2
3-NT	3-Nitrotyrosine
ob/ob	leptin-deficient obese
OCM	one-carbon metabolism
PEPCK	phosphoenolpyruvate carboxykinase
Ppargc1a	peroxisome proliferator-activated receptor γ coactivator 1-α
PVN	paraventricular nucleus
ROS	reactive oxygen species
SAH	S-adenosylhomocystein
SAHH/AHCY	S-adenosylhomocystein hydrolase
SAM	S-adenosylmethionine
SCN	suprachiasmatic nucleus
SNA	sympathetic nerve activity
SOD	superoxide dismutase
SRB	sulfate-reducing bacteria
STZ	streptozotocin
sWAT	subcutaneous white adipose tissue
T2D	type 2 diabetes
TASIR1/TASIR3	taste 1 receptor member 1 and 3
TC	total cholesterol
TG	triglyceride
TMAO	trimethylamine-N-oxide
TRF	time-restricted fasting
TSAA	total sulfur amino acid
WAT	white adipose tissue
WD	western diet

and effects on the transsulfuration and glutathione (GSH) pathways [14,15].

This review will give an overview on the possible interaction of the methionine pathways with the redox status of cells, and in particular the effects of methionine restriction.

2. Methionine metabolism

Methionine is an amino acid that occurs in two chiral forms. While D-methionine hardly occurs in nature, L-methionine is a component of most proteins. Besides cysteine, methionine is the only proteinogenic amino acid containing sulfur [16]. Due to the thioether group, Methionine is less reactive than cysteine, whose sulfur atom is located in a sulfhydryl group. As an essential amino acid, methionine cannot be synthesized endogenously and must be provided by the diet [17]. In metabolism, methionine is a supplier of methyl groups ($-CH_3$) and necessary for cell growth and normal cell function [18]. Furthermore, methionine is involved in the metabolism of polyamines, and GSH plays an important role in oxidative stress resistance [17,19]. Methionine metabolism can be divided into three connected pathways: the methionine cycle, the transsulfuration pathway and the salvage pathway [20] (Fig. 1).

In the methionine cycle, methionine is converted to the universal methyl-donor S-adenosylmethionine (SAM) by the enzyme methionine adenosyltransferase (MAT) [21]. In this reaction, all three phosphates are removed from ATP, indicating the "high-energy" nature of this sulfonium ion. As a principal methyl donor, SAM is involved in different methylation processes of DNA, RNA, and proteins [22]. After donating a methyl group, S-adenosylhomocysteine (SAH) is generated, which is a product inhibitor of SAM-dependent methylation reactions. SAH hydrolase (SAHH/AHCY) catalyzes the reversible hydrolysis of SAH to adenosine and L-homocysteine. The methionine cycle is closed by the followed remethylation of homocysteine to methionine. This process can be conducted via the folate cycle with 5-methyltetrahydrofolate as a methyl donor or by the betaine homocysteine methyltransferase (BHMT) requiring betaine as a methyl donor [23].

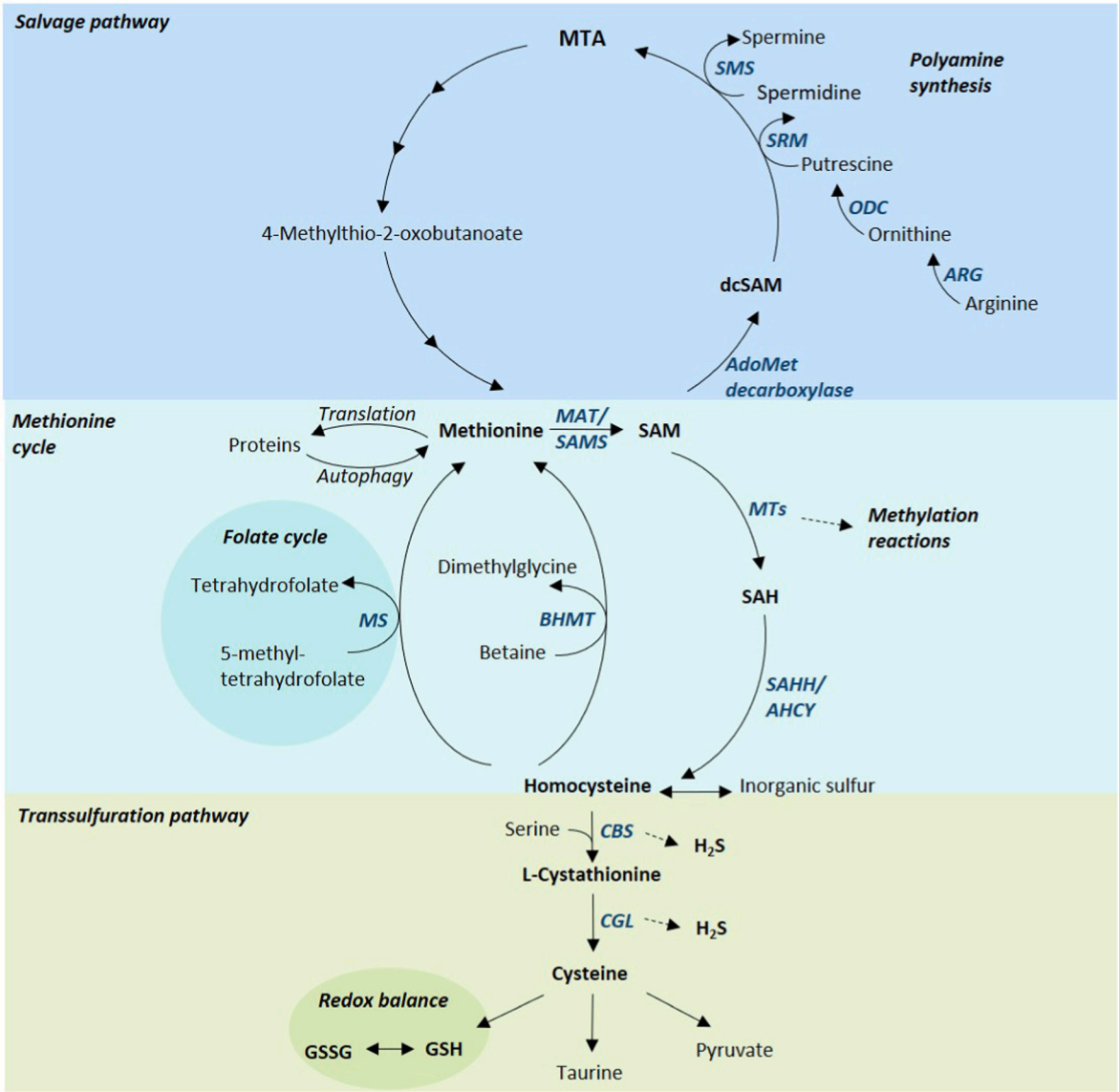

Fig. 1. Schematic methionine metabolism (modified according to Parkhitko et al. [15]). The methionine metabolism can be divided into three main parts. In the methionine cycle the essential amino acid methionine is converted by methionine adenosyltransferase to S-adenosylmethionine (SAM), a principal methyl donor. SAM can be demethylated to S-adenosylhomocysteine and hydrolized to homocysteine by the S-adenosylhomocysteine hydrolase. Homocysteine can be either remethylated back to methionine through the folate cycle or by betaine homocysteine methyltransferase. Another pathway is the transsulfuration of homocysteine. In this route homocysteine is needed for the synthesis of L-cystathionine by cystathionine-β-synthase. L-cystathionine can be hydrolyzed by the cystathionine-γ-lyase to cysteine, a precursor for taurine, pyruvate and glutathione, which is important for the redox balance. As side product of both enzymes, hydrogen sulfide is built. Another possibility to regenerate methionine is through the salvage pathway. Thereby SAM is decarboxylated and serves as aminopropylgroup donor for the synthesis of polyamines like spermidine and spermine. For this synthesis putrescine is formed in parallel through arginase and ornithine decarboxylase activity and then synthesized to spermine and spermidine. The needed decarboxylated SAM here is thereby converted to 5′-methylthioandenosine and synthesized back to methionine. AdoMet = S-adenosylmethionine, ARG = arginase, BHMT = betaine homocysteine methyltransferase, CBS = cystathionine-β-synthase, CGL = cystathionine-γ-lyase, dcSAM = decarboxylated SAM, GSH = glutathione, GSSG = glutathione disulfide, H_2S = hydrogen sulfide, MAT = methionine adenosyltransferase, MS = methionine synthase, MT = methyltransferase, MTA = 5′-methylthioandenosine, ODC = ornithine decarboxylase, SAH = S-denosylhomocysteine, SAHH/AHCY = S-adenosylhomocysteine hydrolase, SAM = S-adenosylmethionine, SMS = spermine synthase, SRM = spermidine synthase.

Besides the remethylation pathway homocysteine can be utilized in the transsulfuration pathway [23]. In this metabolic pathway the transfer of sulfur from homocysteine to cysteine occurs and is the only route for biosynthesis of cysteine. The rate-limiting cystathionine-β-synthase (CBS) synthesizes cystathionine through the condensation of homocysteine and serine. Cystathionine can be hydrolyzed by the cystathionine-γ-lyase (CGL) to produce cysteine, which is involved in the synthesis of proteins, GSH, and taurine [20]. GSH, a tripeptide of cysteine, glutamic acid and glycine, is one of the most important thiol redox buffers and can scavenge ROS. After scavenging ROS, GSH is reversibly oxidized to GSSG [20,24] or S-nitrosoglutathione, the reaction product of •NO and GSH that can be restored by the enzyme S-nitrosoglutathione reductase (GSNOR) in a NADH-consuming manner [25].

GSH is found free or protein bound in eukaryotic cells. Since the GSH reductase is constitutively active and inducible during oxidative stress, free GSH is almost only present in its reduced form. Therefore, the GSH: GSSG ratio is a key redox sensor and can be used as a marker of oxidative stress. Under normal conditions in mammalian cells the molar GSH: GSSG ratio exceeds 100:1 whereas in various oxidative stress models

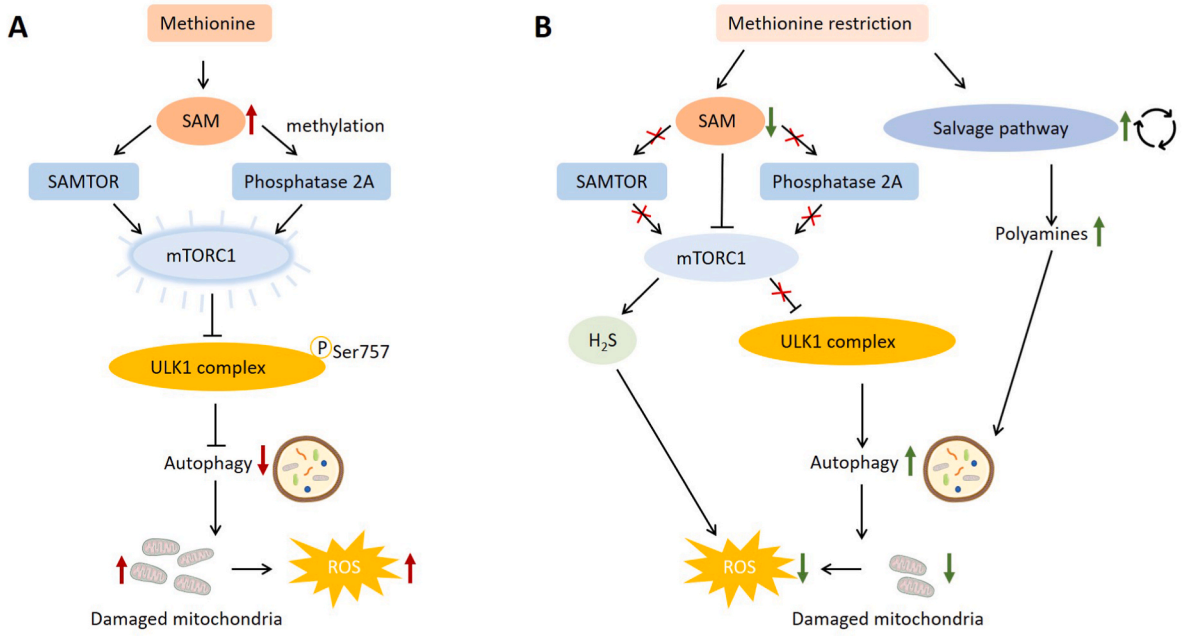

Fig. 2. The possible mechanism of methionine on mTORC1 activity and autophagy. A: Methionine can lead to higher circulating SAM concentrations. This is sensed by SAMTOR leading to an activation of mTORC1. Also intracellular SAM can methylate phosphatase 2A which activates mTORC1. Activated mTORC1 supresses the activity of the ULK1 complex through a specific phosphorylation on SER757 resulting in autophagy inhibition. This can lead to higher levels of damaged cell organelles such as mitochondria producing more ROS. **B:** Under methionine restricition SAM levels are altered leading to a supressed mTORC1 activity. The ULK1 complex is active and promotes autophagy. Also the suppressed mTORC1 can lead to higher H_2S production, a radical scavenger leading to lower ROS levels. Besides, the possible upregulation of the salvage pathway in the methionine cycle by methionine restriction leads to higher levels of polyamines, able to stimulate cytoprotective autophagy. mTORC1 = mammalian target of rapamycin complex 1, SAM = S-adenosylmethionine, ROS = radical oxygen species.

decreased ratios of 10:1 or even 1:1 have been observed [26,27]. The extracellular GSH/GSSG ratio and Cys/cystine ratio in plasma can be used to quantify oxidative stress associated with a number of unhealthy risk factors [28]; in addition, the GSH/GSSG ratio and the Cys/cystine ratio can be influenced by the SAA content of meals [29]. Furthermore, in an SAA-deficient diet, additional intake of drugs, such as therapeutic doses of acetaminophen, may alter SAA metabolism to maintain plasma cysteine/cystine redox potential (E(h)CySS) [30].

It has been shown that an activation of the transsulfuration pathway also promotes the production of the signaling molecule hydrogen sulfide (H_2S) [31]. As a side product of cystathionine-β-synthase and cystathionine-γ-lyase H_2S is generated and has been recognized as the third gaseous signaling molecule together with nitric oxide (NO) and carbon monoxide (CO) [32]. Although it is toxic in high concentrations, under physiological conditions, low concentrations of endogenous H_2S have a protective effect. It protects cells from oxidative stress by modulating neuronal transmission, smooth muscle relaxation, release of insulin, and the inflammatory response [33,34]. Since transsulfuration modulates several physiological processes and plays a central role in maintaining redox balance, dysregulation of this pathway can lead to deleterious effects. Cysteine and H_2S participate in a multitude of signaling processes and need to be highly regulated for normal cellular processes with multi-level controls (details on regulators of transsulfuration can be found in Ref. [31]).

To regenerate methionine, the transsulfuration pathway intersects with the transmethylation pathway, where homocysteine can be remethylated back to methionine as already mentioned above. However, impaired homocysteine remethylation and aberrancy in methyltransferase reactions can lead to methionine deficiency and homocysteine elevation, a process that seems to be associated to NAFLD, metabolic syndrome and cardiovascular risk as well as inflammation, oxidative stress, unfolded protein response, and cell death [35–41].

Another way to regenerate methionine is through the salvage pathway, also known as 5′-methylthioadenosine (MTA) cycle, which regenerates methionine through SAM and is involved in the production of polyamines [42]. Briefly, SAM is decarboxylated by adenosylmethionine decarboxylase to dcSAM (decarboxylated SAM) and can serve as an aminopropyl group donor. In parallel, arginine is converted to ornithine by arginase and then decarboxylated by ornithine decarboxylase to putrescine. Putrescine is involved in the production of spermidine and spermin through spermidine synthase and spermin synthase, which use dcSAM as aminopropyldonor. Meanwhile, dcSAM is converted to MTA and through multiple enzymatic steps synthesized back to methionine [20]. Polyamines produced by this route are thought to play a dual role in maintaining redox balance. Polyamines may act protectively as free radical scavenger of hydroxyl radicals formed by fenton-like reactions, but not against superoxide radicals [43].

In addition, they may influence autophagy and interact with signaling pathways that modulate cellular responses [19]. While low polyamine levels promote growth cessation, high concentrations are associated with rapid proliferation or cancer. Dysregulated polyamine metabolism could lead to an imbalanced metabolic redox state. Therefore, maintaining intracellular polyamine homeostasis seems to be very important [44].

In addition to these three major pathways, several paralogous pathways contribute to methionine metabolism, as described by Sekowska et al. [45]. Studies show that chronic high exposure to methionine can lead to increased oxidative stress and contribute to multiple diseases and methionine metabolism dysregulation [17]. Dietary interventions such as methionine restriction could therefore contribute to the pathogenesis of multiple diseases as well as life span extension [17,23,46–49].

3. Methionine restriction (MR), aging, and diseases

3.1. Aging/lifespan

Life expectancy has been rising in most countries over the past

Table 1
Antioxidant effects of MR.

Studied condition	Model/Species/ Strains	Age	Diet composition/ MR content	Intervention duration	Effects	Ref.
Obesity	(M) C57BL/6J mice	14 weeks old	HFD: 24% Fat; SD: 0.86% Met; MR: 0.17% Met	22 weeks	Body weight ↓; fat mass ↓; lean mass per BW ↑; tissue mass per BW ↑; serum/liver ROS, GSH/GSSG ↑; serum/liver MDA ↓; liver GSH ↓; hepatic Nrf2, HO-1 and NQO-1 genes ↑	[83]
Obesity	(M) C57BL/6J mice	29 weeks old	HFD: 24% Fat; SD: 0.86% Met; MR: 0.17% Met	15 weeks	Plasma SOD ↑; plasma MDA ↓; heart Nrf2, HO-1 and NQO-1 genes ↑	[86]
Healthy	(M) Wistar rats	7 weeks old	SD: 0.86% Met; MR: 0.34% Met	7 weeks	Kidney 8-oxodG -; brain 8-oxodG ↓; kidney/brain GSA, AASA, CEL, CML, MDAL ↓	[92]
Obesity	(M) ob/ob mice	10 weeks old	SD: 0.86% Met; MR: 0.12% Met	14 weeks	Body weight ↓; adiposity ↓; lean body weight ↓; plasma total cholesterol and LDL ↓; hepatic TG ↓; VLDL ↑; serum ALT and AST ↓; hepatic Scd1 gene↓; hepatic FAO ↑	[113]
Obesity	(M and F) C57BL/ 6J mice	18 weeks old	WD: 42% high-fat, high-sucrose SD: 8.2 g/kg Met; MD: 0% Met	5 weeks	Body weight ↓; WAT UCP-1 gene in males ↑; Acc1 and Fasn in females ↑; skeletal muscle mTORC1 ↓	[116]
Healty	(M) F-344 rats	6–7 weeks old	SD: 0.86% Met; MR: 0.17% Met	Short-term study 2 weeks and 4 weeks; long-term study: 1–6 months	Plasma 8-OHdG, 8-isoprostane, protein-bound GSH in long-term study↓; free GSH in long-term study↑; liver and kidney GSH in short-term study ↓; brain GSH in short-term study -; brain GSSG reductase in both short-term study and long-term study; liver GSH peroxidase in both short-term study and long-term study↓; kidney GSH peroxidase in both short-term study and long-term study↑; brain GSH peroxidase in both short-term study and long-term study; liver total SOD activity, Mn-SOD in long-term study	[123]
Obesity	(M) C57BL/6J mice	5 weeks old	HFD: 20% Fat; SD: 0.86% Met; MR: 0.17% Met	22 weeks	Body weight ↓; body fat rate ↓; plasma lipid levels ↓; colon MDA ↓; colon/ileum GSH-Px ↑; colon/ileum GSH/GSSG ↑	[119]
Healty	(M) C57BL/6J mice	6 weeks old	SD: 0.86% Met; MR: 0.17% Met	8 weeks	Insulin sensitivity ↑; hepatic glucose production ↓; hepatic FGF21 ↑; HepG2 cells GSH, GSSG ↓	[139]
Healthy	(M) Wild-type, $Gcn2^{-/-}$	5 weeks old (Exp. 1) 7 weeks old (Exp. 5&6)	SD: 0.86% Met; MR: 0.17% Met	14 weeks (Exp. 1) 8 weeks (Exp. 5&6)	Insulin, glucose ↓(Exp. 1); energy expenditure ↑(Exp. 1); GSH (Exp. 5&6)↓; hepatic NQO-1 gene ↑(Exp. 5&6); targets of Nrf2 (Exp. 5&6)↑	[150]
Healthy	(M) Wild Type, $Nfe2l2^{fl/(Alb)}$	8 weeks old	SD: 0.86% Met; MR: 0.17% Met	8 weeks	Energy expenditure ↑; hepatic Nfe2l2 gene -; serum FGF21 ↑; Nfe2l2 target genes -	[152]
Healthy	(M) Wistar rats	10 weeks old	SD: 0.86% Met; MR: 0.17% Met	7 weeks	Brain 8-oxodG, GSA, AASA, CEL, CML ↓	[173]
Aging	(M) Wistar rats	8 months and 26 months	SD: 0.86% Met; MR: 0.17% Met	8 weeks	Peroxisomal β-oxidation, GSA, 2-SC ↓	[174]
Glioma	The human glioma cell lines U87 and U251	N/A, cell culture	Met-Cys double deprivation	96 h	GSH ↓; ROS ↑; LC3-II ↑	[175]
Aging	(M) C57BL/6J mice	2, 12, and 15 months old	SD: 0.86% Met; MR: 0.34% Met	3 months	Brain NQO-1, HO-1 genes ↑; brain MDA ↓; serum/liver/brain FGF21 ↑	[263]
IBD	(M) ICR mice	Not mentioned	SD: 0.8% Met; MR: 0.14% Met	7 days	Colon MPO ↓; colon SOD, CAT, GPx ↑; colonic nuclear Nrf2 ↑	[251]

a Symbol: ↑ means increase; ↓ means decrease; - means no effects.
b M means male; F means female.
c HFD means high fat diet; SD means standard diets; MR means methionine restriction; MD means methionine deprivation; WD means western diet.

decades, as well as the prevalence of aging-associated pathological conditions [50]. It is suggested that a long-term, low-fat, whole-food vegan diet may increase life expectancy in humans by down-regulating IGF-I activity [51]. The influence of dietary interventions and restrictions, including CR and PR, on (metabolic) health and aging, has been investigated for more than 60 years [52,53]. Recent evidence shows that especially the quantity, source, and amino acid composition are strongly associated with the positive effects on lifespan extension and metabolic health [54].

Dietary methionine restriction prolongs mammalian lifespan [55], although it should be noted that Western diets contain methionine at levels many times higher than dietary requirements [56]. The adverse effects of this amino acid on lifespan have been strongly related to the disadvantageous ability of methionine to promote oxidative stress by several mechanisms, which might promote the aging process.

Methionine restriction (MR) was first reported by Dr. Norman Orentreich in 1993 [55]. They restricted the essential amino acid L-methionine from 0.86 to 0.17% of the diet, resulting in a 30% longer lifespan of male Fischer 344 rats. Similar results have been demonstrated in other models of yeast [57], *Drosophila* [58], *Caenorhabditis elegans* (*C. elegans*) [59], mice [60,61] and rats [55,62,63]. Richie et al. were able to show that 80% MR in Fisher 344 rats resulted in a 44% increase of lifespan compared to controls [63]. In a mouse model of BALB/cJ × C57BL/6J F1 mice, a diet with 0,15% methionine compared to 0,43% methionine led to lifespan extension [60]. The positive effects on lifespan extension are associated with favorable metabolic responses on low-methionine diet in rodents [64,65]. Studies in other species under specific growth conditions support these results. For example, Carbreiro et al. demonstrated that metformin-induced altered methionine metabolism in *Escherichia coli* (*E. coli*) led to MR in *E. coli*, resulting in a prolongation of lifespan in their host *C. elegans* [59]. *Drosophila* fed with MR also had longer lifespans, but only under conditions of a low amino acid status,while a high amino acid status prevented the effect [58]. In cell culture experiments in human diploid fibroblast by Koziel

et al., it was observed that under MR conditions, the replicative lifespan was extended while cellular senescence was postponed [66].

The underlying mechanisms of the beneficial effects of MR on aging are very complex and not yet fully understood [18]. One possibility could be through influencing insulin/IGF-1 and mTORC1 (mammalian target of rapamycin complex 1) signaling, which regulated longevity across species in other dietary restriction and protein restriction models [67–69]. Like growth factors, insulin, and amino acids, methionine can contribute to mTORC1 activation, a complex with several subunits and central regulator of cell functions [70]. Activated mTORC1 is suppressing autophagy by inactivation of Ulk1 (Ser757) through phosphorylation [71] (Fig. 2A). However, autophagy plays an important role in the removal of damaged organelles such as mitochondria. Interestingly, recent data from Plummer et al. suggest that the autophagic activity underlying the lifespan extension by MR could be specifically that of mitophagy (the autophagy-dependent degradation of mitochondria), but not non-specific bulk macroautophagy or any other known form of selective autophagy [12]. Damaged mitochondria produce more ROS [72], therefore mitophagy is important to maintain mitochondrial quality.

Suppression of mTORC1 signaling pathways by MR could therefore extend chronological and replicative lifespan by reducing oxidative stress caused of damaged organelles [49] (Fig. 2B). Studies show that methionine can influence the mTORC1 activity via multiple pathways. On the one hand, SAM, a metabolite of methionine, is sensed by SAM-TOR, resulting in mTORC-1 activation and autophagy suppression. On the other hand, intracellular SAM can methylate protein phosphatase 2A, which also activates mTORC1 [18,70]. MR is thought to alter SAM availability and thereby contribute to lifespan extension by suppressing mTORC1 activity [20]. Also, extracellular methionine is sensed by the taste 1 receptor member 1 and 3 (TASIR1/TASIR3) resulting in mTORC1 activation through phospholipase C, increase in intracellular calcium, and mitogen-activated protein kinase (MAPK) activation [18,73]. Lower extracellular methionine levels could therefore suppress this activation. Further, the induction of autophagy is closely related to the salvage cycle described in chapter 2 [19].

In addition, methionine is indirectly involved in the synthesis of polyamines, as the dcSAM formed in the methionine cycle serves as an aminopropyl donor for polyamine synthesis [20]. Polyamines like Spermidine stimulate cytoprotective autophagy, and it could be shown that supplementation with spermidine could extend lifespan across species [74–77]. Controversially, although methionine is required for the synthesis of spermidine, MR actually resulted in a 10-fold increase in spermidine in studies by Barcena et al. in progeroid mice, leading to an increase in lifespan [61]. The upregulation of the salvage pathway in MR could be a possible target for the positive effect [18]. Another mechanism on lifespan extension could be through the positive effect of MR on aging-associated metabolic diseases. In adult mice fed MR, the negative effects of aging on body mass, obesity, and insulin resistance were reversed by induction of fibroblast growth factor (FGF) 21 in the liver [78].

The positive effects of MR on lifespan extension are partially mediated through reducing oxidative stress, which is closely related to aging and aging-associated diseases. Induction of autophagy, H_2S production, and reduction in free radical leakage from mitochondria seem to contribute there [18]. An increased flux via the transsulfuration pathway has been described in different MR models and is postulated as contributing factor for lifespan extension [79,80]. It could be caused by an enhanced cystathionine y-lyase expression when sulfur-containing amino acids are restricted [81]. Human studies in centenarians also revealed a specific plasma profile associated with an enhanced transsulfuration pathway and highly regulated methionine metabolism [80]. Contributing to the beneficial aging effect appears to be enhanced H_2S synthesis as a byproduct of this pathway. H_2S can act as a ROS scavenger and upregulate antioxidant defense mechanisms [18].

Suppression of the mTOR pathway by MR can also lead to increased H_2S production, as mentioned above [71]. *In vivo* and *in vitro* studies by Wang et al. demonstrated that MR can effectively delay senescence through higher H_2S production and mTOR suppression by AMPK in renal aging [82]. This is supported by various studies across species observing an enhanced H_2S production by MR [83–86]. In addition, the transsulfuration pathway is required for the synthesis of GSH, an important regulator of redox balance [24]. The antioxidant effects of MR are summarized in Table 1. Studies have shown that an 80% MR increases the GSH content in erythrocytes of rats, which correlates with a reduction in age-related diseases and life expectancy [63,87]. However, it was also observed that GSH was reduced by MR in the liver and several tissues, although oxidative stress was not enhanced [63,65,87–89]. The low levels of hepatic GSH could be compensated by increased oxidative capacity [89]. GSH decrease and GSSG:GSH ratio increase are possible to contribute to extend lifespan by MR [62]. However, the influences and mechanisms of MR on GSH and GSH:GSSG ratio are still unclear, and further studies are needed.

In addition, methionine seems to stimulate mitochondrial ROS production. Mitigation of mitochondrial ROS (mtROS) by MR is another mechanism that contributes to the maintenance of a redox balance for healthy aging [18]. Sanz et al. demonstrated that 80% MR decreased mtROS production of complexes I and III in the liver and heart, similar to the results of Caro et al. [90–92]. Lifespan extension could be partially mediated by attenuating mtROS overproduction. The underlying mechanism appears to be a direct and rapid effect of methionine or methionine metabolites on mitochondrial complexes [13]. It has been reported that the reaction of methionine with hydroxyl radicals produces methionine radicals as intermediates and methanethiol as the final gaseous product [93]. Intermediate radicals or methanethiol itself may react with complex I or III in mitochondria, leading to overproduction of mtROS.

In summary, reduction of oxidative stress, induction of autophagy (mitophagy), and activation of the transsulfuration pathway seems to contribute most to lifespan extension by MR, but the mechanisms are very complex and not yet fully understood.

3.2. Cardiovascular disease and associated risk factors

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world and aging is the dominat risk factor for CVD. Aging has remarkable effects on the heart and arterial system, leading to an increase in CVD including atherosclerosis, hypertension, myocardial infarction, and stroke [94]. Inappropriate diet contributes to "unsuccessful" aging and aging-related diseases [95] and is also a major risk factor for CVD, which can thus also be seen as a diet-associated disease. Diets rich in red meat, such as western diet (WD) correlate with increased CVD risk. One reason for the increased CVD risk observed in high red meat diets is thought to be linked to gut microbiota-dependent generation of trimethylamine-N-oxide (TMAO) from L-carnitine, a nutrient abundant in red meat [96]. TMAO is pro-inflammatory, able to impair vascular function and structure, and may up-regulate scavenger receptors and inhibit reverse cholesterol transport.

In general, a westernized diet, such as high fat diet (HFD) is characterized by a high proportion of saturated fat. Increased intake of fat, especially saturated fat, is associated with the increase in cardiometabolic diseases and obesity [97]. In fact, obesity is another independent risk factor for CVD [98]. Obesity is a multifactorial disease caused by the interaction of multiple factors such as genetics, environment, and biology, leading to the expansion of adipose tissue. Both sexes and all ethnic groups are affected by obesity at all ages [99] and obesity is associated with lower life expectancy because of a dramatic increase in the risk of comorbidities such as diabetes and CVD, including hyperglycemia, hypertension, and dyslipidemia. Furthermore, obesity-related diseases appear to accelerate cellular processes also observed in normal aging [100]. MR may delay the occurrence of CVD and associated risk factors. A diet high in animal protein/methionine

increases total homocysteine and methionine concentrations and thus the risk of CVD [101,102], whereas a low-fat vegetarian and vegan diet is associated with a reduction in cardiovascular risk factors [103]. Notably, MR can induce hyperhomocysteinemia in rats, which is a risk factor for the development of CVD [104]. However, Ables et al. [105] consider that MR may improve cardiac adaptability despite hyperhomocysteinemia.

It has been reported that total fat mass increases with age and its distribution changes, especially in the abdominal region [106]. In particular, abdominal obesity is a risk factor for CVD worldwide [107]. MR to alleviate obesity, such as reducing body weight and abdominal fat deposition and increasing energy expenditure, has been extensively studied.

MR was able to prevent weight gain and fat accumulation in both mouse and human studies [108,109]. Restricting methionine content from 0.86% to 0.17% can effectively increase total energy expenditure and core temperature and regulate metabolic flexibility, as shown in F344 rats. Dietary MR produced a persistent increase in uncoupling protein 1 expression in brown and white adipose tissue in combination with decreased leptin and increased adiponectin serum levels [110]. Compared with HFD-induced obese mice, 22-week MR (0.17% Met) significantly increased average heat production during the light and dark cycle [111]. Interestingly, MR also seems to be able to restore the circadian misalignment induced by a HFD. MR (0.17% Met; control diet 0.86% Met) improved the HFD-disrupted cyclical fluctuations of lipidolysis genes and the circulating lipid profile in C57BL/6 J mice. Also, MR improved the expression of clock-controlled genes in the liver and the brown adipose tissue [112].

In addition, obesity may affect heart function through risk factors such as dyslipidemia. MR has been evidenced to improve lipid metabolism. The plasma levels of triglyceride, total cholesterol, and low-density lipoprotein cholesterol were decreased, while high-density lipoprotein cholesterol was increased significantly in HFD-fed mice after MR [84,111]. Similar effects were shown in leptin-deficient obese (ob/ob) mice after 14 weeks of 0.12% MR treatment [113], suggesting that MR can effectively improve the dyslipidemia of obese mice.

Lipid metabolism is a driving force for the pathological changes in CVD, and remodeling lipid metabolism by MR and reducing fat mass could therefore reduce a risk factor for CVD.

A 2011 study showed in 26 obese adults randomized to MR (2 mg Met/kg body weight/day) or control diet (35 mg Met/kg body weight/day) that MR intervention increased fat oxidation and decreased carbohydrate oxidation and resulted in a decrease in intrahepatic lipid content. Comparable weight loss was observed in both groups [114].

In F344 rats it was shown that MR induced a coordinated down-regulation of lipogenic genes in the liver, resulting in a corresponding reduction in the capacity of the liver to synthesize and export lipids [115]. In this study, MR also remodeled the morphology of adipocytes in all three depots (epididymal, visceral and subcutaneous WAT), increased mitochondrial density in two depots (visceral and subcutaneous), increased TCA flux, and increased the capacity of subcutaneous WAT to oxidize palmitate. Changes in gene expression within WAT and liver reveals that dietary MR produced fundamentally different responses between the tissues with respect to lipid metabolism, however the coordinated remodeling of lipogenic gene expression between liver and WAT induced by dietary MR resulted in a significant decrease in circulating and hepatic lipid levels, beneficial to the overall metabolic profile of the animal.

In addition, MR also upregulated genes related to mitochondrial β-oxidation, further reversing hepatic steatosis in ob/ob mice [113]. In a short-term methionine deprivation (MD), genes involved in hepatic fatty acid β-oxidation, including peroxisome proliferator-activated receptor γ coactivator 1-α (*Ppargc1a*), carnitine palmitoyltransferase (*Cpt1a*), and acyl-coenzyme A oxidase 1 (*Acox1*), were significantly upregulated in female C57BL/6J mice, but not in male ones [116]. Consistent with that, greater changes in lipogenic gene expression in the WAT of female mice compared to male mice were detected in that study. An important note from the authors is that they studied only young mice, and the question arises whether the sex-specific effects of MR persist in older animals after the levels of sex hormones, that drive many sexually dimorphic phenotypes, have declined.

In addition to fat deposition and impaired lipid metabolism, systemic oxidative stress appears to be an important link between CVD, associated risk factors, and aging. Chronic or long-lasting oxidative stress may cause cell damage by oxidizing cellular components such as proteins, lipids, and DNA [117], and is closely related to antioxidant enzymes like GSH, glutathione peroxidases (GPx), and superoxide dismutase (SOD) [118]. MR is able to reduce oxidative stress and oxidation-derived damage. In HFD-fed mice it was shown that MR is able to improve intestinal barrier function, inflammatory response, and oxidative stress by regulating the intestinal microbiota and its metabolites [119]. Improved gut homeostasis may be also associated with decreased body weight, body fat rate, blood glucose and plasma lipid levels by MR.

Furthermore, the nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) pathway plays a role in stress response [120]. Nrf2 is a master regulator of multiple antioxidant enzymes, modulates cellular redox balance and senses the status of cellular oxidative stress. This is done by stimulating the activity of components of antioxidant defense, such as SOD, GPx, heme oxygenase-1 (HO-1), glutathione reductase, thioredoxin reductase, ferritin, and NAD(P)H:quinone oxidoreductase (NQO1). Inducing HO-1 in obesity provides an antioxidant environment that can decrease the formation of adipocytes by reducing visceral adipose precursor proliferation, contributing to hyperplastic adipose tissue expansion [121,122]. A diet restricting methionine to 80% (0.17% Met) significantly increases plasma SOD and decreases MDA levels while increasing mRNA expression of Nrf2, HO-1, and NQO-1 in the heart of HFD-fed mice with cardiovascular impairment [86].

In F344 rats MR was associated with a reduction in oxidative stress biomarkers, including plasma 8-hydoxydeoxyguanosine (8-OHdG), 8-isoprostane and erythrocyte protein-bound GSH after one month with levels remaining low for at least six months. However, no changes in the activities of GSH reductase in liver and kidney and SOD in liver were observed as a result of MR feeding, indicating that oxidative stress is reduced by MR feeding in rats, but this effect cannot be explained by changes in the activity of antioxidant enzymes [123].

The mechanism by which MR ameliorates oxidative stress during CVD may be the activation of autophagy and hepatic H_2S generation [85,124]. Activating transcription factor 4 (ATF4) is considered a master regulator of metabolism and is essential for the autophagy gene transcription program [125].

Although ATF4 is not required for many responses to MR, including body weight reduction and body composition shift (towards leanness), it is required for maintenance of redox homeostasis through the transsulfuration pathway leading to production of endogenous H_2S [126]. In *C. elegans*, the ATF4/CTH2/H_2S pathway also increases stress resistance by suppressing mTORC1 [127]. Furthermore plasma H_2S levels are negatively correlated with adiposity [128] and H_2S modulates Sirt1, which in turn is able to interact with mTOR to suppress oxidative stress [129]. In addition, oxidative stress triggers disruption of signaling pathways associated with metabolism and epigenetics, including microRNAs [130]. Similarly, MR regulates miR-328-3p, a type of microRNA that directly targets CGL and modulates endogenous H_2S levels, thereby relieving oxidative stress and ER stress and improving homeostasis and metabolic efficiency in HFD-fed mice [83]. In conclusion, MR can reduce body weight, increase energy expenditure, and balance redox status. However, on the one hand, MR may induce hyperhomocysteinemia, but on the other hand, it may improve cardiac adaptability. Since a sex-specific response to MR has been demonstrated in young C57BL/6J [116], it is important from a translational perspective to also conduct studies at older ages, especially if we want to investigate and better understand the effects of MR on age-related

diseases such as CVD and associated risk factors.

3.3. Type 2 diabetes/insulin resistance

Insulin resistance (IR) is a set of clinical manifestations resulting from a decrease in the sensitivity of target tissue cells in liver, muscle, and adipose tissue to insulin, leading to a decrease in the efficiency of glucose uptake and utilization. IR, in addition to progressive pancreatic islet beta-cell loss, is part of the pathogenesis of type 2 diabetes (T2D). T2D is generally manifested after the age of 40 and is thereby regarded as typical age-related disease [131]. Indeed, recent data from Fazeli et al. [132] suggest as already other data before, that aging is an independent risk factor for T2D and this disorder is closely related to the aging process.

Vegan and vegetarian diets contain lower concentrations of methionine compared to omnivorous diets and this could explain the reduced incidence of diabetes in humans following the former diets [48]. Castaño-Martinez et al. [48] found that vegans had increased insulin sensitivity.

An elevated concentration of circulating fibroblast growth factor 21 (FGF21) has been implicated as a potential underlying mechanism. Although plant based and animal based foods have different amino acid compositions and the beneficial effects of a vegetarian diet have been reported, a study in mice shows that total protein, not amino acid composition, has healthy metabolic effects [133]. Nevertheless, literature data concerning effects of animal and plant protein are contradictory. Pivovarova-Ramich et al. showed in a randomized clinical trial in individuals with T2D, that both plant and animal protein based diets (30% of energy coming from protein in both groups) similarly reduce oxidative stress markers malondialdehyde (MDA) and protein carbonyls, but led to an increase in 3-nitrotyrosine (3-NT) in plasma, related to changes in fasting insulin and insulin resistance [134]. In contrast, it was shown that replacement of red meat with soy protein reduced plasma MDA and increased plasma total antioxidant capacity [135], a beneficial effect that couldn't be confirmed by another study [136]. In accordance with epidemiological studies on red meat intake, a high-methionine diet in rats showed an increased level of MDA and 3-NT in the liver [137]. However, the animal protein based diet in the study from Pivovarova-Ramich et al. was rich in white meat and dairy food and the methionine content of the diet is unknown.

In various animal models, numerous studies have shown that MR improves systemic glucose homeostasis and insulin signaling in peripheral tissues [46,60,138]. MR has beneficial effects on glucose homeostasis in some tissues and organs of the body. In the liver, MR (0.17%) enhanced the inhibitory effect of insulin on glucose production in C57BL/6J mice during the 8-week intervention, which was related to the increase in Akt phosphorylation [139]. Methionine deprivation also rapidly restored normal glucose tolerance and improved insulin-stimulated glucose uptake and suppression of hepatic gluconeogenesis in both female and male mice fed a continuous high-fat, high-sugar diet [116].

In addition, NZO mice treated with MR showed a decreased hepatic glycogen content and increased hepatic phosphoenolpyruvate carboxykinase (PEPCK) protein expression, indicating increased gluconeogenesis [48]. MR resulted in a significant decrease in circulating and hepatic lipid levels through the coordinated transcriptional restructuring of fat metabolism between the liver and WAT, which may also improve insulin sensitivity, shown in F344 rats [115].

In skeletal muscle, MR improved expression and transport of GLUT4 and glycogen levels and increased the expression of glycolysis-related genes (*HK2, PFK, PKM*) in HFD-fed mice [140]. This suggests that MR alleviates insulin resistance and improves glucose utilization by promoting glucose uptake and glycogen synthesis, glycolysis, and aerobic oxidation in skeletal muscle. MR can also increase insulin sensitivity by enhancing mitochondrial biogenesis with increased mtDNA copy number, *TFAM*, and *PGC1-α* mRNA level in HFD-fed mice [140]. In the renal cortex and HK-2 cells (a type of proximal tubule cells of the human kidney) of Gnmt-deficient mice, a low-protein diet (LPD) also had beneficial effects on diabetic kidney disease [141]. LPD protected the kidney by inhibiting mTORC1, which was related to the lower SAM levels caused by low methionine intake in the diabetic mice.

Because MR can maintain systemic glucose homeostasis, it is thought to be a preventive or complementary feeding pattern. Intrauterine growth restriction (IUGR) is prone to the development of T2D. An MR diet reduced hyperglycemia in pigs with IUGR by promoting hepatic protein kinase B signaling and glycogen synthesis [142], suggesting that MR may be a potential dietary strategy to prevent T2D in humans with IUGR.

Chronic inflammation and oxidative stress triggered by obesity and often as a result of inactivity/sedentary lifestyle over years, lead to IR and eventually to T2D [143], which also accelerates aging. Signaling molecules, including hydrogen peroxide, are involved in the regulation of cellular functions. Reactive molecules can lead to abnormal changes in intracellular signaling and cause chronic inflammation and IR [144]. MR improves insulin sensitivity possibly by activating FGF21-mediated antioxidant signaling pathways. FGF21 is a novel target involved in metabolic regulation and has significant effects on enhancing insulin sensitivity. FGF21 and its receptors (FGFRs) are widely distributed in liver, adipose tissue, and pancreas, and FGF21 is a key target and endocrine mediator of the metabolic phenotype induced by dietary MR. MR can increase the expression of hepatic FGF21 by activating GCN2/ATF4/PPARα signaling in liver cells, thereby improving insulin sensitivity, accelerating energy expenditure, and promoting fat oxidation and glucose metabolism [145].

MR also enhances insulin-stimulated phosphorylation of PKB/Akt and S6 in kidneys of 10-month-old mice to lower blood glucose levels [146]. Moreover, MR was able to decrease GSH in HepG2 cells, thereby regulating the activation state of protein tyrosine phosphatases such as PTEN. A lowered presence of GSH limits the GSH-responsive degradation of PIP3 by PTEN, thereby enhancing the PIP3-dependent activation of Akt [139]. Consequently, a decrease of GSH by MR also triggers upregulation of glutathione S-transferase (GSTP), which appears to be initiated by the ERK-AP-1 pathway [147].

It has been reported that upregulation of renal FGF21 expression in a T1D mouse model resulted in renal protection, possibly because of the activation of the Nrf2 antioxidative pathway mediated by PI3K/Akt/GSK3β/Fyn [148]. In $FGF21^{-/-}$ mice, MR failed to increase energy expenditure and reduce serum triglycerides, suggesting that FGF21 is essential in energy metabolism [138,149]. In $GCN2^{-/-}$ mice, MR similarly improved insulin sensitivity and activated hepatic PERK via the GSH-dependent PERK-eIF2-ATF4-Nrf2 pathway [150], implying that FGF21 rather than GCN2 may be essential for the antioxidative effects of MR.

However, MR-activated hepatic Nrf2 (Nfe2l2) possibly also cooperates with hepatic ATF4 to activate various antioxidant stress response reactions [151].

Interestingly, Nfe2l2 does not appear to be essential for mediating the metabolic effects of dietary MR. It was shown that mice with liver-specific deletion of Nfe2l2 (Nfe2l2fl/(Alb)) treated with MR had no effect on the ability of the MR diet to increase FGF21, reduce body weight and adiposity, and increase energy expenditure [152]. Moreover, although FGF21 has been reported to induce adiponectin expression and secretion in WAT [153,154], the beneficial effects on glucose metabolism induced by MR in HFD-fed mice may also be independent of adiponectin and FGF21 [155]. These results could be due to different animal models, different tissues and organs, sex differences, and duration of MR intervention.

Overall, MR could be a preventive nutritional strategy to treat metabolic diseases by improving glucose homeostasis and insulin sensitivity and accelerating energy expenditure. The exact mechanisms by which MR improves these factors need further investigation. MR appears to partially reduce prooxidant factors through FGF21 and

thereby regulate insulin signaling. However, this hypothesis should be further explored in various animal models, taking into account many factors, including sex differences. Whether other signaling pathways synergize with FGF21 to improve insulin resistance after MR remains to be elucidated.

3.4. Brain aging and cognitive disorders

Aging seems to be the greatest risk factor for most neurodegenerative diseases due to the ever-increasing life expectancy and aging of populations. Aging leads to lipid alteration [156], insulin resistance [157], and complex vascular phenotypic changes [158] that render the brain prone to diseases.

The most common neurodegenerative diseases accompanied with cognitive disorders, Alzheimer's disease (AD) and Parkinson's disease (PD), are predominantly observed in elderly individuals, and the risk of these diseases increases with age [159]. A low-protein and low-methionine plant based diet in vegans and vegetarians has been associated with lower risk of ischemic stroke and neurotransmitter metabolism in addition to the cardiovascular and metabolic disease benefits already described [160–165].

A study in Chinese older adults (≥60 years) showed that methionine cycle metabolites (MCMs) elevated by omnivorous diets can lead to mild cognitive impairment (MCI) [166], suggesting a benefit of avoidance of red meat, especially processed meat.

On the one hand, a restricted diet prolongs lifespan in several species; on the other hand, studies have shown that dietary restrictions, such as CR and IF, and improved brain function during aging are associated [167–169].

MR has the potential to affect brain physiology. Brain-derived neurotrophic factor (BDNF) is widely and highly expressed in the brain and plays a critical role in brain and neuron function. In *in vitro* experiments, MR promoted the level of BDNF in C2C12 cells (a kind of mouse myoblast cells) partly by enhancing glycolysis and lactic acid production [170]. Similarly, it is possible that MR stimulates the production of BDNF in the brain and protects neurons from damage. In addition, direct evidence shows that MR can regulate the physiological functions of the brain.

As mentioned above, MR may lead to weight reduction, but at the same time, individuals will have a stronger appetite simultaneously. The central mechanisms are unclear but involve sympathetic nervous signaling [171].

The level of methionine as a methyl donor nutrient affects DNA methylation in one-carbon metabolism. In C57BL/6J mice, it was shown that a diet with reduced methionine content during the developmental phase led to a direct downregulation of genes in the brain that are related to one-carbon metabolism (DNA methyltransferases), reducing anxiety-like behaviors that persist into adulthood [172].

Moreover, MR appears to be an antioxidant strategy for brain redox homeostasis. MR enhances mitochondrial activity and attenuates endogenous oxidative damage in the rat brain (frontal cortex), including fatty acids peroxidizability index, protein oxidation (GSA, CML, CEL, MDAL, AASA, and 2-SC), and mitochondrial DNA oxidation [173,174]. Mitochondrial ROS production, mitochondrial protein oxidation, and glycoxidation were also decreased in brain, whereas mitochondrial oxidative phosphorylation capacity was increased [92].

Double deprivation of methionine and cystine both *in vitro* and *in vivo* resulted in a decrease in GSH content, an increase in ROS levels, and an induction of autophagy in glioma cells [175], suggesting that MR has effects on the oxidative balance of neurons.

The above studies have shown that MR can alter physiological functions of the brain. How MR might mediate the improvement in cognitive functions via FGF21 and H_2S will be discussed in the next two subsections.

3.4.1. FGF21 and brain function

The initial descriptions of FGF21 provided evidence that it is a powerful metabolic regulator in the context of glucose homeostasis, lipid metabolism, and energy balance as already described, but it remains controversial how FGF21 signaling is anatomically organized to produce its diverse physiological effects. FGF21 can act on the different brain regions. Hepatic FGF21 crosses the blood brain barrier (BBB) and acts on the hypothalamus, and the activation of the hypothalamic-pituitary-adrenal (HPA) axis triggers gluconeogenesis [145]. In that process, FGF21 may play a role in the paraventricular nucleus (PVN) or suprachiasmatic nucleus (SCN) of the hypothalamus through ERK1/2 signaling [176]. Moreover, FGF21 enhanced sympathetic nerve activity (SNA) on BAT to induce UCP-1 expression and lipolysis through the central nervous system (CNS) [177]. Interstingly, by using genetic tools to delete FGF21 signaling in the CNS (Klbfl/(CamK2a)mice), little evidence was found that FGF21 signaling plays a significant role in increasing energy expenditure [178]. In contrast, the same study shows that deletion of FGF21 signaling in the brain fully blocked the ability of MR to increase food intake and energy expenditure. However, the authors point out that it is not clear were exactly FGF21 signaling is deleted in the brain of Klbfl/(CamK2a) mice and that is is likely that FGF21 may signal in multiple brain areas through redundant systems to coordinate its response.

A neuroprotective role of FGF21, was demonstrated in obese and insulin-resistant rats. HFD-fed male Wistar rats developed obesity-related insulin resistance and cognitive decline with impaired hippocampal synaptic plasticity, decreased dendritic spine density, brain mitochondrial dysfunction, and increased brain cell apoptosis [179]. These obese and insulin-resistant rats were found to have impaired FGF21 signaling in the brain. Treatment with recombinant human FGF21 was observed to improve peripheral insulin sensitivity, increase synaptic plasticity in the hippocampus, increase dendritic spine density, restore mitochondrial function in the brain, decrease brain cell apoptosis, and increase FGF21 signaling in the brain, resulting in prevention of cognitive decline.

Furthermore, *in vitro* and *in vivo* AD models demonstrated that FGF21 treatment attenuated neuronal apoptosis in the hippocampus and reduced ROS and 8-OHdG levels [180]. Sirt1, an NAD^+-dependent protein deacetylase, can be upregulated by MR and alters the methionine metabolic pathway in kidney and liver [47,146]. Sirt1 may also promote systemic FGF21 signaling by increasing its supply from the liver and increasing the expression of β-klotho in target organs [181]. Furthermore, FGF21 can activate Nrf2 signaling via the FGFR/β-klotho receptor [182].

The above demonstrates that FGF21 and its co-receptors, which are upregulated by MR, are closely related to improved brain function and reduced levels of oxidative stress in the brain. The antioxidant mechanism of FGF21 may regulate NFκB (nuclear factor 'kappa-light-chain-enhancer' of activated B-cells) and AMPKα/Akt signaling pathways to increase antioxidant enzyme activity and also decrease the production of advanced glycation endproducts (AGEs) [183,184]. It is speculated that inhibition of the NFκB pathway could be a potential target for the treatment of AD [185].

The complex interplay of Nrf2 and NFκB signaling pathways can alter the balance of antioxidative or inflammatory responses [186]. Activation of Nrf2 increases *NQO-1* and *HO-1* expression, which efficiently neutralize ROS and detoxify toxic chemicals, thereby inhibiting ROS-mediated NFκB activation [187]. NFκB binds with cAMP-response-element-binding protein (CBP) in a competitive manner and inhibits the binding of CBP with Nrf2, resulting in inhibition of Nrf2 transactivation [188]. MR regulates NFκB [189], suggesting that MR may alter Nrf2 and NFκB signaling through activation of FGF21 to target oxidative stress and neuroinflammation in cognitive disorders.

On the other hand, brain alterations and mood disorders such AD and depression are often accompanied by insulin resistance in the brain [190,191]. The increase of oxidative stress markers is correlated with

insulin receptor activation [192]. Elevated insulin levels can cause oxidative stress, which in turn further aggravates insulin resistance [193]. Akt/GSK-3β has previously been reported to play a key role in regulating insulin/glucose homeostasis, both in peripheral tissues and in the brain [194–197].

FGF21 may also be a potential regulator for the treatment of insulin resistance in the brain. Recombinant human FGF21 promoted Akt/GSK-3β signaling in the hippocampus of HFD-fed mice to sustain neurogenesis [198]. Moreover, Akt/GSK-3β/Fyn signaling increases Nrf2 activity to resist the beta-amyloid (Aβ)-evoked oxidative stress [199]. As mentioned above, MR acts on Akt to regulate insulin homeostasis, but whether MR can further regulate downstream signaling of Akt or other insulin/glucose-related signaling in the brain is unclear.

The above studies suggest that MR improves brain insulin resistance and oxidative stress associated with cognitive disorders. On the one hand, FGF21 acts directly on the brain as an endocrine hormone via the BBB to balance the disturbed redox homeostasis; on the other hand, FGF21 indirectly reduces systemic oxidative stress and thus exerts neuroprotective effects. However, much additional work will be needed to understand how FGF21 mediates the these important neuroprotective responses.

3.4.2. H_2S and brain function

As mentioned previously, H_2S is formed in the transsulfuration pathway and has potential neuroprotective effects as an endogenous gas with physiological activity [200–202].

H_2S could alleviate the impairment of cognition in part by vasoprotection, promotion of autophagy, and reduction of apoptosis. Cerebrovascular aging leads to cognitive impairment, whereas it is possible that H_2S could protect cerebrovascular vessels from aging [203]. H_2S is a vasoactive factor that plays a role in vascular contractility [204]. MR leads to increased H_2S levels, which may partially inhibit mitochondrial electron transport and oxidative phosphorylation before mediating proangiogenic effects [205].

Damage to cerebral vessels can lead to activation of astrocytes and microglial cells [206]. H_2S effectively inhibited reactive glial responses and synaptic damage and induced autophagic flux, thus improving behavioral outcomes [207]. NaHS as an H_2S donor ameliorated diabetes-associated cognitive decline (DACD) and postoperative cognitive dysfunction, with involved mechanisms being improvement of autophagic flux [208], regulation of mitochondria-mediated apoptotic pathways [209], suppression of endoplasmic reticulum (ER) stress [210], enhancement of synaptic plasticity, and neurogenesis in the hippocampus [211].

In addition, H_2S attenuates cognitive dysfunction induced by the systemic pro-aging factor β2-microglobulin (B2M) [211]. Furthermore, in the same study it was shown that the H_2S donor NaHS recovered autophagic flux in the hippocampus of B2M-exposed Sprague-Dawley rats, as evidenced by decreases in the ratio of autophagosomes to autolysosomes and the expression of p62 protein in the hippocampus. NaHS, could also attenuate the development of early brain injury and cognitive dysfunction induced by subarachnoid hemorrhage via Akt/ERK-related anti-apoptosis pathway, and upregulating BDNF-CREB expression in Wistar rats [212].

In streptozotocin (STZ) induced diabetic rats H_2S not only activated the hippocampal PI3K/AKT pathway, as evidenced by the increase of phosphorylated AKT, but also favorably reversed STZ-disturbed hippocampal neurogenesis and subsequently mediate antidepressant- and anxiolytic-like effects [213]. In an AD mouse model, pathological features such as excessive Aβ accumulation [214] and tau hyperphosphorylation [215] were closely connected to the methionine metabolism. H_2S as a product of methionine metabolism, decreased extracellular levels of $A\beta_{40}$ and $A\beta_{42}$, resulting in improved spatial learning and memory acquisition in APP/PS1 mice [216]. Presumably, H_2S may also sulfhydrate GSK3β, inhibit tau hyperphosphorylation, and reduce neurotoxicity in the 3xTg-AD mouse model [217].

In addition, H_2S attenuates oxidative stress associated with cognitive impairment. The exact etiology of neurodegenerative diseases is not understood but oxidative stress, inflammation and synaptic dysfunction are primary hallmarks. Oxidative stress leads to free radical attack on neural cells contributing to protein misfolding, glia cell activation, mitochondrial dysfunction, impairment of DNA repair system and finally cellular death [218]. In the brains of LPS-induced AD mice, H_2S reversed the increased MDA and decreased GSH levels [219]. H_2S may protect neurons from oxidative stress by increasing GSH levels and inhibiting ROS overproduction in both primary cortical neuronal cells and glial cells [220,221].

Furthermore, it is possible that the Nrf2 system is involved in cognitive decline in multiple diseases [222]. Nrf2 regulates, among others, the catalytic and modifying subunit of glutamate cysteine ligase (GCL) to increase GSH levels [223]. Interestingly, it was observed that the expression of CGL, the biosynthetic enzyme for H_2S, was reduced in the cerebral cortex and hippocampus of 3xTg-AD and human postmortem samples [217,224]. Similarly, brain H_2S levels, CBS, and CGL are also significantly decreased and peroxidative markers are increased in chronic hypobaric hypoxia-, chronic osteoarthritis pain- [225] and hyperhomocysteinemia-induced cognitive dysfunction [226]. H_2S can modulate the Nrf2 and glutathione systems in the kidney-brain axis [227], suggesting that H_2S regulates Nrf2 to maintain redox balance in the brain. Also, Hyperhomocysteinemia in late postnatal life is often associated with severe oxidative stress, leading to developmental disorders and lower H_2S and CBS levels in the offspring. Surprisingly, H_2S donors are able to prevent anxiety-like behaviors, spatial memory decline, and oxidative stress (lipid peroxidation and activity of glutathione peroxidase) in the offspring [228].

A specific H_2S concentration as well as activated H_2S synthesizing enzymes may be also a potential biomarker for Alzheimer's disease and other dementias [229]. Total plasma H_2S was shown to be a strong indicator for AD, and partially drove the relationship between cognitive dysfunction and white matter lesion volume, an indicator of microvascular disease.

Changes in dietary patterns appear to activate H_2S production. Late-life every-other-day (EOD) intermittent fasting drives renal H_2S production, and may modulate age-related frailty, including cognitive deficits [230].

In conclusion, increasing H_2S levels by MR may have certain beneficial effects on cognition and emotion, which may depend on the antioxidant and autophagic flux-promoting properties of H_2S.

4. Dietary recommendations for MR and future studies

4.1. Dietary recommendations for MR

Methionine is found in higher levels in animal foods such as pork, beef, dairy products and eggs compared to a plant based diet. The average daily requirement of methionine is 10.4 mg/kg body weight/day [231]. Both excessive and too low methionine in the diet can cause adverse effects.

The digestion efficiency of plant protein is lower than that of animal protein. In general, the utilization rate of animal protein is at least 90%, whereas it is only 80% for plant protein [232–235]. Consequently, omnivores have a higher protein/methionine intake than vegetarians/vegans. This means MR can be achieved with vegan or Mediterranean diets in particular, but there are some recommended foods and supplements. For vegans, isolated soy protein is of high nutritional quality, comparable to that of animal protein sources, and the methionine content is not limiting for adult protein maintenance [234].

Dietary recommendations for MR should be based on individual health status. Certain populations, such as pregnant women, adolescents, and athletes, are not advised to restrict methionine. Methionine, as a nutrient of one-carbon metabolism (OCM), is involved in the methylation pathway.

Table 2
Effects of MR in human studies.

Studied condition	n value	Met concentration	Age (yr)	Sex (M/F)	BMI (kg/m^2)	Intervention duration	Effects	Ref.
Obese subjects	26	33 mg Met/kg body weight/day	44–53	6/20	32.9–38.9	16 wks	Fat oxidation ↑; intrahepatic lipid content ↓; energy expenditure -	[114]
Adenocarcinoma of the colon or rectum	11	Free	48–78	8/3	24.6 ± 3.1	8 wks	Fed state plasma methionine ↓; BMI -; plasma albumin -; plasma prealbumin concentration -	[258]
Metastatic solid tumors	12	2 mg Met/kg/day	Not mentioned	Not mentioned	Not mentioned	8–39 wks	Plasma methionine ↓; BMI ↓; plasma albumin -	[264]
Healthy, normal-weight subjects	14	0.93 g Met/Cys for women, 1.19 g Met/Cys for men	20–40	4/10	20–25	7 days	Plasma methionine ↓; urinary cysteine and taurine ↓; plasma SCD -; total cholesterol ↓	[265]
Overweight or obese subjects	20	Met/Cys 1.6 g/day	23–40	0/20	24.7–34.7	7 days	Subcutaneous adipose tissue ↓; serum FGF21 ↑	[266]
Healthy, normal-weight subjects	14	0.93 g Met/Cys for women, 1.19 g Met/Cys for men	20–38	4/10	21.0–26.6	7 days	Fatty acids ↑; median glucose concentrations ↓	[267]
Healthy subjects	6	2.92 mg/kg/day	49–58	1/5	27.6 ± 4.32	3 wks	Plasma methionine, NAC and glutathione ↓	[259]
Overweight and obese subjects	23	1.4 g Met/day	37.8–42.2	6/17	30.3–31.1	6 months	Vitamin B_{12} intake ↓; folate intake ↑; homocysteine concentrations -	[244]
Normal-weight subjects	72	Vegan/vegetarian diets	32–46	36/36	21.9–26.1	At least 1 yr	Plasma FGF21 ↑; leptin/adiponectin concentrations -	[48]
T2D	37	Plant protein diets	62.2–66.4	24/13	28.4–31.8	6 wks	Uric acid ↓; glycated haemoglobin ↑; diastolic blood pressure ↑; fasting non-esterified fatty acid ↑; insulin sensitivity -; fasting glucose -	[102]
Not mentioned	48	Lacto-ovo vegetarians	19.8–37	16/32	Not mentioned	2–29 yrs	Erythrocyte SOD activity ↓; serum vitamin B_{12} ↓; serum MDA ↓	[268]
Healthy subjects	61	Lacto-ovo vegetarians/vegan	25.3–43.9	61/0	19.8–26.4	Not mentioned	Plasma homocysteine ↑; plasma vitamin B_{12} ↓	[245]

a Symbol: ↑ means increase; ↓ means decrease; - means no effects.
b M means male; F means female.

Although there is no evidence that OCM nutrient intake has significant effects on fetal growth [235], pregnant women are not recommended to use MR. However, the rate of transsulfuration of methionine appears to be higher in the first trimester, suggesting a higher demand for methionine. The high rate of transsulfuration could be also aimed at providing cysteine and glutathione for the fetus [236].

Brain methionine levels increase physiologically after eating as a result of changes in the serum amino acid pattern [237]. Plasma methionine levels tend to be naturally lower when dietary methionine intake is restricted. School-aged children (9.1 ± 2.2 years old) had similar total sulfur amino acid (TSAA) requirements as adults [238]. Moreover, the TSAA levels of children with chronic renal failure did not differ from those of healthy children; in fact, the minimum requirement for methionine was higher in children with chronic renal failure (7.3 mg/kg/day) [239]. This implies that humans may not benefit from a low-methionine diet during development.

Although MR may improve skeletal muscle health in obese and aging mice and, when combined with endurance training, may increase intrinsic bone strength [240,241], this dietary pattern is not recommended for athletes. Methionine intake appears to be positively associated with lower limb muscular fitness in men [242]. Carnitine is necessary for muscle development during exercise [243] and methionine plays a role in endogenous carnitine synthesis and is not sufficiently present in the MR diet to meet the requirement.

In addition, osteoporosis is a significant problem in aging. MR has been shown to improve cognitive impairment in aging mice, while it also decreases bone mass, trabecular bone volume, bone mineralization activities, and bone mineral content in rats with a decrease in serum osteocalcin and C-terminal telopeptide of type 1 [241]. MR may therefore negatively affect the bone growth and development process. To prevent the development of osteoporosis, MR should also be used with caution in the elderly. But as described in the previous chapters, animal studies show that MR has beneficial effects on disorders of glucose and lipid metabolism (obesity, diabetes, CVD), cognitive decline, and life expectancy; therefore, MR should be considered in certain pathological conditions, but with consideration of the adverse effects. More importantly, micronutrient supplementation is required during MR. Dietary vitamin B12 intake was reduced after a 6-month MR intervention [244] and in ovo-lacto vegetarians/vegans [245]. Vitamin B12 should be supplemented at the same time since it is mainly derived from milk, dairy products, meat, and fatty fish [246]. Some vegan cases show that iron intake may be inadequate as well [247]. In addition, a plant based diet tends to result in lower calcium intake [248]. In conclusion, the above factors should be considered by vegans/vegetarians and the principles of a reasonable diet and balanced nutrients must be followed when performing MR.

4.2. Future studies

There have been many reports regarding the benefits of MR in health and longevity, but despite many studies, the mechanisms of lifespan regulation by CR and PR remain incompletely understood. Interestingly, lifespan of *Drosophila melanogaster* was extended by MR under conditions of low amino acid status, while MR did not work under conditions

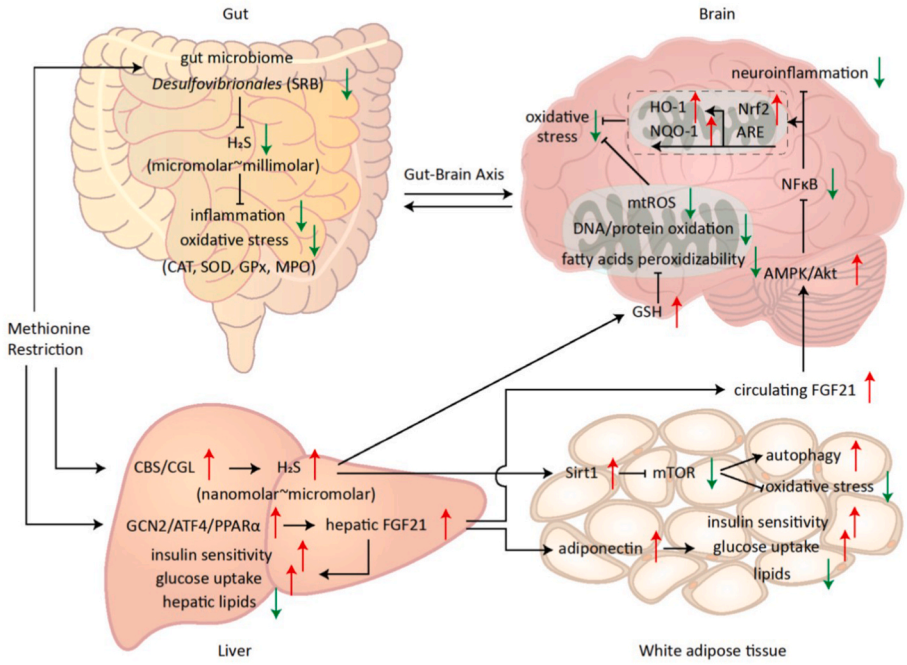

Fig. 3. The possible antioxidant mechanisms of MR in aging and aging-related diseases. [1] FGF21. MR may increase the expression of FGF21 by activating GCN2/ATF4/PPARα nutrition signaling in liver, thereby improving insulin sensitivity, promoting fat oxidation and glucose metabolism in both liver and WAT. Although FGF21 has been reported to induce the adiponectin expression and secretion in WAT, the positive benefits of glucose metabolism induced by MR may be independent of adiponectin and FGF21. Circulating FGF21 released by the liver enters the BBB, regulates AMPK/Akt and inhibits NFκB, further attenuating neuroinflammation and oxidative stress [2]. H_2S (nanomolar to micromolar concentrations) released by the liver. MR produces more H_2S by enhancing the CBS/CGL in transsulfuration pathway. On the one hand, H_2S activates autophagy and inhibits oxidative stress via regulating Sirt1 and mTOR in the WAT. On the other hand, H_2S increases the GSH and improves mitochondrial oxidative damage, including mtROS, DNA/protein oxidation and fatty acids peroxidizability in the brain [3]. Gut microbiome. MR balances the gut microbiome, especially suppresses the *Desulfovibrionales*, a kind of SRB, which could reduce sulfate to produce H_2S (high micromolar to low millimolar concentrations). Lower H_2S decreases the inflammation and oxidative stress in the gut. Moreover, gut and gut microbiome/metabolite homeostasis affects brain function, which is considered as gut-brain axis. FGF21 = fibroblast growth factor 21, WAT = white adipose tissue, BBB = blood brain barrier, CBS = cystathionine-β-synthase, CGL = cystathionine-γ-lyase, H_2S = hydrogen sulfide, GSH = glutathione, mtROS = mitochondrial ROS, SRB = sulfate-reducing bacteria, CAT = catalase, SOD = superoxide dismutase, GPx = glutathione peroxidase, MPO = myeloperoxidase.

of high amino acid status, from which may be concluded that certain conditions must be met for the beneficial effects of MR [58]. For that reason, future studies may benefit from the use of diverse combinations of methionine and other nutrients. In addition, further studies are needed to better understand the molecular mechanisms involved and apply these principles to human nutrition to positively impact aging and/or age-related chronic diseases.

However, humans have considerable difficulties remaining compliant to strict dietary changes. MR is usually implemented with diets consisting of elemental amino acids (AA) that reduce methionine content to ~0.17%. Therefore, practical implementation of MR with diets based on elemental AA is difficult because of poor palatability. The development of methods for the production of highly palatable, low-methionine proteins is a better and innovative approach, as it will solve the problem of compliance and should therefore be a future task. Additionally, a comparison of the physiological responses to different dietary methionine levels or incremental restriction should be a future objective, since it was reported that MR also produces hyperphagia [110,249].

Another experimental strategy to better understand the complex responses to MR is to study the temporal response. In addition, a better understanding of how MR improves tissue-specific and overall insulin sensitivity should also be a focus. The overall metabolic phenotype elicited by MR appears to be the product of a number of responses that require further investigation.

Furthermore, the protective effects of dietary MR on age-related gut barrier dysfunction still remain mainly unclear. Interestingly, the gut microbiome can rapidly respond to diet alterations [250] and has the potential to modulate inflammation and oxidative stress. Inflammatory bowel disease (IBD) is often associated with a severe imbalance of redox homeostasis in the intestine, whereas MR is able to modulate corresponding markers such as catalase (CAT), SOD, GPx activities, and myeloperoxidase (MPO) [251]. In addition, recent evidence suggests that intricate and crucial links between the gut microbiota and the brain involve multiple biological systems and may contribute to neurological disorders [252]. It was shown that time-restricted fasting (TRF) and intermittent energy restriction (IER) prevents colitis mice from gut microbiome composition disorder and gut leakage, thereby reducing oxidative damage in both colon and brain [253]. In addition, immune hemocytes act as signal transducers in the gut and brain, which may also affect chemokines in the brain in response to ROS stress [254]. The above studies show that the balance of the gut microbiome and the integrity of the gut barrier are closely related to redox homeostasis in the brain. A research focus should be on the fact that MR seems to alter gut microbiome/metabolites [255,256] and improve the gut barrier [257]. The interaction of gut and brain function has to be taken into consideration in future MR research.

More importantly, MR not only has beneficial effects on metabolism, but has also been shown to support the feasibility and good tolerability (nutritional status and toxicity) of cancer treatment regimens [258]. MR can specifically affect one-carbon metabolism and redox metabolism in tumor cells involved in chemotherapy and radiation. The response to MR appears to be conserved between humans and mice [259]. This is the basis that MR is likely to be a dietary intervention for adjuvant treatment of diseases such as cancer in the future. In addition, race and region should be better considered in clinical trials in the future. For example, Indian women have different serum OCM markers after methionine exposure than American women [260]. The effects of MR already found in a multitude of human studies are summarized in Table 2.

5. Prospects

The impact of nutrition on longevity and health will continue to be one of the most important issues facing society in the future. Caloric intake and protein intake are of crucial importance here. In the context of sustainability and planetary health, new factors are evolving that are important to be considered. This also affects protein and methionine intake since new protein sources are opened up [261], and new

nutritional habitus will evolve [262]. The possible antioxidant mechanisms of MR in aging and diseases are summarized in Fig. 3, which involves multiple targets. However, whether this leads to a health promotion remains to be elucidated due to many other components of such a diet. One of the future developments with regard to protein and in particular, methionine restriction will be the investigation of the mechanism of action of these diets and the translation of this theoretical knowledge into human studies. However, it must be under the guidance of professionals if implemented.

Declaration of competing interest

The authors Yuyu Zhang, Julia Jelleschitz, Tilman Grune, Weixuan Chen, Yihang Zhao, Mengzhen Jia, Yajie Wang, Zhigang Liu and Annika Höhn declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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References

[1] J. Most, V. Tosti, L.M. Redman, L. Fontana, Calorie restriction in humans: an update, Ageing Res. Rev. 39 (2017) 36–45.
[2] H. Luo, H.H. Chiang, M. Louw, A. Susanto, D. Chen, Nutrient sensing and the oxidative stress response, Trends Endocrinol. Metabol.: TEM (Trends Endocrinol. Metab.) 28 (6) (2017) 449–460.
[3] L.C.D. Pomatto, K.J.A. Davies, The role of declining adaptive homeostasis in ageing, J. Physiol. 595 (24) (2017) 7275–7309.
[4] A. Mladenovic Djordjevic, N. Loncarevic-Vasiljkovic, E.S. Gonos, Dietary restriction and oxidative stress: friends or enemies? Antioxidants Redox Signal. 34 (5) (2021) 421–438.
[5] A. Ionescu-Tucker, C.W. Cotman, Emerging roles of oxidative stress in brain aging and Alzheimer's disease, Neurobiol. Aging 107 (2021) 86–95.
[6] K.J. Min, M. Tatar, Restriction of amino acids extends lifespan in Drosophila melanogaster, Mechanisms of ageing and development 127 (7) (2006) 643–646.
[7] K. Flurkey, C.M. Astle, D.E. Harrison, Life extension by diet restriction and N-acetyl-L-cysteine in genetically heterogeneous mice, J. Gerontol. Biol. Med. Sci. 65 (12) (2010) 1275–1284.
[8] R.C. Grandison, M.D. Piper, L. Partridge, Amino-acid imbalance explains extension of lifespan by dietary restriction in Drosophila, Nature 462 (7276) (2009) 1061–1064.
[9] K. Zou, S. Rouskin, K. Dervishi, M.A. McCormick, A. Sasikumar, C. Deng, et al., Life span extension by glucose restriction is abrogated by methionine supplementation: cross-talk between glucose and methionine and implication of methionine as a key regulator of life span, Sci. Adv. 6 (32) (2020), eaba1306.
[10] S. Nakagawa, M. Lagisz, K.L. Hector, H.G. Spencer, Comparative and meta-analytic insights into life extension via dietary restriction, Aging Cell 11 (3) (2012) 401–409.
[11] S.M. Solon-Biet, A.C. McMahon, J.W.O. Ballard, K. Ruohonen, L.E. Wu, V. C. Cogger, et al., The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice, Cell Metabol. 31 (3) (2020) 654.
[12] J.D. Plummer, J.E. Johnson, Extension of cellular lifespan by methionine restriction involves alterations in central carbon metabolism and is mitophagy-dependent, Front. Cell Dev. Biol. 7 (2019) 301.
[13] J. Gomez, I. Sanchez-Roman, A. Gomez, C. Sanchez, H. Suarez, M. Lopez-Torres, et al., Methionine and homocysteine modulate the rate of ROS generation of isolated mitochondria in vitro, J. Bioenerg. Biomembr. 43 (4) (2011) 377–386.
[14] C. Hine, J.R. Mitchell, Calorie restriction and methionine restriction in control of endogenous hydrogen sulfide production by the transsulfuration pathway, Exp. Gerontol. 68 (2015) 26–32.
[15] A.A. Parkhitko, P. Jouandin, S.E. Mohr, N. Perrimon, Methionine metabolism and methyltransferases in the regulation of aging and lifespan extension across species, Aging Cell 18 (6) (2019), e13034.
[16] J.T. Brosnan, M.E. Brosnan, The sulfur-containing amino acids: an overview, J. Nutr. 136 (6) (2006), 1636S-40S.
[17] Y. Martínez, X. Li, G. Liu, P. Bin, W. Yan, D. Más, et al., The role of methionine on metabolism, oxidative stress, and diseases, Amino Acids 49 (12) (2017) 2091–2098.
[18] M. Kitada, Y. Ogura, I. Monno, J. Xu, D. Koya, Effect of methionine restriction on aging: its relationship to oxidative stress, Biomedicines 9 (2) (2021) 130.
[19] N. Minois, D. Carmona-Gutierrez, F. Madeo, Polyamines in aging and disease, Aging 3 (8) (2011) 716–732.
[20] L. Lauinger, P. Kaiser, Sensing and signaling of methionine metabolism, Metabolites 11 (2) (2021) 83.
[21] J.D. Finkelstein, Methionine metabolism in mammals, J. Nutr. Biochem. 1 (5) (1990) 228–237.
[22] A.K. Weickhmann, H. Keller, J.P. Wurm, E. Strebitzer, M.A. Juen, J. Kremser, et al., The structure of the SAM/SAH-binding riboswitch, Nucleic Acids Res. 47 (5) (2019) 2654–2665.
[23] A.A. Parkhitko, P. Jouandin, S.E. Mohr, N. Perrimon, Methionine metabolism and methyltransferases in the regulation of aging and lifespan extension across species, Aging Cell 18 (6) (2019).
[24] B. Deplancke, H.R. Gaskins, Redox control of the transsulfuration and glutathione biosynthesis pathways, Curr. Opin. Clin. Nutr. Metab. Care 5 (1) (2002) 85–92.
[25] R. Franco, O.J. Schoneveld, A. Pappa, M.I. Panayiotidis, The central role of glutathione in the pathophysiology of human diseases, Arch. Physiol. Biochem. 113 (4–5) (2007) 234–258.
[26] O. Zitka, S. Skalickova, J. Gumulec, M. Masarik, V. Adam, J. Hubalek, et al., Redox status expressed as GSH:GSSG ratio as a marker for oxidative stress in paediatric tumour patients, Oncol. Lett. 4 (6) (2012) 1247–1253.
[27] E. Kalinina, M. Novichkova, Glutathione in protein redox modulation through S-glutathionylation and S-nitrosylation, Molecules 26 (2) (2021) 435.
[28] D.P. Jones, Redefining oxidative stress, Antioxidants Redox Signal. 8 (9–10) (2006) 1865–1879.
[29] Y. Park, T.R. Ziegler, N. Gletsu-Miller, Y. Liang, T. Yu, C.J. Accardi, et al., Postprandial cysteine/cystine redox potential in human plasma varies with meal content of sulfur amino acids, J. Nutr. 140 (4) (2010) 760–765.
[30] Y.O. Mannery, T.R. Ziegler, Y. Park, D.P. Jones, Oxidation of plasma cysteine/cystine and GSH/GSSG redox potentials by acetaminophen and sulfur amino acid insufficiency in humans, J. Pharmacol. Exp. Therapeut. 333 (3) (2010) 939–947.
[31] J.I. Sbodio, S.H. Snyder, B.D. Paul, Regulators of the transsulfuration pathway, Br. J. Pharmacol. 176 (4) (2019) 583–593.
[32] C.-Q. Chen, H. Xin, Y.-Z. Zhu, Hydrogen sulfide: third gaseous transmitter, but with great pharmacological potential, Acta Pharmacol. Sin. 28 (11) (2007) 1709–1716.
[33] O. Kabil, V. Vitvitsky, R. Banerjee, Sulfur as a signaling nutrient through hydrogen sulfide, Annu. Rev. Nutr. 34 (1) (2014) 171–205.
[34] P. Li, H. Liu, X. Shi, V. Prokosch, Hydrogen sulfide: novel endogenous and exogenous modulator of oxidative stress in retinal degeneration diseases, Molecules 26 (9) (2021) 2411.
[35] M. Gulsen, Z. Yesilova, S. Bagci, A. Uygun, A. Ozcan, C.N. Ercin, et al., Elevated plasma homocysteine concentrations as a predictor of steatohepatitis in patients with non-alcoholic fatty liver disease, J. Gastroenterol. Hepatol. 20 (9) (2005) 1448–1455.
[36] G.R. Hajer, Y. van der Graaf, J.K. Olijhoek, M.C. Verhaar, F.L. Visseren, S. S. Group, Levels of homocysteine are increased in metabolic syndrome patients but are not associated with an increased cardiovascular risk, in contrast to patients without the metabolic syndrome, Heart 93 (2) (2007) 216–220.
[37] S.C. de Carvalho, M.T. Muniz, M.D. Siqueira, E.R. Siqueira, A.V. Gomes, K. A. Silva, et al., Plasmatic higher levels of homocysteine in non-alcoholic fatty liver disease (NAFLD), Nutr. J. 12 (2013) 37.
[38] R.C. Austin, S.R. Lentz, G.H. Werstuck, Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease, Cell Death Differ. 11 (Suppl 1) (2004) S56–S64.
[39] H. Refsum, P.M. Ueland, O. Nygard, S.E. Vollset, Homocysteine and cardiovascular disease, Annu. Rev. Med. 49 (1998) 31–62.
[40] A.S. Henkel, M.S. Elias, R.M. Green, Homocysteine supplementation attenuates the unfolded protein response in a murine nutritional model of steatohepatitis, J. Biol. Chem. 284 (46) (2009) 31807–31816.
[41] C. Matte, F.M. Stefanello, V. Mackedanz, C.D. Pederzolli, M.L. Lamers, C.S. Dutra-Filho, et al., Homocysteine induces oxidative stress, inflammatory infiltration, fibrosis and reduces glycogen/glycoprotein content in liver of rats, Int. J. Dev. Neurosci. 27 (4) (2009) 337–344.
[42] P.C. Trackman, R.H. Abeles, Methionine synthesis from 5'-S-Methylthioadenosine. Resolution of enzyme activities and identification of 1-phospho-5-S methylthioribulose, J. Biol. Chem. 258 (11) (1983) 6717–6720.
[43] K.C. Das, H.P. Misra, Hydroxyl radical scavenging and singlet oxygen quenching properties of polyamines, Mol. Cell. Biochem. 262 (1–2) (2004) 127–133.
[44] T.A. Keinänen, M.T. Hyvönen, L. Alhonen, J. Vepsäläinen, A.R. Khomutov, Selective regulation of polyamine metabolism with methylated polyamine analogues, Amino Acids 46 (3) (2014) 605–620.
[45] A. Sekowska, H. Ashida, A. Danchin, Revisiting the methionine salvage pathway and its paralogues, Microb. Biotechnol. 12 (1) (2019) 77–97.
[46] G.P. Ables, C.E. Perrone, D. Orentreich, N. Orentreich, Methionine-restricted C57BL/6J mice are resistant to diet-induced obesity and insulin resistance but have low bone density, PLoS One 7 (12) (2012), e51357.
[47] E.K. Lees, E. Król, L. Grant, K. Shearer, C. Wyse, E. Moncur, et al., Methionine restriction restores a younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21, Aging Cell 13 (5) (2014) 817–827.

[48] T. Castaño-Martinez, F. Schumacher, S. Schumacher, B. Kochlik, D. Weber, T. Grune, et al., Methionine restriction prevents onset of type 2 diabetes in NZO mice, Faseb. J. : Off. Pub. Federation Am. Soc. Exp. Biol. 33 (6) (2019) 7092–7102.

[49] B.C. Lee, A. Kaya, V.N. Gladyshev, Methionine restriction and life-span control, Ann. N. Y. Acad. Sci. 1363 (1) (2016) 116–124.

[50] M. Souza Matos, B. Platt, M. Delibegović, Effects of dietary restriction on metabolic and cognitive health, Proc. Nutr. Soc. 80 (2) (2021) 126–138.

[51] M.F. McCarty, J. Barroso-Aranda, F. Contreras, The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy, Med. Hypotheses 72 (2) (2009) 125–128.

[52] Z.B. Ball, R.H. Barnes, M.B. Visscher, The effects of dietary caloric restriction on maturity and senescence, with particular reference to fertility and longevity, Am. J. Physiol. 150 (3) (1947) 511–519.

[53] G.P. Ables, J.R. Hens, S.N. Nichenametla, Methionine restriction beyond life-span extension, Ann. N. Y. Acad. Sci. 1363 (1) (2016) 68–79.

[54] M. Solon-Biet, Samantha, C. Mcmahon, Aisling, O. Ballard, J. William, K. Ruohonen, E. Wu, Lindsay, C. Cogger, Victoria, et al., The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice, Cell Metabol. 19 (3) (2014) 418–430.

[55] N. Orentreich, J.R. Matias, A. DeFelice, J.A. Zimmerman, Low methionine ingestion by rats extends life span, J. Nutr. 123 (2) (1993) 269–274.

[56] A. Sanz, P. Caro, V. Ayala, M. Portero-Otin, R. Pamplona, G. Barja, Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins, Faseb. J. 20 (8) (2006) 1064–1073.

[57] Z. Wu, L. Song, S.Q. Liu, D. Huang, Independent and additive effects of glutamic acid and methionine on yeast longevity, PLoS One 8 (11) (2013), e79319.

[58] B.C. Lee, A. Kaya, S. Ma, G. Kim, M.V. Gerashchenko, S.H. Yim, et al., Methionine restriction extends lifespan of Drosophila melanogaster under conditions of low amino-acid status, Nat. Commun. 5 (1) (2014).

[59] F. Cabreiro, C. Au, K.-Y. Leung, N. Vergara-Irigaray, M. Cochemé, Helena, T. Noori, et al., Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism, Cell 153 (1) (2013) 228–239.

[60] R.A. Miller, G. Buehner, Y. Chang, J.M. Harper, R. Sigler, M. Smith-Wheelock, Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance, Aging Cell 4 (3) (2005) 119–125.

[61] C. Bárcena, P.M. Quirós, S. Durand, P. Mayoral, F. Rodríguez, X.M. Caravia, et al., Methionine restriction extends lifespan in progeroid mice and alters lipid and bile acid metabolism, Cell Rep. 24 (9) (2018) 2392–2403.

[62] S.N. Nichenametla, D.A.L. Mattocks, V.L. Malloy, Age-at-onset-dependent effects of sulfur amino acid restriction on markers of growth and stress in male F344 rats, Aging Cell 19 (7) (2020), e13177.

[63] J.P. Richie, Y. Leutzinger, S. Parthasarathy, V. Malloy, N. Orentreich, J. A. Zimmerman, Methionine restriction increases blood glutathione and longevity in F344 rats, Faseb. J. 8 (15) (1994) 1302–1307.

[64] L. Sun, A.A. Sadighi Akha, R.A. Miller, J.M. Harper, Life-span extension in mice by preweaning food restriction and by methionine restriction in middle age, J. Gerontol. Ser. A : Biol. Sci. Med. Sci. 64A (7) (2009) 711–722.

[65] S. Maddineni, S. Nichenametla, R. Sinha, R.P. Wilson, J.P. Richie, Methionine restriction affects oxidative stress and glutathione-related redox pathways in the rat, Exp. Biol. Med. 238 (4) (2013) 392–399.

[66] R. Kozieł, C. Ruckenstuhl, E. Albertini, M. Neuhaus, C. Netzberger, M. Bust, et al., Methionine restriction slows down senescence in human diploid fibroblasts, Aging Cell 13 (6) (2014) 1038–1048.

[67] I. Sanchez-Roman, G. Barja, Regulation of longevity and oxidative stress by nutritional interventions: role of methionine restriction, Exp. Gerontol. 48 (10) (2013) 1030–1042.

[68] M. Kaeberlein, P. Kapahi, Cell signaling, Aging is RSKy business. Science. 326 (5949) (2009) 55–56.

[69] P. Kapahi, D. Chen, A.N. Rogers, S.D. Katewa, P.W.-L. Li, E.L. Thomas, et al., With tor, less is more: a key role for the conserved nutrient-sensing tor pathway in aging, Cell Metabol. 11 (6) (2010) 453–465.

[70] M. Kitada, J. Xu, Y. Ogura, I. Monno, D. Koya, Mechanism of activation of mechanistic target of rapamycin complex 1 by methionine, Front. Cell Dev. Biol. 8 (2020) 715.

[71] J. Kim, K.-L. Guan, mTOR as a central hub of nutrient signalling and cell growth, Nat. Cell Biol. 21 (1) (2019) 63–71.

[72] G.Y. Liu, D.M. Sabatini, mTOR at the nexus of nutrition, growth, ageing and disease, Nat. Rev. Mol. Cell Biol. 21 (4) (2020) 183–203.

[73] Y. Zhou, Z. Zhou, J. Peng, J.J. Loor, Methionine and valine activate the mammalian target of rapamycin complex 1 pathway through heterodimeric amino acid taste receptor (TAS1R1/TAS1R3) and intracellular Ca2+ in bovine mammary epithelial cells, J. Dairy Sci. 101 (12) (2018) 11354–11363.

[74] T. Eisenberg, M. Abdellatif, S. Schroeder, U. Primessnig, S. Stekovic, T. Pendl, et al., Cardioprotection and lifespan extension by the natural polyamine spermidine, Nat. Med. 22 (12) (2016) 1428–1438.

[75] T. Eisenberg, H. Knauer, A. Schauer, S. Büttner, C. Ruckenstuhl, D. Carmona-Gutierrez, et al., Induction of autophagy by spermidine promotes longevity, Nat. Cell Biol. 11 (11) (2009) 1305–1314.

[76] T.-T. Xu, H. Li, Z. Dai, G.K. Lau, B.-Y. Li, W.-L. Zhu, et al., Spermidine and spermine delay brain aging by inducing autophagy in SAMP8 mice, Aging 12 (7) (2020) 6401–6414.

[77] F. Madeo, M.A. Bauer, D. Carmona-Gutierrez, G. Kroemer, Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? Autophagy 15 (1) (2019) 165–168.

[78] E.K. Lees, E. Król, L. Grant, K. Shearer, C. Wyse, E. Moncur, et al., Methionine restriction restores a younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21, Aging Cell 13 (5) (2014) 817–827.

[79] H. Kabil, O. Kabil, R. Banerjee, L.G. Harshman, S.D. Pletcher, Increased transsulfuration mediates longevity and dietary restriction in Drosophila, Proc. Natl. Acad. Sci. USA 108 (40) (2011) 16831–16836.

[80] N. Mota-Martorell, M. Jové, C. Borrás, R. Berdún, È. Obis, J. Sol, et al., Methionine transsulfuration pathway is upregulated in long-lived humans, Free Radic. Biol. Med. 162 (2021) 38–52.

[81] C. Hine, E. Harputlugil, Y. Zhang, C. Ruckenstuhl, C. Lee, Byung, L. Brace, et al., Endogenous hydrogen sulfide production is essential for dietary restriction benefits, Cell 160 (1–2) (2015) 132–144.

[82] S.-Y. Wang, W.-J. Wang, J.-Q. Liu, Y.-H. Song, P. Li, X.-F. Sun, et al., Methionine restriction delays senescence and suppresses the senescence-associated secretory phenotype in the kidney through endogenous hydrogen sulfide, Cell Cycle 18 (14) (2019) 1573–1587.

[83] G. Wu, Y. Wang, Y. Yang, Y. Shi, J. Sun, Y. Xu, et al., Dietary methionine restriction upregulates endogenous H(2) S via miR-328-3p: a potential mechanism to improve liver protein metabolism efficiency in a mouse model of high-fat-diet-induced obesity, Mol. Nutr. Food Res. 63 (5) (2019), e1800735.

[84] Y. Xu, Y. Yang, J. Sun, Y. Zhang, T. Luo, B. Li, et al., Dietary methionine restriction ameliorates the impairment of learning and memory function induced by obesity in mice, Food Funct. 10 (3) (2019) 1411–1425.

[85] Y. Yang, Y. Wang, J. Sun, J. Zhang, H. Guo, Y. Shi, et al., Dietary methionine restriction reduces hepatic steatosis and oxidative stress in high-fat-fed mice by promoting H(2)S production, Food Funct. 10 (1) (2019) 61–77.

[86] L. Han, G. Wu, C. Feng, Y. Yang, B. Li, Y. Ge, et al., Dietary methionine restriction improves the impairment of cardiac function in middle-aged obese mice, Food Funct. 11 (2) (2020) 1764–1778.

[87] J.P. Richie, D. Komninou, Y. Leutzinger, W. Kleinman, N. Orentreich, V. Malloy, et al., Tissue glutathione and cysteine levels in methionine-restricted rats, Nutrition 20 (9) (2004) 800–805.

[88] H.M. Brown-Borg, S. Rakoczy, J.A. Wonderlich, V. Armstrong, L. Rojanathammanee, Altered dietary methionine differentially impacts glutathione and methionine metabolism in long-living growth hormone-deficient Ames dwarf and wild-type mice, Longev. Heal. 3 (1) (2014) 10.

[89] S. Ghosh, L.A. Forney, D. Wanders, K.P. Stone, T.W. Gettys, An integrative analysis of tissue-specific transcriptomic and metabolomic responses to short-term dietary methionine restriction in mice, PLoS One 12 (5) (2017), e0177513.

[90] A. Sanz, P. Caro, V. Ayala, M. Portero-Otin, R. Pamplona, G. Barja, Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins, Faseb. J. 20 (8) (2006) 1064–1073.

[91] P. Caro, J. Gómez, M. López-Torres, I. Sánchez, A. Naudí, M. Jove, et al., Forty percent and eighty percent methionine restriction decrease mitochondrial ROS generation and oxidative stress in rat liver, Biogerontology 9 (3) (2008) 183–196.

[92] P. Caro, J. Gomez, I. Sanchez, A. Naudi, V. Ayala, M. López-Torres, et al., Forty percent methionine restriction decreases mitochondrial oxygen radical production and leak at complex I during forward electron flow and lowers oxidative damage to proteins and mitochondrial DNA in rat kidney and brain mitochondria, Rejuvenation Res. 12 (6) (2009) 421–434.

[93] I. Spasojevic, J. Bogdanovic Pristov, L. Vujisic, M. Spasic, The reaction of methionine with hydroxyl radical: reactive intermediates and methanethiol production, Amino Acids 42 (6) (2012) 2439–2445.

[94] E.G. Lakatta, D. Levy, Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease, Circulation 107 (1) (2003) 139–146.

[95] D. Mozaffarian, Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review, Circulation 133 (2) (2016) 187–225.

[96] J.A. Buffa, K.A. Romano, M.F. Copeland, D.B. Cody, W. Zhu, R. Galvez, et al., The microbial gbu gene cluster links cardiovascular disease risk associated with red meat consumption to microbiota L-carnitine catabolism, Nat Microbiol 7 (1) (2022) 73–86.

[97] R.H. Eckel, J.M. Jakicic, J.D. Ard, J.M. de Jesus, N. Houston Miller, V.S. Hubbard, et al., AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines, Circulation 129 (25) (2013) S76–S99, 2014.

[98] F.B. Ortega, C.J. Lavie, S.N. Blair, Obesity and cardiovascular disease, Circ. Res. 118 (11) (2016) 1752–1770.

[99] G. Yosipovitch, A. DeVore, A. Dawn, Obesity and the skin: skin physiology and skin manifestations of obesity, J. Am. Acad. Dermatol. 56 (6) (2007) 901–916, quiz 17-20.

[100] R.S. Ahima, Connecting obesity, aging and diabetes, Nat. Med. 15 (9) (2009) 996–997.

[101] P. Verhoef, T. van Vliet, M.R. Olthof, M.B. Katan, A high-protein diet increases postprandial but not fasting plasma total homocysteine concentrations: a dietary controlled, crossover trial in healthy volunteers, Am. J. Clin. Nutr. 82 (3) (2005) 553–558.

[102] S. Sucher, M. Markova, S. Hornemann, O. Pivovarova, N. Rudovich, R. Thomann, et al., Comparison of the effects of diets high in animal or plant protein on metabolic and cardiovascular markers in type 2 diabetes: a randomized clinical trial, Diabetes Obes. Metabol. 19 (7) (2017) 944–952.

[103] C.R. Pischke, G. Weidner, M. Elliott-Eller, L. Scherwitz, T.A. Merritt-Worden, R. Marlin, et al., Comparison of coronary risk factors and quality of life in coronary artery disease patients with versus without diabetes mellitus, Am. J. Cardiol. 97 (9) (2006) 1267–1273.
[104] A.K. Elshorbagy, M. Valdivia-Garcia, H. Refsum, A.D. Smith, D.A. Mattocks, C. E. Perrone, Sulfur amino acids in methionine-restricted rats: hyperhomocysteinemia, Nutrition 26 (11–12) (2010) 1201–1204.
[105] G.P. Ables, J.E. Johnson, Pleiotropic responses to methionine restriction, Exp. Gerontol. 94 (2017) 83–88.
[106] J.L. Kuk, T.J. Saunders, L.E. Davidson, R. Ross, Age-related changes in total and regional fat distribution, Ageing Res. Rev. 8 (4) (2009) 339–348.
[107] S. Yusuf, S. Hawken, S. Ounpuu, T. Dans, A. Avezum, F. Lanas, et al., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, Lancet (London, England) 364 (9438) (2004) 937–952.
[108] H.M. Brown-Borg, R. Buffenstein, Cutting back on the essentials: can manipulating intake of specific amino acids modulate health and lifespan? Ageing Res. Rev. 39 (2017) 87–95.
[109] N.E. Cummings, D.W. Lamming, Regulation of metabolic health and aging by nutrient-sensitive signaling pathways, Mol. Cell. Endocrinol. 455 (2017) 13–22.
[110] B.E. Hasek, L.K. Stewart, T.M. Henagan, A. Boudreau, N.R. Lenard, C. Black, et al., Dietary methionine restriction enhances metabolic flexibility and increases uncoupled respiration in both fed and fasted states, Am. J. Physiol. Regul. Integr. Comp. Physiol. 299 (3) (2010) R728–R739.
[111] Y. Yang, J. Zhang, G. Wu, J. Sun, Y. Wang, H. Guo, et al., Dietary methionine restriction regulated energy and protein homeostasis by improving thyroid function in high fat diet mice, Food Funct. 9 (7) (2018) 3718–3731.
[112] L. Wang, B. Ren, Q. Zhang, C. Chu, Z. Zhao, J. Wu, et al., Methionine restriction alleviates high-fat diet-induced obesity: involvement of diurnal metabolism of lipids and bile acids, Biochim. Biophys. Acta, Mol. Basis Dis. 1866 (11) (2020), 165908.
[113] V.L. Malloy, C.E. Perrone, D.A. Mattocks, G.P. Ables, N.S. Caliendo, D. S. Orentreich, et al., Methionine restriction prevents the progression of hepatic steatosis in leptin-deficient obese mice, Metab. Clin. Exp. 62 (11) (2013) 1651–1661.
[114] E.P. Plaisance, F.L. Greenway, A. Boudreau, K.L. Hill, W.D. Johnson, R.A. Krajcik, et al., Dietary methionine restriction increases fat oxidation in obese adults with metabolic syndrome, J. Clin. Endocrinol. Metabol. 96 (5) (2011) E836–E840.
[115] B.E. Hasek, A. Boudreau, J. Shin, D. Feng, M. Hulver, N.T. Van, et al., Remodeling the integration of lipid metabolism between liver and adipose tissue by dietary methionine restriction in rats, Diabetes 62 (10) (2013) 3362–3372.
[116] D. Yu, S.E. Yang, B.R. Miller, J.A. Wisinski, D.S. Sherman, J.A. Brinkman, et al., Short-term methionine deprivation improves metabolic health via sexually dimorphic, mTORC1-independent mechanisms, Faseb. J. 32 (6) (2018) 3471–3482.
[117] H. Sies, Oxidative stress: a concept in redox biology and medicine, Redox Biol. 4 (2015) 180–183.
[118] M.J. Picklo, E.K. Long, E.E. Vomhof-DeKrey, Glutathionyl systems and metabolic dysfunction in obesity, Nutr. Rev. 73 (12) (2015) 858–868.
[119] Y. Yang, Y. Zhang, Y. Xu, T. Luo, Y. Ge, Y. Jiang, et al., Dietary methionine restriction improves the gut microbiota and reduces intestinal permeability and inflammation in high-fat-fed mice, Food Funct. 10 (9) (2019) 5952–5968.
[120] K. Itoh, N. Wakabayashi, Y. Katoh, T. Ishii, K. Igarashi, J.D. Engel, et al., Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain, Genes Dev. 13 (1) (1999) 76–86.
[121] G. Wagner, J. Lindroos-Christensen, E. Einwallner, J. Husa, T.C. Zapf, K. Lipp, et al., HO-1 inhibits preadipocyte proliferation and differentiation at the onset of obesity via ROS dependent activation of Akt2, Sci. Rep. 7 (2017), 40881.
[122] Z. Zhang, S. Zhou, X. Jiang, Y.H. Wang, F. Li, Y.G. Wang, et al., The role of the Nrf2/Keap1 pathway in obesity and metabolic syndrome, Rev. Endocr. Metab. Disord. 16 (1) (2015) 35–45.
[123] S. Maddineni, S. Nichenametla, R. Sinha, R.P. Wilson, J.P. Richie Jr., Methionine restriction affects oxidative stress and glutathione-related redox pathways in the rat, Experimental biology and medicine (Maywood, NJ) 238 (4) (2013) 392–399.
[124] Y. Yang, J. Qian, B. Li, M. Lu, G. Le, Y. Xie, Metabolomics based on (1)H-nmr reveal the regulatory mechanisms of dietary methionine restriction on splenic metabolic dysfunction in obese mice, Foods (Basel, Switzerland) 10 (10) (2021).
[125] W. B'Chir, A.C. Maurin, V. Carraro, J. Averous, C. Jousse, Y. Muranishi, et al., The eIF2α/ATF4 pathway is essential for stress-induced autophagy gene expression, Nucleic Acids Res. 41 (16) (2013) 7683–7699.
[126] W.O. Jonsson, N.S. Margolies, E.T. Mirek, Q. Zhang, M.A. Linden, C.M. Hill, et al., Physiologic responses to dietary sulfur amino acid restriction in mice are influenced by Atf4 status and biological sex, J. Nutr. 151 (4) (2021) 785–799.
[127] C. Statzer, J. Meng, R. Venz, M. Bland, S. Robida-Stubbs, K. Patel, et al., ATF-4 and hydrogen sulfide signalling mediate longevity in response to inhibition of translation or mTORC1, Nat. Commun. 13 (1) (2022) 967.
[128] M. Whiteman, K.M. Gooding, J.L. Whatmore, C.I. Ball, D. Mawson, K. Skinner, et al., Adiposity is a major determinant of plasma levels of the novel vasodilator hydrogen sulphide, Diabetologia 53 (8) (2010) 1722–1726.
[129] T. Meng, W. Qin, B. Liu, SIRT1 antagonizes oxidative stress in diabetic vascular complication, Front. Endocrinol. 11 (2020), 568861.
[130] A. Włodarski, J. Strycharz, A. Wróblewski, J. Kasznicki, J. Drzewoski, A. Śliwińska, The role of microRNAs in metabolic syndrome-related oxidative stress, Int. J. Mol. Sci. 21 (18) (2020).
[131] L. Spazzafumo, F. Olivieri, A.M. Abbatecola, G. Castellani, D. Monti, R. Lisa, et al., Remodelling of biological parameters during human ageing: evidence for complex regulation in longevity and in type 2 diabetes, Age (Dordrecht, Netherlands) 35 (2) (2013) 419–429.
[132] P.K. Fazeli, H. Lee, M.L. Steinhauser, Aging is a powerful risk factor for type 2 diabetes mellitus independent of body mass index, Gerontology 66 (2) (2020) 209–210.
[133] M.R. MacArthur, S.J. Mitchell, J.H. Treviño-Villarreal, Y. Grondin, J.S. Reynolds, P. Kip, et al., Total protein, not amino acid composition, differs in plant-based versus omnivorous dietary patterns and determines metabolic health effects in mice, Cell Metabol. 33 (9) (2021), 1808-19.e2.
[134] M. Markova, L. Koelman, S. Hornemann, O. Pivovarova, S. Sucher, J. Machann, et al., Effects of plant and animal high protein diets on immune-inflammatory biomarkers: a 6-week intervention trial, Clin. Nutr. 39 (3) (2020) 862–869.
[135] L. Azadbakht, M. Kimiagar, Y. Mehrabi, A. Esmaillzadeh, F.B. Hu, W.C. Willett, Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome, Br. J. Nutr. 98 (4) (2007) 807–813.
[136] Z. Hematdar, N. Ghasemifard, G. Phishdad, S. Faghih, Substitution of red meat with soybean but not non- soy legumes improves inflammation in patients with type 2 diabetes; a randomized clinical trial, J. Diabetes Metab. Disord. 17 (2) (2018) 111–116.
[137] S. Yalcinkaya, Y. Unlucerci, M. Giris, V. Olgac, S. Dogru-Abbasoglu, M. Uysal, Oxidative and nitrosative stress and apoptosis in the liver of rats fed on high methionine diet: protective effect of taurine, Nutrition 25 (4) (2009) 436–444.
[138] D. Wanders, L.A. Forney, K.P. Stone, D.H. Burk, A. Pierse, T.W. Gettys, FGF21 mediates the thermogenic and insulin-sensitizing effects of dietary methionine restriction but not its effects on hepatic lipid metabolism, Diabetes 66 (4) (2017) 858–867.
[139] K.P. Stone, D. Wanders, M. Orgeron, C.C. Cortez, T.W. Gettys, Mechanisms of increased in vivo insulin sensitivity by dietary methionine restriction in mice, Diabetes 63 (11) (2014) 3721–3733.
[140] T. Luo, Y. Yang, Y. Xu, Q. Gao, G. Wu, Y. Jiang, et al., Dietary methionine restriction improves glucose metabolism in the skeletal muscle of obese mice, Food Funct. 10 (5) (2019) 2676–2690.
[141] M. Kitada, Y. Ogura, I. Monno, J. Xu, D. Koya, Methionine abrogates the renoprotective effect of a low-protein diet against diabetic kidney disease in obese rats with type 2 diabetes, Aging 12 (5) (2020) 4489–4505.
[142] Z. Ying, H. Zhang, W. Su, L. Zhou, F. Wang, Y. Li, et al., Dietary methionine restriction alleviates hyperglycemia in pigs with intrauterine growth restriction by enhancing hepatic protein kinase B signaling and glycogen synthesis, J. Nutr. 147 (10) (2017) 1892–1899.
[143] P.W. Sullivan, E.H. Morrato, V. Ghushchyan, H.R. Wyatt, J.O. Hill, Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S, 2000-2002, Diabetes Care 28 (7) (2005) 1599–1603.
[144] J.L. Evans, B.A. Maddux, I.D. Goldfine, The molecular basis for oxidative stress-induced insulin resistance, Antioxidants Redox Signal. 7 (7–8) (2005) 1040–1052.
[145] Q. Liang, L. Zhong, J. Zhang, Y. Wang, S.R. Bornstein, C.R. Triggle, et al., FGF21 maintains glucose homeostasis by mediating the cross talk between liver and brain during prolonged fasting, Diabetes 63 (12) (2014) 4064–4075.
[146] L. Grant, E.K. Lees, L.A. Forney, N. Mody, T. Gettys, P.A. Brown, et al., Methionine restriction improves renal insulin signalling in aged kidneys, Mechanisms of ageing and development 157 (2016) 35–43.
[147] C.W. Tsai, A.H. Lin, T.S. Wang, K.L. Liu, H.W. Chen, C.K. Lii, Methionine restriction up-regulates the expression of the pi class of glutathione S-transferase partially via the extracellular signal-regulated kinase-activator protein-1 signaling pathway initiated by glutathione depletion, Mol. Nutr. Food Res. 54 (6) (2010) 841–850.
[148] Y. Cheng, J. Zhang, W. Guo, F. Li, W. Sun, J. Chen, et al., Up-regulation of Nrf2 is involved in FGF21-mediated fenofibrate protection against type 1 diabetic nephropathy, Free Radic. Biol. Med. 93 (2016) 94–109.
[149] S. Sharma, T. Dixon, S. Jung, E.C. Graff, L.A. Forney, T.W. Gettys, et al., Dietary methionine restriction reduces inflammation independent of FGF21 action, Obesity 27 (8) (2019) 1305–1313.
[150] D. Wanders, K.P. Stone, L.A. Forney, C.C. Cortez, K.N. Dille, J. Simon, et al., Role of GCN2-independent signaling through a noncanonical PERK/NRF2 pathway in the physiological responses to dietary methionine restriction, Diabetes 65 (6) (2016) 1499–1510.
[151] J. Mimura, A. Inose-Maruyama, S. Taniuchi, K. Kosaka, H. Yoshida, H. Yamazaki, et al., Concomitant Nrf2- and ATF4-activation by carnosic acid cooperatively induces expression of cytoprotective genes, Int. J. Mol. Sci. 20 (7) (2019).
[152] H. Fang, K.P. Stone, S. Ghosh, L.A. Forney, L.C. Sims, L. Vincik, et al., Hepatic Nfe2l2 is not an essential mediator of the metabolic phenotype produced by dietary methionine restriction, Nutrients 13 (6) (2021).
[153] Z. Lin, H. Tian, K.S. Lam, S. Lin, R.C. Hoo, M. Konishi, et al., Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice, Cell Metabol. 17 (5) (2013) 779–789.
[154] W.L. Holland, A.C. Adams, J.T. Brozinick, H.H. Bui, Y. Miyauchi, C.M. Kusminski, et al., An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice, Cell Metabol. 17 (5) (2013) 790–797.
[155] D. Cooke, D. Mattocks, S.N. Nichenametla, R.P. Anunciado-Koza, R.A. Koza, G. P. Ables, Weight loss and concomitant adipose autophagy in methionine-restricted obese mice is not dependent on adiponectin or FGF21, Obesity 28 (6) (2020) 1075–1085.
[156] R. Pamplona, C. Borras, M. Jové, I. Pradas, I. Ferrer, J. Viña, Redox lipidomics to better understand brain aging and function, Free Radic. Biol. Med. 144 (2019) 310–321.

[157] S.E. Arnold, Z. Arvanitakis, S.L. Macauley-Rambach, A.M. Koenig, H.Y. Wang, R. S. Ahima, et al., Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums, Nat. Rev. Neurol. 14 (3) (2018) 168–181.
[158] Z. Ungvari, G. Kaley, R. de Cabo, W.E. Sonntag, A. Csiszar, Mechanisms of vascular aging: new perspectives, J. Gerontol. Biol. Med. Sci. 65 (10) (2010) 1028–1041.
[159] Y. Hou, X. Dan, M. Babbar, Y. Wei, S.G. Hasselbalch, D.L. Croteau, et al., Ageing as a risk factor for neurodegenerative disease, Nat. Rev. Neurol. 15 (10) (2019) 565–581.
[160] K. He, F.B. Hu, G.A. Colditz, J.E. Manson, W.C. Willett, S. Liu, Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women, Int. J. Obes. Relat. Metab. Disord. : J. Int. Assoc. Stud. Obes 28 (12) (2004) 1569–1574.
[161] F.B. Hu, Plant-based foods and prevention of cardiovascular disease: an overview, Am. J. Clin. Nutr. 78 (3 Suppl) (2003), 544s-51s.
[162] J.W. Finley, The antioxidant responsive element (ARE) may explain the protective effects of cruciferous vegetables on cancer, Nutr. Rev. 61 (7) (2003) 250–254.
[163] J.J. Carrero, A. González-Ortiz, C.M. Avesani, S.J.L. Bakker, V. Bellizzi, P. Chauveau, et al., Plant-based diets to manage the risks and complications of chronic kidney disease, Nat. Rev. Nephrol. 16 (9) (2020) 525–542.
[164] D.B. Ibsen, A.H. Christiansen, A. Olsen, A. Tjønneland, K. Overvad, A. Wolk, et al., Adherence to the EAT-lancet diet and risk of stroke and stroke subtypes: a cohort study, Stroke 53 (1) (2022) 154–163.
[165] B. Strasser, J.M. Gostner, D. Fuchs, Mood, food, and cognition: role of tryptophan and serotonin, Curr. Opin. Clin. Nutr. Metab. Care 19 (1) (2016) 55–61.
[166] J. Fu, Q. Liu, M. Zhang, C. Sun, Y. Du, Y. Zhu, et al., Association between methionine cycle metabolite-related diets and mild cognitive impairment in older Chinese adults: a population-based observational study, Nutr. Neurosci. (2021) 1–14.
[167] Z. Liu, X. Dai, H. Zhang, R. Shi, Y. Hui, X. Jin, et al., Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment, Nat. Commun. 11 (1) (2020) 855.
[168] B. Martin, M.P. Mattson, S. Maudsley, Caloric restriction and intermittent fasting: two potential diets for successful brain aging, Ageing Res. Rev. 5 (3) (2006) 332–353.
[169] R. de Cabo, M.P. Mattson, Effects of intermittent fasting on health, aging, and disease, N. Engl. J. Med. 381 (26) (2019) 2541–2551.
[170] R. Antony, Y. Li, BDNF secretion from C2C12 cells is enhanced by methionine restriction, Biochem. Biophys. Res. Commun. 533 (4) (2020) 1347–1351.
[171] T.G. Anthony, D.W. Gietzen, Detection of amino acid deprivation in the central nervous system, Curr. Opin. Clin. Nutr. Metab. Care 16 (1) (2013) 96–101.
[172] D. Ishii, D. Matsuzawa, S. Matsuda, H. Tomizawa, C. Sutoh, E. Shimizu, Methyl donor-deficient diet during development can affect fear and anxiety in adulthood in C57BL/6J mice, PLoS One 9 (8) (2014), e105750.
[173] A. Naudí, P. Caro, M. Jové, J. Gómez, J. Boada, V. Ayala, et al., Methionine restriction decreases endogenous oxidative molecular damage and increases mitochondrial biogenesis and uncoupling protein 4 in rat brain, Rejuvenation Res. 10 (4) (2007) 473–484.
[174] M. Jové, R. Cabré, N. Mota-Martorell, M. Martin-Garí, È. Obis, P. Ramos, et al., Age-related changes in lipidome of rat frontal cortex and cerebellum are partially reversed by methionine restriction applied in old age, Int. J. Mol. Sci. 22 (22) (2021).
[175] H. Liu, W. Zhang, K. Wang, X. Wang, F. Yin, C. Li, et al., Methionine and cystine double deprivation stress suppresses glioma proliferation via inducing ROS/autophagy, Toxicol. Lett. 232 (2) (2015) 349–355.
[176] A.L. Bookout, M.H. de Groot, B.M. Owen, S. Lee, L. Gautron, H.L. Lawrence, et al., FGF21 regulates metabolism and circadian behavior by acting on the nervous system, Nat. Med. 19 (9) (2013) 1147–1152.
[177] B. Cannon, J. Nedergaard, Brown adipose tissue: function and physiological significance, Physiol. Rev. 84 (1) (2004) 277–359.
[178] L.A. Forney, H. Fang, L.C. Sims, K.P. Stone, L.Y. Vincik, A.M. Vick, et al., Dietary methionine restriction signals to the brain through fibroblast growth factor 21 to regulate energy balance and remodeling of adipose tissue, Obesity 28 (10) (2020) 1912–1921.
[179] P. Sa-Nguanmoo, P. Tanajak, S. Kerdphoo, P. Satjaritanun, X. Wang, G. Liang, et al., FGF21 improves cognition by restored synaptic plasticity, dendritic spine density, brain mitochondrial function and cell apoptosis in obese-insulin resistant male rats, Horm. Behav. 85 (2016) 86–95.
[180] S. Chen, S.T. Chen, Y. Sun, Z. Xu, Y. Wang, S.Y. Yao, et al., Fibroblast growth factor 21 ameliorates neurodegeneration in rat and cellular models of Alzheimer's disease, Redox Biol. 22 (2019), 101133.
[181] S. Matsui, T. Sasaki, D. Kohno, K. Yaku, A. Inutsuka, H. Yokota-Hashimoto, et al., Neuronal SIRT1 regulates macronutrient-based diet selection through FGF21 and oxytocin signalling in mice, Nat. Commun. 9 (1) (2018) 4604.
[182] Z. Yu, L. Lin, Y. Jiang, I. Chin, X. Wang, X. Li, et al., Recombinant FGF21 protects against blood-brain barrier leakage through Nrf2 upregulation in type 2 diabetes mice, Mol. Neurobiol. 56 (4) (2019) 2314–2327.
[183] Y. Yu, F. Bai, W. Wang, Y. Liu, Q. Yuan, S. Qu, et al., Fibroblast growth factor 21 protects mouse brain against D-galactose induced aging via suppression of oxidative stress response and advanced glycation end products formation, Pharmacol. Biochem. Behav. 133 (2015) 122–131.
[184] K. Kang, P. Xu, M. Wang, J. Chunyu, X. Sun, G. Ren, et al., FGF21 attenuates neurodegeneration through modulating neuroinflammation and oxidant-stress, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 129 (2020), 110439.
[185] L. Fão, S.I. Mota, A.C. Rego, Shaping the Nrf2-ARE-related pathways in Alzheimer's and Parkinson's diseases, Ageing Res. Rev. 54 (2019), 100942.
[186] F. Sivandzade, S. Prasad, A. Bhalerao, L. Cucullo, NRF2 and NF-κB interplay in cerebrovascular and neurodegenerative disorders: molecular mechanisms and possible therapeutic approaches, Redox Biol. 21 (2019), 101059.
[187] I. Bellezza, A. Tucci, F. Galli, S. Grottelli, A.L. Mierla, F. Pilolli, et al., Inhibition of NF-κB nuclear translocation via HO-1 activation underlies α-tocopheryl succinate toxicity, J. Nutr. Biochem. 23 (12) (2012) 1583–1591.
[188] H. Yang, N. Magilnick, X. Ou, S.C. Lu, Tumour necrosis factor alpha induces co-ordinated activation of rat GSH synthetic enzymes via nuclear factor kappaB and activator protein-1, Biochem. J. 391 (Pt 2) (2005) 399–408.
[189] J.E. Johnson, F.B. Johnson, Methionine restriction activates the retrograde response and confers both stress tolerance and lifespan extension to yeast, mouse and human cells, PLoS One 9 (5) (2014), e97729.
[190] D. Kellar, S. Craft, Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches, Lancet Neurol. 19 (9) (2020) 758–766.
[191] M.K. Singh, S.M. Leslie, M.M. Packer, Y.V. Zaiko, O.R. Phillips, E.F. Weisman, et al., Brain and behavioral correlates of insulin resistance in youth with depression and obesity, Horm. Behav. 108 (2019) 73–83.
[192] C. Lanzillotta, A. Tramutola, G. Di Giacomo, F. Marini, D.A. Butterfield, F. Di Domenico, et al., Insulin resistance, oxidative stress and mitochondrial defects in Ts65dn mice brain: a harmful synergistic path in down syndrome, Free Radic. Biol. Med. 165 (2021) 152–170.
[193] J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes 52 (1) (2003) 1–8.
[194] R. Xiong, X.L. Wang, J.M. Wu, Y. Tang, W.Q. Qiu, X. Shen, et al., Polyphenols isolated from lychee seed inhibit Alzheimer's disease-associated Tau through improving insulin resistance via the IRS-1/PI3K/Akt/GSK-3β pathway, J. Ethnopharmacol. 251 (2020), 112548.
[195] R.B. Mansur, F. Delgado-Peraza, M. Subramaniapillai, Y. Lee, M. Iacobucci, F. Nasri, et al., Exploring brain insulin resistance in adults with bipolar depression using extracellular vesicles of neuronal origin, J. Psychiatr. Res. 133 (2021) 82–92.
[196] B. Kim, K.A. Sullivan, C. Backus, E.L. Feldman, Cortical neurons develop insulin resistance and blunted Akt signaling: a potential mechanism contributing to enhanced ischemic injury in diabetes, Antioxidants Redox Signal. 14 (10) (2011) 1829–1839.
[197] S.O. Rahman, B.P. Panda, S. Parvez, M. Kaundal, S. Hussain, M. Akhtar, et al., Neuroprotective role of astaxanthin in hippocampal insulin resistance induced by Aβ peptides in animal model of Alzheimer's disease, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 110 (2019) 47–58.
[198] Q. Wang, J. Yuan, Z. Yu, L. Lin, Y. Jiang, Z. Cao, et al., FGF21 attenuates high-fat diet-induced cognitive impairment via metabolic regulation and anti-inflammation of obese mice, Mol. Neurobiol. 55 (6) (2018) 4702–4717.
[199] H. Rong, Y. Liang, Y. Niu, Rosmarinic acid attenuates β-amyloid-induced oxidative stress via Akt/GSK-3β/Fyn-mediated Nrf2 activation in PC12 cells, Free Radic. Biol. Med. 120 (2018) 114–123.
[200] D.R. Linden, M.D. Levitt, G. Farrugia, J.H. Szurszewski, Endogenous production of H2S in the gastrointestinal tract: still in search of a physiologic function, Antioxidants Redox Signal. 12 (9) (2010) 1135–1146.
[201] R. Wang, Two's company, three's a crowd: can H2S be the third endogenous gaseous transmitter? Faseb. J. : Off. Pub. Federation Am. Soc. Exp. Biol. 16 (13) (2002) 1792–1798.
[202] J. Selhub, Homocysteine metabolism, Annu. Rev. Nutr. 19 (1999) 217–246.
[203] J. Mun, H.M. Kang, J. Jung, C. Park, Role of hydrogen sulfide in cerebrovascular alteration during aging, Arch Pharm. Res. (Seoul) 42 (5) (2019) 446–454.
[204] W. Zhao, J. Zhang, Y. Lu, R. Wang, The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener, EMBO J. 20 (21) (2001) 6008–6016.
[205] A. Longchamp, T. Mirabella, A. Arduini, M.R. MacArthur, A. Das, J.H. Treviño-Villarreal, et al., Amino acid restriction triggers angiogenesis via GCN2/ATF4 regulation of VEGF and H(2)S production, Cell 173 (1) (2018) 117–129, e14.
[206] C.S. McKimmie, G.J. Graham, Astrocytes modulate the chemokine network in a pathogen-specific manner, Biochem. Biophys. Res. Commun. 394 (4) (2010) 1006–1011.
[207] D. Xin, X. Chu, X. Bai, W. Ma, H. Yuan, J. Qiu, et al., l-Cysteine suppresses hypoxia-ischemia injury in neonatal mice by reducing glial activation, promoting autophagic flux and mediating synaptic modification via H(2)S formation, Brain Behav. Immun. 73 (2018) 222–234.
[208] X. Kang, C. Li, Y. Xie, L.L. He, F. Xiao, K.B. Zhan, et al., Hippocampal ornithine decarboxylase/spermidine pathway mediates H(2)S-alleviated cognitive impairment in diabetic rats: involving enhancment of hippocampal autophagic flux, J. Adv. Res. 27 (2021) 31–40.
[209] S. Ma, D. Zhong, P. Ma, G. Li, W. Hua, Y. Sun, et al., Exogenous hydrogen sulfide ameliorates diabetes-associated cognitive decline by regulating the mitochondria-mediated apoptotic pathway and IL-23/IL-17 expression in db/db mice, Cell. Physiol. Biochem. : Int. J. Exp. Cell Physiol. Biochem. Pharmacol. 41 (5) (2017) 1838–1850.
[210] W. Zou, J. Yuan, Z.J. Tang, H.J. Wei, W.W. Zhu, P. Zhang, et al., Hydrogen sulfide ameliorates cognitive dysfunction in streptozotocin-induced diabetic rats: involving suppression in hippocampal endoplasmic reticulum stress, Oncotarget 8 (38) (2017) 64203–64216.
[211] S.M. Chen, M. Li, J. Xie, S. Li, S.S. Xiang, H.Y. Liu, et al., Hydrogen sulfide attenuates postoperative cognitive dysfunction through promoting the pathway of

Warburg effect-synaptic plasticity in hippocampus, Toxicol. Appl. Pharmacol. 409 (2020), 115286.
[212] T. Li, H. Liu, H. Xue, J. Zhang, X. Han, S. Yan, et al., Neuroprotective effects of hydrogen sulfide against early brain injury and secondary cognitive deficits following subarachnoid hemorrhage, Brain pathology (Zurich, Switzerland) 27 (1) (2017) 51–63.
[213] W. Jiang, Y.Y. Tang, W.W. Zhu, C. Li, P. Zhang, R.Q. Li, et al., PI3K/AKT pathway mediates the antidepressant- and anxiolytic-like roles of hydrogen sulfide in streptozotocin-induced diabetic rats via promoting hippocampal neurogenesis, Neurotoxicology 85 (2021) 201–208.
[214] A. McCampbell, K. Wessner, M.W. Marlatt, C. Wolffe, D. Toolan, A. Podtelezhnikov, et al., Induction of Alzheimer's-like changes in brain of mice expressing mutant APP fed excess methionine, J. Neurochem. 116 (1) (2011) 82–92.
[215] B. Wu, H. Cai, S. Tang, Y. Xu, Q. Shi, L. Wei, et al., Methionine-mediated protein phosphatase 2A catalytic subunit (PP2Ac) methylation ameliorates the tauopathy induced by manganese in cell and animal models, Neurotherapeutics : J. Am. Soc. Exp. Neurotherapeutics 17 (4) (2020) 1878–1896.
[216] X.L. He, N. Yan, H. Zhang, Y.W. Qi, L.J. Zhu, M.J. Liu, et al., Hydrogen sulfide improves spatial memory impairment and decreases production of Aβ in APP/PS1 transgenic mice, Neurochem. Int. 67 (2014) 1–8.
[217] D. Giovinazzo, B. Bursac, J.I. Sbodio, S. Nalluru, T. Vignane, A.M. Snowman, et al., Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulfhydrating GSK3β and inhibiting Tau hyperphosphorylation, Proc. Natl. Acad. Sci. U. S. A 118 (4) (2021).
[218] H. Kahroba, B. Ramezani, H. Maadi, M.R. Sadeghi, H. Jaberie, F. Ramezani, The role of Nrf2 in neural stem/progenitors cells: from maintaining stemness and self-renewal to promoting differentiation capability and facilitating therapeutic application in neurodegenerative disease, Ageing Res. Rev. 65 (2021), 101211.
[219] B.E. Aboulhoda, L.A. Rashed, H. Ahmed, E.M.M. Obaya, W. Ibrahim, M.A. L. Alkafass, et al., Hydrogen sulfide and mesenchymal stem cells-extracted microvesicles attenuate LPS-induced Alzheimer's disease, J. Cell. Physiol. 236 (8) (2021) 5994–6010.
[220] Y. Kimura, N. Shibuya, H. Kimura, Sulfite protects neurons from oxidative stress, Br. J. Pharmacol. 176 (4) (2019) 571–582.
[221] W.L. Yin, J.Q. He, B. Hu, Z.S. Jiang, X.Q. Tang, Hydrogen sulfide inhibits MPP(+)-induced apoptosis in PC12 cells, Life Sci. 85 (7–8) (2009) 269–275.
[222] L. Chen, R. Shi, X. She, C. Gu, L. Chong, L. Zhang, et al., Mineralocorticoid receptor antagonist-mediated cognitive improvement in a mouse model of Alzheimer's type: possible involvement of BDNF-H(2) S-Nrf2 signaling, Fund. Clin. Pharmacol. 34 (6) (2020) 697–707.
[223] Y. Jin, Z.L. Huang, L. Li, Y. Yang, C.H. Wang, Z.T. Wang, et al., Quercetin attenuates toosendanin-induced hepatotoxicity through inducing the Nrf2/GCL/GSH antioxidant signaling pathway, Acta Pharmacol. Sin. 40 (1) (2019) 75–85.
[224] K. Eto, T. Asada, K. Arima, T. Makifuchi, H. Kimura, Brain hydrogen sulfide is severely decreased in Alzheimer's disease, Biochem. Biophys. Res. Commun. 293 (5) (2002) 1485–1488.
[225] G. Batallé, X. Bai, E. Pouso-Vázquez, G. Roch, L. Rodríguez, O. Pol, The recovery of cognitive and affective deficiencies linked with chronic osteoarthritis pain and implicated pathways by slow-releasing hydrogen sulfide treatment, Antioxidants (Basel, Switzerland) 10 (10) (2021).
[226] G. Kumar, A. Chhabra, S. Mishra, H. Kalam, D. Kumar, R. Meena, et al., H2S regulates hypobaric hypoxia-induced early glio-vascular dysfunction and neuro-pathophysiological effects, EBioMedicine 6 (2016) 171–189.
[227] V. Calabrese, M. Scuto, A.T. Salinaro, G. Dionisio, S. Modafferi, M.L. Ontario, et al., Hydrogen sulfide and carnosine: modulation of oxidative stress and inflammation in kidney and brain Axis, Antioxidants (Basel, Switzerland) 9 (12) (2020).
[228] O. Yakovleva, K. Bogatova, R. Mukhtarova, A. Yakovlev, V. Shakhmatova, E. Gerasimova, et al., Hydrogen sulfide alleviates anxiety, motor, and cognitive dysfunctions in rats with maternal hyperhomocysteinemia via mitigation of oxidative stress, Biomolecules 10 (7) (2020).
[229] E. Disbrow, K.Y. Stokes, C. Ledbetter, J. Patterson, R. Kelley, S. Pardue, et al., Plasma hydrogen sulfide: a biomarker of Alzheimer's disease and related dementias. Alzheimer's & dementia, the journal of the Alzheimer's Association. 17 (8) (2021) 1391–1402.
[230] Y.O. Henderson, N. Bithi, C. Link, J. Yang, R. Schugar, N. Llarena, et al., Late-life intermittent fasting decreases aging-related frailty and increases renal hydrogen sulfide production in a sexually dimorphic manner, GeroScience 43 (4) (2021) 1527–1554.
[231] M.E. Nimni, B. Han, F. Cordoba, Are we getting enough sulfur in our diet? Nutr Metab (Lond) 4 (2007) 24.
[232] D.H. Calloway, M.J. Kretsch, Protein and energy utilization in men given a rural Guatemalan diet and egg formulas with and without added oat bran, Am. J. Clin. Nutr. 31 (7) (1978) 1118–1126.
[233] C.A. Hudson, A.A. Betschart, J.R. Turnlund, M.J. Kretsch, H.E. Sauberlich, Protein utilization by young women consuming animal or plant protein diets at various levels of vitamin B-6 intake, Am. J. Clin. Nutr. 49 (4) (1989) 636–640.
[234] V.R. Young, M. Puig, E. Queiroz, N.S. Scrimshaw, W.M. Rand, Evaluation of the protein quality of an isolated soy protein in young men: relative nitrogen requirements and effect of methionine supplementation, Am. J. Clin. Nutr. 39 (1) (1984) 16–24.
[235] M. Lecorguillé, S. Lioret, B. de Lauzon-Guillain, E. de Gavelle, A. Forhan, F. Mariotti, et al., Association between dietary intake of one-carbon metabolism nutrients in the year before pregnancy and birth anthropometry, Nutrients 12 (3) (2020).
[236] J. Dasarathy, L.L. Gruca, C. Bennett, P.S. Parimi, C. Duenas, S. Marczewski, et al., Methionine metabolism in human pregnancy, Am. J. Clin. Nutr. 91 (2) (2010) 357–365.
[237] R.A. Rubin, L.A. Ordonez, R.J. Wurtman, Physiological dependence of brain methionine and S-adenosylmethionine concentrations on serum amino acid pattern, J. Neurochem. 23 (1) (1974) 227–231.
[238] J.M. Turner, M.A. Humayun, R. Elango, M. Rafii, V. Langos, R.O. Ball, et al., Total sulfur amino acid requirement of healthy school-age children as determined by indicator amino acid oxidation technique, Am. J. Clin. Nutr. 83 (3) (2006) 619–623.
[239] R. Elango, M.A. Humayun, J.M. Turner, M. Rafii, V. Langos, R.O. Ball, et al., Total sulfur amino acid requirements are not altered in children with chronic renal insufficiency, but minimum methionine needs are increased, J. Nutr. 147 (10) (2017) 1954–1959.
[240] A. Swaminathan, A. Fokin, T. Venckūnas, H. Degens, Methionine restriction plus overload improves skeletal muscle and metabolic health in old mice on a high fat diet, Sci. Rep. 11 (1) (2021) 1260.
[241] T.H. Huang, J.L. Lewis, H.S. Lin, L.T. Kuo, S.W. Mao, Y.S. Tai, et al., A methionine-restricted diet and endurance exercise decrease bone mass and extrinsic strength but increase intrinsic strength in growing male rats, J. Nutr. 144 (5) (2014) 621–630.
[242] L. Gracia-Marco, S. Bel-Serrat, M. Cuenca-Garcia, M. Gonzalez-Gross, R. Pedrero-Chamizo, Y. Manios, et al., Amino acids intake and physical fitness among adolescents, Amino Acids 49 (6) (2017) 1041–1052.
[243] E.P. Brass, Supplemental carnitine and exercise, Am. J. Clin. Nutr. 72 (2) (2000), 618s-23s.
[244] N. Haulrik, S. Toubro, J. Dyerberg, S. Stender, A.R. Skov, A. Astrup, Effect of protein and methionine intakes on plasma homocysteine concentrations: a 6-mo randomized controlled trial in overweight subjects, Am. J. Clin. Nutr. 76 (6) (2002) 1202–1206.
[245] N.J. Mann, D. Li, A.J. Sinclair, N.P. Dudman, X.W. Guo, G.R. Elsworth, et al., The effect of diet on plasma homocysteine concentrations in healthy male subjects, Eur. J. Clin. Nutr. 53 (11) (1999) 895–899.
[246] H.J. Powers, Riboflavin (vitamin B-2) and health, Am. J. Clin. Nutr. 77 (6) (2003) 1352–1360.
[247] D. Alexander, M.J. Ball, J. Mann, Nutrient intake and haematological status of vegetarians and age-sex matched omnivores, Eur. J. Clin. Nutr. 48 (8) (1994) 538–546.
[248] P. Appleby, A. Roddam, N. Allen, T. Key, Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford, Eur. J. Clin. Nutr. 61 (12) (2007) 1400–1406.
[249] D. Wanders, D.H. Burk, C.C. Cortez, N.T. Van, K.P. Stone, M. Baker, et al., UCP1 is an essential mediator of the effects of methionine restriction on energy balance but not insulin sensitivity, Faseb. J. 29 (6) (2015) 2603–2615.
[250] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, et al., Diet rapidly and reproducibly alters the human gut microbiome, Nature 505 (7484) (2014) 559–563.
[251] G. Liu, L. Yu, J. Fang, C.A. Hu, J. Yin, H. Ni, et al., Methionine restriction on oxidative stress and immune response in dss-induced colitis mice, Oncotarget 8 (27) (2017) 44511–44520.
[252] L.H. Morais, HLt Schreiber, S.K. Mazmanian, The gut microbiota-brain axis in behaviour and brain disorders, Nat. Rev. Microbiol. 19 (4) (2021) 241–255.
[253] X. Zhang, Q. Zou, B. Zhao, J. Zhang, W. Zhao, Y. Li, et al., Effects of alternate-day fasting, time-restricted fasting and intermittent energy restriction DSS-induced on colitis and behavioral disorders, Redox Biol. 32 (2020), 101535.
[254] S.C. Wu, Z.S. Cao, K.M. Chang, J.L. Juang, Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila, Nat. Commun. 8 (1) (2017) 24.
[255] L. Wang, B. Ren, Y. Hui, C. Chu, Z. Zhao, Y. Zhang, et al., Methionine restriction regulates cognitive function in high-fat diet-fed mice: roles of diurnal rhythms of SCFAs producing- and inflammation-related microbes, Mol. Nutr. Food Res. 64 (17) (2020), e2000190.
[256] G. Wu, Y. Shi, L. Han, C. Feng, Y. Ge, Y. Yu, et al., Dietary methionine restriction ameliorated fat accumulation, systemic inflammation, and increased energy metabolism by altering gut microbiota in middle-aged mice administered different fat diets, J. Agric. Food Chem. 68 (29) (2020) 7745–7756.
[257] B. Ren, L. Wang, A. Mulati, Y. Liu, Z. Liu, X. Liu, Methionine restriction improves gut barrier function by reshaping diurnal rhythms of inflammation-related microbes in aged mice, Front. Nutr. 8 (2021), 746592.
[258] X. Durando, M.C. Farges, E. Buc, C. Abrial, C. Petorin-Lesens, B. Gillet, et al., Dietary methionine restriction with FOLFOX regimen as first line therapy of metastatic colorectal cancer: a feasibility study, Oncology 78 (3–4) (2010) 205–209.
[259] X. Gao, S.M. Sanderson, Z. Dai, M.A. Reid, D.E. Cooper, M. Lu, et al., Dietary methionine influences therapy in mouse cancer models and alters human metabolism, Nature 572 (7769) (2019) 397–401.
[260] P. Katre, S. Joshi, D.S. Bhat, M. Deshmukh, N. Gurav, S. Pandit, et al., Effect of multi-nutrient insufficiency on markers of one carbon metabolism in young women: response to a methionine load, Eur. J. Clin. Nutr. 70 (6) (2016) 687–693.
[261] O. Shikha, B. Alaa El-Din, G. Tilman, K.S. Oliver, Bioavailability of nutrients from edible insects, Curr. Opin. Food Sci. 41 (2021) 240–248.
[262] W. Isabelle, O. Mario, W. Petra, S. Monika, N. Susanne, K. Rebecca, et al., Sustainable food protein supply reconciling human and ecosystem health: a Leibniz Position, Global Food Secur. 25 (2020), 100367.
[263] B. Ren, L. Wang, L. Shi, X. Jin, Y. Liu, R.H. Liu, et al., Methionine restriction alleviates age-associated cognitive decline via fibroblast growth factor 21, Redox Biol. 41 (2021), 101940.

[264] D.E. Epner, S. Morrow, M. Wilcox, J.L. Houghton, Nutrient intake and nutritional indexes in adults with metastatic cancer on a phase I clinical trial of dietary methionine restriction, Nutr. Cancer 42 (2) (2002) 158–166.
[265] T. Olsen, B. Øvrebø, C. Turner, N.E. Bastani, H. Refsum, K.J. Vinknes, Combining dietary sulfur amino acid restriction with polyunsaturated fatty acid intake in humans: a randomized controlled pilot trial, Nutrients 10 (12) (2018).
[266] T. Olsen, B. Øvrebø, N. Haj-Yasein, S. Lee, K. Svendsen, M. Hjorth, et al., Effects of dietary methionine and cysteine restriction on plasma biomarkers, serum fibroblast growth factor 21, and adipose tissue gene expression in women with overweight or obesity: a double-blind randomized controlled pilot study, J. Transl. Med. 18 (1) (2020) 122.
[267] T. Olsen, B. Øvrebø, C. Turner, N.E. Bastani, H. Refsum, K.J. Vinknes, Effects of short-term methionine and cysteine restriction and enrichment with polyunsaturated fatty acids on oral glucose tolerance, plasma amino acids, fatty acids, lactate and pyruvate: results from a pilot study, BMC Res. Notes 14 (1) (2021) 43.
[268] M.M. Boancă, H.A. Colosi, E.C. Crăciun, The impact of the lacto-ovo vegetarian diet on the erythrocyte superoxide dismutase activity: a study in the Romanian population, Eur. J. Clin. Nutr. 68 (2) (2014) 184–188.