Thesis

Psychoimmunological Interfaces
A systematic analysis of barrier markers in people with depressive disorders

submitted by

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Graz, 11.05.2026 *Sarah Niloufar Meyer m.p*

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Zusammenfassung

Hintergrund: Depressive Störungen stellen ein zunehmendes globales Gesundheitsproblem dar, wobei die Zahlen voraussichtlich bis 2030 weiter ansteigen werden. Da sich präventive und therapeutische Strategien hauptsächlich auf psychotherapeutische Interventionen und Antidepressiva konzentrieren, untersuchen neuere Studien das Potential des Darmmikrobioms in der Behandlung von Patienten mit Depressionen. In den letzten zehn Jahren sind das Darmmikrobiom, die Darmbarriere und die Blut-Hirn-Schranke zu einem Schwerpunkt von Untersuchungen zu ihrer möglichen Beteiligung bei depressiven Störungen geworden. Um diese Zusammenhänge zu entschlüsseln könnten Biomarker ein diagnostisches Tool darstellen, das eine indirekte Beurteilung der Funktion und Integrität von Barrieren ermöglicht und die komplexe Pathophysiologie depressiver Störungen weiter aufzuklären vermag.

Zielsetzung: Das Ziel dieser systematischen Übersichtsarbeit ist es, den aktuellen Stand der Wissenschaft zu den Biomarkern FABP2, FABP7 und GFAP, sowie ihre möglichen Zusammenhänge mit depressiven Störungen und Symptomschwere darzulegen und zusammenzufassen.

Methodik: Eine systematische Literatursuche nach den PRISMA Richtlinien wurde im September 2024 durchgeführt. PubMed, Embase, Web of Science und Google Scholar wurde nach Primärstudien durchsucht, die einen der drei Biomarker; FABP2, FABP7 oder GFAP, in Personen mit Depressionen und einer gesunden Kontrollgruppe untersuchen. Die Newcastle-Ottawa Skala für Fall-Kontroll-Studien wurde zur Qualitäts- und Bias-Risikoeinschätzung der eingeschlossenen Studien verwendet. Aufgrund der Heterogenität der Studien wurde eine narrative Synthese durchgeführt.

Ergebnisse: Diese Übersichtsarbeit hat Querschnitt- und Fall-Kontroll-Studien eingeschlossen. Insgesamt erfüllten zehn Studien die vordefinierten Einschlusskriterien und wurden in die systematisch Übersichtsarbeit aufgenommen. Von diesen untersuchten sechs Studien GFAP Konzentrationen und vier Studien erfassten FABP2 Serum Konzentrationen. Es wurde keine den Einschlusskriterien

entsprechende Studie für FABP7 gefunden. Insgesamt umfasste die Untersuchung von FABP2 234 Personen mit einer depressiven Störung und 166 gesunde Kontrollen. Die Studien zu GFAP umfassten insgesamt 339 Personen mit einer depressiven Störung und 218 gesunde Kontrollen. Die Ergebnisse für FABP2 waren konsistent und zeigten positive Zusammenhänge mit depressiven Störungen, während die Ergebnisse für GFAP inkonsistent waren. Fünf Studien untersuchten zusätzlich mögliche Zusammenhänge mit der Schwere der Symptome und lieferten heterogene Ergebnisse. Eine Studie untersuchte FABP2 Level und suizidales Verhalten und zeigte positive Zusammenhänge.

Diskussion und Schlussfolgerung: Die Limitationen dieser systematischen Übersichtsarbeit bestehe in einer begrenzten Anzahl von passenden Studien mit insgesamt relativ kleiner Stichprobengröße und einem Fehlen longitudinaler Studien. Die Ergebnisse dieses Reviews zeigten eine relevante Forschungslücke für FABP7 auf. Des Weiteren deuten die Ergebnisse für FABP2 auf Zusammenhänge mit depressiven Störungen hin, die die Rolle der Darmbarriere bei Depressionen unterstreichen. Es wurde kein eindeutiger Zusammenhang zwischen Symptomschwere und FABP2 als auch GFAP gefunden. Die Ergebnisse zu GFAP in Bezug auf mögliche Zusammenhänge mit Depressionen waren nicht schlüssig. Weitere Forschung, die sich auf Subgruppen depressiver Störungen und spezifische klinische Merkmale konzentriert, erscheint sinnvoll.

Abstract

Background: Depressive disorders represent a rising global health problem with numbers estimated to further increase by 2030. As prevention and therapeutic strategies mainly concentrate on psychotherapeutic interventions and antidepressants, recent studies have examined the potential of targeting the gut microbiome of patients suffering depression. Over the past decade, the gut microbiome, the intestinal barrier and the blood-brain barrier have become focus of investigations on their potential involvement in depressive disorders. To clarify these associations barrier markers may represent a diagnostic tool to indirectly assess barrier function and integrity and help elucidate the complex pathophysiology of depressive disorders.

Objectives: This systematic review aims to summarize the current evidence on the biomarkers FABP2, FABP7 and GFAP and their potential associations with depressive disorders and symptom severity.

Methods: A systematic literature review, following the PRISMA guidelines, was conducted in September 2024. PubMed, Embase, Web of Science and Google Scholar were searched for studies investigating one of the three biomarkers, FABP2, FABP7, or GFAP, in patients with depressive disorders and in healthy control subjects. The Newcastle-Ottawa Scale for case-control studies was used to evaluate the risk of bias and quality of the included studies. Due to heterogeneity, a narrative synthesis was conducted.

Results: This review included cross-sectional and case-control studies. Ten studies met the eligibility criteria and were included in this review. Of these, six studies assessed GFAP concentrations and four studies investigated FABP2 serum levels. No eligible study was found for FABP7. In total, the studies examining FABP2 included 234 individuals with depressive disorder and 166 healthy controls. All included studies investigating GFAP comprised a number of 339 individuals with depressive disorder and 218 healthy controls. The findings for FABP2 were consistent and showed positive associations with depressive disorders, whereas the results for GFAP were inconsistent. Five studies additionally examined potential

associations with symptom severity and yielded heterogeneous results. One study investigated FABP2 levels and suicidal behavior and found positive associations.

Discussion and Conclusion: The limitations of this review consist in a limited number of studies with overall relatively small sample sizes and a lack of longitudinal studies. The findings of this review revealed a significant research gap for FABP7. Furthermore, the results indicate associations with FABP2 and depressive disorders, highlighting the role of the intestinal barrier in depression. No concrete link between symptom severity and both FABP2 and GFAP were found. The findings for GFAP on potential associations with depression were inconclusive. Further research focusing on subgroups of depressive disorders and specific clinical features seems relevant.

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Abbreviations

ANS	Autonomic nervous system
B-FABP	Brain-fatty-acid-binding-protein
BBB	Blood-brain barrier
BDI-II	Beck-Depressions-Inventar II
BLBP	Brain lipid-binding protein
CDRS-R	Children's Depression Rating Scale – Revised)
CGI	Clinical Global Impressions Scale
CGI-I	Clinical Global Impressions Scale - Improvement
CGI-S	Clinical Global Impressions Scale - Severity
CIDI	Composite International Diagnostic Interview
CNS	Central nervous system
CPRS	Comprehensive Psychopathological Rating Scale
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DALYs	Disability-adjusted life-years
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELISA	Enzyme-linked immunosorbent assay
ENS	Enteric nervous system
FABP2	Fatty-acid-binding protein 2
FABP7	Fatty-acid-binding protein 7
FABPB	Fatty-acid-binding protein brain
FABPs	Fatty-acid-binding proteins
GABA	Gamma-amino butyric acid
GBD	Global Burden of Disease
GFAP	Glial fibrillary acidic protein
HAMA	Hamilton Anxiety Rating Scale
HAMD	Hamilton Depression Rating Scale
HAMD-17	17-item Hamilton Depression Rating Scale
HAMD-6	6-item Hamilton depression Rating Scale
HDRS	Hamilton Depression Rating Scale
HPA	Hypothalamic–pituitary–adrenal axis

I-FABP	Intestinal-fatty acid-binding-protein
IBD	Inflammatory bowel disease
ICD-10	International Statistical Classification of Diseases and Related Health Problems10th Revision
ICD-11	International Classification of Diseases 11th Revision
IIH	Idiopathic intracranial hypertension
IL	Interleukin
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime
LBP	Lipopolysaccharid-binding protein
LPS	Lipopolysaccharides
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MGBA	Microbiota-gut-brain axis
MINI	Mini International Neuropsychiatric Interview
MRG	*Synonym for FABP7*
NDRIs	Norepinephrine/dopamine reuptake inhibitors
NOS	Newcastle-Ottawa Scale
nsMDD	Non-suicidal major depressive disorders
PISCO-S	*Acronym for:* Population, Indicator, Control, Outcome, Study design
PNIE	Psychoneuroimmunoendocrinology
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RCTs	Randomized controlled trials
SCFAs	Short-chain fatty acids
SCID	Structured Clinical Interviews of DSM
Simoa	Single molecule array
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
SUAS	Suicide Assessment Scale
SUAS-S	Suicide Assessment Scale Self-report version

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1 Introduction

1.1 Global burden and relevance of depressive disorders

Depressive disorders represent a major global health problem with rising prevalence across all age groups (1). Around 5,7% of adults are estimated to experience depressive disorders, with women being more likely than men to suffer from depression (2). One third of mental health disorders arise before the age of 14 (3). Among adolescents (10-19 years), the estimated prevalence of major depressive disorders (MDD) is around 8%, while elevated depressive symptoms occur in approximately 34% of adolescents, with a rising prevalence since 2001 (4). Worldwide, around 332 million people are suspected to suffer from depression (2). According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) of 2019, depressive disorders accounted for a higher percentage of disability-adjusted life-years (DALYs) in 2019 (1,8 %) than in 1990 (1,1%) across all age groups. Among individuals aged 10 to 24 years, depressive disorders accounted for 3,7 % of DALYs in 2019, compared to 2,9 % in 1990. In the 25 to 49-year age group, depressive disorders ranked sixth among causes of DALYs in 2019, whereas they ranked eighth in 1990 (5). According to the World Health Organization (WHO) projections, depression will be the leading cause of DALYs by 2030 (6). For those affected, depression causes severe distress in everyday life due to great impairment of well-being and self-esteem. Depressive disorders are widely associated with various secondary effects including increased rates of sick leave, further social isolation and somatic comorbidities. Statistical analysis show two times higher mortality rates among patients with depression compared to the general population (7).

One potential consequence of depressive disorders is suicide, ranking among leading causes of death in young people between the ages of 15 to 29 (2). Positive associations between depression during adolescence and suicidal behavior in adulthood have been found (8), accentuating the importance of prevention strategies, treatment options and new diagnostic tools such as biomarkers in body fluids. As the diagnosis of depressive disorders is currently made through

conversations and questionnaires only (9), additional instruments providing measurable values or images could be beneficial.

1.2 Definition and diagnosis of depressive disorders

Depressive disorders belong to the spectrum of mental disorders, more specifically to the group of mood disorders, and are characterized by central symptoms such as depressed mood, anhedonia and loss of interest in activities. These symptoms must be present for at least two weeks and can be accompanied by neurovegetative, cognitive, or behavioral symptoms including sleeping disturbances, concentration problems, loss of appetite, psychomotor agitation or retardation, and suicidal thoughts (10).

According to the 11th revision of the “International Classification of Diseases” (ICD-11), depressive disorders are classified into the following categories which can be further subdivided in specific diagnostic subcategories:

6A70: Single episode depressive disorder
6A71: Recurrent depressive disorder
6A72: Dysthymic disorder
6A73: Mixed depressive and anxiety disorder
GA34.41: Premenstrual dysphoric disorder
6A7Y: Other specified depressive disorders
6A7Z: Depressive disorders, unspecified

With regard to single episode depressive disorders and recurrent depressive disorders, ICD-11 divides depressive symptoms into three clusters.

Cluster 1 symptoms consist of depressed mood and loss of interest and are categorized as affective symptoms.
The symptoms in cluster 2 are classified as cognitive and behavioral impairments and include symptoms such as concentration difficulties, hopelessness or suicidal thoughts.

Cluster 3 comprises neurovegetative disorders including sleeping disturbances, loss of appetite, psychomotor agitation or retardation, and fatigue.

To diagnose a single episode or a recurrent depressive disorder, one or more symptoms of cluster 1 must be present. Furthermore, at least 5 or more symptoms out of all cluster symptoms must occur in the patient nearly every day for a period of at least two weeks (10, 11).

Essential for the diagnosis of depressive disorders is a psychiatric anamnesis, including a specific anamnesis of social life, a potential history of addiction and suicidal thoughts or behavior. A history of manic, hypomanic or mixed episodes must be excluded. Furthermore, the exclusion of somatic causes by a physical exam and blood tests is important. Potential somatic differential diagnoses include hypo- and hyperthyroidism, cardiovascular conditions (e.g. coronary heart disease, myocardial infarction etc.), chronic inflammatory bowel disease, chronic nephritis or lues (12). Laboratory analyses cover a complete blood count, electrolytes, thyroid-stimulating hormone, iron status, transaminases, creatinine, vitamin D3 and C-reactive protein (CRP), among others (12, 13).

The use of standardized diagnostic interviews such as the Structured Clinical Interview for DSM (SCID), the Composite International Diagnostic Interview (CIDI) or the Mini International Neuropsychiatric Interview (MINI) are established instruments for the diagnosis of depression (14). The MINI, for example, is a structured interview for 17 different psychiatric diagnoses. It covers 16 categories (15) with each 8 to 10 questions that can be answered with “yes” or “no” (16). The MINI has been adapted for children and adolescents, called the MINI-KID (17).
Helpful tools for evaluating depressive symptoms include questionnaires such as the Hamilton Depression Rating Scale (HAMD or HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS) or the Beck-Depressions-Inventar II (BDI-II) for self-assessment.

1.3 Assessment of depressive symptoms and symptom severity

As previously mentioned, symptoms are mainly assessed with self-questionnaires or rating scales for medical professionals. The HAMD or HDRS is a 17- or 21-item scale used by medical professionals to assess and quantify depressive symptoms during a clinical interview with the patient. It is mostly used for adults with a diagnosis of an affective disorder to evaluate effectiveness of antidepressant treatment. The symptoms can be classified as mild, moderate or severe. Each symptom can be awarded up to two to four points (18). There are no standardized values categorizing symptoms to their severity. Suggested cut-off scores for the 17-item scale are nine to 16 points for mild, 17 to 24 points for moderate and over 25 points for severe depressive symptoms (19).

The HAMD-6 is an adapted version of the HAMD-17, often used in clinical studies, analyzing six of the 17-items including the core depressive symptoms (i.e. depressed mood, feelings of guilt, work and interests, psychomotor retardation, psychic anxiety and somatic symptoms). A systematic review by Timmerby et al. investigated the clinimetric quality of the HAMD-6 compared to the HAMD-17 and the MADRS and found the HAMD-6 to outperform both ranking scales in terms of their clinimetric properties (20).

The MADRS consists of 10 items addressing depressive symptoms. It is used by medical professionals in the context of a clinical interview. The MADRS evaluates symptom severity and can also be used to monitor changes under antidepressive treatment. Each item can be rated from zero to six points, summing up to a maximum total of 60 points. The suggested rating scale categorizes mild depressive symptoms within a range from 13 to 21 points, moderate symptoms from 22 to 28 points and severe depressive symptoms over a score of 29 points (21).

The BDI-II is a self-assessment questionnaire where patients decide on different statements for 21 questions concerning their depressive symptoms over the past two weeks. Each question will be awarded with an assigned number of points, depending on the chosen statement. A total of up to 63 points can be awarded. Depressive symptoms are categorized as mild when ranging between a score of 14

to 19 points. With a total of 20 to 28 points symptoms are classified as moderate, while severe symptoms are identified with a score over 29 points (19).

To assess symptom severity and categorize specific symptoms such as anxiety or suicidality in more detail, further questionnaires/scales are available. A sample of theses scales is briefly presented in the following table which additionally includes two diagnostic interviews specifically for minors (Table 1).

Table 1. Additional sample of scales for symptom assessment

Name of questionnaire/scale	Overview
HAMA (Hamilton Anxiety Rating Scale)	14-items measuring symptoms of anxiety (psychic and somatic anxiety), indicated for all ages groups. Each item is awarded zero to four points depending on its severity, with zero to 56 points in total. Mild: < 17 points Mild to Moderate: 18 to 24 points Moderate to severe: 25 to 30 points (22, 23)
SUAS (Suicide Assessment Scale) Modified Swedish version developed by Nimeus et al. (24) as a self-report instrument: SUAS-S	Assessment of suicidal risk over time evaluated with 21 items each rewarded zero to four points with a possible total score of zero to 80 points. Five areas are covered: affect, bodily states, emotional reactivity control, coping, and suicidal thoughts and behavior (25, 26).
CPRS (Comprehensive Psychopathological Rating Scale)	Assessment of psychiatric symptom severity and changes over time evaluated with 65 items, each awarded zero to three points (27, 28).

CGI (Clinical Global Impressions Scale)	Assessment of overall symptom severity and improvement of symptoms under medication over time. It consists of two components: the CGI-severity (CGI-S) and the CGI-improvement (CGI-I). The CGI-S evaluates the severity of the condition over a period of seven days on a scale ranging one to seven points (normal to extremely ill). The CGI-I evaluates the improvement of the condition after initiation of medication compared to the overall clinical state seven days before start of medication on a seven point scale (1 = very much improved, 7 = very much worse) (29).
SHAPS (Snaith-Hamiltion Pleasure Scale)	Self-assessment tool specifically evaluating anhedonia across different domains. The SHAPS concentrates on consummatory pleasure. 14 items with a four-point rating scale and a total sum of 14 – 56 points (increasing anhedonia with higher sum) (30).
CDRS-R (Children's Depression Rating Scale – Revised)	A semi-structured interview used for assessing depressive symptoms in minors. 17 items, each awarded one to five or one to seven points with a score of 40 points or above indicating depressive symptomatology (31).
K-SADS-PL (Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime)	A semi-structured diagnostic interview to evaluate the presence of affective disorders and schizophrenia in the present state and lifetime. 20 categories

	with a total of 82 symptoms and a scoring system of zero to three and zero to two points. Depending on the screen interview, additional diagnostic supplements (five possible categories) should be applied if the child reaches a threshold rating (32).

However, as symptoms of depressive disorders can mimic other disorders (e.g. anxiety disorders, adjustment disorders, post-traumatic stress disorders, dementia, etc.) (12), the correct diagnosis of depression requires experience and expertise as it relies on subjective interpretation (33) and additionally on the patient's description of symptoms, which can be biased by various factors. A meta-analysis by Mitchell et al. observed that only 47,3 % of cases were diagnosed correctly with a depressive disorder by a general practitioner (34), highlighting the need of objective instruments. Biomarkers are suggested to perform as such objective diagnostic tools for depressive disorders, reflected by the increasing interest in different markers of inflammatory, metabolic and endocrinologic pathways, supposedly involved in the pathogenesis of depressive disorders (33). However, there are currently no established diagnostic biomarkers for use in clinical practice.

1.4 Risk factors and epidemiological aspects

Depressive disorders affect both females and males of all ages. Various factors are known to influence the development of depression. Among these, the lack of a stable social environment in terms of family, friends or trusted individuals, is a known risk factor for developing depressive symptoms. Regarding socioeconomic factors, higher levels of education and a secure employment status are associated with a reduced risk of depression (7).

According to a global meta-analysis of recent studies, the rate of depression among the general population demographic in developed countries is estimated to be higher in urban than rural areas. Two theories try to explain these findings: the

breeder hypothesis suggests that people living in urban areas are more exposed to factors inducing depressive symptoms (e.g. air pollution, noise pollution, reduced contact with nature etc.); the drift hypothesis suggests that people suffering depression tend to move to urban areas in order to receive better medical care or to escape higher stigmatization in rural areas. However, the definite causes remain unclear and require further investigation including the aspects of modern lifestyle (35).

Although depressive disorders concern both sexes, the prevalence among women is reported to be about two times higher (36). There is emerging evidence indicating unambiguous differences between the sexes and the development of depressive disorders. These variations are suggested to be caused by distinct routes in the development of immune pathways and neuronal structures in early life, as well as hormonal fluctuations throughout a woman's lifespan. As a result of these interactions, women may be more prone to microglial reactivity and neuroinflammation in response to stress (37). Recent literature indicates that estrogen may be a central modulator of neuroinflammatory processes, having neuroprotective as well as neurotoxic effects, depending on serum levels (38). Furthermore, estrogen may affect emotional and cognitive functions by modulating neurotransmitter systems and neurotrophic processes. One of those neurotransmitter systems is the serotonergic system. Considering its suggested role in the development of depressive disorders, estrogens influence on the latter is highly conceivable (39). Similarly, interactions with the gut microbiome have been implied. A specialized subset of the microbiome, widely referred to as the "estrobolome", influences estrogen metabolism. The enzyme beta-glucuronidase, expressed by parts of the estrobolome, alters bioavailability of estrogen by deconjugating bound estrogen and preventing it from being excreted. The deconjugated, active hormone then returns to the bloodstream (38). A prior study by Li et al. suggested that estradiol in depressed women was more likely to be degraded through bacteria of the gut than in non-depressed women. Additionally, the authors found changes in the gut microbiota composition of individuals with depression (36), going in line with earlier studies (40-44). Imbalance of the microbiome, also referred to as dysbiosis (45), may be triggered by factors such as

nicotine consumption (46, 47), poor diet (e.g. processed food, low dietary fiber, saturated and trans-fats, high sugars etc.) (46, 48), infection, inflammation and medication (48, 49).

1.5 Current treatment strategies and limitations

Depending on the age of patients, the severity and duration of depressive disorders therapeutic interventions are established by way of shared decision-making. Moderate to severe depressive episodes often require additional pharmacological treatment alongside psychotherapeutic interventions such as behavioral or cognitive therapy. The primary medication recommendation are second-generation antidepressants (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or norepinephrine/dopamine reuptake inhibitors (NDRIs) (50), of which SSRIs are mainly prescribed. As SSRIs are associated with individual response rates, varying therapeutic efficacy and adverse side effects (51), new therapeutic strategies are needed. By elucidating the complex mechanisms behind the pathogenesis of depression, novel therapeutic targets may unfold. Considering the increasing relevance of the gut microbiome, the intestinal barrier, neuroinflammatory processes and the blood-brain barrier (BBB) in the development of depressive disorders (51, 52), biomarkers potentially providing information about barrier function and integrity (53-55) may help to better understand the pathophysiologic background of depressive disorders, which could lead to new possibilities in therapeutic interventions.

1.6 Pathophysiology of depressive disorders

The exact etiology of depressive disorders is suspected to be multifactorial but still remains not fully understood. The so-called “vulnerability-stress model” assumes that the presence of vulnerability factors in combination with psychosocial stressors may be a possible cause for depressive disorders (7).

Previous literature has proposed different theories of the complex pathogenesis of depression, including an imbalance of monoamine neurotransmitters, dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, endocrine disturbances, inflammation and oxidative stress, as well as hypotheses of neuroplasticity and neurotrophy (56).

Over the past two decades the role of the gut microbiome in the development of depressive disorders has become an increasingly important subject in research. Several reviews have investigated the bidirectional communication between the microbiome and the central-nervous system, forming the “gut-brain axis” or “microbiota-gut-brain axis” (MGBA) (45, 57-59). One pathway of communication is suggested to be via bacterial metabolites (e.g. gamma-amino butyric acid (GABA) or serotonin etc.) of the gut microbiome, functioning as neurotransmitters and regulating mood, cognitive and behavioral functions (57). Dysbiosis is suspected to increase intestinal permeability, which in turn might lead to local and systemic inflammatory processes (49, 60), potentially altering the BBB and thereby generating neuroinflammatory processes (61). Furthermore, as suggested by previous studies, alterations in immune pathways, potentially provoked by bacterial translocation through increased intestinal permeability, may lead to neuroinflammation and dysfunction of the BBB (56). There is emerging evidence of an inflammatory subtype of depression as some patients suffering depressive disorders show significantly higher markers of inflammation (e.g. CRP or interleukin (IL) - 6) compared to control populations. Moreover, the presence of increased inflammatory markers has been associated with specific symptoms such as fatigue, anhedonia and sleeping disturbances (62).

Collectively, all these hypotheses are considered to contribute to the development of depressive disorders by way of complex interplay. However the pathogenesis of depression has not yet been conclusively established (56) and remains a relevant focus for future research to help establish more effective treatment and preventive strategies.

1.7 Psychoneuroimmunoendocrinology

The scientific field of psychoneuroimmunoendocrinology (PNIE) comprises the intricate interactions between the immune system, the endocrine system, neuronal circuits and processes and their influence on psyche. As several studies have shown a significant presence of inflammation in some patients with depressive disorders (62, 63), research in PNIE has outlined the relevance of the immune system and the effects of its dysfunction on affective disorders. Ortega et al. have described the numerous and intertwined mechanism of PNIE in affective disorders in a comprehensive review (64), which will be briefly summarized in the following section.

The complex interactions of the different systems are reciprocal, which makes it difficult to determine cause and consequence. However, a dysfunction of the immune system is suspected to cause inflammatory processes that influence endocrine and neural pathways, potentially leading to the development of affective disorders. A central aspect of immune system dysfunction may be an imbalance of pro- and anti-inflammatory cytokines and antibodies. Various causes considered to promote dysfunction of the immune system are to be found in genetics and external factors. Concerning the latter, psychological and psychosocial stress are suspected to play a centrale role in the development of depressive disorders. Both early-life stress and chronic stress may lead to hyperactivation of the HPA axis, which results in hypercortisolemia. As cortisol can cross the BBB, increased hormone levels are suggested to intensify neuroinflammatory processes, again activating the HPA axis. Other suspected consequences of stress include alterations of the autonomic nervous system (ANS), resulting in increased activity of the sympathetic nervous system, causing an inflammatory response to stress. As the ANS comprises the enteric nervous system (ENS) and the vagus nerve, alterations of the ANS also affect the MGBA, which is considered to play a key role in the development of neuropsychiatric disorders. There is evidence indicating a negative influence of psychological and -social stress on the gut ecosystem, specifically promoting dysbiosis. Moreover, alterations of afferent (e.g. vagus nerve) and efferent pathways, due to dysbiosis, could in turn accelerate the latter. That imbalance of microbiota in the gut potentially causes a disruption of the intestinal barrier,

promotes intestinal inflammation and increases permeability, collectively further altering the immune system and fueling systemic inflammation. Similarly, diet and malnutrition are considered to cause changes of the microbiome, potentially contributing to inflammatory processes (64). External factors such as mode of delivery, feeding practices during infancy or urban lifestyle may affect diversity of microbiota in the gut (65). As stress is likely to promote unhealthy and addictive habits such as substance abuse, unhealthy sleeping routines or poor diet, stress triggers inflammatory processes through various ways (64). Chronic and early life stress, including childhood maltreatment, may cause epigenetic modifications of stress response genes (e.g. NRC31, SLCA4, FKBP5) potentially associated with accelerated reactions to stress and the presence of depressive disorders (66). Collectively, all these factors and mechanisms are regarded to induce dysfunction of the immune system, leading to systemic inflammation and neuroinflammation.

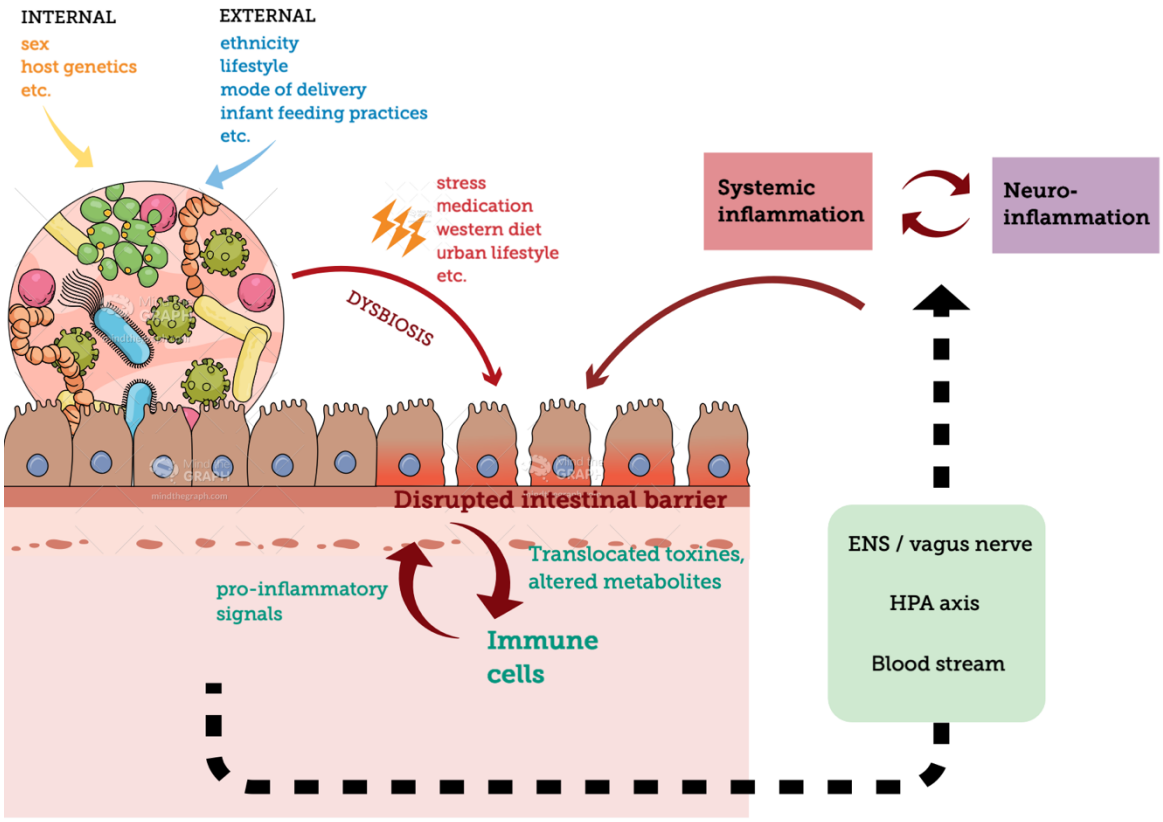

Figure 1. Simplified illustration of the microbiome and some suspected interactions leading to the development of depressive disorders. Created by the author with mindthegraph.com.

ENS: enteric nervous system
HPA axis: hypothalamic-pituitary-adrenal axis

The development of MDD may be triggered and exacerbated by systemic inflammation and neuroinflammation in a bidirectional manner. As previously mentioned, inflammatory processes are suggested to be promoted and exacerbated by various factors including psychological and psychosocial stress, metabolic and endocrine changes, unhealthy lifestyle factors (e.g. malnutrition, sedentary lifestyle), or dysbiosis. Intense, prolonged or chronic inflammatory reactions may cause alterations of neural homeostasis, intestinal integrity and endocrine pathways. The continuous release of pro-inflammatory cytokines, such as IL-1β, IL-6 or tumor necrosis factor-α, potentially disrupts different systems and pathways including neurotransmitters, neuroendocrine axes and neuroplasticity. Elevated levels of pro-inflammatory cytokines also activate the HPA axis, leading to “sickness behavior”, a physiologic reaction to infection or inflammation. However, prolonged or chronic activation of the HPA axis can result in significant mood changes through accelerated cortisol production and alterations of the BBB, again provoking neuroinflammatory processes.

The importance of the BBB and the intestinal barrier in the etiopathogenesis of neuropsychiatric disorders is highlighted by these associations. Further research is required as investigations of these barriers may provide novel treatment targets and a better pathophysiologic understanding of depressive disorders (64).

1.8 Psychoimmunological interfaces

Interfaces within multicellular organisms primarily separate different compartments from one another to maintain homeostasis, provide protection against pathogens and regulate translocation across barriers (67). The cells forming these barriers are connected through cell contacts, including gap-junctions, which enable communication within and across tissue. In vitro models have demonstrated that these gap junction-coupled cells show similar responses to inflammatory stimuli. When this network of cells becomes target of inflammatory processes, pro-inflammatory signals and substances can spread across organs and lead to systemic inflammation. A potential consequence of inflammation is the disruption of

in body barriers, allowing the transfer of inflammatory signals into the organism, further spreading inflammation (68).

The intestinal barrier and the BBB represent such dynamic interfaces. Both barriers also take part in regulating immune responses (58, 69) and directly and indirectly modulating neurotransmitters (53, 70). Growing evidence reinforces the concept of a bidirectional communication system between the gut, including the microbiome, and the central nervous system (CNS). Signaling pathways supposedly include the autonomic nervous system, the immune and endocrine system, as well as metabolites, such as short-chain fatty acids (SCFAs), lipopolysaccharides (LPS) or neurotransmitters (58, 71-73). The MGBA is therefore considered to play a key role in regulating neuroinflammatory processes, stress response, neurotransmission and neurogenesis. Recent data additionally emphasizes the potential influence of the MGBA on the pathogenesis of neurological disorders, including depression (52).

1.8.1 Blood-brain barrier

The BBB is a semi-permeable membrane between the peripheral blood and the brain. It is formed by the inner layer of cerebral blood vessels, consisting of special endothelial cells, tight junctions, pericytes and astrocyte end-feet (74). This barrier plays a crucial role in maintaining brain homeostasis, strictly controlling the passage of exogenous, endogenous and water-soluble molecules (53). Among protective functions, the BBB is also considered as a mediator between the immune system and the CNS (75), as it regulates the impact of peripheral immune responses on the brain. Inflammatory signals from the periphery can be conducted via neural, humoral and cellular pathways, indicating the brain to reconcile a systemic response. During that process, microglia is activated and induces a range of changes in neurotransmitters like serotonin and dopamine, which results in “sickness behavior”. This general reaction includes symptoms such as tiredness, loss of appetite, reduced mobility and overall depressive-like behavior, with the purpose to accelerate healing capacities of the host (69). Over the past decade, growing evidence supports the suggestion of low-grade systemic inflammation relevantly contributing to the development of depressive disorders in some patients (63). With

regard to the physiologic reactions of the BBB to peripheral inflammation, chronic low-grade inflammatory processes appear likely to alter the BBB.

1.8.2 Intestinal barrier

The intestinal barrier serves as a filter between the external and the internal environment. It is summarized as a semi-permeable membrane acting through a mechanical barrier and immunological defense mechanisms, protecting the host from external, potentially harmful, substances and microorganisms (76-78). The physical barrier is formed by the mucus layer, mostly consisting of transmembrane mucins (glycocalyx) and gel-forming mucins, which separates the intestinal lumen from the epithelium. These underlying epithelial cells are mainly connected through tight and adherens junction as well as desmosomes and contribute to the physical barrier. Both lamina propria and mucus contain immunological components acting as the chemical defense mechanism of the intestinal barrier (76, 78).

The gut microbiota, which consists of an abundance of microorganisms, plays a key role in maintaining this barrier stable. These microorganisms, including bacteria, fungi, viruses and archaea, are specific to the host and are suspected to depend on various factors such as mode of delivery, genetics and multiple environmental and external influences (e.g. (Western) diet, stress, xenobiotics, smoking, etc.) (70).

Previous literature indicates that a balanced microbiome is crucial for preserving intestinal barrier integrity. Among other factors, such as the bile acid metabolism, SCFAs, which are bacterial metabolites, may play an important role in maintaining intestinal homeostasis (79) by compensating the effect of pro-inflammatory signals, stimulating mucus secretion and influencing the formation of tight-junctions. They are suggested to inherit many more functions as mouse models have shown a neuroprotective effect of these metabolites (52, 70). A shift in bacterial colonization leads to a conceivable change of bacterial metabolites, potentially negatively affecting intestinal integrity. A disruption of this barrier is considered to amplify intestinal inflammation (80), which in turn, is suspected to cause dysfunction of the BBB and alter CNS functions (75, 81) by substances translocated in the

bloodstream, such as LPS (82). Similarly, microbiome imbalance has been associated with depressive-like behavior in several animal studies (83), and gastrointestinal dysfunctions have been observed in patients with psychiatric disorders (71).

1.8.2.1 Assessing intestinal integrity

To assess intestinal integrity, different biomarkers have been investigated over the past decade. In general, there are two groups of biomarkers that can be distinguished: endogenous and exogenous biomarkers. The category of exogenous biomarkers comprises sugars like lactulose and mannitol, and degradation products including D-lactic-acid and LPS. Substances including fatty-acid-binding protein 2 (FABP2), zonulin, lipopolysaccharide-binding protein (LBP) or diamine oxidase, are classified as endogenous biomarkers.

An established method for assessing barrier integrity of the small intestines is the use of lactulose and mannitol. As both sugars can be catabolized by the microbiome of the colon, a triple combination, additionally including sucralose, is thought to provide a more precise measuring method for barrier integrity of the whole gut. However, the use of a triple combination for clinical practice is still being investigated. Endogenous biomarkers may reflect barrier integrity and its permeability for the whole digestive tract more precisely. Most detection methods use the enzyme-linked immunosorbent assay (ELISA), although results require some time and have shown low specificity for zonulin for instance. FABP2 has been conceived as a promising biomarker for integrity and function assessment of the intestinal barrier, yet further research is required to provide more accurate and rapid detection methods for use in clinical practice (84).

1.9 Measuring methods of biomarker concentrations

For assessing and measuring concentrations of biomolecules (e.g. hormones, cytokines, proteins, viruses) in biological fluids, such as blood or cerebrospinal fluid (CSF), different detection methods are available. A widely known and established

test is the ELISA. To quantify substance concentrations ELISA utilizes antigens and enzyme-marked antibodies (85, 86). The specificity of antibodies allows the detection of biomolecules with very low concentrations, such as vitamins or proteins, enabling quantification of these molecules (87). Different variants of ELISA can be distinguished including the indirect, the direct and the sandwich ELISA. The basic principle of the indirect and direct ELISA relies on specific antigens fixated at the bottom of a microplate that will bind matching antibodies if present in the tested medium. Subsequently, the biomolecules that do not bind to the antigens are washed out, leaving only the targeted substance. The indirect ELISA uses a secondary antibody that is marked with an enzyme (e.g. alkaline phosphatase or peroxidase) and binds to the primary antibody, whereas the direct variant implies a primary antibody already marked with an enzyme. Then, another substrate (e.g. P-nitro-phenyl phosphate or 5 amino salicylic acid and orthophenylenediamine) that reacts with the enzyme is added and catalyzes a reaction visible with a change of color. The intensity defines the substance concentration. On the contrary, the sandwich ELISA, which is considered highly sensitive, uses “coating antibodies” instead of “coating antigens”. Specific antigens bind to the fixated primary antibody. A secondary antibody, marked with an enzyme, binds to a different epitope of the antigen. The subsequent steps follow the basic principle of the indirect or direct ELISA, respectively (87).

Single molecule arrays (Simoa) present a novel and more sensitive detection tool for low-concentrated biomolecules as they allow a digital detection of single protein molecules via fluorescent signals. The basic principle is equivalent to the sandwich ELISA technology, whereas Simoa uses paramagnetic beads coated with enzyme-marked antibodies instead of coated microplates. These beads are added to the sample solution, followed by the addition of detection antibodies. Subsequently, the sample is transferred into the single molecule array with femtoliter-sized wells that hold one bead only. An oil solution washes away excess beads and seals the wells. Fluorescent signals can then be measured digitally (88). Simoa is stated to offer extremely sensitive quantification of molecules in very low concentrations (89), exceeding ELISAs sensitivity (88, 90).

1.10 Biomarkers

1.10.1 Fatty acid-binding proteins

Fatty acid-binding proteins (FABPs) are small (~15 kDa), water-soluble cytoplasmic proteins expressed in different tissues with active fatty acid metabolism and belong to the family of lipid-binding proteins (80, 91). By binding lipophilic molecules and their metabolites, FABPs contribute to the regulation of tissue-specific lipid metabolism. A wider range of functions have been proposed but has not yet been clearly established (92).
Presently, 10 isoforms of FABPs have been identified in mammals (93).

1.10.1.1 Fatty acid-binding protein 2

FABP2 (intestinal fatty acid-binding-protein, I-FABP) is located in the enterocytes of the small intestine and, to a lesser extent, in the colon, and performs as a biomarker for enterocyte damage and intestinal injury (94, 95). Accordingly, elevated plasma levels of FABP2 may indicate intestinal epithelial damage associated with loss of intestinal barrier integrity and increased intestinal permeability (80, 95).

Current literature examines various potential biomarkers to non-invasively assess the integrity of the intestinal barrier. As the measurement of lactulose/mannitol ratio is one of the most established tools for evaluating intestinal permeability, the identification of other biomarkers that are less time-consuming and allow retrospective analyses of intestinal barrier integrity, have gained increasing attention in research (96). FABP2 is currently a promising biomarker for assessing gut injury in necrotizing enterocolitis (97) and may also serve for other diseases involving impairment of the gut. As outlined in a review by Wasiak et al., FABP2 concentrations in the blood are physiologically very low, which is why elevated levels, potentially caused by translocation to the blood, may indicate increased intestinal permeability, besides enterocyte damage (82). Findings of a meta-analysis investigating associations of FABP2 concentrations in patients with mood disorders indicates a positive correlation of serum FABP2 levels and patients compared to a healthy control population. However, the author stated that

interpretation should be made with caution as patients mostly received medication (98), which may contribute to dysbiosis and thereby impairment of the intestinal barrier (49). The hypothesized mechanism between microbiome imbalance, increased serum concentrations of FABP2, and neuroinflammation, is depicted in a simplified graphic below (Figure 1).

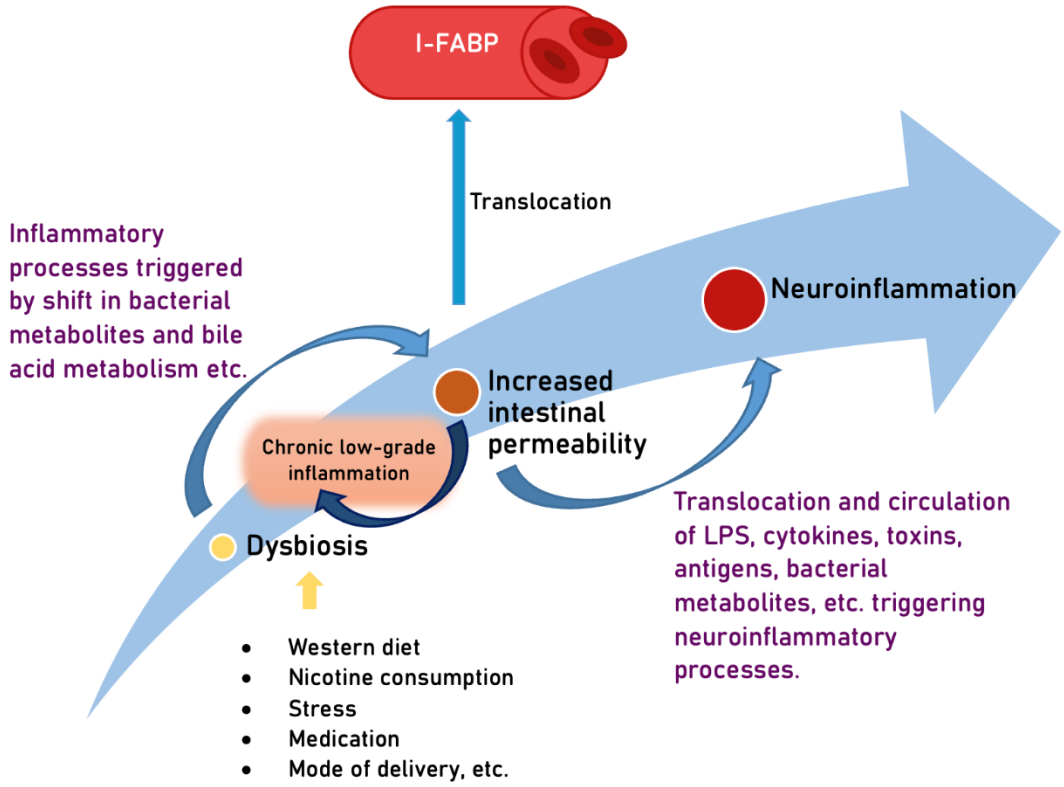

Figure 2. Simplified illustration of dysbiosis leading to neuroinflammation. Created by the author.

I-FABP: intestinal-fatty acid binding protein
LPS: lipopolysaccharides

1.10.1.2 Fatty acid-binding protein 7

FABP7 (brain fatty acid-binding protein, B-FABP) is a lipid transporter predominantly expressed in glia cells in the brain. Previous reviews have reported expression in astrocytes and oligodendrocytes (93), while others have summarized evidence of expression in astrocytes and radial glia cells (95, 99). As astrocytes compose a vast proportion of neuronal glia cells in the brain (100), FABP7 is considered to play an

important role in brain and central nervous system development, primarily in the early stages of life (93, 95, 99).

Recent animal studies have suggested a potential involvement of FABP7 in neuropsychiatric and neurodegenerative disorders, based on findings indicating that FABP7 may regulate inflammatory processes, influence neurogenesis and modulate signaling pathways involved in maintaining BBB integrity (100, 101). In the same context, mice exposed to chronic-unpredictable mild stress developed depressive-like behaviors accompanied by decreased FABP7 and glial-fibrillary-acidic protein (GFAP) expression levels in the hippocampus. Interestingly, an upregulation of FABP7 expression resulted in a reduction of inflammatory response and depressive-like behaviors as well as increased expression levels of GFAP (100).

The use of FABP7 as a diagnostic biomarker of symptom severity in patients with schizophrenia has been suggested in a study by Koga et al. Among other symptoms, depression and anxiety in schizophrenia have been positively associated with elevated FABP7 levels (102).

1.10.2 Glial-fibrillary-acidic protein

Astrocytes, also referred to as astroglia, are structural cells of the brain (26). They belong to the non-neuronal cell group of macroglia and inherit diverse functions (103). While they are considered to play a role in the conduction of stimuli (104), the maintenance of the BBB integrity and the transmission of nutrients (58), a large part of their functions remains not fully understood and undefined (103).

Astrocytes contain specific intermediate filament III proteins called GFAPs. These proteins enable glia cells to form a stable cellular framework and support the blood-brain-barrier. GFAPs are also expressed in parts of the peripheral nervous system and the ENS (105).

As a response to pathologies like brain injury, infection or inflammation, astrocytes switch into a “reactive” state. This process is characterized by functional and morphological changes, proliferation and hypertrophy of astroglia, also referred to as reactive astrogliosis (104-106). It has been shown that GFAP concentrations increase during that process, suggesting potential use as a diagnostic biomarker for diseases involving reactive astrogliosis (105, 107). A recent study by Agnello et al. observed significantly higher GFAP serum concentrations in patients with Alzheimer's disease compared to age-matched healthy controls (107), which were also reported in a previous review (108). There is evidence suggesting GFAP as a diagnostic biomarker for neurological disorders and a possible indicator for disease severity (109). However, the existing evidence implicates discrepancies regarding the correlation between elevated GFAP levels and the extent of reactive astrogliosis and neural damage. Some studies observed direct correlations (107) whereas others indicated no definite generalizability (106). Nevertheless, most studies mainly investigated neurodegenerative or demyelinating disorders, while research in individuals with depression is scarce. As alterations in astrocytic functions and morphology are suspected to be involved in the development of depressive disorders (59), further investigation appears to be relevant.

1.11 Research question and objectives

In light of the current evidence, the development of depressive disorders supposedly results from a complex interplay of immune and inflammatory processes, potentially triggered by external stressors. Both the intestinal barrier and the BBB are suspected to play a key role in disease development and progression. With regard to the MGBA, alterations of the microbiome or the intestinal homeostasis affect both the BBB and the brain (83). Similarly, intestinal functions are influenced by the brain and indirectly by the BBB (110). These associations and their proposed involvement in depressive disorders opened a field of research that gained increasing attention over the past decade. The growing evidence on the bidirectional relationship between the gut and the brain indicates that therapeutic strategies targeting one barrier likely affects the other. As the proteins FABP2, FABP7 and GFAP indirectly represent function or integrity of the intestinal and the blood-brain barrier, a

comprehensive summary of the current state of evidence is relevant to further assess the need of research which could help unravel the complex pathogenesis of depressive disorders, establish biomarkers for the diagnosis of depression, identify subgroups of depressive disorders or early detection tools, evaluate therapeutic success on the basis of biomarkers, and give rise to potential new therapeutic strategies and targets, respectively.

Consequently, this review sets out to examine recent literature on potential associations of the three biomarkers FABP2, FABP7 and GFAP with depressive disorders and symptom severity and to discuss their potential use in clinical practice. The primary objective of this review was to investigate potential associations of the biomarkers FABP2, FABP7 and GFAP with depressive disorders.

Precisely, this review aimed to (i) assess potential differences of FABP2, FABP7 and GFAP concentrations in body fluids between individuals suffering depressive disorders and healthy individuals, and (ii) to estimate whether symptom severity is associated with biomarker concentrations.

Based on the current evidence, it is hypothesized that (i) the three biomarkers may be positively correlated with the presence of depression and that (ii) the levels of the investigated biomarkers may be directly associated with symptom severity.

The findings obtained in this review aim to evaluate the potential use of the investigated biomarkers in clinical practice and whether future research appears to be beneficial and reasonable.

2 Methodology

This systematic review aims to synthesize the available evidence from clinical studies investigating the biomarkers FABP2, FABP7, and GFAP in individuals with depressive disorders compared with healthy controls. Alongside, investigations on associations with symptom severity, if included in the available studies, are being reviewed.

2.1 Eligibility Criteria

Inclusion and exclusion criteria are summarized in Table 2. Eligibility criteria were defined according to the PICOS (population, indicator, control, outcome, study design) framework. In general, observational studies investigating the biomarkers FABP2, FABP7 and GFAP (indicator) in individuals with depressive disorder (population) and healthy controls (control) were identified to examine biomarker levels and potential associations with depression and symptom severity (outcome). A publication window within the last 20 years was chosen to capture contemporary scientific evidence while minimizing the inclusion of outdated methodologies. Studies published in languages other than English were excluded to ensure accurate interpretation of reported results and methodological details. The focus on the specific barrier markers FABP2, FABP7, and GFAP was determined based on their established relevance in psychoimmunological research and their potential role in depression.

Table 2. Table of inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. **Population:** Studies including humans diagnosed with depressive disorders (e.g., major depression, clinically diagnosed depression).	1. **Population:** Studies exclusively investigating animals or cell cultures. Studies that do not provide a clear diagnosis of depressive disorders in human participants. Studies including

	participants with additional comorbid conditions (e.g., inflammatory bowel disease or multiple sclerosis) alongside a clear diagnosis of depression.
2. **Topic Relevance:** Studies investigating the relationship between psychoimmunological interfaces of the gut and brain and the barrier markers FABP2, FABP7, and GFAP.	2. **Topic Relevance:** Studies that do not focus on the psychoimmunological interfaces of the gut and brain or the specific barrier markers FABP2, FABP7, and GFAP. Studies that do not provide clear data or results regarding these barrier markers in relation to depression.
3. **Study Types:** Original research articles, including randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional studies. Only peer-reviewed studies are considered.	3. **Study Types:** Case reports, commentaries, editorials, conference abstracts without full-text availability, and non-peer-reviewed articles. Theoretical papers or opinion articles lacking empirical data.
4. **Language:** Studies published in English.	4. **Language:** Studies published in languages other than English without an available English translation.
5. **Publication Period:** Studies published within the last 20	5. **Publication Period:** Studies published before the defined 20-

years to ensure the inclusion of current scientific findings.	year period, unless they are of historical significance and provide essential information.

2.2 Data bases and search strategy

The systematic review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero, Registration Number: CRD42024558773) on June 16, 2024.
Following registration, a systematic literature search was conducted in September 2024, using databases; Pubmed, Web of Science, Google Scholar and Embase. The search was performed using the following terms:

"FABP7" OR "FABP2" OR "GFAP" OR "glial fibrillary acidic protein" OR "fatty acid binding protein 2" OR "fatty acid binding protein 7" OR "brain lipid-binding protein" OR BLBP OR "B-FABP" OR "FABPB" OR "brain fatty acid-binding protein" OR "brain-type fatty acid-binding protein 7" OR "MRG" OR "I-FABP" OR "I-FABP2" OR "FABPI" OR "Intestinal-type fatty acid-binding protein" OR "fatty acid binding proteins") AND ("Depression*" OR depressed OR MDD OR "major depressive disorder" OR "major depression").

The results were filtered to include only publications in English within a publication period from 2004 to September 2024. The search strategy was slightly adapted to each database and is presented in the appendix. Systematic reviews were screened for additional primary studies but were not included in the analysis.

2.3 Study selection and data extraction

The screening of the retrieved literature was conducted by a single reviewer using Rayyan (111). Following automatic de-duplication and manual removal of remaining duplicates, titles and abstracts were screened. Full texts were retrieved when titles

and abstracts did not provide sufficient information to assess eligibility. In cases of uncertainty, the thesis supervisor was consulted, and disagreements were resolved through discussion. Subsequently, a detailed full-text assessment was performed. In addition, the reference lists of all included articles were screened to identify additional relevant studies.

Data extraction was carried out by the same reviewer. The following data were extracted from the included studies: (i) study characteristics (author, year, country, study design, diagnosis, symptom assessment, protein examined, sample material, assay method); (ii) participant characteristics (sample size, gender, median age, medication status); and (iii) outcome data (measured protein levels, statistical significance and clinical relevance, other relevant correlations, confounding factors and study limitations, both reported and independently identified).

All data were entered into a predesigned extraction form, presented in the appendix, to ensure consistency and facilitate comparison across studies.

One additional relevant study (112) was identified through manual reference screening after the main screening process and was therefore not included in the formal analysis.

2.4 Quality assessment of the included studies

The same reviewer conducted a methodological quality assessment using the Newcastle-Ottawa Scale (NOS) for non-randomized studies (113) to differentiate between high- and low-quality studies. The NOS evaluates three domains: (i) selection of study groups, (ii) comparability of groups, and (iii) ascertainment of exposure. A maximum of one “star” can be awarded for each item within the Selection and Exposure categories, and up to two “stars” can be awarded for Comparability. Thus, each study can receive a maximum of nine stars in total.

Studies receiving seven or more stars were classified as high quality, while those scoring below four were considered low quality. Studies rated between four and six stars were categorized as moderate quality.

2.5 Synthesis

Due to the heterogeneous results of the primary studies, a qualitative research synthesis in terms of a narrative summary was conducted.

3 Results

3.1 Study selection

The systematic literature search identified 1,776 records across four databases. After removal of duplicates using the automatic de-duplication function in Rayyan (111) and additional manual duplicate removal, 297 records were excluded. A total of 1,479 records remained and were screened at the title and available abstract level. In cases where eligibility could not be clearly determined, full-text screening was performed. During the screening process, 1,443 records were excluded. Subsequently, 36 articles were retrieved and assessed for eligibility through full-text review. Ultimately, 10 studies met the predefined inclusion criteria and were included in the final synthesis (114-123). The screening process is additionally presented in the PRISMA 2020 flow diagram (Figure 3).

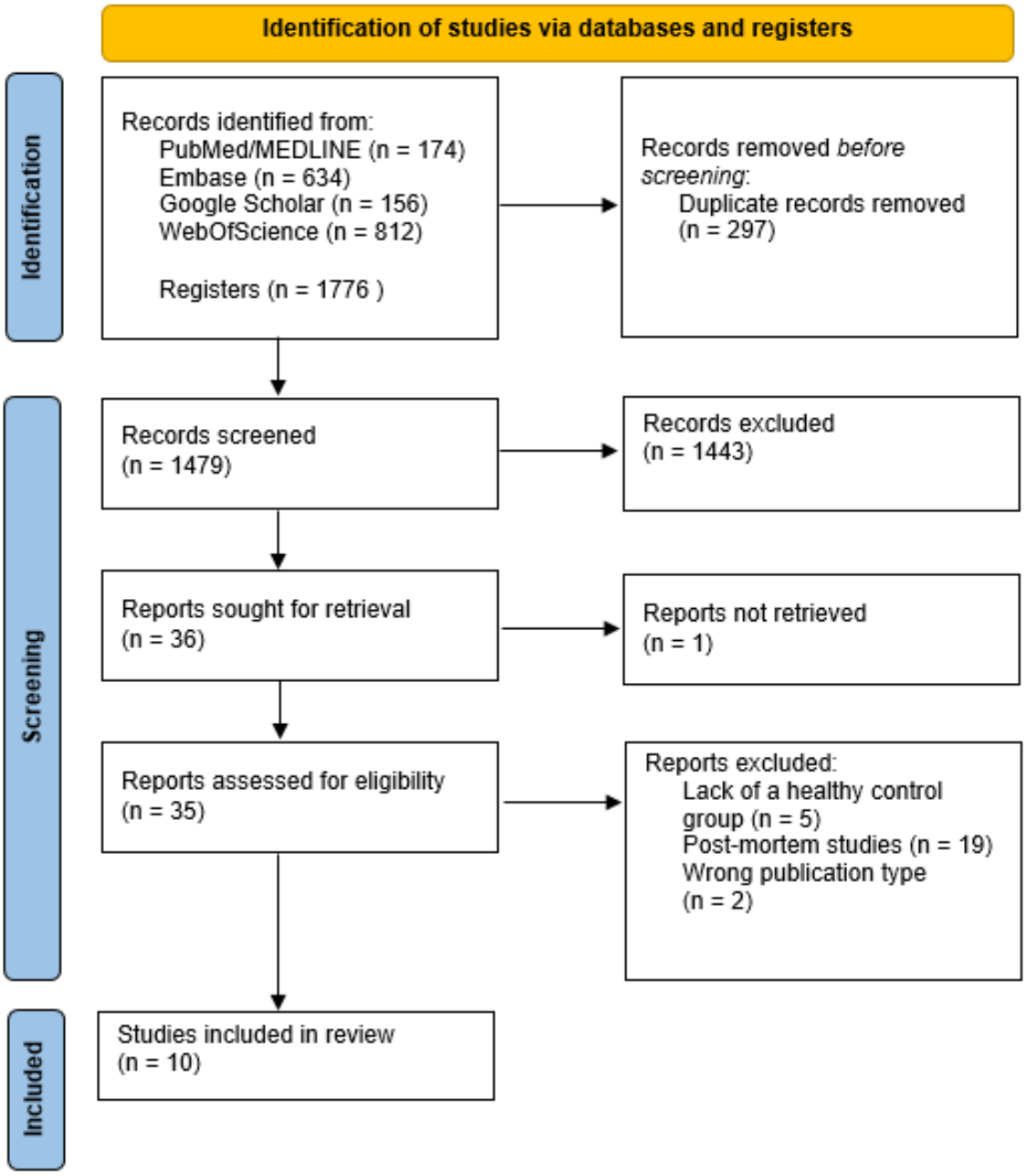

Figure 3. PRISMA 2020 flow diagram for new systematic reviews

3.2 Study characteristics

All included studies were published between 2010 and 2024 and were either case-control or cross-sectional studies. These studies included patients with a DSM or ICD-10 diagnosis of depression and a healthy control group without a history of psychiatric illness. All studies assessed biomarker levels in patients with depressive disorder and compared them to concentrations in healthy controls. Although FABP7

was included in the review question, no studies met the predefined inclusion criteria. Sample sizes ranged from 11 to 110 for patients and from 14 to 95 for healthy controls. In total, all studies comprised a sample size of 573 patients with a diagnosis of depressive disorder and 384 healthy controls. The studies examining FABP2 concentrations included 234 individuals with depressive disorder and 166 healthy controls. All included studies investigating GFAP comprised a number of 339 individuals with depressive disorder and 218 healthy controls.
Median age varied from 16 to 73.9 in patients and from 15 to 73.9 in the healthy control group. Two studies specifically focused on young patients with a median age of 16 (114, 117). One study focused on elderly women only (120). The studies originated from Sweden (n = 2) (118, 120), Russia (n = 2) (121, 122), China (n = 1) (114), Denmark (n = 1) (115), Germany (n = 1) (116), Iraq (n = 1) (119), Spain (n = 1) (123) and Switzerland (n = 1) (117). The assay method used for measuring FABP2 levels was ELISA. For GFAP quantification, either ELISA or Simoa was utilized. Symptom assessment tools varied in the included studies and can be found in the data extraction table (Table 4) presented in the appendix.

All included studies investigated patients with psychiatric disorders and comprised participants with a diagnosis of depression as well as a control group without a history of psychiatric illness and comorbid conditions. In all studies, additional biomarkers were assessed alongside those included in the review question. Five studies employed a case-control design (115-117, 119, 122), while five studies used a cross-sectional design (114, 118, 120, 121, 123). One study analysed serum GFAP levels at two time points (115); all other studies measured biomarker concentrations at a single time point.

3.3 Findings for FABP2

Four studies investigated serum FABP2 levels (114, 117, 118, 123). All four reported significant differences between FABP2 levels in participants with depressive disorder compared to healthy controls.

3.4 Findings for GFAP

Six studies assessed GFAP levels (115, 116, 119-122) . Five of these measured serum GFAP levels, while one study analysed GFAP concentrations in CSF (120). Of the five studies investigating serum GFAP levels, two studies reported significantly elevated serum GFAP levels in participants with depression compared to healthy controls (116, 119), one study found significantly lower serum GFAP levels in treatment-naïve patients compared to healthy controls (115), and two Russian studies observed no statistically significant differences between serum GFAP levels in participants with depressive disorder and healthy controls (121, 122). The study by Gudmundsson et al. (120), which investigated CSF GFAP levels in elderly women, found no statistically significant association between GFAP levels and the presence of a depressive disorder.

3.5 Association with symptom severity

Five of the ten included studies directly investigated potential associations between biomarker concentrations and symptom severity. The studies revealed heterogeneous results.

Two studies examined FABP2 levels and a potential correlation with symptom severity and suicidal behavior, respectively. One found a significant positive correlation with suicidal behavior but did not report on associations with symptom severity (118). The other study did not observe significant associations between FABP2 levels and depression scores but found a positive association between FABP2 levels and anxiety (114).

Four studies investigated potential correlations between GFAP levels and symptom severity (115, 116, 119, 121). Hviid et al. (115) and Levchuk et al. (121) did not observe significant associations, whereas Steinacker et al. (116) and Al-Hakeim et al. (119) reported a statistically significant positive correlation between GFAP levels and the severity of depressive symptoms. The remaining two studies did not report on any associations with symptom severity (120, 122).

3.6 Risk of bias

The methodological quality of the included studies was assessed using the NOS (113). All included studies were categorised moderate to low risk of bias as seen in table 3, therefore none was classified as high risk of bias.

Table 3. Table of NOS Quality Assessment

Study	Selection	Comparability	Exposure	Total stars	Risk of bias
H. Wu et al., 2022, China: Biomarkers of intestinal permeability and blood-brain barrier permeability in adolescents with major depressive disorder	2	2	2	6	moderate
C.V.B. Hviid et al, 2023, Denmark: Serum glial fibrillary acidic protein and neurofilament light chain in treatment-naïve patients with unipolar depression	3	2	2	7	low
P. Steinacker et al., 2021, Germany: Glial fibrillary acidic protein as blood biomarker for differential diagnosis and severity of major depressive disorder.	2	2	2	6	moderate
E. Osuna et al., 2024, Switzerland: Iron status in Swiss adolescents with paediatric major depressive disorder and healthy controls: a matched case-control study.	4	2	2	8	low
Ohlsson et al., 2019, Sweden: Leaky gut biomarkers in depression and suicidal behavior	2	2	2	6	moderate

H.K. Al-Hakeim et al., 2023, Iraq: The physio-affective phenome of major depression is strongly associated with biomarkers of astroglial and neuronal projection toxicity which in turn are associated with peripheral inflammation, insulin resistance and lowered calcium.	2	2	2	6	moderate
Gudmundsson et al., 2010, Sweden: Is there a CSF biomarker profile related to depression in elderly women?	4	1	3	8	low
Galkin, Levchuk, Simutkin, et al., 2022, Russia: Electroencephalogram Coherence and Peripheral Markers of Nervous Tissue Damage in Depressive Disorders	2	1	2	5	moderate
Levchuck et al., 2023, Russia: Serum Levels of S100B Protein and Myelin Basic Protein as a Potential Biomarkers of Recurrent Depressive Disorders	2	0	2	4	moderate
Alvarez-Mon et al., 2019, Spain: Abnormal Distribution and Function of Circulating Monocytes and Enhanced Bacterial Translocation in Major Depressive Disorder	2	2	2	6	moderate

3.7 Summary of findings

Out of the 10 included studies, four investigated serum FABP2 levels and found significantly positive associations with depression (114, 117, 118, 123). Two of these four studies included additional analyses on symptom severity and suicidal behavior, respectively, and potential associations with biomarker concentrations (114, 118). Only one found a positive association with suicidal behavior (118).

Six studies examined GFAP concentrations, yielding mixed results (115, 116, 119-122). Three of the six studies found significant associations with biomarker levels in individuals with depressive disorders (115, 116, 119), while two were directly (116, 119) and one inversely (115) correlated. The remaining three studies did not observe any significant differences (120-122). Four studies additionally examined potential associations with symptom severity (115, 116, 119, 121). Two of these studies reported a positive trend between serum GFAP levels and the severity of depressive symptoms (116, 119), whereas the other two found no correlation with symptom severity (115, 121).

All data extracted from the included studies was entered in a predefined extraction table that is presented in the appendix.

Overall, the available evidence suggests a consistent increase in serum FABP2 levels in individuals with depressive disorders, whereas findings regarding GFAP are inconsistent across studies. Considering the findings of the five studies additionally investigating symptom severity, the results yielded were inconsistent.

4 Discussion

4.1 Summary of main findings

This systematic review synthesizes the available evidence on studies investigating associations between depressive disorders, symptom severity and the barrier markers FABP2, FABP7 and GFAP compared to healthy controls. Overall, the findings indicate consistent alterations in serum FABP2 levels in patients with depression, whereas results for GFAP were heterogeneous across studies. Notably, no eligible studies investigating FABP7 were identified.

A potential correlation between biomarker levels and symptom severity was not consistently evident within the included studies. Finally, with the exception of one study, biomarker measurements were obtained at a single time point, precluding longitudinal assessment.

4.2 Interpretation of findings for FABP2

Across the included studies, serum FABP2 levels were generally higher in patients with depressive disorders than in healthy controls. These findings are broadly consistent with previous literature, although evidence is heterogeneous. While some meta-analyses reported significantly elevated serum FABP2 levels in individuals with depressive symptoms (124), an earlier systematic review by Safadi et al. found no significant differences between FABP2 serum concentrations in patients with psychiatric disorders and healthy controls (125). However, the authors observed elevations in other biomarkers of intestinal inflammation, suggesting that intestinal barrier alterations may not be consistently reflected by FABP2 across psychiatric disorders. Taken together with our findings, these observations indicate that serum FABP2 elevations could be episode- or symptom- specific, particularly given the heterogeneity of depressive disorders (126). Supporting this notion, an external study reported higher FABP2 levels and evidence of “gut inflammation” in patients with severe mental illness compared to healthy controls, reflecting potential alterations in intestinal epithelial integrity in context of psychiatric disorders (127).

4.2.1 Symptom Severity

As only one of the included studies directly compared depression scores with FABP2 concentrations (114), conclusions regarding potential associations with symptom severity are very limited. Notably, Wu et al. did not observe significant correlations with depression scores (114). A recently published study by Chen et al. supports these findings, although it was published after completion of the systematic review (128). However, Wu et al. reported significant elevations of serum FABP2 levels in MDD patients with severe to moderate anxiety relative to those with moderate to mild symptoms of anxiety. In contrast, Ohlsson et al. found increased serum FABP2 levels in MDD patients with a recent suicide attempt compared to non-suicidal participants (nsMDD). However, they did not evaluate associations between FABP2 levels and symptom severity within the nsMDD group (118). Overall, these findings are compatible with the notion of elevated FABP2 concentrations potentially being associated with specific clinical features rather than overall depressive-symptom severity.

4.2.2 Age and intestinal barrier

As age has been associated with intestinal inflammation and dysfunction of the intestinal barrier (129), age-related changes may have had an impact on the results of the included studies. The four included studies investigated FABP2 levels in populations of different age groups (adolescents and adults). While the overall findings concerning associations between FABP2 and depression are consistent across all age groups, the results regarding symptom severity show discrepancies. As mentioned before, only one study directly compared scores of symptom severity with FABP2 levels, which included solely adolescents. Age may have had an impact on the results. A link between chronic low-grade inflammation and older populations has been reported. Moreover, age-related intestinal inflammation and barrier dysfunction, potentially leading to leaky gut, have been observed in previous studies. Changes of microbial composition and alterations of the immune system in the elderly may promote these processes (129). Hypothetically, impaired intestinal barrier function in older populations could be associated with more severe symptoms of depression, as, for example, the study by Ohlsson et al. (118) found

associations between suicidal behavior and increased FABP2 concentrations in adult population. However, the median age of the population examined was 38,5 years for patients and 34,4 years for healthy controls. Additionally, the evidence on age-related alterations of intestinal permeability is inconsistent (129). Any concrete conclusions are hampered and limited by a relatively small sample size and the lack of studies that could be compared with one another. Age may have influenced findings on symptom severity but cannot be concluded on results of these reviews findings.

4.2.3 Potential influence of medication

Findings from a systematic review and meta-analysis by Safadi et al., indicated associations between gut dysbiosis biomarkers and symptom severity, irrespective of medication status. However, FABP2 levels were not increased in depressed patients, therefore suggesting that serum FABP2 levels do not correlate with symptom severity (125). Additionally, findings of a recent study by Gawlik-Kotelnicka et al., observed no significant association between serum FABP2 levels and symptom severity in subjects with depressive disorders. However, the authors reported a significant difference of FABP2 levels in patients receiving antidepressant treatment compared to those without medication. Most of the patients were treated with SSRIs, while other antidepressants were not directly classified (130). Previous studies in mice have suggested antimicrobial effects of antidepressants, particularly SSRIs and SNRIs, influencing the “richness” of the gut microbiome (131). As the microbiome is suspected to affect intestinal integrity (49, 60, 79, 80), altered FABP2 concentrations may be promoted by antidepressant use, as it is considered a biomarker to assess intestinal barrier integrity (84). Similarly, these observations might indicate an association between increased FABP2 levels and treatment status, which should be considered when interpreting the findings of the four eligible studies, as medication status varied (114, 117, 118, 123).

4.2.4 Sex-specific differences

Beyond the main findings on FABP2, potential sex-specific differences warrant consideration. Previous literature has shown that women are more likely to develop

depressive disorders (132, 133), further reflected by data of the WHO (2), suggesting possible associations with sex. Notably, prior research has reported a significant difference in serum levels of zonulin, a potential biomarker of intestinal inflammation and altered intestinal permeability, between female and male participants (134). Mouse models of stress-induced depressive-like behavior have shown that female and male mice not only developed depressive-like behavior at different time points but also experienced different inflammatory response pathways and tight junction alterations in the jejunum. Moreover, microbiota composition differed in female and male mice after experiencing chronic stress (135). Existing evidence suggests sex-specific differences of the microbiome already exist from birth (e.g. reduced α-diversity in males). As sex hormones are suspected to influence microbial diversity and composition (136), sex-dependent alterations of the intestinal barrier appear conceivable. These findings suggest that sex-specific differences may also be present in serum FABP2 concentrations. However, none of the available studies performed subgroup analyses or reported main effects of sex. Importantly, the frequent adjustment for sex across studies should not be interpreted as evidence for the absence of sex effects, as adjustment primarily addresses confounding factors.

4.2.5 Geographic location and dietary habits

Western diet, consisting of high-processed foods and a high intake of unsaturated fats and sugars, among others (70), is considered to negatively affect intestinal barrier function and microbial diversity. Recent evidence indicates potential associations between Western dietary habits and chronic inflammation as they may directly and indirectly trigger inflammatory processes (137). As mentioned previously in this review, chronic low-grade inflammation is suggested to play an important role in the pathophysiology of depressive disorders (63), particularly in the inflammatory subtype of depression (62). Eating patterns as found in Western diet trigger dysbiosis which can in turn initiate inflammatory responses and affect intestinal integrity (138). Henceforth, diet and its influencing factors should be contemplated when interpreting the findings of this review. As dietary habits were not specifically taken into account and compared between healthy controls and

individuals with depressive disorders, as well as within the latter group, conclusions concerning the impact of diet on the measured biomarker levels remain limited.

Dietary habits seem to be influenced by various factors including age, gender, and socio-economic status. Likewise, differences between world regions have been observed, particularly between high- and low-income countries (139). However, over the past decade Western diet has become increasingly widespread globally (140), which may constrain associations with world region. Of the four included studies investigating FABP2 levels, three were conducted in Europe (i.e. Sweden (118), Switzerland (117) and Spain (123)) and one in China (114). Notably, Spain belongs to the countries surrounding the Mediterranean Sea, where the Mediterranean diet originated (141). Several studies have observed positive effects of Mediterranean diet patterns on health, with one demonstrating negative correlations with inflammatory markers in blood serum (137). However, a recent systematic review and meta-analysis by Alfaro-González et al. reported that young people (2-24 years) in Spain showed a decreasing adherence to the Mediterranean diet since 2011 and are more likely to follow a low-quality diet (142). An observational study of 2025, which examined dietary patterns of immigrant and native populations in Spain found that the consumption of whole foods, vegetables and fruits, were higher with increasing age, irrespective of the population's origin (143). For Asian countries, a shift in traditional dietary patterns towards westernized eating patterns has been observed (144, 145). Given this trend and all four studies (114, 117, 118, 123) observing elevated FABP2 levels in depressed individuals compared to healthy controls, western dietary habits may indirectly have influenced FABP2 serum levels. However, eating habits are individual and without particularly assessing diet and residence, correlations between diet, world region and FABP2 concentrations cannot be implicated. To further address this matter, studies investigating populations in other regions of the world may help to clarify associations between diet, world region and depressive disorders. The question remains whether dietary habits differed significantly between depressed individuals and healthy controls and influenced FABP2 levels or whether the depressive disorder itself or other pathophysiologic processes led to alterations of biomarker concentrations in patients.

4.2.6 Longitudinal Changes

Although increased serum FABP2 levels were generally reported across the included studies, conclusions regarding temporal dynamics or associations with symptom severity remain limited, as all biomarker measurements were taken at a single time point. Additionally, the lack of studies investigating FABP2 in depressed and healthy individuals, as well as potential confounding by medication status, environmental factors such as diet and relatively small sample sizes must be acknowledged.

4.3 Interpretation of findings for GFAP

The results for GFAP levels in body fluids of depressed and healthy individuals observed in this review were heterogeneous, reflecting the inconsistent evidence reported in the existing literature. GFAP concentrations in previous studies have been measured in blood samples, CSF or post-mortem brain tissue of subjects with depressive disorders. While post-mortem studies have reported more consistent findings of decreased GFAP concentrations and reduced astroglial density in patients with depressive disorders compared to non-depressed controls (146, 147), measurements in blood or CSF samples have yielded mixed results.

4.3.1 Measurements in CSF

In a recent study by Michel et al., CSF samples from patients with unipolar depression were compared to those of controls with idiopathic intracranial hypertension (IIH) (148). Findings of that study have shown significantly increased CSF GFAP levels in patients with depression. However, as the control group suffered from IIH, interpretation for comparison with the healthy general population is only possible to a limited extent, as IIH may affect CSF dynamics and GFAP concentrations. The only study included in this review investigating CSF GFAP levels in depressed patients compared to healthy controls reported no significant differences (120). To our knowledge, the study by Gudmundsson et al., is the only study to date that assessed GFAP concentrations in CSF and compared them to healthy control subjects. Nevertheless, the generalizability of these findings is

limited by the inclusion of elderly women only and a small sample size of 11 subjects with MDD. A comparison of the inconsistent evidence is limited, as subjects in both groups differed considerably (120, 148). These observations highlight the need for further research across a broader age range, greater sample sizes, both sexes and well-matched healthy controls.

4.3.2 Measurements in blood serum and medication status

Serum GFAP concentrations were measured in five studies (115, 116, 119, 121, 122). The median age in these studies was relatively comparable, ranging from 37 to 46 years. One study, which exclusively included treatment-naïve patients with depressive disorder, found significantly decreased GFAP levels in patients compared to healthy controls (115). It should be noted, however, that these treatment-naïve individuals did not receive any antidepressant medication two months prior to the intervention, and that data reporting any previous antidepressant treatment was not stated (115). In contrast, Steinacker et al. observed significantly elevated serum GFAP levels in patients with MDD who all received psychotropic treatment but did not further define which antidepressants were taken (116). Another study that reported significantly increased serum GFAP levels did not specify medication status (119). Notably, psychotropic treatment may influence GFAP expression, as post-mortem studies have shown higher GFAP levels in premedicated compared to treatment-naïve subjects (149). Furthermore, a recent study that investigated GFAP serum levels in individuals with post-traumatic stress disorder and a control population found GFAP concentrations to be higher in participants on SSRI treatment than in participants not taking SSRIs (150). These findings suggest a potential influence of SSRIs on GFAP levels, which should be considered when interpreting the findings of this review for GFAP. Moreover, it raises the question of how long the effects of taking an SSRI last on GFAP levels. Since the remaining two studies included within this review lacked information on medication status or did not directly compare premedicated patients with other subgroups (121, 122), interpretation regarding the effect of psychotropic treatment on GFAP levels should be made with caution. To identify potential associations between GFAP serum levels and depressive disorders, studies integrating non-

medicated individuals with depression may provide results with greater generalizability.

4.3.3 Serum versus CSF

A comparison between serum and CSF GFAP measurements is not possible due to the lack of studies examining CSF GFAP concentrations. However, previous literature reported that CSF GFAP measurements are more sensitive to pre-analytical variables than serum analyses (151, 152). This may have influenced the results of Gudmundsson et al. (120). Considering the suggested adaptions to stabilize GFAP in CSF samples (e.g. the use of sealed and completely filled microtubes) as outlined by Evertsson et al. (151), the question remains whether CSF samples outperform blood samples with regard to accuracy and sensitivity, or whether phlebotomy is overall more efficient due to a simpler collection method and lower burden on patients.

4.3.4 Sex-specific differences

Recent evidence suggests that women are more sensitive to neuroinflammatory processes assumedly due to genetics, epigenetics and hormonal fluctuations modulating immune responses and neuroplasticity (37). Sex-specific differences between biomarker levels therefore appear conceivable. Two studies directly assessed the main effect of sex and found no significant differences (115, 121), while the remaining studies primarily adjusted for sex. However, there cannot be drawn any conclusions from these findings and further research would be needed to investigate potential associations between sex and biomarker levels.

4.3.5 Symptom severity

As only four studies additionally investigated potential associations with symptom severity, reporting mixed results, concrete conclusions cannot be drawn. Steinacker et al. observed a significant correlation of serum GFAP levels with MADRS scores after excluding one outlier (116), which demonstrates the possible effect of relatively small sample sizes on the stability of results. The only study with a greater sample

size in MDD patients did not observe statistically significant associations between serum GFAP levels and symptom severity (115); though the authors stated that symptoms were less severe compared to the depressed subjects included in the study by Steinacker et al.

These findings suggest that differences in GFAP levels across studies may partly reflect the inclusion of patients at different stages or episodes of depression, with varying symptom severity. Elevated serum GFAP concentrations may therefore be restricted to specific symptoms or more severe cases, particularly in light of the heterogeneity of depressive disorders and their diverse manifestations (126). Additionally, a recent review by Patani et al. stated that astrocytic reactivity, provoked by brain injury, neurodegeneration or neuroinflammation, presents itself in various subforms (e.g. dyshomeostasis, cytotoxicity) even within a disease.

As GFAP is a marker of astrocytic reactivity, this might suggest that GFAP elevations are potentially associated with specific states of astrocytic reactivity (103, 153) varying within depressive disorders, especially supported in the light of the heterogeneous findings in this review.

4.4 Interpretation of findings for FABP7

Although one study has assessed FABP7 in depression (102), it lacked a healthy control group and was therefore not eligible for inclusion. Notably, this study reported no significant association between FABP7 serum levels and symptom severity in subjects with depressive disorders (102). Nevertheless, recent animal studies have observed that FABP7 may act as a modulator of inflammatory responses and signaling pathways involved in maintaining BBB integrity (100, 101). Furthermore, depressive-like behavior in mice was reduced by upregulation of FABP7 expression (100), indicating a potential role for FABP7 in the development or severity of psychiatric disorders.

No other eligible studies investigating FABP7 in depression were identified, revealing a clear gap in the literature and a potential avenue for future research.

4.5 Limitations and strengths

There are notable limitations of the studies included in this review. Overall, sample sizes for both healthy controls and participants with depressive disorders were relatively small, which may limit robustness and generalizability of the findings. With regard to participant recruitment, most studies enrolled individuals from a single clinical or research center, which further limits generalizability. Although all included studies performed symptom assessment, different rating scales were used (e.g. HAMD-17, HAMD-6, HAMA, MADRS, BDI-II, SUAS, CPRS etc.). This heterogeneity may have affected how symptom severity was quantified and makes comparisons across studies difficult, thereby limiting the interpretability of associations with biomarker levels. In the same context, variations in medication status should also be taken into account when evaluating the results of this review. All studies, with one exception, measured at single time points only, which limits the ability to detect temporal changes or assess longitudinal associations. Finally, all studies were case-control or cross-sectional studies, which precludes any conclusions to be drawn about cause and consequence.

To ensure a systematic and transparent approach, this review was conducted following the PRISMA guidelines. Nonetheless, this systematic review has potential methodological limitations that should be acknowledged. First, the review was conducted by a single reviewer, which may have increased the risk of bias. Relevant studies or important data may have been inadvertently omitted during the screening and data extraction process. However, the thesis supervisor was consulted in cases of uncertainty and disagreements were resolved through discussion. Second, only a limited number of studies met the predefined eligibility criteria. Although one study investigated FABP7, it did not fulfill the inclusion criteria and was therefore excluded from the analysis. Third, the database PsycInfo was not searched due to lack of institutional access, which may have limited the comprehensiveness of the literature retrieved.

Despite these limitations, several strengths of this review should be acknowledged. First, the systematic search strategy across multiple databases and the registration of the review protocol in PROSPERO ensured methodological transparency.

Second, the inclusion of studies assessing different biological matrices (serum and CSF) provided a broader overview of biomarker research in depression. Finally, this systematic review was one of the first reviews of primary studies investigating the biomarkers FABP2, FABP7 and GFAP in individuals with depression and healthy controls.

4.6 Clinical implications and future perspectives

In this review, the findings for FABP2 were the most consistent and positive, as elevated serum concentrations were reported across all included studies compared with the other biomarkers examined.

In the context of clinical practice, FABP2 may hold potential as a diagnostic biomarker for depressive disorders, particularly when used in combination with other biomarkers, as suggested in a previous study (114). However, the existing limitations of this review's findings have to be considered. Given the lack of longitudinal studies, FABP2 does not yet appear suitable as a routine diagnostic biomarker for depressive disorders in current clinical practice. It is plausible that elevations in FABP2 levels may be present in a broader range of individuals with depressive disorders, as a significant correlation with symptom severity has not been reported. To ascertain this hypothesis, further research employing longitudinal studies is essential.

In light of current literature describing FABP2 as an endogenous biomarker for enterocyte damage and intestinal barrier disruption (80, 95) the consistently increased FABP2 concentrations observed in this review may indirectly reflect the presence of intestinal inflammation (64, 80, 127), intestinal barrier dysfunction (64, 80) and increased intestinal permeability (64, 96, 154), which is also referred to as "leaky gut" (94, 124, 155, 156), in depressive disorders. Given this notion, FABP2 could be an indirect marker for leaky gut. From a clinical perspective, this points to the intestinal barrier as a potential therapeutic target for patients with depressive disorders. Over the past decade, the field of nutritional psychiatry has gained increasing attention. Epidemiological data has shown associations between mental health and diet and highlighted the potential possibilities of nutrition-based approaches in the treatment of mental health disorders (157). In several studies,

the microbiome as part of the intestinal barrier has already been targeted with pro- and prebiotics, amongst others. A recent systematic review by Ribera et al. summarizes findings of those studies, reporting positive effects on depressive symptoms (158). Future therapeutic strategies for MDD patients with elevated FABP2 serum levels could implement treatment of gut dysbiosis and potential leaky gut, for example as outlined in a review by Aleman et al. (159). Nevertheless, it should be noted that the gut microbiome is host specific and therapeutic strategies may need to be adapted and individualized to the patients (160) displaying increased FABP2 serum concentrations. Moreover, the decision regarding a potential treatment for leaky gut should not only be based on FABP2 as the sole biomarker, but rather in combination with other biomarkers such as fecal zonulin or serum LBP (96) and LPS (95). Furthermore, exclusion of other diseases such as coeliac disease or inflammatory bowel disease (IBD) should be performed as they can present not only with elevated FABP2 levels (161, 162) but patients may show depressive symptoms (163, 164). An established non-invasive method for coeliac disease detection is the assessment of IgA antibodies against tissue-glutaminase (163) and the measurement of fecal calprotectin for IBD detection (165). However, these suggestions are based on the notion of FABP2 indirectly representing the presence of leaky gut and therefore remain hypothetical until definite associations with MDD are evident.

Considering the MGBA and the assumed inflammatory processes associated with depression or subtypes of depression (166); the findings of this review indirectly support the inflammatory hypothesis (167, 168) and the relevance of an inflammatory subtype of depression (62, 169). As dysbiosis could lead to a disruption of the intestinal barrier by way of inducing inflammatory processes and subsequently altering permeability (64), the suggested inflammatory subtype may be connected with an impaired intestinal barrier and increased intestinal permeability. Given this notion, leaky gut could be associated with subtypes of depressive disorders, particularly the inflammatory subtype. However, more research is required to clarify whether inflammatory processes represent a cause or consequence of depressive disorders and how to possibly prevent such processes.

The findings for GFAP are more heterogeneous and hamper any concrete conclusion. However, in the light of current evidence the use of GFAP as a diagnostic biomarker for depressive disorders does not yet appear to be suitable. It is nevertheless conceivable that GFAP may serve as a diagnostic tool, as previous studies have reported positive correlations with neurodegenerative disorders, such as Alzheimer´s disease (170), in which neuroinflammation is suggested to affect both disease development and progression (171). Similarly, this is proposed for depressive disorders (172). As there may be different states of astrocytic reactivity within a disease (103, 153), GFAP as a marker for astroglial reactivity, could be relevant for identifying subtypes of depression rather than serving as a general diagnostic biomarker. To identify potential links between GFAP and subgroups of depression and clinical symptoms respectively, further investigations focusing on symptom severity and specific clinical features are necessary. Elucidating these associations may help to distinguish clinically relevant subgroups of depressive disorders.

In light of previous literature suggesting that FABP7 may play a role in stabilizing the BBB and potentially modulating GFAP expressions (100), future research is crucial to clarify its function and potential associations with depressive disorders. As a previous study suggested important effects of FABP7 on adult neurogenesis and thereby potential novel therapeutic targets for depressive disorders (173), clinical studies are needed.

Addressing the current research gap regarding FABP7 could contribute to the identification of a more effective biomarker for depressive or other psychiatric disorders and expand the possibilities of effective treatment options.

4.7 Future research

As depressive disorders depict a rising mental health condition, new treatment strategies and effective diagnostic tools delineate important focus in future research. To clearly establish potential associations between the three biomarkers and depressive disorders, studies incorporating a longitudinal design and larger sample

sizes among patients and controls are necessary. Furthermore, a wider age range across both genders and recruitment from diverse clinical institutions or community settings are required. Subgroup analyses considering medication status, potentially treatment resistant patients, specific symptom clusters, gender, and diet, are proposed to identify potential associations.

5 Conclusion

In conclusion, the available evidence on the three biomarkers - FABP2, FABP7 and GFAP - has yielded heterogeneous findings.
This review reveals a significant research gap concerning FABP7, underscoring the need for further investigation in order to determine its role in depressive disorders, potentially establishing new therapeutic approaches.

The findings for GFAP regarding its role and diagnostic potential in depressive disorders are inconclusive. The findings for GFAP may have been influenced by different factors including sex, stage/episode and clinical presentation of depression and medication status. GFAP may more likely serve as a biomarker to differentiate between subgroups of depression or specific clinical symptoms rather than detecting depressive disorders in general. To clarify these associations and fully evaluate its potential usefulness as a biomarker in clinical practice, further studies with a longitudinal design and subgroup analyses are necessary.

With respect to FABP2, the overall findings are more consistent and indirectly support the existing hypothesis of alterations in intestinal barrier integrity and intestinal inflammation in depressive disorders, although it remains unclear whether these processes are a cause or a consequence of depression. Notably, patient characteristics including sex, medication status, diet and subtype of depression, may have affected the results for FABP2. However, the acquired findings indicate the necessity for future research on potential therapeutic strategies related to the gut barrier, as they appear to be promising, especially given the growing importance of the field of nutritional psychiatry.

Overall, this review highlights the complexity of depressive disorders and adds to the growing body of evidence suggesting that alterations in gut–brain barrier integrity and neuroimmune interactions may contribute to their pathophysiology, emphasizing the need for further investigation of subgroup-specific biomarker alterations.

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7 Appendix

The following tool was used to optimize language in parts of this thesis: ChatGPT GPT 5 and gpt-5-mini, OpenAI, (https://chatgpt.com).

Additional link to access the extraction table (table4) on page 70 in a bigger version: https://1drv.ms/x/c/a2f9c3a7242f874d/IQDoYcDF0Y7IS467AI3i_iylAQygJonqQAyhPCjvaOSjNxA

Search strategy

Search String Embase:

1	depression.ab,fx,hw,kf,ot,sh,ti,tw.	845574
2	"depressive disorder".ab,fx,hw,kf,ot,sh,ti,tw.	59033
3	"major depressive disorder".ab,fx,hw,kf,ot,sh,ti,tw.	46307
4	"depress* ".ab,fx,hw,kf,ot,sh,ti,tw.	940519
5	GFAP.ab,fx,hw,kf,ot,sh,ti,tw.	31530
6	"glial fibrillary acidic protein".ab,fx,hw,kf,ot,sh,ti,tw.	40741
7	"FABP2".ab,fx,hw,kf,ot,sh,ti,tw.	597
8	"fatty acid protein 2".ab,fx,hw,kf,ot,sh,ti,tw.	12
9	"intestinal-type fatty acid binding protein".ab,fx,hw,kf,ot,sh,ti,tw.	32
10	"I-FABP".ab,fx,hw,kf,ot,sh,ti,tw.	961
11	"FABPI".ab,fx,hw,kf,ot,sh,ti,tw.	28
12	FABP7.ab,fx,hw,kf,ot,sh,ti,tw.	551
13	"B-FABP".ab,fx,hw,kf,ot,sh,ti,tw.	78
14	"BLBP".ab,fx,hw,kf,ot,sh,ti,tw.	266
15	"FABPB".ab,fx,hw,kf,ot,sh,ti,tw.	0
16	"brain fatty acid-binding protein".ab,fx,hw,kf,ot,sh,ti,tw.	65
17	"brain lipid-binding protein".ab,fx,hw,kf,ot,sh,ti,tw.	183
18	depression/ or major depression/	557265
19	fatty acid binding protein 2/ec [Endogenous Compound]	1243
20	fatty acid binding protein 7/ec [Endogenous Compound]	439
21	glial fibrillary acidic protein/ec [Endogenous Compound]	27571
22	1 or 2 or 3 or 4 or 18	940519
23	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 16 or 17 or 19 or 20 or 21	54734
24	22 and 23	1545
25	limit 24 to (human and english)	668
26	limit 25 to (english language and yr="2004 -Current")	634

Search string PubMed:

("FABP7 protein, human" [Supplementary Concept] OR "FABP2 protein, human" [Supplementary Concept] OR "GFAP protein, human" [Supplementary Concept] OR "glial fibrillary acidic protein" OR "fatty acid binding protein 2" OR "fatty acid binding protein 7" OR "FABP2" OR "FABP7" OR GFAP OR "brain lipid-binding protein" OR BLBP OR "B-FABP" OR "FABPB" OR "brain fatty acid-binding protein" OR "brain-type fatty acid-binding protein 7" OR "MRG" OR "I-FABP" OR "I-FABP2" OR "FABPI" OR "Intestinal-type fatty acid-binding protein" OR "fatty acid binding proteins") AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR Depression* OR depressed OR MDD OR "major depressive disorder") Filters: Clinical Study, Comparative Study, Multicenter Study, Observational Study, Randomized Controlled Trial, Research Support, N.I.H., Extramural, Research Support, N.I.H., Intramural, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, Non-P.H.S., Research Support, U.S. Gov't, P.H.S., Research Support, U.S. Gov't, Humans, English, German

Search string Web of Science:

("FABP7" OR "FABP2" OR "GFAP" OR "glial fibrillary acidic protein" OR "fatty acid binding protein 2" OR "fatty acid binding protein 7" OR "brain lipid-binding protein" OR BLBP OR "B-FABP" OR "FABPB" OR "brain fatty acid-binding protein" OR "brain-type fatty acid-binding protein 7" OR "MRG" OR "I-FABP" OR "I-FABP2" OR "FABPI" OR "Intestinal-type fatty acid-binding protein" OR "fatty acid binding proteins") AND ("Depression*" OR depressed OR MDD OR "major depressive disorder" OR "major depression")
Filters: English language, 2004 - 2024

Search string Google Scholar:

(intitle:"FABP7" OR intitle:"FABP2" OR intitle:"GFAP" OR intitle:"fatty acid binding proteins" OR intitle:"fatty acid binding protein 7" OR intitle:"fatty acid binding protein 2" OR intitle:“glial fibrillary acidic protein” OR intitle:"B-FABP") AND (Depression OR "depressive disorder" OR "major depressive disorder" OR MDD OR "mental health" OR "psychiatric disorders") AND (human OR humans OR patient OR patients), Filters: 2004-current, only English

Table 4. Extraction table

Author, year, country	Study design	Diagnosis	Sample Size N (F/M) Patients	Sample size N (F/M) healthy controls	Median Age Patients	Median Age Healthy Controls	Symptom Assessment	Medication status	Biomarkers measured	Sample material	Assay Method	Biomarker Levels in Patients	Biomarker Levels in Helathy Controls	Primary finding regarding the research question of the systematic review	Statistical Significance	Other relevant correlations	Confounding Factors	Study Limitations
H. Wu et al., 2022, China	Cross-sectional study	MDD (DSM 5)	50 (35/25)	40 (27/13)	16	15	HAMD-17 and HAMA-14, for patients and HC	No anti-depressants, mood-stabilizers or neuroleptics in the previous month	I-FABP, Zonulin, Claudin-5, LPS	Venous blood (serum)	ELISA	I-FABP (ng/ml) 4.95 ± 0.83	I-FABP (ng/ml) 4.01 ± 0.69	Elevated I-FABP levels in patients compared to HC	yes (p<0,001)	No correlation between I-FABP and depression scores; higher I-FABP levels in MDD patients with anxiety than without anxiety; no correlation between suicidal behavior and non-suicidal behavior	Adjusted: age, gender, BMI; Not adjusted: economic status, dietary habits, other psycho-social factors	Stated by the authors: No longitudinal analysis, small sample size, no evaluation of intestinal microbiota, economic status, dietary habits, and other psychosocial factors not evaluated Further: Recruitment from one medical institution only
C.V.B. Hvid et al, 2023, Denmark	Case-control Study	mild to moderate unipolar depression (DSM-IV)	110 (72/38)	33 (23/10)	42	39	HAMD-17 and HAMD-6, BDI II, Danish version of the MINI for patients and HC (of previous study).	No anti-depressants in the previous two months	GFAP, NfL	Venous blood (serum) from the DEMO-II trial (Biobank material) (Krogh et al., 2012)	Simoa	GFAP (approx. mean value estimated from boxplot diagramm) 70 pg/ml	GFAP (approx. mean value estimated from boxplot diagramm) 75 pg/ml	Reduced serum GFAP levels of treatment-naïve patients with unipolar depression compared to healthy controls	yes (p=0,03)	No significant change in GFAP levels over 3 months; No significant correlations of GFAP levels with depression scores; significantly positive association with age (p < 0.001); significantly negative association with BMI (p=0,01); no association with sex.	Adjusted: age, gender, BMI Not adjusted for: multiple testing	Stated by the authors: Use of biobank material from a different study, mild depression severity, serum sample use only, small sample size in healthy control group, high intermediate precision of GFAP assay
P. Steinacker et al., 2021, Germany	Case-control study	MDD (DSM 5)	45 (29/16)	16 (12/4)	48	45	MADRS for all patients	Single or combinatorial medication with anti-depressants, benzo-diazepines or anti-psychotics (all MDD patients)	GFAP, NfL	Venous blood (serum)	Simoa	GFAP (mean value) 211 ± 90 pg/ml	GFAP (mean value) 147 ± 61 pg/ml	Elevated serum GFAP levels in patienzs with MDD compared to healthy controls	yes (p = 0.0178)	Diagnostic discrimination of MDD from HC (sensitivity 87%, specificity 56%, cut-off 128 pg/ml); Significantly positive association of GFAP with age in MDD and HC (p < 0.001); No correlation for the MDD group of GFAP with the albumin quotient as measure of the blood-CSF-barrier function	Not adjusted for age, sex, BMI	Stated by the authors: No longitudinal data, small sample sizes, potential influence of medication status Further: serum sample analyses only, patient recruitment from one single institution only
E. Osuna et al., 2024, Switzerland	(matched) Case-control Study	paediatric MDD (DSM - IV)	95 (55/40)	95 (55/40)	16,1	16	M.I.N.I. KID for HC. K-SADS-PL and CDRS-R for patients.	38% (36 participants) of cases used anti-depressants	I-FABP, AGP alpha-1-acid-glycoprotein; CRP; SF serum ferritin; sTfR soluble transferrin receptor	Venous blood (serum)	ELISA	I-FABP (pg/ml) 307 (17, 515)	I-FABP (pg/ml) 232 (163, 357)	Elevated I-FABP levels in patients compared to HC.	yes (p=0,047)	I-FABP did not correlate with any other biomarker measured	Matched cases and controls according to sex, age group (13 to < 16 and 16 to < 18 years) and education level	Stated by the authors: *only concerning primary endpoint (iron status correlation)* Further: No longitudinal data, small sample sizes
Ohlsson et al., 2019, Sweden	Cross-sectional study	MDD (with and without recent suicide attempt; DSM-IV)	67 (37/30) rSA (n = 54; 30/24), nsMDD (n = 13; 7/6)	17 (8/9)	rSA: 38,5 nsMDD: 34,5	34,4	MADRS and SUAS	No treatment with antidepressants, neuroleptics or mood stabilizers in the previous month in the nsMDD group.	I-FABP, Zonulin, soluble CD14, IL-6	Venous blood (serum)	ELISA	I-FABP (pg/ml) in - rSA: 2027.5 (1277.8–2723.8) - nsMDD: 559.8 (431.4–976.5)	I-FABP (pg/ml) 667.8 (474.6–1378.0)	Significantly positive correlation between I-FABP levels and severity of depression and suicidal symptoms (MADRS [r = 0.25, P < 0.05] and SUAS scores [r = 0.38, P < 0.001]; also significantly positive correlation of SUAS scores in the nsMDD group (r = 0.60, P < 0.05).	yes (p < 0,001)	In all participants I-FABP correlated negatively with Zonulin and positively with IL-6.	Adjusted: age, gender, BMI, substance use; Not adjusted: alcohol intake, economic status, smoking, dietary habits and other.	Stated by the authors: Small sample size, no longitudinal data, possible confounding by unadjusted factors, diagnostic heterogeneity in the rSA group Further: Blood sample storage for a prolonged period (mean 12 ± 2 years) prior to analysis, which may have affected long-term biomarker stability and limits comparability with other studies.
H.K. Al-Hakeim et al., 2023, Iraq	Case-control study	MDD (DSM 5)	94 (52/42) BDI < 34: 53 (34/19) BDI ≥ 34: 41 (18/23)	47 (25/22)	BDI < 34: 37,2 BDI ≥ 34: 39,5	38.0	BDI-II, HAMA, Fibromyalgia and Chronic Fatigue Syndrome Rating Scale	Not stated.	GFAP, NfL, p-tau 217, PDGFRbeta, CRP, magnesium, calcium, fasting blood glucose, insulin	Venous blood (serum)	ELISA	GFAP (pg/ml) - BDI <34: 169.9 ± 10.6 - BDI ≥ 34: 225.4 ± 12.1	GFAP (pg/ml) 116.7 ± 11.2	GFAP levels are higher in MDD than HC, GFAP levels correlated positively with the severity of depression.	yes (p<0,001)	No other concerning GFAP.	Adjusted: age, sex, BMI, tobacco use disorder, education	Stated by the authors: none stated. Further: No longitudinal data, small sample size, no statement regarding the use of psychothropic substances/medication in patients, recruitment from a single institution only, serum sample analyses only.
Gudmundsson et al., 2010, Sweden	Cross-sectional study	MDD (DSM-III-R)	11 (11/0)	67 (67/0)	All participants: 73.9	All participants: 73.9	CPRS and MADRS	23, 1 % of all women in the study used benzodiazepines, 24,4 % used anxiolytics, 3,8% used antidepressants	GFAP, Nfl	CSF	ELISA	GFAP (ng/l) 946 ± 196	GFAP (ng/l) 887 ± 308	CSF-GFAP levels did not correlate with the diagnosis of MDD.	no (p = 0.247)	No other concerning GFAP.	Adjusted: age Not adjusted: BMI, alcohol intake, economic status, smoking	Stated by the authors: Specific demographic group, ethnicity and sex, small sample size, Healthy controls were defined as individuals without dementia. Further: GFAP analyses in CSF only, potential effect of prolonged storage (max. 5 years), unadjusted confounding factors
Galkin, Levchuk, Simutkin, et al., 2023, Russia	Case-control study	F32 or F33 (single depressive episode or recurrent depressive disorder), ICD-10 criteria	30 (22/8)	30 (23/7)	46	44	HDRS-17	Not stated.	GFAP, serum calcium-binding protein S100b, myelin basic protein (MBP)	Venous blood (serum)	ELISA	GFAP (ng/ml) 0.3 (0.11; 1.25)	GFAP (ng/ml) 0.37 (0.15; 1.21)	GFAP levels in patients with depression did not significantly differ from levels in HC.	no (p = 0.112)	Significant correlations between EEG coherence coefficients: alpha-, beta- and delta-rhythm in the right-hemisphere and GFAP, as well as inflammatory changes in the brain in patients with depression.	Sex and age matched controls. Not adjusted: BMI, alcohol intake, economic status, smoking	Stated by the authors: none stated. Further: No longitudinal data, small sample size, no statement regarding the use of psychothropic substances/medication in patients
Levchuck et al., 2023, Russia	Cross-sectional study	Depressive episode and recurrent depressive disorder (RDD), F32 or F33, ICD-10 criteria	DE 28 (20/8) RDD 21 (18/3)	25 (12/13)	DE: 44.5 (31; 54.75); RDD: 47 (40.5; 60.5)	38 (32.5; 42.5)	HDRS-17, HARS, CGI-S and SHAPS	SSRI therapy in 16 patients with RDD.	GFAP, MBP, S100B	Venous blood (serum)	ELISA	GFAP (ng/mL) DE: 0.31 (0.06; 1.36) RDD: 0.12 (0.08; 1.32)	GFAP (ng/ml) 0.38 (0.13; 1.07)	No significant differences in GFAP levels of patients and HC.	No (p= 0.537)	GFAP levels in patients with RDD correlated negativley with the duration of the last therapeutic remission. No correlation with symptom severity.	Not adjusted: age, sex, BMI, economic status, alcohol intake, smoking	Stated by the authors: heterogeneity of groups Further: No longitudinal data, small sample size, GFAP serum analyses only, potential influence of SSRI treatment, recruitment from a single institution only.
Alvarez-Mon et al., 2019, Spain	Cross-sectional study	MDD (DSM-V)	22 (13/9)	14 (8/6)	40,3	40,8	HDRS-17, MINI (to exclude patients with concomitant psychiatric illness)	No medication: 2 (9,09 %) Antidepressants: 19 (86,36 %) Anxiolytics or hypnotics: 17 (77,27 %) Mood stabilizers: 5 (22,72 %) Atypical antipsychotics: 6 (27,27 %)	I-FABP, LBP, Zonulin, CD14++CD16- (classical), CD14++CD16++ (intermediate), CD14-CD16++ (nonclassical) monocytes, TNF-α, IL-1β, IL-6, IL-10	Venous blood (serum)	ELISA	I-FABP (no values given)	I-FABP (no values given)	Significantly increased I-FABP levels in patients compared to HC.	Yes (no p-value reported)	No other concerning I-FABP. A low-grade systemic inflammation was observed in MDD patients.	Sex-, age- and BMI-matched controls from the same epidemiological area. Not adjusted: smoking and drinking habits, employment and economic status.	Stated by the authers: none stated. Further: No longitudinal data, small sample size, potential influence of medication, recruitment from a single institution only, no assessment of dietary habits and psychosocial factors