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Alzheimer's disease and gastrointestinal microbiota; impact of *Helicobacter pylori* infection involvement

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Abstract: Background: Alzheimer disease (AD) is a leading cause of global burden with great impact on societies. Although research is working intensively on promising therapy, the problem remains up-to-date. Among the various proposed hypotheses regarding causality and therapy, emerging evidence supports the hypothesis that gastrointestinal microbiota through the so-called 'gut-brain axis' interacts with immune system and brain and shape the balance between homeostasis and disease; the involvement of gastrointestinal microbiota in the pathophysiology of AD is less defined, even though the role of 'gut-brain axis' has been well verified for other neurodegenerative conditions. **Methods:** We performed a systematic review of PubMed/MEDLINE database from 1st January 1990 to 17th October 2018, to investigate the accessible literature regarding possible association between AD and gastrointestinal microbiota. Inclusion criteria were available full text in English language, original clinical papers implicating AD patients and any sort of gastrointestinal microbiota. **Results:** Through our query, an initial number of 241 papers has been identified. After removing duplicates and through an additional manual search, twenty-four papers met our inclusion criteria. The great majority of eligible publications supported a possible connection between AD and gastrointestinal microbiota. The most common investigated microorganism was *Helicobacter pylori*. **Conclusion:** Our own systematic review, showed a possible association between AD and gastrointestinal microbiota mainly including *Helicobacter pylori*, and thus further research is required for substantiation of causality as well as for the establishment of promising novel therapies.

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Alzheimer's disease and gastrointestinal microbiota; impact of *Helicobacter pylori* infection involvement

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Conflict of interest

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Abstract

Background: Alzheimer disease (AD) is a leading cause of global burden with great impact on societies. Although research is working intensively on promising therapy, the problem remains up-to-date. Among the various proposed hypotheses regarding causality and therapy, emerging evidence supports the hypothesis that gastrointestinal microbiota through the so-called “gut-brain axis” interacts with immune system and brain and shape the balance between homeostasis and disease; the involvement of gastrointestinal microbiota in the pathophysiology of AD is less defined, even though the role of “gut-brain axis” has been well verified for other neurodegenerative conditions.

Methods: We performed a systematic review of PubMed/MEDLINE database from 1st January 1990 to 17th October 2018, to investigate the accessible literature regarding possible association between AD and gastrointestinal microbiota. Inclusion criteria were available full text in English language, original clinical papers implicating AD patients and any sort of gastrointestinal microbiota.

Results: Through our query, an initial number of 241 papers has been identified. After removing duplicates and through an additional manual search, twenty-four papers met our inclusion criteria. The great majority of eligible publications supported a possible connection

between AD and gastrointestinal microbiota. The most common investigated microorganism was *Helicobacter pylori*.

Conclusion: Our own systematic review, showed a possible association between AD and gastrointestinal microbiota mainly including *Helicobacter pylori*, and thus further research is required for substantiation of causality as well as for the establishment of promising novel therapies.

Keywords: Alzheimer, dementia, gastrointestinal microbiota, gastrointestinal bacteria, *helicobacter pylori*

Introduction

Alzheimer's disease (AD), widely known as “senile dementia” or “cognitive disorder”, is the most common form of dementia classified as neurodegenerative pathology of central nervous system (CNS). It is characterized by progressive impairments in diverse behavioral and cognitive functions that exert a prominent impact on AD patients, their families, caregivers, and society. AD natural history is progressive and irreversible and its hallmarks consist of cognitive, functional and psychiatric components [1].

Pathophysiology of AD is complex and has not yet been fully elucidated. However, there have been proposed several cellular and molecular mechanisms like free radical oxidative stress, proteotoxicity and mitochondrial dysfunction. Typical histopathological findings include the extracellular senile plaque formation of amyloid- β peptide ($A\beta$) as well as the intracellularly accumulating neurofibrillary tangles with neuropil threads, which are a direct

consequence of amyloid precursor protein processing to A β , and tau protein hyperphosphorylation [2–5]. Overexpression of hyperphosphorylated and aggregated tau seems to damage the axonal transport, resulting in abnormal mitochondrial distribution, mitochondrial dysfunction and neuronal damage [6].

Changes in composition of the so-called “gastrointestinal microbiota”, apart from various intestinal disorders, influence CNS disorders including AD [1]. In this respect, bidirectional communication between gastrointestinal tract (GIT) and the brain occurs both in health and disease [7]. The term “gut-brain axis” encompasses bidirectional communication between enteric nervous - endocrine systems and CNS [8]. This interplay integrates regulation of immune responses in the intestine and brain, and all aspects of this system seem to be significantly influenced by the activity of gastrointestinal microbiota [9]. Gastrointestinal microbiota, both commensal and pathogenic, is regarded as a pivotal regulator that modulates immune, neuronal, metabolic and endocrine pathways and also assists the regulation of the hypothalamic-pituitary-adrenal axis activation state [2,4,10]. Likewise, both commensal and pathogenic microorganisms are known to produce several neuromodulators and neurotransmitters, as well as amyloids [11]. Gastrointestinal microbiota alterations might lead to distorted equilibrium in the lamina propria immune response, followed by systemic inflammatory downstream reactions at distal sites including CNS [9].

Specifically, accumulating evidence from germ-free mice as well as from ones exposed to pathogenic microbial infections, antibiotics, probiotics, or fecal microbiota transplantation suggest a role for the gastrointestinal microbiota in host cognition or AD-related pathogenesis. Increased gut and blood-brain barrier (BBB) permeability through microbial dysbiosis might contribute to neurodegenerative pathogenetic mechanisms. Bacteria may cross the BBB/blood cerebrospinal fluid barrier (BCSFB) to access the CNS by transcellular

penetration or paracellular entry or via infected monocytes from the peripheral circulation (the “Trojan horse” mechanism), thereby leading to neurodegeneration [1,4,9,12–14].

More specifically, regarding the “Trojan horse” mechanism, it appears to be a general mechanism described for several brain disorders including Alzheimer’s disease, Parkinson’s disease and multiple sclerosis [15]. Moreover, the “Trojan horse” mechanism is also applied for infected leukocytes with bacterial pathogens such as *Chlamydia pneumonia*, group B *streptococcus* or *Lysteria monocytogenes* that may cross the BBB/BCSFB as mentioned previously [14,16]. Likewise, activated monocytes, possibly infected by *Helicobacter pylori* (*Hp*) or altered gastrointestinal microbiota systemic dissemination due to dysbiosis may transigrate the BBB/BCSFB, thus triggering the development and progression of brain pathologies [9,17,18]. However, these considerations warrant further elucidation.

In respect to *Hp* contribution to gut-brain cross-talk, there is adequate piece of evidence, that *Hp* can influence microbiota composition, causing imbalance of microbial phyla and dysbiosis and therefore be implicated in the aforementioned pathogenetic cascade. More specifically, studies on *Hp*-positive patients revealed an overall decrease in bacterial diversity with the absolute prevalence at phyla level of *Proteobacteria*, followed by *Bacteroidetes*, *Actinobacteria* and *Firmicutes* [19]. Further studies demonstrated that the same patients are characterized by increased amounts of potential pathogenic *Succinivibrio*, *Coriobacteriaceae*, *Enterococcaceae*, and *Rikenellaceae* phyla in their stools as well as increased abundance of *Candida glabrata* and other unclassified Fungi. These microbial changes may contribute to intestinal mucosal barrier disruption and its consequences[20]. Additionally, *Hp* might exert direct neurotoxic effects, that result in gut-brain axis dysregulation, by activating neurogenic inflammatory processes or by microelement deficiency as a consequence of anatomical and functional changes of GIT [21].

Alterations in overall diversity and the relative abundance of microbial species is connected with CNS autoimmunity. Gastrointestinal microbiota imbalance can induce inflammation that is connected with the pathogenesis of metabolic syndrome (MetS)- related disorders including AD. Moreover, gastrointestinal microbiota can secrete large amounts of amyloids and lipopolysaccharides, which might contribute to the modulation of signaling pathways and the production of pro-inflammatory cytokines that are associated with AD pathogenesis and cerebral amyloid accumulation. These pro-inflammatory cytokines might relay peripheral immune signals to the CNS via sensory nerves, circumventricular organs and BBB cells. As a consequence, the brain could induce mediators, triggering additional immune modulation dysfunction, and activating inflammation through interaction with immune cells, thereby leading to neurodegeneration [1,4,9,12–14].

Taken all together, growing evidence supports the idea of existing an association between gastrointestinal microbiota and AD. However, the contribution of gastrointestinal microbiota to the development of cognitive impairment and dementia is less described, even though the model of "gut-brain axis" has been well established for other neuropsychiatric disorders [22]. Within this study, we review all accessible to us clinical studies investigating AD participants and any sort of gastrointestinal microbiota implication to elucidate if a possible association is reported.

Methods

Protocol: We performed a systematic review of the accessible literature, in order to investigate the above addressed issue. Bibliographical search has been planned and performed according to the described methods of Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses [23]. We also followed the Cochrane collaboration methodology for overviews of reviews [24].

Strategy: An electronic search was conducted in Pubmed/MEDLINE database from 1st January 1990 – 17th October 2018. Software for the reference management of retrieved results and avoidance of duplicates was Mendeley for Mac, version 1.19.2 (Elsevier Inc, New York, USA). PICO items included the following: (P) adult population with AD, (I) involvement of any type of gastrointestinal microbiome, (C) respective population without dementia/cognitive decline, (O) whether an association exists or not. Keywords used for Boolean search were the following with all possible combinations: “alzheimer”, “dementia”, “microbiota”, “gastrointestinal bacteria”, “dysbiosis” and “probiotics”. Further articles were identified through a manual search based on the initial literature results.

Inclusion/exclusion criteria: All criteria have been defined *a priori*, in order to identify all studies investigating a possible association between AD and gastrointestinal microbiota. Only publications written in English language with available and eligible to us full text were considered. Original clinical studies with patients and case reports/series discussing the aforementioned correlation were included, irrespectively of their retrospective or prospective design. Reviews and preclinical studies using animal models or cell cultures were excluded.

Data extraction:

Two investigators (M.D., G.K.) performed independently data extraction from selected papers to Excel sheet (Office 2011 for Mac, Microsoft, Redmond, WA, USA). Extracted data were tabulated (Tables 1-2) and reviewed by first author (M.D.). In cases of conflict, a consensus has been achieved by intervention of last author (J.K.). All data have been stored and managed on a secure server. Collected data consisted of the following parameters: year of

publication, geographical topography, type of study, number of patients and controls, follow-up, basic demographical characteristics (age, gender), type of gastrointestinal microbiota and possible mechanism of action along with type of investigation. In cases where direct demographic data were not available, such as absolute number of participants, gender and rest demographic parameters were calculated indirectly by using relevant study material (e.g. known ratios and absolute number of a (sub)population). Outcomes of review are discussed in “Results” section.

Results

The initial PubMed/MEDLINE electronic search yielded a total number of 241 results (Figure 1). After removal of duplicates, the number of available manuscripts initially confined to 124. Out of them, after reviewing all titles and abstracts were further removed: 55 reviews, 24 (partially or fully) irrelevant clinical studies, 15 letters to the editor, 9 basic research papers (5 mouse models and 4 non-rodent basic research) and 3 editorials. A total number of 14 papers met the inclusion criteria. Another 10 studies were manually identified through an in-hand search of similar articles. Finally, 24 studies were eligible for the purposes of this review. Main outcome of this review was that the vast majority of investigated papers reported a positive association between gastrointestinal microbiota and deterioration of AD. The most common reported microorganism was *Hp*, one of the identified bacterial pathogens in humans which its role is principally as a pathogen or a commensal [25]. Interestingly, a wide variety of different proposals for the pathogenesis have been reported by the authors of the reviewed articles, such as chronic inflammation, immunological mechanisms, apoptosis, disruption of BBB, intestinal dysbiosis and MetS-related atherosclerosis. However, there were also studies without attributing the positive association to a possible mechanism, or studies revealing no association (Table 2).

Discussion

The section of discussion has been structured according to the abovementioned categories of postulated mechanisms of action, which were retrieved by reviewed articles. However, a classification according to pathogenetic mechanism constitutes only an artificial - distinction, which serves the better comprehension of reader. Human pathophysiology involves complex and multiple mechanisms, which co-exist and often synergistically shape the final effect. For instance, immunological aspects share overlapping fields with inflammatory mechanisms.

Inflammation

Inflammation either acute or chronic constitutes one fundamental way of how organism replies to diverse stimuli and invaders. It is characterized by the five best-known signs: *dolor* (pain), *calor* (heat), *rubor* (redness), *tumor* (swelling) and *functio laesa* (loss of function). Ultimate result of inflammation is the elimination of the causative factor as well as the repair of the damaged tissue [26]. Inflammatory components have been frequently described from gut-axis scientists who would like to explain the distant effect of gastrointestinal microbiota on AD development. The gastrointestinal microbiota is directly related with dementia pathogenesis via triggering metabolic diseases and low-grade inflammation progress [10]. In particular, the gastrointestinal microbiota (mainly bacteria) by releasing amyloid peptides and lipopolysaccharides, activates inflammatory signaling via the induction of cytokines, with potential effects on the pathophysiological cascade of AD [27]. Likewise, aging is characterized by a gradual increase in proinflammatory status and this process has been linked with cognitive decline in normal and pathological aging [28]. Equally, accumulating data indicate that inflammation is involved in the pathophysiology of AD [29] and neuroinflammation appears to be a hallmark of AD [30,31].

In this respect, a large scale US survey [32] claimed that *Hp* achieved its action also via inflammatory responses. Furthermore, the Northern Manhattan Study (NOMAS) [33] examined in a prospective study with 1625 participants the infectious burden of *Hp*, *Cytomegalovirus* (CMV), *Herpes simplex virus* (HSV)-1 and HSV-2. The authors concluded that past infections might contribute to cognitive impairment. One of the attributed mechanisms was the chronic infection. Moreover, a French study [34] supported the hypothesis that *Hp* mediates its effect on dementia through cerebrospinal fluid and generally neuroinflammation. Additionally, others [35] postulated that periodontal disease could be linked to cognitive impairment, among others, via systemic inflammation. Finally, the aim of a recent interesting study [36], was to investigate the presence of the bacterial exotoxins rhamnolipids in serum and cerebrospinal fluid of AD patients and healthy subjects. The authors reported a significant elevation in both fluids of AD patients (measured with dot blot and ELISA, respectively) compared to controls and this finding was correlated to disease severity, assessed by the valid Mini Mental State Test. The attributed mechanisms included chronic inflammation associated with intestinal dysbiosis and release of rhamnolipids.

Immunological mechanisms

In the analysis of papers performed, we identified an immunological hypothetical impact on how microbiota can achieve its distant effect. However, an overlapping with inflammatory pathways, as previously commented, is possible. For instance, it was examined the possible association between infectious burden of *Hp*, *Chlamydomphila pneumoniae*, CMV, *Borrelia burgdoferi*, HSV-1 and AD [37]. The authors deduced that mechanism of action might include triggering of autoantibodies and subsequent infection with neuronal loss. Furthermore, another research team [38] studied the association of brain amyloidosis with microbiota *Escherichia/Shigella*, *Pseudomonas aeruginosa*, *Eubacterium rectale*,

Eubacterium hallii, *Faecalibacterium prausnitzii*, and *Bacteroides fragilis*. They included, for this purpose, 40 patients with cognitive impairment in a cross-sectional multicenter study. The authors concluded, that an increase in the abundance of a pro-inflammatory gastrointestinal microbiota taxa of *Escherichia/Shigella* and a reduction in the abundance of an anti-inflammatory *E. rectale*, may be correlated with peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis. Moreover, other investigators [39] tried to determinate whether periodontitis in AD is associated with both increased dementia severity and cognitive decline, and an increased systemic pro-inflammatory state. The study population included twenty-two subjects in a prospective way. It was found that antibodies to periodontal *Porphyromonas gingivalis* were associated with an increase in serum C-reactive protein (CRP), tumor necrosis factor (TNF)- α and TNF- α / interleukin (IL)-10 ratios in participants with AD. Besides, we have proposed in the past [40] that *Hp* could also act via immune-mediated mechanisms. Particularly, we have suggested mechanistically, the release of proinflammatory and vasoactive factors, such as cytokines IL-1, IL-6, IL-8, IL-10, IL-12, TNF- α , interferon- γ , eicosanoids (leukotrienes, prostaglandins catalyzed by cyclooxygenase enzymes) and acute phase proteins (fibrinogen, CRP). We further postulated a possible stimulation of mononuclear cells to produce a tissue factor-like procoagulant, which converts fibrinogen to fibrin. Current evidence of abnormalities of both humoral and cellular immunity that play important roles in the *Hp*-associated gastric pathologies and other degenerative disorders including AD neuropathy have been recently reviewed, in details, by us [1].

Another study [41] suggested that cognitive impairment in case of *Hp* infection might be mediated through anti-*Hp* IgG brain inflammation. A further study stemming from the USA [42] compared serum antibody levels against bacteria of periodontal disease (see also Table 2) between participants who eventually converted to AD and control subjects. The authors demonstrated elevated antibodies to periodontal disease bacteria in subjects, years prior

cognitive impairment and suggested that periodontal disease might potentially contribute to the risk of AD onset or even progression. Pathogenically, it was postulated an IL-11 stimulation through a Th2 cell polarization. Furthermore, it was hypothesized, that chronic diseases, like periodontitis, might elevate the overall “set point” of systemic inflammation in individual patients, which would also increase the risk for onset or progression of AD. A US case control study [43] of 24 subjects researched whether Gram-negative bacterial molecules are linked to AD. Interestingly, the authors reported that lipopolysaccharides and *Escherichia coli* K99 pili protein in vessels and ependymal cells might contribute to vessel injury and ependymal injury as well as white matter injury brains of AD patients. Finally, an Iranian case-control study [44], where 80 patients with AD were included, demonstrated statistically significant elevated serum levels of TNF- α in AD patients with concomitant periodontitis compared to AD patients with healthy periodontium.

Apoptosis

Apoptosis, plays an important role in the pathogenesis of neurological diseases [45] and microbiota related-apoptosis might be an aggravator of neurodegenerative disease including AD [46]. Apoptosis-induced neuronal death is an important factor contributing to the progression of AD [47]. In this respect, probiotics appear to prevent several destructive effects of aging including reduced neurotransmitter concentrations, chronic inflammation, oxidative stress and apoptosis, all of which are contributors to neurodegenerative diseases' pathophysiology [46]. Of note, under the term apoptosis is defined the programmed death cell and involves mainly two pathways the extrinsic and intrinsic one. The class of cysteine proteases, such as caspase-8, caspase-9, and caspase-3, is frequently involved in these pathways [1]. We [40] as well as other authors [32] speculated that *Hp* achieves this pathogenicity, also, via activation of T cell-mediated apoptotic pathways.

Disruption of BBB

The BBB is located at the level of cerebral microvessels and represents the largest interface for blood-brain exchange. The main constituent of the BBB is the brain microvascular endothelial cell connected to pericytes and astrocytes by a common basement membrane comprised extracellular matrix proteins. A physical barrier is formed at the interendothelial cleft by complex junctions that regulate the flux of ions, polar molecules, and macromolecules from the systemic circulation [9]. A potential break down of this selective “filter” might have disastrous consequences for organisms [48,49]. We [9,40] and other investigators [32] reported such a mechanism as a plausible interpretation of *Hp* pathogenicity. The second group added the hypothesis of secondary accumulation of amyloid cerebrally after the disruption of BBB.

MetS-related atherosclerosis

One of the described mechanisms includes the implication of MetS-related atherothrombosis cascade, which affects both heart and brain disorders frequently associated with MetS [50,51]. Epidemiological data indicate that several well-recognized risk factors for AD, including MetS-related disorders (diabetes mellitus, atherosclerosis, hypertension, stroke, transient ischemic attacks, microvessel pathology and smoking), have a vascular component that decreases cerebral perfusion. In this respect, regional cerebral hypoperfusion can preclinically recognize individuals at risk for AD and precedes hypometabolism, neurodegeneration and cognitive decline in AD [52]. Moreover, carotid atherosclerosis, a significant independent factor associated with MetS, seems to be a predictive agent concerning the cognitive impairment progression in AD patients [53]. Likewise, arterial stiffness, a hallmark of the

aging process and atherosclerosis, is an emergent risk factor for dementia via its repetitive associations with cognition, cerebral small vessel disorder, and A β deposition [54].

The level of IgG antibodies against periodontal microbiota was studied in serum of 110 patients with AD (matched respectively to cognitively intact controls) [35] and found a statistically significant increase of IgG in AD patients group. Furthermore, the authors showed a strong positive association with apolipoprotein E (APOE), which seems to have an emerging role as independent risk factor for both cardiovascular disease and AD [1,34,42]. Moreover, NOMAS [33] revealed that infectious burden of common pathogens (Table 2) in a sample of 1625 individuals was associated with stroke and atherosclerosis and independently with cognitive status. Likewise, we investigated in a series of clinical studies[40,55–58] the impact of *Hp* infection on patients with AD. There has been found a strong positive association and one of the proposed mechanisms was hyperhomocysteinemia and atherothrombotic disorders. *Hp* infection is known to cause atrophic gastritis, which can secondarily lead through folate and B12 deficiency to hyperhomocysteinemia [34,41]. Moreover, hyperhomocysteinemia is regarded as an independent risk factor for cardiovascular disease, which is the main cause of global morbidity and mortality[59]. Likewise, hyperhomocysteinemia is further connected with the MetS [60]. Interestingly, two successive French studies[34,61], where 53 and 603 subjects were included, respectively, showed that *Hp* infection was associated with AD. One of the suggested mechanisms that could interpret *Hp* pathogenicity was the mentioned hyperhomocysteinemia and atheromatic plaque formation. The same conclusion and postulation mechanistically reached by others investigators [41], who verified the above mentioned association between *Hp* serology and AD in a case control study of thirty participants. Likewise, additional authors [32] in a relatively large cross sectional study with more than two thousand included subjects, examined the association between *Hp* and AD. The researchers reported a positive linkage,

which was attributed, among others, to atherosclerosis development and subsequent strokes through cytotoxic strains as well as to endothelial dysfunction owing to hyperhomocysteinemia. Important to note that, *Hp* infection has been correlated significantly with the gastrointestinal microbiota negative interactions [62]. Moreover, *Hp* can modify the gastric microbiota composition, thereby the resulting changes may play a role in the development of *Hp*-related diseases [19].

Various mechanisms

A plethora of different attributed mechanisms have been identified in the selected papers, which they could not albeit be classified to a single category. An Iranian randomized, double-blind and controlled clinical trial [63], which included 60 AD patients evaluated the effects of *Lactobacillus acidophilus*, *L. casei*, *L. fermentum* and *Bifidobacterium bifidum* on cognitive function and metabolic status. The authors claimed that probiotic consumption for 12 weeks could affect positively both examined parameters of AD patients, which were attributed to a potential adjustment of brain activity through contributing in the neurotransmitter synthesis or receptor expression. Regarding the mentioned NOMAS [33], another hypothesized mechanism included the toxic effect of some neurotropic agents in the development of cognitive impairment. Interestingly, above mentioned authors [32] again, hypothesized that nitric oxide and molecular mimicry of host structures might consist mechanisms that explain an etiological linkage between *Hp* and AD. Additionally, we [40] supported the idea, that *Hp* might also be implicated in the AD pathogenesis through promotion of platelet and platelet–leukocyte aggregation, production of reactive oxygen metabolites and circulating lipid peroxides or additional MetS-related mechanisms [9]. An alternative possible mechanism of periodontitis impact on AD is the endothelial dysfunction

with accompanying white matter hyperintensities, described in two of above analyzed papers [34,35]. *Hp*-associated neural loss consists another pathogenetic explanation [64].

Association without suggested mechanism

An analysis of rectal samples collected during a prospective observational study [65] was conducted among residents of nursing home with advanced dementia and *Clostridium difficile*. The authors concluded that subjects with advanced dementia were characterized by a significant gut dysbiosis. Noteworthy is also a case report of a patient with co-occurring AD and neuroborreliosis [66]. The authors discussed a possible exacerbation of the symptoms of either neuroborreliosis or AD through this co-infection.

Emergent data indicates a role of gastrointestinal microbiota in regulating innate immunity and influencing brain function. The gastrointestinal microbiota society diversity can regulate host innate immunity mechanisms that impact A β amyloidosis [67]. In this respect, recent evidence suggest that altered gastrointestinal microbiota, including *Actinobacteria*, *Bacteroides*, *Ruminococcus*, *Lachnospiraceae*, and *Selenomonadales*, could be contributed to AD pathophysiology [68]. Moreover, recent experimental data indicated that gastrointestinal microbiota modulates a host's health and disorder including AD by producing several substances, such as short-chain fatty acids (SCFAs) among others [69]. The gastrointestinal microbiota dysregulation may contribute to AD pathophysiology by modulating SCFA concentrations. Particularly, the amounts of *Acetobacter* and *Lactobacillus* as well as *Acetate*, the most rich SCFAs derived from the dysregulated microbiota, diminish considerably in AD [70]. The composition and diversity of gastrointestinal microbiota are disturbed and the SCFAs concentrations are decreased in AD mice, predicting changes in more than 30 metabolic pathways, that could be connected with amyloid deposition and ultrastructural irregularities in AD mouse intestine. These findings underscore the important alteration of

gastrointestinal microbiota on the level of phylum, genus, and species with age, as well as the potential cause of the altered gastrointestinal microbiota in AD mice. Moreover they provide new ways for therapeutic intervention in AD [71]. Prolonged shifts in gastrointestinal microbiota composition and diversity produced by long-term broad-spectrum antibiotics reduce A β plaque deposition with reduction of plaque-localized glial reactivity and change in microglial morphology [67].

No association

Nevertheless, there have been also identified some works, which did not find an association between investigated pathologies. A Japanese study, [72] examined the potential relationship between *Hp* infection and AD in a population sample of 385 Japanese subjects, did not find an association between the infection and AD. However, two critical concerns regarding the methodological limitations might render the results of this study highly debatable. The first is that both age and sex, found to be associated with AD were not matched in the two study groups. Therefore, comparisons between AD patients and controls cannot be expected to establish any firm conclusions. The second concern is that the very high *Hp* infection prevalence in the general Japanese population around 70 years old, reported by the authors, and, deductively, in the control group of the study, renders the study underpowered, meaning it requires probably thousands of participants to prove whether an association between AD and *Hp* infection can be established or excluded [73]. A Swedish research team [74] performed a study in 47 AD patients, whereas 59 vascular dementia subjects and 8 MCI were also included. Control sample consisted of 101 participants. Although the authors found an association between AD and homocysteine, *Hp* antibodies failed to reveal a correlation between examined study groups. Important to note that *Hp* serum antibodies are not regarded as the gold standard for *Hp* gastritis, since they fail to distinguish

between new and past infections. Histological substantiation of *Hp* is regarded nowadays as the diagnostic modality of choice [75]. Finally, a Chinese team[76] investigated recently in a case control study of 75 AD patients with corresponding number of control subjects, the possible impact of *Toxoplasma gondii* on AD. A percentage of 61.3 % of AD patients and 62.6 % of healthy volunteers were positive for anti-Toxoplasma IgG but all participants were negative for anti-Toxoplasma IgM. No significant differences were found between AD with their controls regarding anti-Toxoplasma IgG antibody.

The results of this systematic review should be in the light of several limitations. Risk and reporting of bias has not been fully performed. Moreover, although beyond the scopes of our own brief review, additional concerns warranted further research may focused on whether there are different data in gastrointestinal microbiota between *Hp*-positive and *Hp*-negative AD patients. Furthermore, we have included papers only from 12 different countries (out of 196 totally). Of note, prevalence of main involved pathogen, *Hp* is exceptionally high in many developing, albeit, not included countries.

Conclusion

Pathogenesis of AD remains currently largely unclear. Gastrointestinal microbiota seems to interact pleiotropically with immune system in homeostasis and disease and shape immune responses. Through our review we conclude that gastrointestinal microbiota, particularly *Hp*, is associated with cognitive impairment. Further large-scale studies are however, warranted, in order a deep understanding and substantiation of postulated mechanisms to be achieved. For instance, biomarkers of gastrointestinal microbiota that could be found in the near future might contribute to an early diagnosis, thereby offering more efficiently to the control of the AD course.

Conflict of interest

Authors declare no conflict of interest. No financial support or any funds have been used for this work

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Figure Legends

Figure 1:Flow chart of the selection process

Figure 2: Simplified graphical representation of the main postulated theories - mechanisms of action of **gastrointestinal** microbiota on AD: i. Disruption of blood brain barrier and apoptosis. ii. MetS-related Atherosclerosis and infected monocytes “Trojan horse theory” iii. Intestinal dysbiosis, chronic (bacterial) inflammation and immunological mechanisms

Abbreviations: A β ; Amyloid β -peptide, AD; Alzheimer’s disease, APOE; apolipoprotein E, BBB; blood brain barrier, BCSFB; BBB/blood cerebrospinal fluid barrier, CMV; cytomegalovirus, CNS; central nervous system, CRP; C-reactive protein, GIT; gastrointestinal tract, *Hp*; *Helicobacter pylori*, HSV; herpes simplex virus, IL; interleukin, MetS; metabolic syndrome, PICO; Patient Intervention Comparison and Outcome, TNF; tumor necrosis factor