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Insulin resistance in Alzheimer's disease: The genetics and metabolomics links

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease with significant socioeconomic burden worldwide. Although genetics and environmental factors play a role, AD is highly associated with insulin resistance (IR) disorders such as metabolic syndrome (MS), obesity, and type two diabetes mellitus (T2DM). These findings highlight a shared pathogenesis. The use of metabolomics as a downstream systems' biology (omics) approach can help to identify these shared metabolic traits and assist in the early identification of at-risk groups and potentially guide therapy. Targeting the shared AD-IR metabolic trait with lifestyle interventions and pharmacological treatments may offer promising AD therapeutic approach. In this narrative review, we reviewed the literature on the AD-IR pathogenic link, the shared genetics and metabolomics biomarkers between AD and IR disorders, as well as the lifestyle interventions and pharmacological treatments which target this pathogenic link.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease which affects peoples' psychological, physical, emotional, and social abilities extensively. AD claimed 134,242 people in 2020 according to the Centers for Disease Control and Prevention (CDC) of the of the United States [1]. According to the recent fact sheet of the World Health Organization (WHO), there are 50 million suffering from dementia globally wherein 60–70 % of the cases are caused by AD [2]. Based on the recent report of the Alzheimer's Association, AD is the fifth leading cause of death among Americans older than 65-year and the sixth leading cause of deaths among all ages [3]. To date, there is no curative treatment for AD [2,3]. However, identifying biomarkers which predict risk populations and implicated pathophysiological factors may help to prevent and probably combat the progressive course of the disease.

The hallmark pathogenic features of AD are the accumulation of beta amyloids (Aβ) outside neurons and the hyperphosphorylation and aggregation of tau proteins inside neurons [3–6]. Other substantial AD features may also present such as brain atrophy, particularly hippocampal and neocortex atrophy [7], and the large volume of white matter hyperintensities (WMH) [8]. Furthermore, reduced levels of neurotransmitters' such as acetylcholine and catecholamines such as norepinephrine and dopamine had been indicated in AD [9–11]. AD is a multifactorial disease where genetic variants and other environmental or non-genetic factors may cause and aggravate the disease progression [12–18]. The environmental or the non-genetic factors include, but not limited to, aging, cardiovascular diseases (CVDs) including ischemic stroke and coronary artery disease (CAD), type 2 diabetes (T2DM), metabolic syndrome (MS), obesity, depression, women particularly postmenopausal, cognitive inactivity, dyslipidemia, smoking, substance abuse, and unhealthy dietary habits [2,13,15,16,19–23]. These environmental factors may lead, in a way or another, to some pathogenic pathways which cause or aggravate AD development. These pathways include, but not limited to, oxidative stress, mitochondrial dysfunction, chronic inflammation, reduced glucose utilization and energy metabolism as well as brain insulin resistance (IR) [6,24–27].

IR disorders such as MS, obesity and T2DM are highly associated with AD [24,28–32]. However, the mechanisms by which this association occur are not fully understood. It could be linked to shared genetic variants or rather downstream factors which may had induced the disease manifestations [18,24,33–36]. One of the downstream systems' biology (omics) approaches is metabolomics which identifies metabolic traits associated with diseases, exposures, and responses to therapy [37–39]. Metabolomics has the advantage of being close to the

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phenotype as well as reflecting upper stream systems' biology approaches such as genomics, transcriptomics and proteomics [37]. In a recent review by the first author, common metabolomics biomarkers and metabolic pathways among cardiometabolic diseases (CMDs) were reviewed [40]. The reviewed CMDs included IR disorders (MS, obesity and T2DM), CVDs and cerebrovascular diseases. Almost 40 metabolomics biomarkers were common between those CMDs representing a shared metabolic trait and pathways (CMDs Metabotype). We conceptualized that the AD-IR pathogenic link is accentuated on the metabolomics level as well. However, to the best of our knowledge this has not been reviewed in the literature previously. The shared metabolic trait between AD and IR disorders may assist early diagnosis and guide therapy. Therefore, we aimed to sight the presence of the previously reviewed CMDs metabolic trait in AD. Towards that end, we reviewed the literature on the pathogenic link between AD and IR disorders and their shared genetics and metabolomics biomarkers. We also applied a web-based metabolic pathway analysis for the common metabolites between AD and IR disorders to indicate implicated metabolic pathway in the link between them. Furthermore, we also reviewed the therapeutic approaches which may interfere with these interlinked pathogenic and metabolic pathways. The MEDLINE through PubMed database was used to retrieve literature on the AD-IR disorders link including genetic factors involved in this link. Moreover, we searched for the AD metabolomics studies which include the CMDs Metabotype that has been reported previously [40]. The review contains four main sections besides the introduction (First section) and the conclusion (Last section). In the second section, the AD and IR disorders pathogenic link is discussed. In the third section, the shared genetics biomarkers between AD and IR disorders are discussed. The fourth section focuses on the shared metabolomics biomarkers between AD and IR disorders. The fifth section discusses the current state of therapeutics which can target the AD-IR link and the proposed future investigations in this direction.

2. AD and IR disorders pathogenic link:

The role of impaired insulin signaling in the pathogenesis of AD gained attention in the past two decades [27,41,42]. In fact, both insulin deficiency and insulin resistance (IR) have detrimental consequences on the brain [43,44]. In the context of IR, there are several plausible pathways that may explain the link between AD and IR. In the insulin resistance state, three detrimental elements are present, the IR, the compensated peripheral hyperinsulinemia and the consequent hyperglycemia or glucose intolerance. Simply put, IR is the reduced response to insulin which can occur due to genetic and/or environmental factors [45]. When developed, IR is compensated by increased secretion of insulin (i.e., Hyperinsulinemia) to achieve normoglycemia leading to the vicious cycle of IR ↔ Hyperinsulinemia [46,47]. This vicious cycle is implicated in AD pathogenesis in a way or another [25,48,49]. Since the transport of molecules across the blood brain barrier (BBB) is highly affected by the variation in their peripheral levels, peripheral hyperinsulinemia leads to elevation in brain insulin [43,50]. Insulin is degraded by the insulin degrading enzyme (IDE), an enzyme which degrades Aβ protein as well [36,43]. However, insulin competes with Aβ protein for IDE with higher IDE-insulin affinity compared to Aβ protein [36]. Thus, a state of hyperinsulinemia can lead to Aβ protein accumulation, one of the important hallmarks of AD [36,43]. Moreover, insulin increases Aβ protein in the extracellular spaces [36]. Accumulated Aβ proteins interfere with the bindings of insulin to insulin receptors which aggravates IR [25,27,36,51]. On the other hand, IDE dysfunction increases the accumulation of Aβ. The reduced metabolic activity of IDE can happen due to some genetic polymorphisms or due to some conditions such as Type one diabetes mellitus (T1DM) [52–56]. Therefore, considering the pathogenic interaction between Aβ and impaired insulin signaling, it is not surprising that impaired cerebral glucose metabolism usually proceeds AD signs and symptoms by several years [26,57,58]. In fact, IR as well as hyperglycemia affect memory performance and neuronal growth which play role in cognitive dysfunction, a key clinical feature of AD [59]. Post-prandial glucose in T2DM patients had been found associated with white matter hyperintensities (WMH) and brain atrophy, both are indicative of AD risk and progression [8,19]. In another way, IR has been linked to tau hyperphosphorylation tauopathy which are crucial pathogenic features in AD [60]. In addition, IR affects neurotransmitters' levels [10,61]. For instance, impaired insulin signaling reduces acetylcholine level in the brain leading to crucial cholinergic perturbations which are largely implicated in AD progression [9,10,61]. In fact, the synthesis of acetylcholine from choline and acetyl-Coenzyme A (Acetyl-Co-A) is reduced significantly in AD patients [9,10]. Besides the direct detrimental effect of hyperinsulinemia in the brain, it may lead to brain insulin deficiency. Indeed, the chronic state of hyperinsulinemia interferes with the saturable transport of insulin through the BBB, eventually leading to the reduction of insulin levels in the central nervous system (CNS) [27,43,50]. CNS insulin deficiency is associated with AD pathogenesis and progression as well [43,62]. In other words, AD represents a state of type 3 diabetes where combined effects of IR and insulin deficiency are implicated in the pathogenesis [63,64].

There are other shared pathogenic pathways between AD and IR disorders. For instance, chronic inflammation and oxidative stress are involved in the pathogenesis of AD and IR disorders [15,25,65]. Another pathogenic link is the association between IR disorders and the disturbed gut microbiota which may lead to disrupted gut-brain axis [66–70]. Disturbed gut-microbiota has been linked to neurodegenerative diseases including AD [71–73]. In this pathway, the gut-microbiota-brain-axis plays important role in modulating brain's functions and behaviors suggesting the hypothesis of "AD may begin in the gut" [72]. Similarly, IR may explain the link between AD and CVDs. AD had been found associated with CVDs, cerebrovascular diseases (CVAs), intima-media thickness of carotid arteries as well as high platelets reactivity and endothelial dysfunction [2,23,48,74–76]. In fact, some reports suggested that the AD-CVDs association might be bidirectional and mediated by the Aβ protein [76,77]. Indeed, IR is highly implicated in CVDs where the vicious cycle of IR ↔ hyperinsulinemia is involved in CVDs' pathogenesis [49,78]. This vicious cycle is associated with the atherogenic dyslipidemia, one of the main risk factors of stroke and other CVDs [79–82]. Furthermore, it is also associated with high platelets reactivity and endothelial dysfunctions which increases CVDs risk in people suffering from IR disorders [83–86]. Moreover, intima-media thickness of common carotid arteries is associated with IR, hyperinsulinemia and high blood glucose levels [87–89]. Fig. 1 illustrates the role of IR ↔ Hyperinsulinemia vicious cycle and related conditions in AD development.

3. Genetics variabilities shared between AD and IR disorders

There have been enormous efforts exerted to identify AD genetic associations, however, the genetic overlapping of AD with other diseases gained substantial focus to delineate risk groups. IR-AD genetic links had been identified in various literature. For instance, the genetic link of the obesity-brain atrophy association was investigated by Ho and colleagues [33]. In their study, they used magnetic resonance imaging (MRI) to generate regional brain 3D maps for 206 healthy elderly subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Subjects were classified to carriers and non-carriers of the risk allele for the single-nucleotide polymorphism (SNP) rs3751812 within the fat mass and obesity-associated (*FTO*) gene. Healthy elderly subjects who were carriers of the rs3751812 SNP-obesity-risk allele had a systematic brain volume deficit [33]. The same SNP (rs3751812) had been found associated with MS and T2DM as well [90]. Other obesity-risk-associated SNPs from the *FTO* gene such as, rs17817449, rs9939609, rs8050136 and rs1421085 had been linked to changes in cognition and brain function [33,35,91]. Furthermore, the rs1421085 SNP was found to be associated with obesity, changes in brain functions and decreased

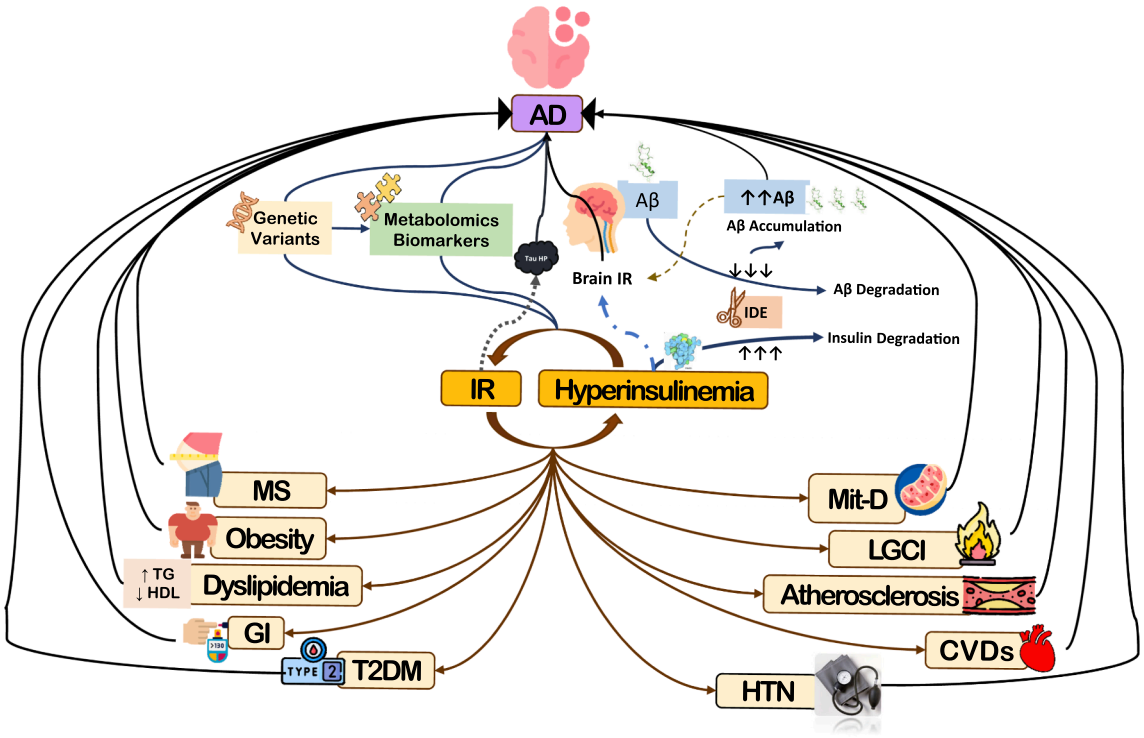

Fig. 1. The role of Insulin resistance (IR), Hyperinsulinemia and their associated conditions in AD.
AD is multifactorial where genetic and non-genetic factors interact in the pathogenesis. Cardiometabolic Diseases such as MS, obesity, T2DM, and CVDs share the vicious cycle of IR ↔ hyperinsulinemia which affects the brain in several pathways. High insulin levels competes with Aβ protein for IDE with higher IDE-insulin affinity compared to Aβ leading to Aβ accumulation. Aβ protein interferes with the bindings of insulin-to-insulin receptors causing brain IR. Tau hyperphosphorylation has been linked to IR. Metabolomics is close to the disease phenotype and reflects genetics and other environmental factors implicated in the pathogenesis of the disease which is manifested by the common metabolic biomarkers between AD and IR disorders. The IR ↔ hyperinsulinemia vicious cycle and related conditions (Below the vicious cycle part) is adapted and modified with permission from Amin, A. M. (2021). "The metabolic signatures of cardiometabolic diseases: Does the shared metabotype offer new therapeutic targets?" Lifestyle Medicine 2(1): e25. Abbreviations, AD: Alzheimer's disease, IR: Insulin resistance, MS: Metabolic Syndrome, Mit-D: Mitochondrial dysfunction, HTN: Hypertension, GI: Glucose intolerance, CVDs: Cardiovascular diseases, LGCI: Low Grade Chronic Inflammation, Aβ: Amyloid beta. IDE: Insulin Degrading Enzyme. Obesity, T2DM, GI, brain, MS, Inflammation, Mitochondria and Atherosclerosis icons from free icon website (www.flaticon.com). Insulin molecule icon from: https://pdb101.rcsb.org/motm/14. Aβ molecule icon created from pdb file 2lfm (public database) by Jeff Brender (biophysik) which is licensed under Creative Commons Attribution-Share Alike 3.0 (https://creativecommons.org/licenses/by-sa/3.0/deed.en).

medial prefrontal cortical function among subjects from the Baltimore Longitudinal Study of Aging (BLSA) [91]. Noteworthy, the aforementioned *FTO* gene SNPs (rs3751812, rs17817449, rs9939609, rs8050136 and rs1421085) had been found associated with other IR disorders, particularly MS and T2DM [90,92–94]. There are several plausible mechanisms which may explain the role of the *FTO* gene in the pathophysiological overlapping between AD and IR disorders [95]. The *FTO* gene risk alleles are positively associated with plasma ghrelin, an orexigenic hormone, however they are negatively associated with leptin, a satiety promoting hormone [96]. This may lead to impaired satiation and weight gain. As consequence, hyperinsulinemia and IR will develop causing disorders such as, MS, obesity and T2DM [97,98]. Although a neuroprotective role of ghrelin had been proposed [99], increased plasma levels of ghrelin and acyl-ghrelin, the functional form of ghrelin, were associated with reduced cognitive function suggesting that elevation in acyl-ghrelin/des-acyl-ghrelin ratio, as well as changes in ghrelin receptors or ghrelin sensitivity might be implicated in AD pathogenesis [97,100,101]. In fact, ghrelin had been considered an AD biomarker [102]. Therefore, the *FTO*-ghrelin-IR pathway may have substantial role in the association between IR disorders and AD.

There are other genetic variants which are associated with both T2DM and AD. In a study by Wang et al., 2017 [34], 8 novel pleiotropic SNPs were found associated with both AD and T2DM among European population [34]. This was indicated through the analysis of Genome-wide association study (GWAS) datasets from the IGAP and the DIAGRAM consortia [34]. The eight novel pleiotropic SNPs were rs896854, rs6859, rs2075650, rs6982393, rs4734295, rs7812465, rs10510109, and rs2421016. For these genetic variants, they are linked to oxidative stress, mitochondrial dysfunction, autophagy activation, the regulation of phosphoinositide-3-kinase (PI3K), and apolipoprotein E (ApoE) [34,103]. These aforementioned pathways are highly implicated in the pathogenesis of AD and IR disorders [43]. Some of the SNPs which were identified by Wang and colleagues [34] had been found associated with obesity and ischemic stroke (IS) as well as one or more of the metabolic features of MS such as dyslipidemia, glucose intolerance and IR. For instance, the rs6859 SNP had been found associated with dyslipidemia among Chinese Maonan population [104]. Another example, the rs 2075650 SNP had been found associated with dyslipidemia and carotid artery disease risk [105]. Yamase and colleagues indicated that the rs2075650 SNP is associated with IS in Japanese population [106]. The rs2075650 SNP is associated with CAD as well [107,108]. Both IS and CAD are risk factors of AD [21,48,74]. They are also metabolically linked to IR disorders as previously discussed in this review. The role of the IDE in the AD-IR pathogenic link is mediated by genetic polymorphisms as well. In fact, there are several SNPs in the *IDE* gene which are associated with either AD or T2DM [52,109–111]. The rs1887922 SNP from the *IDE* gene had been linked to both diseases. It had been found associated with late onset of AD among Chinese population samples [52,110]. This association was accentuated in men and non-carriers of the apolipoprotein E (*ApoE*) ε4 allele of the *ApoE* gene

[52]. Similarly, the rs1887922 SNP had been found associated with fasting plasma glucose, mean fasting plasma glucose, HbA1c and T2DM [109]. It was accentuated in men as well. Furthermore, the rs1887922 SNP had been found associated with reduced insulin sensitivity and T2DM risk in German cohort [111]. There are several plausible mechanisms to explain the role of the rs1887922 SNP risk allele in AD and T2DM. This role might be related to a reduced expression of *IDE* or reduced IDE metabolic activity which may increase Aβ accumulation [52–54]. On the other hand, the rs1887922 SNP risk allele is associated with reduced hepatic insulin degradation, an indication of early IR state [111]. It is worthy to mention that the rs1887922 SNP risk allele had been found associated with CAD, a risk factor of AD [53].

The effect of some AD genetic variants might be accentuated when their carriers endure another AD risk factor. For instance, the apolipoprotein E (*ApoE*) ε4 allele of the *ApoE* gene is associated with AD in subjects with T2DM, hypertension, chronic low-grade inflammation and postmenopause [12,13,15,16,18,112]. In fact, the *ApoE* ε4 genetic variant is associated with MS and obesity [14,113]. In a similar way, T2DM accentuates the association between the C allele of the apolipoprotein J/clusterin (*APOJ/CLU*) rs11136000 genetic variant and AD [17,114,115]. On the contrary, the T allele of the same SNP may offer a protective effect against AD [114]. The *APOJ* – rs11136000 genetic variant association with neural inefficiency is present in healthy subjects as well [116]. In fact, several loci in the *APOJ/CLU* gene showed significant association with Aβ deposition [117]. The *APOJ/CLU* gene encodes for clusterin which has been considered a biomarker of AD, particularly in AD patients suffering from IR conditions [118–121]. Indeed, clusterin dysregulation has been implicated in several diseases such as AD, CVDs, cancer and T2DM [118–120,122,123]. Clusterin perturbation causes IR which explains its role in the AD-IR pathogenic link [119,124]. Noteworthily, the rs11136000-AD association is not consistent among ethnicities, yet considering age may adjust towards the existence of the association in people over 75 years [17,125]. Besides the interactions of risk diseases with the AD genetic variants, currying dual polymorphisms of AD-IR genetic variants increases AD risk. For instance, carriers of both the *FTO*- (rs9939609) - AA genotype and the *ApoE* ε4 genetic variants have higher risk for AD, particularly dementia [126]. As previously discussed, *FTO* is associated with obesity, T2DM and MS. Another example had been shown in a Chinese population-based study where carriers of the *NDUFAF6*- (rs6982393) and *ApoE* ε4 genetic variants had higher risk for AD [112]. Both polymorphisms are associated with IR disorders. In Table 1, some of the SNPs and genes that are common between AD and IR disorders are presented.

4. Metabolomics biomarkers shared between AD and IR disorders:

Metabolomics is one of the main systems' biology (omics-level) personalized medicine approaches which comes after genomics, epigenomics, transcriptomics and proteomics [129–131]. Metabolomics has the advantage of reflecting previous omics levels and being close to the phenotype. Therefore, a metabolomics link between diseases may reflect associated metabolic pathways which can't be indicated in the upstream genetic link. In metabolomics studies, a spectroscopical analysis of biosamples is used to cluster metabolites based on certain phenotype such as disease, condition or exposure to treatment [57,73,130–134]. This sheds light on the metabolic pathways' perturbations which gives better understanding of the pathogenicity, as well as assisting diagnosis and guiding therapy [37,57,135]. In a previous review, the shared metabolic biomarkers of CMDs were presented [40]. Upon literature review for the current review, we found that most of such metabolites along with other metabolites are common between AD or cognitive decline/impairment and IR disorders. In Table 2, we present more than 50 metabolites which are commonly perturbed in AD and IR disorders (i.e., AD-IR link metabotype). Most of these metabolites are involved in several metabolic pathways implicated in both AD and IR disorders.

Glucose, mannose and fructose are common metabolic biomarkers of IR disorders and AD [26,134,136–142]. As early mentioned, impaired cerebral glucose metabolism plays vital role in AD pathogenesis and it usually proceeds AD clinical symptoms by several years [26,57]. Biomarkers indicating perturbation in lipid metabolism had been found in several AD metabolomics and lipidomic studies. For instance, ceramides which are an essential sphingolipids precursor were perturbed in AD [57,143,144]. In a human study by Han and colleagues, ceramides were significantly higher in AD patients compared to controls [143]. In a more recent study by Yi and colleagues, ceramides and sphingolipids were elevated in cerebral cortices of AD rats [144]. Ceramides are commonly altered in IR disorders such as T2DM, metabolic syndrome and obesity [145–147]. Ceramides usually indicate an alteration in mitochondrial function, inflammation and IR [147–149]. Such pathogenic pathways are implicated in AD as previously discussed in this review. Metabolic biomarkers of gut microbiota dysbiosis are highly presented in the common metabolites between AD and IR disorders

Table 1
Examples of SNPs and genetic variabilities associated with both AD and IR disorders.

SNP/allele	Gene/Chromosome	AD	T2DM	MS/ MS Features (IR, elevated HOMA-IR, Dyslipidemia, Glucose Intolerance)	Obesity
rs3751812	*FTO*/Chr16	[33]	[90]	[90]	[33,90]
rs1421085	*FTO*/Chr16	[91,35]	–	[92]	[91]
rs17817449	*FTO*/Chr16	[35]	[94]		[35]
rs9939609	*FTO*/Chr16	[35]	[93,94]	[92]	[35]
rs8050136	*FTO*/Chr16	[35]	[93]	[92]	[35]
ApoE ε4	*APoE*/Chr19	[16,18]	[16,127]	[113]	[14]
rs11136000	*APOJ* (*CLU*)/Chr8	[17,125]	[115,127]	[127,17]	–
rs2075650	*TOMM40*/Chr19	[34]	[34]	[105]	[14]
rs896854	*TP53INP1*/Chr8	[34]	[34]	[128]	–
rs6859	*PVRL2*/Chr19	[34]	[34]	[104]	–
rs6982393	*TP53INP1*/Chr8 *C8orf38 NDUFAF6*	[112,34]	[34]	–	–
rs4734295	*TP53INP1*/Chr8 *C8orf38*	[34]	[34]	–	–
rs7812465	*C8orf38*/Chr8	[34]	[34]	–	–
rs10510109	*BTBD16*/Chr10	[34]	[34]	–	–
rs2421016	*PLEKHA1*/Chr10	[34]	[34]	–	–
rs1887922	*IDE*/Chr10	[52,110]	[111,109]	–	–

AD: Alzheimer Disease, SNP: Single nucleotide polymorphism, *FTO:* fat mass and obesity-associated gene, T2DM: Type 2 Diabetes Mellitus, MS: Metabolic syndrome, *APoE*: apolipoprotein E, APOJ: apolipoprotein J, NDUFAF6: NADH Ubiquinone Oxidoreductase Complex Assembly Factor 6.

Table 2
Examples on metabolic biomarkers associated with both AD and IR disorders.

Metabolites	AD/CD	MS/ IR / Dyslipidemia/ GI	Obesity	T2DM	Metabolic Pathway
Acetoacetate	[134]	[160]	[160,209]	[142,152,134]	• Butanoate metabolism • Synthesis and degradation of ketone bodies • Valine, leucine and isoleucine degradation
Adenosine	[178,210,181,211,134],	[212,186]	[213,214]	[213,214]	• Purine metabolism
Aspartate	[135,215,181]	[216]	[183]	[182]	• Alanine, aspartate and glutamate metabolism • Aminoacyl-tRNA biosynthesis • beta-Alanine metabolism • Histidine metabolism • Nicotinate and nicotinamide metabolism • Pantothenate and CoA biosynthesis • Urea Cycle
Acylcarnitines	[178,57,180]	[145,160,189]	[217,145,218,141]	[142,145,162]	• Carnitine Metabolism • Gut-Microbiota metabolism
Arginine	[215,219,167]	[160]	[66]	[193,184]	• Aminoacyl-tRNA biosynthesis • Arginine and proline Metabolism • Arginine biosynthesis
Alanine	[178,215,167]	[207,139]	[66,206,141]	[142,152,184]	• Aminoacyl-tRNA biosynthesis • Alanine, aspartate and glutamate Metabolism • Urea Cycle
Betaine	[167]	[220,221]	[222,223,224]	[225]	• Glycine, serine and threonine metabolism • Gut-Microbiota metabolism
BCAAs: Leucine, Isoleucine, Valine	[57,215,181,180]	[185,204,146,186]	[185,66,218]	[203,142,184,185,162]	• Aminoacyl-tRNA biosynthesis • Valine, leucine and isoleucine biosynthesis and degradation • Pantothenate and CoA biosynthesis
Ceramides	[143,144,57]	[145,146]	[145]	[145,147]	• Aminoacyl-tRNA biosynthesis • Sphingolipid metabolism
Choline	[178,134,167]	[139220]	[66]	[162,68]	• Glycine, serine and threonine metabolism • Glycerophospholipid metabolism • Gut-Microbiota Metabolism
Citrate	[226]	[227]	[228]	[229]	• Alanine, aspartate and glutamate Metabolism • Citrate Cycle • Urea Cycle • Warburg Effect
Creatine	[178,134,226]	[160,139]	[66]	[162,152]	• Arginine and proline metabolism • Creatine biosynthesis and degradation • Creatine and creatinine Metabolism • Glycine, serine and threonine metabolism
Creatinine	[178,131,210]	[160]	[66]	[142]	• Creatine degradation • Creatine and creatinine metabolism
4-Cresol *p*-Cresol	*p*-cresol sulfate [167], *p*-cresol glucuronide [230]	*p*-cresol sulfate [231]	*p*-cresol sulfate [232]	[233]	• Gut-Microbiota metabolism
DMA	[179]	[234,227]	[232]	[229]	• Methylamines metabolism • Gut-Microbiota metabolism
DMG	[235]	[227]	[236]	[236,68]	• Glycine, serine and threonine metabolism • Methylamines metabolism • Gut-Microbiota metabolism
Fructose	[134,136]	[139,204]	[140,141]	[142,134]	• Fructose and mannose pathway • Amino sugar and nucleotide sugar metabolism
Formate (Formic Acid)	[131]	[237,238]	[239]	[162,152]	• Arginine and proline metabolism
Glucose	[26,17,134,181,136]	[137]	[170,141]	[142,162]	• Glycolysis and Gluconeogenesis pathway
Glutamine	[235,178,215]	[160,139,204]	[160]	[152],	• Aminoacyl-tRNA biosynthesis • Arginine biosynthesis • Glutamine and glutamate metabolism

(*continued on next page*)

Table 2 (*continued*)

Metabolites	AD/CD	MS/ IR / Dyslipidemia/ GI	Obesity	T2DM	Metabolic Pathway
Glutamate	[135,215]	[139]	[66,218,141]	[142]	• Alanine, aspartate and glutamate metabolism • Glyoxylate and dicarboxylate metabolism • Nitrogen Metabolism • Purine metabolism • Aminoacyl-tRNA biosynthesis • Arginine and proline metabolism • Alanine, aspartate and glutamate metabolism • Arginine biosynthesis • Butanoate metabolism • Glutamine and glutamate metabolism • Glyoxylate and dicarboxylate metabolism • Glutathione metabolism • Histidine metabolism • Nitrogen Metabolism • Urea Cycle
Glycine	[215]	[160,161]	[66,218,160]	[162]	• Glycine, serine and threonine metabolism • Aminoacyl-tRNA biosynthesis • Glyoxylate and dicarboxylate metabolism • Glutathione metabolism
Hippurate	[131]	[161,237]	[66,170,237]	[240]	• Phenylalanine Metabolism • Gut-Microbiota Metabolism
Histidine	[178]	[207,189]	[218,206]	[152]	• Aminoacyl-tRNA biosynthesis • Histidine metabolism • beta-Alanine metabolism
3-hydroxybutyrate (β-hydroxybutyrate)	[131]	[161,241,186]	[209]	[242]	• Butanoate metabolism • Synthesis and degradation of ketone bodies
Imidazole Propionate	[168]	[69175]	[176](2)	[175]	• Gut-Microbiota metabolism
3-indoxyl sulfate	[167][168]	[169]	[170], [171]	[172173] (1)	• Gut-Microbiota metabolism
Lactic acid	[210,215,181]	[160,139]	[66,218,160]	[142,162]	• Pyruvate Metabolism • Glycolysis and Gluconeogenesis pathway
Lysine	[134]	[160,208]	[66,206,160]	[162]	• Aminoacyl-tRNA biosynthesis
Mannose	[134]	[138]	[138,218,140,141]	[142], [138]	• Fructose and mannose pathway
3-Methyl-histidine	[167]	[243]	[232,243,206]	[142]	• Aminoacyl-tRNA biosynthesis • Histidine metabolism
Myoinositol	[215]	[160]	[160]	[142]	• Ascorbate and aldarate metabolism • Galactose metabolism • Phosphatidylinositol signaling system • Inositol phosphate metabolism
Nicotinamide	[135,134]	[186]	[244]	[133], [134]	• Nicotinate and nicotinamide metabolism
L-Ornithine	[181]	[207]	[206]	[142,152,193]	• Arginine and proline metabolism • Arginine biosynthesis • Glutathione metabolism • Urea Cycle
2-oxoglutarate (α-ketoglutarate)	[178,131,181]	[245,246,146,189]	[246,66,140]	[152]	• Glutamine and glutamate metabolism • Butanoate metabolism • Alanine, aspartate and glutamate metabolism
Phenylalanine	[134,181]	[160,204]	[66,218]	[142],	• Arginine biosynthesis • Aminoacyl-tRNA biosynthesis • Nitrogen Metabolism Phenylalanine Metabolism • Phenylalanine, tyrosine and tryptophan biosynthesis
Phenylacetylglycine	[211,168]	[247]	[170]	[152]	• Phenylalanine metabolism • Gut-Microbiota metabolism
Proline	[180]	[207,204]	[206]	[142]	• Aminoacyl-tRNA biosynthesis • Arginine and proline metabolism
Pyruvate	[226]	[160]	[66,228]	[142]	• Arginine and proline metabolism • Alanine, aspartate and glutamate metabolism • Glyoxylate and dicarboxylate metabolism

(*continued on next page*)

Table 2 (*continued*)

Metabolites	AD/CD	MS/ IR / Dyslipidemia/ GI	Obesity	T2DM	Metabolic Pathway
					• Cysteine and methionine metabolism • Glycolysis and Gluconeogenesis pathway • Pyruvate Metabolism • Urea Cycle
SCFAs: Acetate, Valerate, Butyrate	[73], [130], [163], [131]	[160,161]	[66]	[162]	• Glyoxylate and dicarboxylate metabolism (Acetate) • Pyruvate Metabolism • Gut-Microbiota metabolism
Serine	[215,136]	[242,160]	[242,66]	[242,184]	• Aminoacyl-tRNA biosynthesis • Glycine, serine and threonine metabolism • Glyoxylate and dicarboxylate metabolism • Sphingolipid metabolism • Cysteine and methionine metabolism
Succinate	[215,131]	[216,234]	[248,249,232]	[229]	• Citrate Cycle • Butanoate metabolism • Warburg Effect • Gut-Microbiota metabolism
Taurine	[250,131,134]	[160,139]	[66]	[152]	• Taurine and hypotaurine metabolism
Threonine	[136]	[207,208]	[209]	[242,184,162]	• Glycine, serine and threonine metabolism • Aminoacyl-tRNA biosynthesis • Valine, leucine and isoleucine biosynthesis
TMAO	[157,156]	[70,231]	[151,66]	[152,67]	• Methylamines metabolism, Gut-Microbiota metabolism
TMA	[131]	[234,227]	[251]	[152]	• Methylamines metabolism • Gut-Microbiota metabolism

SCFAs: Short chain fatty acids, AD: Alzheimer's Disease, MS: Metabolic Syndrome, GI: Glucose Intolerance, CI: Cognitive Dysfunction, IR: Insulin resistance, TMA: Trimethylamine, TMAO: Trimethylamine-oxide, DMA: Dimethylamine, DMG: Dimethylglycine. [1] In [173] study, 3-indoxyl sulfate increased in diabetic patients with nephropathy compared to diabetic with normal renal function. [2] In [176] study, the correlation imidazole propionate was with hypertension in obese subjects

(Table 2). Some of these dysbiotic gut microbiota metabolites are directly derived microbiome metabolites and some are derived by combinatory metabolism of microbiome and host. In general, dysbiotic gut microbiota metabolites are associated with IR and chronic low grade inflammation [150]. For instance, trimethyl-amine-oxide (TMAO) is a gut microbiota metabolite which is one of the metabolic biomarkers of IR disorders such as T2DM, obesity and MS [66,67,70,151,152]. TMAO has been found associated with atherosclerosis, as well as a predictor of CVDs and mortality in T2DM patients [153–155]. Not surprisingly, TMAO is also associated with neuro-degenerative diseases such as AD [156,157]. In fact, inhibiting the gut-microbiota production of TMAO through dietary compounds such as 3,3-dimethyl-1-butanol (DMB) and resveratrol reduces atherosclerosis [158,159]. Whether this dietary or supplementation approach consequently reduces AD risk warrants further clinical study. Other AD-IR gut microbiota dysbiosis metabolic biomarkers include short chain fatty acids (SCFAs), 3-indoxyl sulfate, imidazole propionate, choline, betaine, and 4-cresol. Variations in SCFAs are associated with IR disorders and cognitive impairment [66,73,130,160–163]. Modulation of SCFAs had been found associated with improvements in insulin sensitivity, glucose metabolism and weight [130,164,165]. Therefore, dietary interventions toward favorable SCFAs modulation has beneficial effect in AD and IR disorders [130,166]. The 3-indoxyl sulfate (indoxyl sulfate) is gut microbiota derived metabolite which is associated with IR disorders and AD [167–172]. Indoxyl sulfate has been found elevated in diabetic patients with nephropathy compared to diabetic with normal renal function [173]. This metabolite promoted vascular calcification in chronic kidney disease (CKD) rat model where that association was linked to IR and elevated glucose [174]. Another gut derived metabolite is imidazole propionate which has been found associated with T2DM and prediabetes [175]. This association was highly linked to the dysbiosis in gut microbiota. Imidazole propionate positively correlated with elevated blood pressure in obese subjects as well [176]. Imidazole propionate causes an impairment to insulin signaling and glucose metabolism, two crucial pathogenic factors in the AD-IR link [69,175]. Although its role in AD not yet elucidated, imidazole propionate as well as other gut-derived metabolites can cross BBB and have been recently detected in the forebrains of mice [168]. Much more details on imidazole propionate molecular mechanisms in humans are expected to thrive the discussion on this topic by an ongoing Sweden study [177]. Branched chain amino acids (BCAAs), acylcarnitines, lactate, pyruvate, serine, threonine, alanine, histidine, glutamine, adenosine, nicotinamide, proline, arginine, and aspartate were found perturbed metabolites in AD [57,134,167,178–181]. Similarly, these metabolites were associated with IR disorders such as T2DM, MS and obesity [133,137,139–142,182–186]. Elevated levels of BCAAs; L-leucine, L-isoleucine and L-valine are proinflammatory, induces oxidative stress and mitochondrial dysfunction [185,187,188]. They are indicative of IR as well [185,188]. Similarly, acylcarnitines promotes inflammation, oxidative stress, mitochondrial dysfunction and IR [145,189–191]. Such pathways are highly implicated in AD pathogenesis which explain their presence in AD metabolic biomarkers [57,178,180]. The metabolites: arginine, ornithine, proline, pyruvate, and glutamate are associated with the metabolic pathway of arginine and proline metabolism. In fact, alterations in arginine metabolism precede behavioral changes in AD mice model [192]. The accumulation of proline and ornithine may indicate increased activity of the arginase enzyme, a state which is not uncommon in IR disorders and it is associated with endothelial dysfunction and CVDs [193]. Increased arginase enzyme activity hinders the formation of nitric oxide (NO), and thus increasing the reactive oxygen species and mitochondrial dysfunction, as well as endothelial dysfunction and vascular complications [179,194,195]. The NO

pathway is implicated in neurodegenerative diseases including AD since decreased NO impairs cerebral blood flow [195]. Arginase inhibitors have been proposed as novel therapy to hinder AD progression, however, clinical investigations are in their early stage [196]. Collectively, the AD-IR link metabotype indicates common metabolic pathogenic pathways not only between AD and IR disorders but also between AD and IR disorders complications. Therefore, it is not surprising to us that most of the AD-IR linked metabolites had been linked to CVDs as well [197–201].

To shed more light on the most significant and impactful metabolites' sets and metabolic pathways in the AD-IR link metabotype (i.e. metabolites' list in Table 2), we applied enrichment over representation analysis (ORA) and metabolic pathway analysis for the metabolites' list in the AD-IR link metabotype using the web-based free software MetaboAnalyst 5.0 [202]. We considered p value <0.05 and false discovery rate (FDR) <0.1 for the listing of the implicated metabolites' sets and metabolic pathway, as shown in Tables 3 and 4, respectively. The enrichment ORA demonstrated that eleven metabolites' sets were significantly overrepresented, as shown in Table 3. Of these metabolites' sets, Glycine and Serine Metabolism, Urea Cycle, Ammonia Recycling, Glucose-Alanine Cycle, Arginine and Proline Metabolism and Alanine Metabolism had the most significance ($p < 0.001$ and FDR < 0.02). Other significant metabolites' sets can be sought from Table 3 ($p < 0.05$ and FDR < 0.1). Fig. 2.A and 2.B show Bar Chart and Dot plot views of the ORA, respectively. The metabolic pathway analysis of the AD-IR link metabotype based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) showed that fourteen metabolic pathways were significantly perturbed ($p < 0.05$ and FDR < 0.1), as shown in Table 4. Metabolic pathways of: Aminoacyl-tRNA biosynthesis, Alanine, aspartate and glutamate metabolism, Arginine biosynthesis, Butanoate metabolism, Glyoxylate and dicarboxylate metabolism, Glycine, serine and threonine metabolism, Valine, leucine and isoleucine biosynthesis, D-Glutamine and D-glutamate metabolism, Arginine, and proline metabolism had the most significance with extremely low FDR ($p < 0.001$ and FDR < 0.008). Other significant metabolic pathways can be sought from Table 4 ($p <$ 0.05 and FDR < 0.1). Out of the fourteen significant metabolic pathways, the most impactful were: Synthesis and degradation of ketone bodies, Glycine, serine and threonine metabolism, Alanine, aspartate and glutamate metabolism, D-Glutamine and D-glutamate metabolism and Arginine and proline metabolism, respectively. Fig. 2.C depicts the metabolic pathway analysis topology. Looking to the most significant and impactful metabolites' sets and metabolic pathways, one can contemplate the large overlapping between AD and IR disorders on a metabolomics level which supports the understanding of the AD-IR pathogenic link. Perturbations in these metabolites' sets and metabolic pathways had been previously reported in AD and IR disorders [66,139,142,160,162,167,168,184,185,192,203–208].

5. AD-IR pathogenic link as a therapeutic target for AD treatment

There are several non-pharmacological and pharmacological therapeutic strategies that have been studied for AD management. However, the non-pharmacological strategies might be more effective than current pharmacological strategies [3]. Physical activity, social care, cognitive stimulation, and dietary interventions are some of the proposed lifestyle interventions. Among suggested dietary therapies are the Calorie restricted (CR) diet, intermittent fasting (IF), the low carbohydrate high fat (LCHF) diet or the Ketogenic diet and the Mediterranean (MEDT) diet. The effectiveness of some of these therapeutic approaches could be explained, in part, by their role in targeting the AD-IR pathogenic link. The current pharmacological treatments of AD do not stop the progression of the disease, yet they may manage some of the symptoms [3]. The Food and Drug Administration (FDA) approved AD-drugs manage AD symptoms by two main approaches. The first one is through the inhibition of acetylcholine esterase enzyme (AChE), an enzyme which breaks-down the acetylcholine neurotransmitter [3,252]. This increases the level of acetylcholine neurotransmitter. These drugs include donepezil, rivastigmine and galantamine. The second approach is through the antagonization of *N*-methyl D-aspartate (NMDA) receptor by Memantine [3]. Memantine which is FDA approved AD-drug reduces the excitatory effect of increased glutamate in subjects suffering from AD [252]. It is available alone or in combination with donepezil. A recent drug which is still under FDA review is Aducanumab which works by reducing Aβ in the brain [3,252]. None of the current AD-drugs targets the IR pathogenic pathway in AD. Some T2DM drugs have been proposed to play role in AD treatment [61,253–255]. This includes drugs such as metformin, sodium-glucose co-transporter-2 inhibitors (SGLT2i) or gliflozins and glucagon-like peptide-1 receptor (GLP-1) agonists [61,253,254]. In the following sub-sections, the lifestyle and the

Table 3
Enrichment ORA analysis of the AD-IR link metabotype.

	Overrepresented metabolite sets (1)	Implicated Metabolites (2)	Total (3)	Hits (4)	Raw p (5)	Holm p (6)	FDR (7)
1	Glycine and Serine Metabolism	Creatine; Betaine, Dimethylglycine; Glycine; L-Glutamic acid; L-Alanine; L-Threonine; L-Serine; Oxoglutaric acid; Ornithine; Pyruvic acid; L-Arginine	59	12	1.21E-05	0.00119	0.00119
2	Urea Cycle	L-Glutamic acid; L-Alanine; L-Aspartic acid; Oxoglutaric acid; Ornithine; Pyruvic acid; L-Arginine; L-Glutamine	29	8	4.17E-05	0.00405	0.00205
3	Ammonia Recycling	Glycine; L-Glutamic acid; L-Histidine; L-Serine; L-Aspartic acid; Oxoglutaric acid; Pyruvic acid; L-Glutamine	32	8	9.11E-05	0.00875	0.00298
4	Glucose-Alanine Cycle	D-Glucose; L-Glutamic acid; L-Alanine; Oxoglutaric acid; Pyruvic acid	13	5	0.00024	0.0228	0.00587
5	Arginine and Proline Metabolism	Creatine; Glycine; L-Glutamic acid; L-Proline; L-Aspartic acid; Oxoglutaric acid; Ornithine; Succinic acid; L-Arginine	53	9	0.000758	0.0712	0.0149
6	Alanine Metabolism	Glycine; L-Glutamic acid; L-Alanine; Oxoglutaric acid; Pyruvic acid	17	5	0.000988	0.0919	0.0161
7	Glutamate Metabolism	Glycine; L-Glutamic acid; L-Alanine; L-Aspartic acid; Oxoglutaric acid; Pyruvic acid; Succinic acid; L-Glutamine	49	8	0.00202	0.186	0.0283
8	Carnitine Synthesis	L-Carnitine; Glycine; L-Lysine; Oxoglutaric acid; Succinic acid	22	5	0.00348	0.316	0.0426
9	Aspartate Metabolism	Acetic acid; L-Glutamic acid; L-Aspartic acid;Oxoglutaric acid; L-Arginine; L-Glutamine	35	6	0.00605	0.544	0.0594
10	Warburg Effect	Citric acid; D-Glucose; L-Glutamic acid; L-Lactic acid; Oxoglutaric acid; Pyruvic acid; Succinic acid; L-Glutamine	58	8	0.00606	0.544	0.0594
11	Malate-Aspartate Shuttle	L-Glutamic acid; L-Aspartic acid; Oxoglutaric acid;	10	3	0.0109	0.96	0.0972

This Metabolites enrichment analysis was generated by MetaboAnalyst 5.0 web-based program using the shared AD-IR link metabotype metabolites' list. See Fig. 2.A and 2.B for bar chart and dot plot visualization of this analysis. (1) Only pathway metabolites' sets with $p < 0.05$ and FDR < 0.1 are shown in the Table. 2 Implicated metabolites from shared AD-IR link metabotype. (3) Total number of metabolites in the metabolites' set. (4) Hits: number of metabolites from the AD-IR link metabotype involved in the metabolites' set. (5) Raw p: original p value calculated from the enrichment analysis. (6) Holm p: adjusted raw p value by Holm-Bonferroni method. (7) FDR: false discovery rate.

Table 4
Metabolic pathways Analysis for the AD-IR link metabotype.

	Metabolic Pathway (1)	Implicated Metabolites (2)	Total (3)	Hits (4)	Raw *p* (5)	- Log (*p*) (6)	Holm *p* (7)	FDR (8)	Impact (9)
1	Aminoacyl-tRNA biosynthesis	L-Histidine; L-Phenylalanine; L-Arginine; L-Glutamine; Glycine; L-Aspartate; L-Serine; L-Valine; L-Alanine; L-Lysine; L-Isoleucine; L-Leucine; L-Threonine; L-Proline; L-Glutamate.	48	15	1.19E-12	11.926	9.96E-11	9.96E-11	0.16667
2	**Alanine, aspartate and glutamate metabolism**	**L-Aspartate; L-Alanine; L-Glutamate; L-Glutamine; Citrate; Pyruvate; Succinate; 2-Oxoglutarate.**	**28**	**8**	**9.05E-07**	**6.0432**	**7.51E-05**	**3.80E-05**	**0.58254**
3	Arginine biosynthesis	L-Glutamate; L-Arginine; L-Aspartate; L-Ornithine; L-Glutamine; 2-Oxoglutarate.	14	6	1.60E-06	5.796	0.000131	4.48E-05	0.2538
4	Butanoate metabolism	(R)-3-Hydroxybutanoate; Acetoacetate; L-Glutamate; Butanoic acid; 2-Oxoglutarate; Succinate.	15	6	2.60E-06	5.5844	0.000211	4.69E-05	0.11111
5	Glyoxylate and dicarboxylate metabolism	Citrate; L-Serine; Glycine; L-Glutamate; Acetate; Pyruvate; Formate; L-Glutamine.	32	8	2.79E-06	5.5545	0.000223	4.69E-05	0.1799
6	**Glycine, serine and threonine metabolism**	**L-Serine; Choline; Betaine; N,*N*-Dimethylglycine; L-Glycine; L-Threonine; Creatine; Pyruvate.**	**33**	**8**	**3.60E-06**	**5.4441**	**0.000284**	**5.03E-05**	**0.58578**
7	Valine, leucine and isoleucine biosynthesis	L-Threonine; L-Leucine; L-Isoleucine; L-Valine.	8	4	5.19E-05	4.2852	0.004045	0.000622	0
8	**D-Glutamine and D-glutamate metabolism**	**L-Glutamate; L-Glutamine; 2-Oxoglutarate.**	**6**	**3**	**0.000523**	**3.2817**	**0.040249**	**0.005489**	**0.5**
9	**Arginine and proline metabolism**	**L-Arginine; Creatine; L-Proline; L-Glutamate; L-Ornithine; Pyruvate.**	**38**	**6**	**0.000834**	**3.0786**	**0.06342**	**0.007788**	**0.34441**
10	Histidine metabolism	L-Glutamate; L-Histidine; N(pi)-Methyl-L-histidine; L-Aspartate.	16	4	0.001122	2.95	0.084154	0.009425	0.22131
11	Citrate Cycle (TCA Cycle)	2-Oxoglutarate; Succinate; Citrate; Pyruvate.	20	4	0.002726	2.5645	0.20171	0.020815	0.22801
12	Glycolysis / Gluconeogenesis	Pyruvate; (S)-Lactate; beta-D-Glucose; Acetate.	26	4	0.007335	2.1346	0.53543	0.051342	0.12971
13	**Synthesis and degradation of ketone bodies**	**3-Hydroxybutyrate; Acetoacetate.**	**5**	**2**	**0.00885**	**2.0531**	**0.6372**	**0.057184**	**0.6**
14	Nitrogen Metabolism	L-Glutamate; L-Glutamine.	6	2	0.013014	1.8856	0.92396	0.078081	0

This pathway analysis was generated by MetaboAnalyst 5.0 web-based software. (1) Only metabolic pathways with $p < 0.05$ and FDR < 0.1 are shown in the Table 2 Implicated metabolites from the shared AD-IR link metabotype as presented in Table 2. (3) Total number of metabolites in the pathway. (4) Hits: number of metabolites from the shared AD-IR link metabotype involved in the pathway. (5) Raw *p*: original *p* value calculated from the pathway analysis. (6) -log (*p*): negative log of (*p*) value. (7) Holm *p*: adjusted raw *p* value by Holm-Bonferroni method. (8) FDR: false discovery rate. (9) Impact: impact of the pathway as calculated from pathway topology analysis. Pathways in bold have the highest impact (impact > 0.3).

pharmacological approaches interfering with the AD-IR pathogenic link are discussed. Fig. 3 summarizes these approaches.

5.1. Lifestyle modifications interfering with the AD-IR pathogenic link

Exercise is one of the effective non-pharmacological strategies in AD management [3,256–258]. Exercise improves physical fitness and cognitive functions in elderly AD patients [256]. It is also associated with reduced Aβ deposition [259]. In monkeys' model of aging, physical activity had been found to decrease brain atrophy [260]. In fact, exercise improves insulin sensitivity and glucose metabolism which is an effective lifestyle-strategy in the treatment of IR disorders and CVDs [261]. It is reasonable to contemplate that exercise mitigates the pathogenic effect of AD-IR pathway by improving glucose metabolism and insulin signaling leading to the documented positive outcomes in AD [258]. Interestingly, exercise may hamper the effect of genetic variants associated with the AD-IR pathogenic link. For instance, physical activity may have better effect on reducing Aβ deposition in *ApoE* ε4 carriers compared to non-carriers [259]. Another example, the effect of the increased BMI risk allele *FTO*-SNP rs3751812 can be mitigated by physical activity [262]. Whether this effect can be extrapolated for AD, should be one of future investigations. On a metabolomics level, the data on variations in the metabolome of people suffering from cognitive impairment or at higher risk of AD is scarce. However, in a study which investigated serum metabolomics variations post exercise in men suffering from metabolic syndrome showed a favorable metabolic variation including improvements in BCAAs and gut microbiota derived metabolites such as choline and betaine [221]. These variations may indicate improvement in IR which can be extrapolated to AD, however further investigations are warranted.

CR diet and IF are among the proposed dietary approaches for AD management [263,264]. CR diet and IF had been studied as nutritional therapy for IR disorders such as obesity, MS and T2DM [265–267]. Both dietary approaches had shown promising results in preventing and reducing AD progression [35,264,268–270]. However, extreme CR should be considered cautiously to avoid possible negative impacts [271]. The role of CR diet and IF in AD management may be mediated by several mechanisms. CR diet and IF maintain low level of insulin due to the calorie restriction or the reduction of feeding window (feeding hours), respectively. Sustained reduction in elevated insulin levels to the baseline or the fasting insulin level breaks the vicious cycle of IR ↔ Hyperinsulinemia and thus improves insulin sensitivity and glucose metabolism. Accordingly, this interferes with the AD-IR pathogenic link. Essentially, CR diet and IF reduce blood glucose, blood pressure, IR, hyperinsulinemia, and inflammation which are risk factors of AD development [267,269,272,273]. Furthermore, autophagy, the process of body's self-renovation and recycling, is induced by CR diet and IF [274,275]. This increases longevity and reduces aging effects. Dysfunction of autophagy leads to neuronal cell death which is common pathogenic feature in neurodegenerative diseases such as AD and Parkinson's disease (PD) [275]. Therefore, dietary approaches which induce autophagy such as CR and IF can play vital role in AD management by confronting neuronal death and neuronal aging. CR diet prevents amyloid plaque development [35,264,268–270]. IF promotes Aβ removal from the brain [276]. Both CR diet and IF increase the level of ketone bodies such as β-hydroxybutyrate (βHB) which has several therapeutic roles in improving AD symptoms [276,277]. The role of βHB in AD management is furtherly discussed in the following paragraph as we discuss the ketogenic diet. It is worthy to mention that the CR diet with focus on limiting calories from carbohydrates mediated modulation

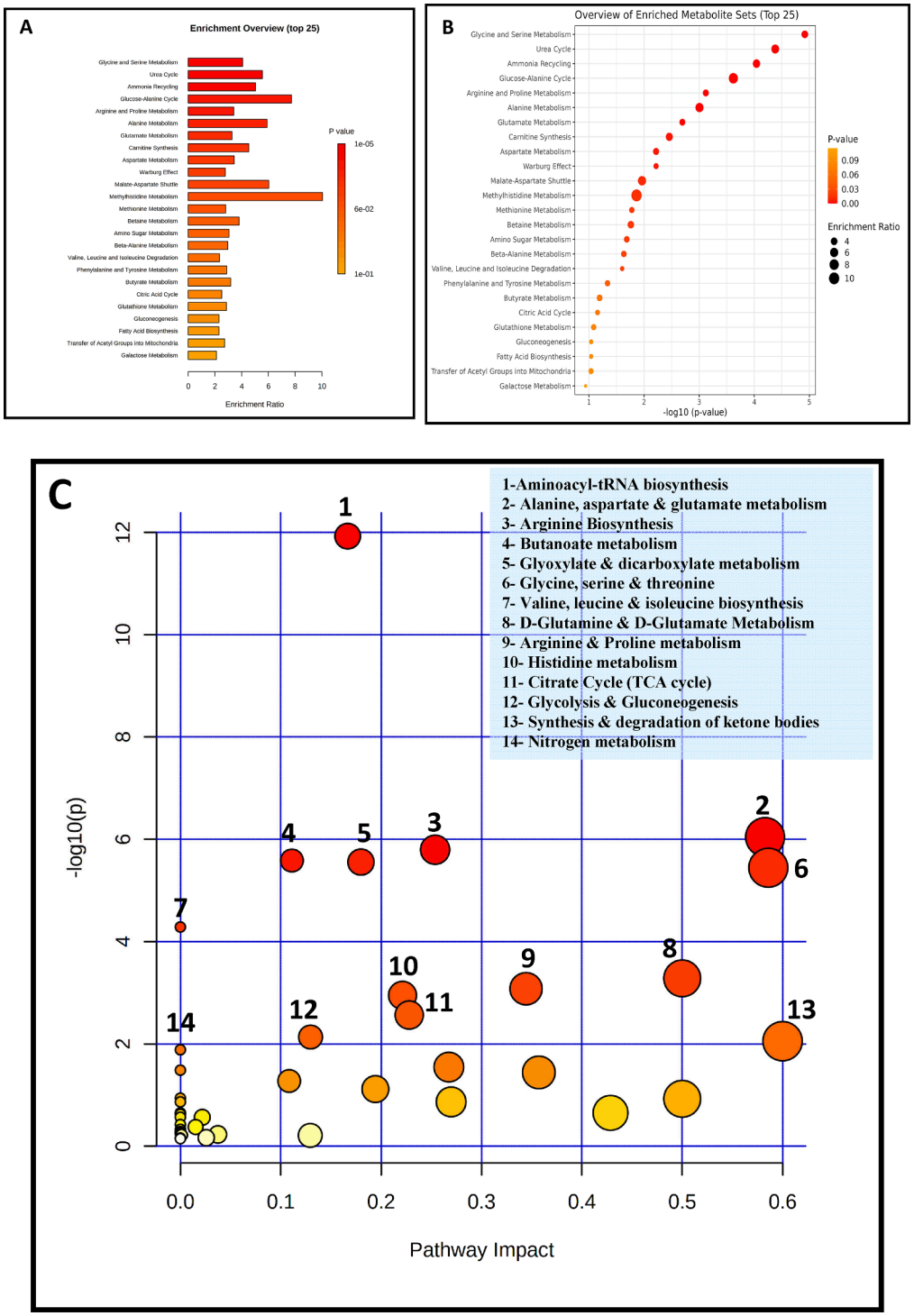

Fig. 2. Over representation Enrichment analysis and metabolic pathway analysis of the AD-IR link metabotype as generated by MetaboAnalyst 5.0 web-based software.

Fig. 2.A: Bar chart view of the over representation Enrichment overview based on Small Molecule Pathway Database (SMPDB). Metabolites' sets in the over representation Enrichment analysis are sorted based on fold enrichment and *p* value. Glycine and Serine Metabolism, Urea Cycle, Ammonia Recycling, Glucose-Alanine Cycle and Arginine and Proline Metabolism had the most significance, respectively. Refer to Table 3 for further details on each metabolites' set - related metabolites, *p* value and FDR value of each metabolites' set. Fig. 3.B: Dot Plot view of the over representation Enrichment overview based on Small Molecule Pathway Database (SMPDB). Metabolites' sets are sorted based on fold enrichment and *p* value. Glycine and Serine Metabolism, Urea Cycle, Ammonia Recycling, Glucose-Alanine Cycle and Arginine and Proline Metabolism had the most significance, respectively. Refer to Table 3 for further details on each metabolites' set - related metabolites, *p* value and FDR value of each metabolites' set. Fig. 2.C: Pathway analysis of the AD-IR link metabotype metabolites based on the Kyoto Encyclopaedia of Genes and Genomes (KEGG) showed that Aminoacyl-tRNA biosynthesis followed by Alanine, aspartate and glutamate metabolism had the highest significance, while Synthesis and degradation of ketone bodies followed by Glycine, serine and threonine had the highest impact. Refer to Table 4 for further details on each pathway: related metabolites, *p* value, FDR value and impact.

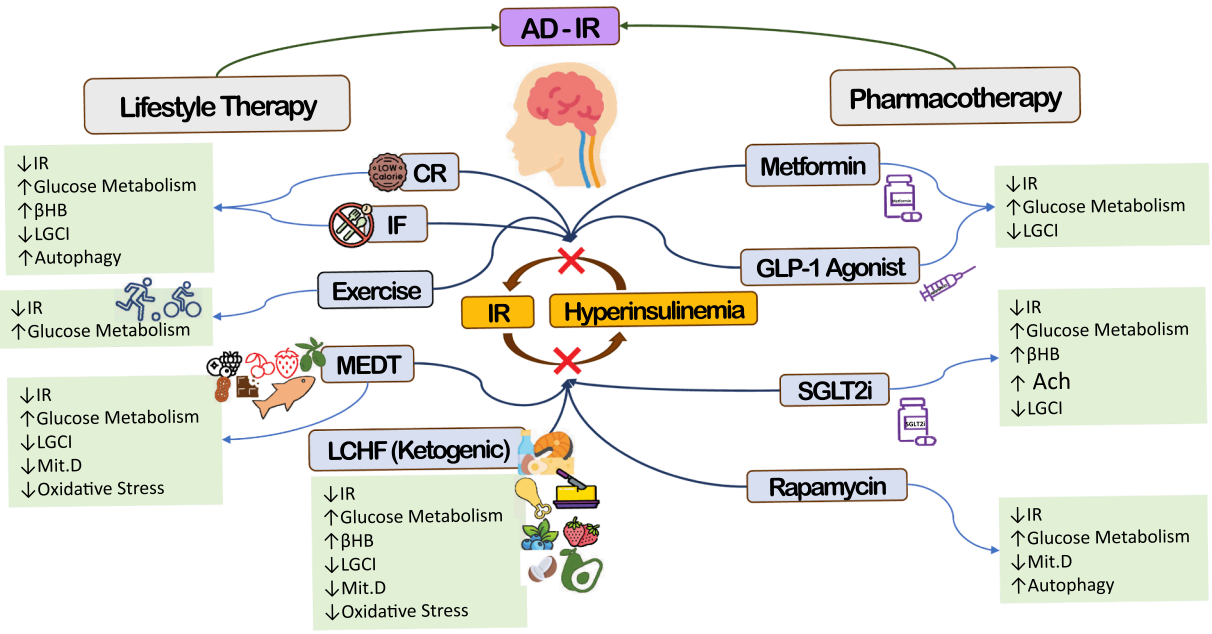

Fig. 3. Therapeutic approaches targeting AD-IR Link and their proposed Mechanisms.
The pathogenic link between AD and IR disorders can be targeted with lifestyle and pharmacological therapies. This will help to break the vicious cycle of IR ↔ Hyperinsulinemia and thereupon interfere with the AD-IR pathogenic link. ↑: indicates Increase or Improve. ↓: indicates Decrease or Inhibit. Abbreviations, IR: Insulin Resistance, AD: Alzheimer's diseases, CR: Calorie restriction, IF: Intermittent Fasting, LGCI: Low grade chronic inflammation, MEDT: Mediterranean Diet, Mit. D: Mitochondrial Dysfunction, LCHF: Low carbohydrates high fat diet, SGLT2i: Sodium-glucose Cotransporter 2 Inhibitors, GLP-1: glucagon-like peptide 1, βHB: β-hydroxybutyrate and ACh: Acetylcholine. CR, IF, brain, blue berries, strawberry, butter and coconut icons from www.flaticon.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of gut microbiota favoring AD reversal in female mice [278]. There are CR mimetic compounds such as resveratrol and rapamycin which mimic the therapeutic effect of CR diet on AD [269]. These compounds are expected to have auspicious role in AD management warranting further study.

The role of the ketogenic diet or the low carbohydrate healthy fat (LCHF) diet in the nutritional therapy of AD has gained attention [130,279–282]. LCHF diet focuses on reducing carbohydrates, maintaining moderate protein and allowing healthy fat up to satiation [277,283,284]. Since carbohydrates is restricted on the LCHF diet, low level of insulin is maintained which shifts energy metabolism towards fat metabolism and ketogenesis [277,283,285,286]. Ketogenesis usually happens in the liver, and it includes the formation of ketone bodies form fatty acids derived from endogenous and exogenous fat [277,282,283,286]. Ketogenic (i.e., LCHF) diet is an effective nutritional therapy option for pharmacological-resistant epilepsy [287,288]. LCHF diet has beneficial effects on the fundamental clinical features of IR disorders. It improves glucose metabolism, reduces IR and normalizes HbA1c as well as decreasing medications use in T2DM patients [283,284,289–291]. Furthermore, it is effective in reducing inflammation, oxidative stress, dyslipidemia, and excess weight in subjects suffering from IR disorders such as MS and obesity [292–295]. LCHF diet enhances cardiac biomarkers and reduces cardiovascular risk in individuals enduring IR disorders [292–296]. Therefore, it has been recommended by several guidelines as one of the nutritional therapy options for T2DM [297–300]. LCHF diet role in the nutritional therapy of AD is achieved through more than one plausible mechanism. First, restricting carbohydrates maintains low insulin level which increases insulin sensitivity (i.e., decreases IR) [286]. Reducing IR will lead to subsequent further reduction in the peripheral insulin level which in turn will hamper the detrimental effect of hyperinsulinemia on the brain [25,27,301]. Second, it normalizes blood glucose level which will limit the effect of elevated blood glucose in the AD-IR pathogenic link as discussed earlier in this review [25,301]. Third, ketogenesis is induced by LCHF diet which leads to the production of ketone bodies such as acetoacetate and βHB [277,286]. The latest breeds several curative pathways in CMDs diseases including IR disorders and CVDs [40,277]. In fact, βHB has vasodilating effect [302–304]. Besides, it reduces oxidative stress, inflammation, and IR, as well as it improves mitochondrial respiration [277,281,302–304]. These beneficial effects not only hamper AD risk factors but also reduce AD progression [281]. βHB serves as an energy source in the brain, particularly for cells suffering from IR [301,305,306]. Fourth, metabolism of fatty acids in the mitochondria generates Acetyl-Co-A [286] which is important for the synthesis of acetylcholine. Since cholinergic perturbations, in particular reduced acetylcholine synthesis, is involved in AD pathogenesis [9,10], it is reasonable to conceptualize that LCHF diet increases acetylcholine synthesis through increasing Acetyl-Co-A availability. Fifth, the abundance of fatty acids on a restricted carbohydrate diet (i.e., LCHF diet), particularly if enriched with medium chain triglycerides (MCT) reduces Aβ levels and improves cognitive ability [285,306,307]. The role of MCT was highly significant in carriers of *ApoE ε4* [307]. Besides, MCT consumption was associated with elevation in ketone bodies (β-hydroxybutyrate and acetoacetate). Sixth, the ketogenic diet enhances the biogenesis of mitochondria which improves brain metabolism [308]. Lastly, similar to the CR and IF, the ketogenic diet induces autophagy [275]. As previously discussed in this review, autophagy reduces neuronal death and neuronal aging. Considering the aforementioned mechanisms, the favorable effect of LCHF diet in AD treatment is promising. Therefore, and not surprisingly, the LCHF diet had been found to increase daily function and quality of life in AD patients [301]. It also had positive effects on CVDs risk components such as the level of high density lipoprotein (HDL). In a recent systematic review, the LCHF diet was found effective in reducing AD cognitive symptoms [309]. Similarly, Lilamand and colleagues narrated an updated review of 12 preclinical and clinical studies of LCHF diet in AD treatment [305]. LCHF diet reduced cerebral inflammation, Aβ and tau protein hyperphosphorylation in preclinical studies. In clinical studies, it showed improvements in cognitive functions, brain metabolisms, and AD biomarkers. The metabolomics variations following the exposure to LCHF

diet has been investigated in several diseases such as epilepsy, cancer, and psoriasis [310–312]. However, the metabolomics data is limited in regard to the application of the LCHF in AD. Nonetheless, the LCHF exposure metabolomics studies in other diseases indicated perturbations in some of the common metabolic biomarkers between AD and IR disorders. For instance, LCHF diet exposure led to reductions in ceramides, lactic acid, isoleucine, leucine, and alanine which are known metabolic biomarkers of AD, as shown in Table 2 [310–312]. Considering the aforementioned mechanisms for the therapeutic role of LCHF diet in the treatment of IR disorders and AD as well as the effectiveness shown in preclinical and clinical studies, one could speculate that incorporating LCHF diet in AD management is hopeful. However, long-term clinical studies to assess metabolic biomarkers and symptoms' improvement are warranted.

The Mediterranean (MEDT) diet has been investigated in the protection and management of IR disorders and AD [313–319]. MEDT diet is one of the effective nutritional therapy in IR disorders (T2DM, MS, obesity) and CVDs, particularly when designed to restrict carbohydrates and enrich certain dietary components such as nuts, olive oil and berries on their meal plans [313–315,320–322]. Similarly, adherence to the MEDT is associated with lower risk of cognitive decline and AD [316,317,323]. In regard to the AD-IR pathogenic link, there are several plausible explanations to the role of the MEDT in reducing cognitive decline and improving AD symptoms. MEDT diet is prosperous with fatty fish, extra virgin olive oil, seeds, nuts, vegetables, berries fruits, fibers, and resistant starch [313–315,324]. Many of those dietary components play vital role in reducing inflammation, oxidative stress, and IR [324,325]. Berries fruits, extra virgin olive oil, nuts, dark chocolate, and green tea are rich in polyphenol compounds which had been found effective in reducing IR and inflammation as well as improving lipid profile in subjects suffering from CMDs diseases [326–328]. This largely explains their nutritional therapy role in reducing cardiovascular risk in subjects suffering from IR disorders [328,329]. Comparably, they are competent in improving cognitive decline [323,330]. Besides their anti-inflammatory, anti-oxidant, and insulin sensitization roles, polyphenols have anti-amylogenic activity and they interfere with tau hyperphosphorylation and accumulation [324,331]. In a *meta*-analysis of 80 randomized clinical trials (RCT), dietary flavonoids, a class of polyphenols, had positive effect on cognitive performance, particularly flavonoids from MEDT dietary components such as cocoa, gingko and berries [323]. One of the main dietary polyphenols which is found in olive oil, grapes, pistachios, cocoa, and berries has been extensively studied in AD [332]. Resveratrol is an anti-inflammatory, anti-oxidant, and epigenetic and mitochondrial modulator [332,333]. Resveratrol has been shown to improve insulin sensitization and both glucose and lipid metabolism [334]. Resveratrol has a CR mimetic effect and reduces age related deterioration [335]. Resveratrol has a cardioprotective role by reducing mitochondrial and endothelial dysfunction and increasing endothelial production of NO [333,336,337]. As previously mentioned, reduction in NO is implicated in endothelial dysfunction and reduced cerebral blood flow, one of the pathogenic pathways of AD [195]. Besides, resveratrol modulates gut microbiota which reduces the synthesis of the gut derived metabolite TMAO, an effect which can lead to reduced atherosclerosis [159]. Furthermore, resveratrol has autophagy induction and antiaging properties [338–340]. Such pleiotropic effects of resveratrol explain great portion of its positive role in improving cognitive function [332]. Noteworthily, resveratrol induced favorable metabolomics changes in diet-induced metabolic syndrome model in mice [341]. In addition to the promising effect of polyphenols, the MEDT dietary components such as fish, nuts and extra virgin olive oil are rich in the Omega 3 long-chain polyunsaturated fatty acids which have crucial role in the prevention of CVDs and cognitive decline [324]. Omega 3 fatty acids are known for their anti-inflammatory function which is critical for cardiac and cognitive protection [325]. Since both the MEDT and the Ketogenic diet showed promising results as a preventive and probably treatment lifestyle intervention for AD, the combination of both diets or the modification of the MEDT diet with food components from the LCHF (Ketogenic) diet had gained scientific interest [130,280,342]. For instance, the enrichment of MEDT diet with coconut oil improved cognitive functions in AD patients [316]. Coconut oil, an MCT rich fat, increases the production of ketone bodies such as, βHB which is effective in reducing inflammation and IR as well as it can be used as an alternative source of energy in IR- areas of the brain. There is also the Spanish Ketogenic Mediterranean Diet (SKMD) or the modified Mediterranean ketogenic diet (MMKD) which is a ketogenic diet (i.e., LCHF diet) where its main protein source is fish and the extra virgin olive oil is a main source of fat [130,343]. This diet has been found effective in reducing cardiovascular risk factors and improving glucose metabolism [343]. Furthermore, it had been found associated with favorable modulation of gut microbiota and improvement of AD biomarkers in the cerebrospinal fluids (CSF) [130]. Nutrimetabolomics studies showed that the MEDT diet remitted ceramides, BCAAs and acylcarnitines in CVDs [321,322,344]. These metabolites are associated with AD and IR disorders as demonstrated in Table 2. Nuts such as almond and pistachios represent important portion of a well-designed MEDT meal plan. They were found to modulate gut microbiota and remit microbiota dysbiosis metabolic biomarkers such as TMAO, Hippurate and 4-cresol in IR disorders [345,346]. Similarly, blueberries consumption reduced methylamines (TMA & DMA), acetone, acetoacetate and succinate in IR disorders [347]. MEDT dietary fibers such as arabinoxylan and resistant starch modulated dysbiotic gut microbiota and increased fecal SCFAs such as acetate and butyrate in subjects suffering from MS [166]. In a pilot randomized cross-over study comparing the MMKD to the American Heart Association (AHA) diet, it was found that the MMKD increased fecal propionate and butyrate, however, it reduced acetate and lactate [130]. As previously discussed, SCFAs compounds improve insulin sensitivity which in turn may play vital role in targeting the IR-AD pathogenic link [130,164,165]. Considering the aforementioned therapeutic targets and the metabolomics variations post MEDT dietary intervention in AD, it could be well conceptualized that a well-designed MEDT plan enriched with certain foods or modified to the SKMD or the MMKD is auspicious nutritional therapy approach.

5.2. *Pharmacological treatments interfering with the AD-IR pathogenic link*

Several T2DM medications have been proposed for AD-pharmacological therapy. These drugs work by strategies such as reducing blood glucose, IR, oxidative stress, inflammation, and cardiovascular events as well as increasing acetylcholine and ketone bodies [61,253,254]. Metformin is the first line T2DM medication since it works on the root cause of T2DM by increasing sensitivity to insulin which will lead to subsequent reduction in peripheral hyperinsulinemia [348]. Furthermore, metformin has cardioprotective role by reducing atherosclerosis and platelets reactivity which thereupon reduces cardiovascular and cerebrovascular events [349–351]. Metformin has been suggested for the treatment of AD [254]. Metformin was found to increase life span and healthy aging in mice [352]. The AD protective role of metformin can be attributed to its role in reducing IR, atherosclerosis, oxidative stress, inflammation, mitochondrial dysfunction, and ailing aging [254,350,353–355]. Metformin has been investigated in several IR disorders metabolomics studies. In a urine metabolomics rat-model study, metformin altered several gut-microbiota derived metabolites as well as other metabolites from the shared AD-IR linked metabolites presented in Table 2 [356]. In another diabetic rat-model study, metformin normalized the diabetic pattern through modulating more than 15 metabolites of the AD-IR shared metabolites [229]. In a review by Kim [357], he indicated that metformin altered many of the metabolic biomarkers of IR including large number of the shared metabolic biomarkers presented in Table 2 in the current review. Future metabolomics studies investigating the role of metformin in AD prevention and

treatment including variations in the human metabolome worth further study.

Gliflozins or SGLT2i such as empagliflozin, dapagliflozin and canagliflozin exert their anti-diabetic effect through the inhibition of SGLT2 enzyme which reduces the reabsorption of glucose by renal tubules [358]. This causes increased excretion of glucose, and hence reducing blood glucose and IR. While reducing blood glucose and IR has a neuroprotective effect, SGLT2i may help improving AD through several other mechanisms [61,253]. First, SGLT2i reduces blood glucose, thus targeting one of the detrimental pathogenic pathways in the AD-IR link [358]. Second, SGLT2i reduces IR and hence decreases peripheral hyperinsulinemia, thereupon targets fundamental element in the AD-IR link [358]. Third, SGLT2i increases the level of ketone bodies such as βHB which can be used as an alternative fuel for IR areas in the brain [253,305,306,358]. As previously discussed in this review, βHB reduces oxidative stress, inflammation and has vasodilating effect [302,303]. These factors, in turn decrease the risk for cardiovascular and cerebrovascular events which are risk factors of AD [302,303,358]. Fourth, besides the inhibitory effect of gliflozins on the SGLT2 transporter, they possess inhibitory effect on acetylcholine esterase enzyme (AChE), the degrading enzyme of acetylcholine [255,359]. Accordingly, this increases the level of brain acetylcholine which is one of the crucial AD treatment strategies. Taken together, it can be speculated that SGLT2i drugs have promising role in AD management meriting further investigation for effectiveness and safety. Metabolomics studies investigating SGLT2i effect in T2DM and Type one DM (T1DM) indicated metabolomics variations post exposure [360–362]. In a study by Mulder and colleagues, dapagliflozin le-d to increase in 9 out of 13 urinary metabolites that has been linked to mitochondrial dysfunction in T2DM patients [361]. In another recent metabolomics study, T2DM patients had elevated levels of BCAAs, lactate, betaine, myoinositol and ketone bodies in urine post-dapagliflozin treatment [362]. In a metabolomics study on T1DM, empagliflozin led to significant metabolic pathway variations in plasma and urine [360]. The metabolomics variations proposed mitochondrial function improvement post empagliflozin use in T1DM. To the best of our knowledge, there is no study investigating SGLT2i metabolomics effect in AD. In this context, it is worthy to mention that SGLT2i should be used with caution due to its well-established euglycemic ketoacidosis side effect [358,363]. Therefore, SGLT2i is not advocated in people following dietary approaches that may increase ketone bodies' levels such as the LCHF (Ketogenic) diet to avoid developing of ketoacidosis [364]. Furthermore, judicial clinical decision should consider SGLT2i risk of fractures on the early weeks of treatment, particularly in elderly since they are at higher risk of falls and fractures [365]. Collectively, SGLT2i may play effective role in AD treatment. However, further clinical studies are required.

Similar to Metformin and SGLT2i, the GLP-1 agonists are T2DM drugs which have been recently proposed for the treatment of AD [366]. Liraglutide is one of the commonly used GLP-1 agonists in clinical practice in T2DM and obesity and it recently gained attention in AD. Its role in AD can be linked to the improvements in glucose metabolism and insulin signaling as well as the reduction of IR and inflammation [367]. Clinicians are looking forward for the results of an ongoing clinical trial of liraglutide in AD patients [368]. On a metabolic biomarkers' level, a study of two weeks treatment of liraglutide in diet-induced-obesity mice indicated favorable perturbations in several obesity related metabolites such as nicotinamide and taurine [244]. These metabolites were associated with obesity, fat, glucose intolerance and leptin levels [244]. Considering that these metabolites are shared between AD and other IR disorders as early elucidated in this review (Table 2), it can be speculated that liraglutide may have promising role in AD treatment. Again, further clinical investigations are warranted to evaluate liraglutide effectiveness and safety in AD treatment.

Rapamycin (Sirolimus) is an inhibitor drug for the mechanistic target of rapamycin kinase (mTOR) which has been proposed for AD management [369]. Rapamycin targets the aging process through mTOR inhibition which leads to autophagy induction and mitochondrial modulation [370,371]. Similar to resveratrol, rapamycin mimics the therapeutic effect of CR diet and IF [269]. Rapamycin reduced IR in T2DM rats [371]. It also improved cardiac function in aged mice [372]. Thus, it may have promising effect in AD, particularly if combined with dietary approaches such as LCHF or MEDT diet. However, the clinical studies as well as the metabolomics investigations on rapamycin use in AD are scarce which limits the current recommendation of it.

6. Conclusion

It can be concluded that AD and IR disorders are extremely linked. The link between AD and IR disorders is multifactorial where genetic and environmental factors are shared and implicated in their pathogenesis. The presence of more than one factor, including polymorphisms, has an additive effect in the development of the disease course often hindering management. Metabolomics biomarkers shed more light on the implicated pathways in the AD-IR pathogenic link. If used effectively, metabolomics biomarkers may offer early detection of the disease and follow-up of the treatment. However, metabolomics studies assessing treatment approaches are scarce. The pathogenic link between AD and IR disorders may be fended with nutritional and pharmacological treatments. Metabolomics analysis offers fast and reliable method to follow up treatment efficacy. However, further researching is warranted. Whether AD management plan that apply-one or more of dietary approaches such as CR, IF, LCHF and MEDT, in addition to pharmacological drugs targeting AD-IR link is effective and safe warrants further investigations.

CRediT authorship contribution statement

Arwa M. Amin: Conceptualization, Writing – original draft. **Hamza Mostafa:** Visualization. **Hani M.J. Khojah:** Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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