Uloga depresije u razvoju blagog kognitivnog poremećaja

/ The Role of Depression in the Development of Mild Cognitive Impairment

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Blagi kognitivni poremećaj (BKP) smatra se stanjem između zdravog starenja i demencije, različitih etioloških čimbenika, kliničkih prezentacija i progresivnosti profila. Cilj rada je dati cjelovit pregled spoznaja o ulozi depresije u razvoju BKP-a. Značajna povezanost depresije s incidencijom BKP-a potvrđena je u većini istraživanja. Depresija može biti rizični čimbenik za razvoj BKP-a. Povezanost depresije i BKP-a ostvaruje se i zajedničkim čimbenicima – vaskularnim lezijama, patologijom Alzheimerove demencije (AD), genetskom vezom. Depresivni simptomi i promjene bijele tvari mogu imati aditivni ili sinergistički učinak za razvoj BKP-a. Rizični čimbenici za incidenciju BKP-a u depresivnih osoba su starija životna dob, kumulativni depresivni simptomi, dulje trajanje depresije, veći intenzitet depresivnih simptoma, niska, ali i visoka zastupljenost patologije AD-a, sinergistička aditivna interakcija nedostatka tjelesne aktivnosti i poteškoća spavanja, depresije i anksioznosti, muški rod, niži stupanj formalnog obrazovanja, aktualno posjedovanje recepta za korištenje antidepresiva. Zaštitni čimbenici koji pospješuju reverziju u uredno kognitivno funkcioniranje u depresivnih osoba su mlađa dob, neamnestički BKP, manji intenzitet depresivnih simptoma ili pak smanjenje depresivnih simptoma.

/ Mild cognitive impairment (MCI) is understood as a condition between normal aging and dementia, with different etiological factors, clinical presentations and progression profiles. The aim of this paper was to provide a comprehensive overview of the role of depression in the development of MCI. Most studies have confirmed that there is a significant connection between depression and the incidence of MCI. Depression can be a risk factor for the development of MCI. The connection between depression and MCI is achieved through common factors such as vascular lesions, Alzheimer's disease pathology and genetic links. Depressive symptoms and changes in white matter may have an additive or synergistic effect on the development of MCI. Risk factors for the incidence of MCI in individuals with depression include older age, cumulative depressive symptoms, longer duration of depression, higher severity of depressive symptoms, low, but also high burden of Alzheimer's pathology, synergistic additive interaction of lack of physical activity and sleep difficulties, depression and anxiety, male gender, lower level of formal education and current prescription of antidepressants. Protective factors that promote the reversion to normal cognitive functioning in depressed individuals include younger age, non-amnestic MCI, lower severity of depressive symptoms or a reduction in depressive symptoms.

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UVOD

Blagi kognitivni poremećaj, BKP (engl. *mild cognitive impairment*), klinički je koncept koji su Petersen i suradnici 1997. godine definirali kao stanje između zdravog starenja i demencije (1). Prevalencija u općoj populaciji varira u istraživanjima od 0,8 do 11,1 % (2). BKP raste s dobi te zahvaća 15-20 % populacije starije od 60 godina (1). Značajnim dijelom je riječ o incipijentnoj demenciji (3) što potvrđuju neuropatološka istraživanja koja su pronašla dokaze patologije Alzheimerove demencije (AD) i godinama prije pojave kliničkih simptoma (5). Svoje začetke BKP ima u 1962. godini, kada je Kral (6) opisao razlike između nedeteriorirajućih i deteriorirajućih smetnji pamćenja. BKP obilježavaju subjektivne teškoće pamćenja, objektivno oštećenje kognitivnih funkcija uobičajeno procijenjeno neuropsihologijskim testovima, odsutnost drugih kognitivnih poremećaja uz očuvano svakodnevno funkcioniranje, očuvano generalno kognitivno funkcioniranje i odsutnost demencije (7). Koncept se razvio od svojih početaka (8). U klasifikacijama MKB-11 (9) i DSM-5 (10) konceptualiziran je kao blagi neurokognitivni poremećaj (9).

BKP može zahvaćati oštećenje jednog ili pak više aspekata kognitivnog funkcioniranja. Razlikuju se podtipovi i ovisno o tome je li oštećeno pamćenje, što se naziva amnestičkim BKP-om, ili su oštećene druge kognitivne funkcije, što se naziva neamnestičkim BKP-om. Nadalje se može dijeliti na različite podtipove ovisno o kliničkoj prezentaciji, npr. BKP povezan s AD-om. Dijagnoza se postavlja nizom kliničkih i dijagnostičkih postupaka koji uključuju ispitivanje anamneze, procjenu kognitivnog funkcioniranja, funkcionalnog statusa, utjecaja lijekova, neuroloških ili psihijatrijskih abnormalnosti, i laboratorijsko testiranje (11). BKP je heterogeni sindrom s različitim etiološkim čimbenicima, kliničkim prezentacijama i progresivnosti. Navedeno rezultira postojanjem različitih kombinacija kriterija za BKP (12). Za

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical concept defined by Petersen et al. in 1997 as a state between healthy aging and dementia (1). Studies have shown that its prevalence in the general population varies from 0.8% to 11.1% (2). The prevalence of MCI increases with age, affecting 15-20% of the population over 60 years old (1). For the most part, these data refer to incipient dementia (3), which is confirmed by the results of neuropathological research indicating signs of Alzheimer's disease (AD) pathology years before the appearance of clinical symptoms (5). The origins of MCI date back to 1962 when Kral (6) described the differences between non-deteriorating and deteriorating memory impairments. MCI is characterized by subjective memory complaints, objective impairment of cognitive functions usually assessed through neuropsychological tests, the absence of other cognitive disorders with preserved daily functioning, preserved general cognitive functioning and the absence of dementia (7). The concept has evolved since its inception (8). In the ICD-11 (9) and DSM-5 classification systems (10), it is conceptualized as mild neurocognitive disorder (9).

MCI can affect the impairment of one or more aspects of cognitive functioning. It can be divided into subtypes depending on whether memory is impaired, which is referred to as amnestic MCI, or if other cognitive functions are impaired, known as non-amnestic MCI. Furthermore, it can be categorized into different subtypes based on clinical presentation, e.g. MCI associated with AD. The diagnosis involves a series of clinical and diagnostic procedures, including taking medical history, assessing cognitive functioning, functional status, medication effects, neurological or psychiatric abnormalities, and laboratory testing (11). MCI is a heterogeneous syndrome with various etiological factors, clinical presentations and progression, leading to different combinations of MCI criteria (12). Clinical guidelines for selecting neuropsychological tests are required

procjenu BKP-a potrebne su kliničke smjernice za odabir neuropsihologijskih testova (13). Sugerirani su degenerativni, vaskularni, traumatski, infektivni, ali i psihijatrijski etiološki čimbenici BKP-a (14). Razvijaju se dijagnostičke metode za razlikovanje različitih vrsta BKP-a i metode liječenja. Učinak farmakoterapije i psihoterapije na liječenje BKP-a nije jednoznačno razjašnjen (3, 15,16).

Jedan od sugeriranih psihijatrijskih etioloških čimbenika BKP je depresija. **Depresija** je naziv za niz depresivnih poremećaja, primarno obilježenih sniženim raspoloženjem ili anhedonijom, ali i negativnim samovrednovanjem, poremećajem spavanja i apetita, značajno smanjenom funkcionalnosti, u trajanju od dva tjedna i više (8). Smanjenje kognitivne učinkovitosti jedno je od ključnih obilježja depresivnih poremećaja. Ispitivanje odnosa kognicije i depresije predmet je istraživanja posljednjih četrdesetak godina, prvotno usmjerenih na sadržaj misli i obilježja obrade informacija, a potom na razumijevanje kognitivnih deficita. Veliki depresivni poremećaj u odraslih nerijetko se manifestira kognitivnim oštećenjem, blagim deficitima pamćenja, brzine procesuiranja i izvršnih funkcija (17), ali i oštećenjem vizuospacijalnih sposobnosti (18), oslabjelom pažnjom i koncentracijom (19). Depresija u starijoj dobi obilježena je većom vjerojatnošću disfunkcije izvršnih funkcija i usko povezanog oštećenja adaptivnog funkcioniranja (17,20,21), kao i obilnijim somatskim komorbiditetom, varijabilnim terapijskim učinkom (22-25). Neka istraživanja navode da povezanosti između komponenata izvršne disfunkcije i funkcionalne nesposobnosti ne ovise o depresiji, već o vaskularnim rizičnim čimbenicima (26).

Dok neki autori navode da je 26 % osoba s BKP-om depresivno (27), drugi izvještavaju o čak 63,3 % depresivnih u populaciji s BKP-om (28). Brojna istraživanja ukazuju na povezanost BKP-a i depresije (27-32), ali njihov vremenski tijek javljanja, kauzalnost, kao i me-

for MCI assessment (13). Proposed etiological factors for MCI include degenerative, vascular, traumatic, infectious and psychiatric factors (14). Diagnostic methods are being developed to differentiate between various types of MCI and treatment methods. The impact of pharmacotherapy and psychotherapy on MCI treatment has not been definitively clarified (3, 15, 16).

One of the suggested psychiatric etiological factors of MCI is depression. **Depression** refers to a range of depressive disorders, primarily characterized by low mood or anhedonia, as well as negative self-evaluation, sleep and appetite disturbances, significantly reduced functionality, which can all last for two weeks or more (8). Reduced cognitive efficiency is one of the key features of depressive disorders. Research on the connection between cognition and depression has been ongoing for the past forty years, initially focusing on thought content and information processing characteristics, and later on understanding the cognitive deficits. Major depressive disorder in adults often manifests with cognitive impairment, mild memory deficits, as well as processing speed and executive function deficits (17), in addition to impairments in visuospatial abilities (18), reduced attention and concentration (19). Depression in older age is characterized by a higher likelihood of executive function dysfunction and closely related adaptive functioning impairment (17, 20, 21), as well as a greater somatic comorbidity and variable therapeutic response (22-25). Some studies suggest that the correlation between components of executive dysfunction and functional impairment is not dependent on depression, but on vascular risk factors (26).

While some authors report that 26% of individuals with MCI are depressed (27), others report results as high as 63.3% of depressed individuals among the population suffering from MCI (28). Numerous studies indicate that there is a link between MCI and depression (27-32), but the timing of their occurrence, causality and underlying correlation mechanisms have not been sufficiently clarified. Brain imaging studies were mostly

hanizmi u osnovi međuodnosa nisu dovoljno razjašnjeni. Istraživanja oslikavanja mozga uglavnom su odvojeno ispitivala depresivne skupine (33-35) i one s BKP (36-37). Zajedničke strukturne promjene i za depresiju i za BKP su smanjenje volumena u brojnim moždanim regijama: insuli, gornjem temporalnom girusu, donjem frontalnom girusu, amigdali, hipokampusu i talamusu (38). Pretpostavlja se da je smanjenje volumena u insuli i gornjem temporalnom girusu odraz komunikacijskih deficita i deprivacije od kognitivno i socijalno-stimulirajućih aktivnosti, rizičnih čimbenika i za depresiju i za BKP. Depresivne osobe s BKP-om imaju abnormalnu moždanu aktivnost u odnosu na nedepresivne osobe s BKP-om (39). Moguće je da depresivni simptomi smanjuju kapacitet kognitivnog funkcioniranja i povećavaju rizik od razvoja BKP-a (40), ali i da BKP povećava rizik od depresivnih simptoma (41).

Slabo postignuće na kognitivnim testovima snažan je prediktor progresije BKP-a u AD, prema nekim istraživanjima snažniji i od biomarkera (42-44). Neuropsihologijska procjena važan je alat procjene BKP-a, a neki autori sugeriraju da može identificirati one koji će razviti BKP i prije pojave prvih simptoma (9).

Psihodijagnostika je grana kliničke psihologije koja se bavi praktičnim i metodološkim pitanjima dijagnostike i psihološke procjene (45). U kliničkoj psihologijskoj praksi koriste se intervju, dijagnostička opservacija, upitnici i projektivne tehnike sa svrhom dijagnostike uzroka poremećaja i preporuke tretmana (45). Razvijeni su i validirani psihologijski mjerni instrumenti za diferencijalnu dijagnostičku procjenu, te projektivne tehnike (46). Klinička neuropsihologija se bavi bihevioralnom ekspresijom disfunkcije mozga (47) koja se manifestira u tri funkcionalna sustava: kogniciji, emocijama i izvršnim funkcijama (47). Kognitivne funkcije Lezak (48) dijeli na receptivne funkcije, pamćenje i učenje, mišljenje i ekspresivne funkcije.

used to examine depressive groups (33-35) and those with MCI (36-37) separately. Common structural changes in both depression and MCI include reduced volume in various brain regions: insula, superior temporal gyrus, inferior frontal gyrus, amygdala, hippocampus and thalamus (38). It is assumed that volume reduction in the insula and superior temporal gyrus reflects communication deficits and deprivation of cognitively and socially stimulating activities, risk factors for both depression and MCI. Depressed individuals with MCI exhibit abnormal brain activity compared to non-depressed individuals with MCI (39). It is possible that depressive symptoms reduce cognitive functioning capacity and increase the risk of MCI (40), but also that MCI increases the risk of depressive symptoms (41).

Poor results on cognitive tests represent a strong predictor of MCI progression to AD, even stronger than biomarkers according to some studies (42-44). Neuropsychological assessment is an important tool for evaluating MCI, and some authors suggest that it can help identify those individuals who will develop MCI even before the appearance of the first symptoms (9).

Psychodiagnostics is a branch of clinical psychology that deals with practical and methodological issues concerning diagnostics and psychological assessment (45). In clinical psychological practice, interviews, diagnostic observation, questionnaires and projective techniques are used to diagnose the causes of disorders and recommend treatments (45). Psychometric instruments for differential diagnostic assessment and projective techniques have also been developed and validated (46). Clinical neuropsychology deals with the behavioral expression of brain dysfunction (47), which manifests in three functional systems: cognition, emotions, and executive functions (47). Lezak (48) divides cognitive functions into receptive functions, memory and learning, thinking and expressive functions.

Clinical neuropsychological assessment, rather than the sole results of neuropsychological tests,

Klinička neuropsihologijska procjena, a ne sami rezultati neuropsihologijskih testova, neophodna je za postavljanje dijagnoze BKP, jer se neuropsihologijski profili različitih poremećaja preklapaju, a postignuća na testovima ovise o brojnim čimbenicima koje kliničar uzima u obzir pri interpretaciji (9). Dijagnosticiranjem BPK-a otkrivaju se rana obilježja demencija i omogućuju potencijalno odgađanje progresije (49). Osobe s BKP-om vjerojatnije će razviti demenciju od osoba urednog kognitivnog funkcioniranja (10), a vjerojatnost raste ako se BKP javlja u komorbiditetu s depresijom (50). Osobe s komorbidnom depresijom i BKP u anamnezi čak su i po kognitivnom oporavku i remisiji depresije u većem riziku za razvoj demencije od depresivnih (51). Rizični i zaštitni čimbenici za BKP u osoba s depresijom malo su istraživani.

CILJ

Cilj ovog rada je dati pregled spoznaja o ulozi depresije u razvoju BKP-a:

1. Ustanoviti jesu li dosadašnja istraživanja pokazala povezanost depresije i incidencije BKP-a;
2. Saznati na koji se način u dosadašnjim istraživanjima depresija objašnjava kao rizični čimbenik za BKP;
3. Dati pregled do sada istraživanih rizičnih i zaštitnih čimbenika koji se nalaze u podlozi odnosa depresije i BKP-a.

METODE

Pretraživanjem elektronskih znanstvenih baza podataka *Pubmed, Web of Science, Science Direct, PsychInfo, Scopus* i OVID prikupljeni su radovi objavljeni zaključno s 9.5.2022, prema ključnim riječima: depresija, depresivni poremećaj, disruptivni poremećaj disregulacije raspoloženja, veliki depresivni poremećaj, velika depresija, velika depresivna epizoda, depresivna

is essential for diagnosing MCI because neuropsychological profiles of different disorders tend to overlap, and test scores depend on numerous factors that clinicians take into account when interpreting them (9). Diagnosing MCI reveals early signs of dementia and allows for potential delay in progression (49). Individuals with MCI are more likely to develop dementia than those with normal cognitive functioning (10), and the likelihood increases if MCI co-occurs with depression (50). Even in cognitive recovery and remission of depression, individuals with a history of comorbid depression and MCI are at a greater risk of developing dementia than those with depression alone (51). Risk and protective factors for MCI in individuals with depression have not been extensively researched.

OBJECTIVE

The objective of this paper is to provide an overview of the knowledge gained with regard to the role of depression in the development of MCI:

1. To determine whether previous research has shown a correlation between depression and the incidence of MCI.
2. To understand how depression is explained as a risk factor for MCI in previous research.
3. To provide an overview of the risk and protective factors underlying the connection between depression and MCI that have been researched so far.

METHODS

By reviewing the electronic scientific databases such as Pubmed, Web of Science, Science Direct, PsychInfo, Scopus and OVID, papers published up to May 9, 2022, were collected using the following keywords in English: depression, depressive disorder, disruptive mood dysregulation disorder, major depressive disorder, major depression, major depressive episode, depres-

epizoda, distimija, perzistentni depresivni poremećaj, premensturalni disforični poremećaj i blagi kognitivni poremećaj, na engleskom jeziku. Uključena su istraživanja koja su ispitivala povezanost depresivnih poremećaja, ali i (sub) kliničkih depresivnih simptoma s BKP-om. Termin depresija koristi se kao općeniti termin, a detaljnije će se opisati klinička skupina. S obzirom da je blagi neurokognitivni poremećaj usko povezan s BKP-om uključena su i istraživanja koja su ispitivala odnos blagog neurokognitivnog poremećaja i depresije. Zbog kliničke i metodološke heterogenosti nije provedena meta-analiza, već je prikazan pregledni članak narativne forme. Obuhvaćena su istraživanja na svim uzorcima neovisno o dobi, rodu, dobi javljanja i trajanju depresivnog poremećaja. Isključeni su radovi koji nisu na engleskom ili hrvatskom jeziku, studije slučaja, sekundarna istraživanja, radovi čije su metode saznavanja isključivo nepsihologijske obrade (slikovni prikazi mozga, biomarkeri), te istraživanja koja su ispitivala skupine osoba s komorbidnim poremećajima.

REZULTATI

Pretraživanjem baza podataka pronađeno je ukupno 12404 radova, od kojih je iz daljnje obrade uklonjen 4071 duplikat pa je u daljnju selekciju ušlo 8333 radova. Dio radova isključen je prema kriterijima nakon pregleda na razini naslova i sažetka, a dio nakon čitanja rada. U konačnici su odabrana 33 istraživanja.

Povezanost depresije i incidencije BKP

Značajna povezanost depresije s incidencijom BKP-a potvrđena je u većini longitudinalnih istraživanja koja su pratila depresivne osobe urednog kognitivnog funkcioniranja do BKP-a, u rasponu od OR =1,7, 95 %, CI, 1,1-2,8 do OR=16,16, 95 %, 1,12-2,32 (tablica 1).

sive episode, dysthymia, persistent depressive disorder, premenstrual dysphoric disorder and mild cognitive impairment. Studies that examined the connection of depressive disorders and (sub)clinical depressive symptoms with MCI were included. The term "depression" is used as a general term, and the clinical group will be described in more detail. Since mild neurocognitive impairment is closely associated with MCI, studies examining the connection between mild neurocognitive impairment and depression were also included. Due to clinical and methodological heterogeneity, a meta-analysis was not conducted and a narrative review article was presented instead. Studies that covered all samples regardless of age, gender, age of onset and duration of depressive disorder were included. Studies not published in English or Croatian, case studies, secondary research, studies with exclusively non-psychological methods (brain imaging, biomarkers), and studies that examined groups with comorbid disorders were excluded.

RESULTS

A total of 12,404 papers were found through database searches, of which 4,071 duplicates were removed, leaving 8,333 papers available for further selection. Some papers were excluded based on criteria after reviewing their titles and abstract reviews, while others were excluded after reading the full text. In the end, 33 studies were selected.

Connection between depression and the incidence of MCI

A significant connection between depression and the incidence of MCI was confirmed in most longitudinal studies that monitored individuals with depression and normal cognitive functioning to MCI, with odds ratios ranging from 1.7 (95% CI, 1.1-2.8) to 16.16 (95% CI, 1.12-2.32) (Table 1). Out of the 33 studies that

TABLICA 1. Pregled istraživanja longitudinalnog nacrta koja su ispitivala kognitivno funkcioniranje depresivnih osoba
TABLE 1. A review of longitudinal design studies investigating the cognitive functioning of individuals with depression

Prezime autora i godina istraživanja / Author's surname and year of research	Uzorak / Sample	Interval praćenja / Monitoring interval Kontrola A) AD patologije B) vaskularnih rizičnih čimbenika C) gena / Control variable A) AD pathology B) vascular risk factors C) genes	Procjena depresije / Assessment of depression	Procjena BKP-a / Assessment of MCI	Rezultati Prevalencija BKP-a Povezanost depresije i BKP / Results Prevalence of MCI Connection between depression and MCI	Mehanizam u osnovi povezanosti depresije i BKP-a / The mechanism underlying the connection between depression and MCI				
						Različiti meh. rane i kasne depresije / Different mechanisms of early and late depression	Depresija kao rizični čimbenik BKP-a / Depression as a risk factor for MCI	Vaskularne lezije i depresija / Vascular lesions and depression	DEP I BKP posljedica AD patologije / Depression and MCI consequence of AD pathology	Genetska povezanost / Genetic link	DEP i BKP nisu povezani / Depression and MCI are not connected
Adler, Chwalek, & Jajcevic, (2004); (96)	N=27, M dobi ± SD: 73,4 ± 6.5 g). >60 g pacijenata gerontopsihijatrijske klinike s dg. depresivnog poremećaja (MKB-10), N (DEP+BKP)=15 N(DEP)=12 / N=27, M age ± SD: 73.4 ± 6.5 y. >60 y patients of gerontho-psychiatric clinic with diagnosed depressive disorder (ICD-10), N(DEP+MCI)=15 N(DEP)=12	6 mj.; uredne rutinske lab.pretrage, EKG, EEG i CT ili MRI bez psihotropnih lijekova posljednji tjedan, bez komorbiditeta / 6 months; regular routine lab tests, EKG, EEG, and CT or MRI without psychotropic drugs in the last week, without comorbidities	Hamiltonova ljestvica depresije (HAM-D) / Hamilton depression rating scale (HAM-D)	Strukturirani intervju za dijagnozu demencije Alzheimerovog tipa, multiinfarktnu demenciju i druge demencije prema MKB-10 i DSM-III-R (SIDAM), Barthelov indeks i Ljestvica instrumentalnih aktivnosti IADL, <46 bodova na Strukturiranom intervjuu SISCO / SIDAM – Structured Interview for the diagnosis of Dementia of the Alzheimer type, Multi-infarct dementia and dementias of other aetiology according to ICD-10 and DSM-III-R (SIDAM), Barthel index, The Lawton instrumental activities of daily living (IADL) scale, <46 points on Structured Interview SISCO	Od 15 pacijenata s BKP-om u inicijalnoj procjeni, 12 ima i nakon 6 mjeseci. Svih 12 urednog kognitivnog funkcioniranja nakon 6 mjeseci ima uredno kognitivno funkcioniranje. Oporavak kognitivnog funkcioniranje može trajati dulje nego oporavak od depresije. Nije ustanovljena povezanost težine depresije i BKP, niti povezanost težine depresije i remisije od BKP-a. / Out of 15 patients initially assessed with MCI, 12 still have MCI after 6 months. All 12 of these patients with normal cognitive functioning, after 6 months still have normal cognitive functioning. Recovery of cognitive functioning may take longer than recovery from depression. There is no established connection between the severity of depression and MCI, or between the severity of depression and remission from MCI.						✓
Almeida et al. (2016); (29)	Kohortno istraživanje, N=3113 muškaraca , M dobi=77.1 ± 3.6 g, 3 skupine: uredno kognitivno funkcioniranje (UKF), BKP, DEM / A cohort study, N=3113 men, M age=77.1 ± 3.6 y, 3 groups: normal cognitive functioning (NCF), MCI, DEM	5 godina, / 5 years,	Gerijatrijska ljestvica depresije (GDS) ≥7 / Geriatric Depression Scale (GDS) ≥7	≥24 bodova na MMSE; TICS (Telefonski intervjuu kognitivnog statusa, Knopman i sur., 2010), 27-31 bodova / ≥24 points on MMSE; TICS (Telephone Interview for Cognitive Status , Knopman et al.., 2010), scores amount to 27-31	11,6 % sudionika je razvilo BKP. Aktualni klin. znač. depr. simptomi povezani su s pov. rizikom od BKP-a (RR = 2,59, 95 % CI = 1,57–4,27) . Povijest klinički značajnih depresivnih simptoma u anamnezi nije povezana s povećanim rizikom od javljanja BKP-a. / 11.6% of participants developed MCI. Current clinically significant depressive symptoms are associated with an increased risk of MCI (RR = 2.59, 95% CI = 1.57–4.27). A history of clinically significant depressive symptoms in the anamnesis is not associated with an increased risk of MCI.	✓	**X**				
Barnes et al. (2006), (27)	Populacijsko prospektivno istraživanje, sudionici *the Cardiovascular Health Study Cognition Study;* N(UKF)=2220 M= 74 godine / Population Prospective Study,*the Cardiovascular Health Study Cognition Study participants;* N(NCF)=2220 M= 74 y	6 godina, B / 6 years, B	Ljestvica depresije Centra za epidemiološke studije (CES-D); 3-7 blagi, >=8 umjereni i teški dep. simptomi. / Center for Epidemiologic Studies Depression Scale (CES-D); 3-7 mild, >=8 moderate and severe depressive symptoms	Pojedinci koji nisu zadovoljili kriterije za demenciju ali imaju deficit kognitivnih funkcija u odnosu na prvo mjerenje Neuropsihologijka baterija / Individuals who do not meet the criteria for dementia but have cognitive function deficits compared to the initial neuropsychological assessment battery	13 % sudionika je razvilo BKP. Depresivni simptomi u prvoj točki mjerenja povezani su s povećanim rizikom od BKP-a (10,0 %, 13,3 %, and 19,7 %, za one bez depresivnih simptoma, s blagim, odnosno umjerenim ili teškim depresivnim simptomima). Vaskularna bolest i depresija su međusobno neovisni rizični čimbenici za BKP. / 13% of participants developed MCI. Depressive symptoms at the first measurement point are associated with an increased risk of MCI (10.0%, 13.3%, and 19.7% for those without depressive symptoms, with mild or with moderate to severe depressive symptoms, respectively). Vascular disease and depression are muutally independent risk factors for MCI.		**?**	**X**	**?**		

Bhattarai, Oehlert, Multon, i Sumerall, (2019) (130)	Retrospektivno kohortno istraživanje N=800 ratnih veterana s prosjekom dobi 64,57 godina (SD = 2,58) / Retrospective cohort study N=800 war veterans, M age= 64.57 y (SD = 2.58)		Dijagnoza MKB-9 preuzeta iz med. dokumentacije / ICD-9 diagnosis taken from medical documentation	Dijagnoza MKB-9 / ICD-9 diagnosis	7 % sudionika je dijagnosticirano demencijom ili drugom formom kognitivnog oštećenja / 7% of participants diagnosed with dementia or another form of cognitive impairment.	✓		
Burhanullah etl al. (2020), (97)	Populacijsko istraživanje N (UKF)= 470 65 godina i stariji / Population study N (NCF)= 470 65 years and older	M=5,73 godine / M=5.73 y	Inventar neuropsihijatrijskih simptoma (NPI). /The Neuropsychiatric Inventory, NPI.	Modificirani upitnik mini mental statusa (3MS) ili Upitnik kognitivnog propadanja za informanta, kognitivni testovi / Modified Mini-Mental State Test (3MS) or Cognitive Decline Questionnaire for Informants and cognitive tests	Ukupno opterećenje NPS-om bilo je povezano s longitudinalnim kognitivnim padom. Rezultat na NPI-**depresija nije bio** povezan s longitudinalnim padom ni na jednoj mjeri ishoda. /The total burden of NPS (Neuropsychiatric Symptoms) was associated with longitudinal cognitive decline. However, the score on the NPI-depression scale was not associated with longitudinal decline on any outcome measure.			✓
Chan et al. (2020), (87)	Populacijsko istraživanje, podaci derivirani iz BIOCARD studije; N (UKF)=216, M dobi = 57 godina / Population study, data derived from BIOCARD study; N (NCF)=216, M age= 57 y	20 godina, M= 12.7 godina, A analiza biomarkera AD (beta,(Aβ)1-42) , t-tau, and p-tau) iz cerebrospinalne tekućine / 20 y M= 12.7 y A Analysis of AD biomarkers (beta,(Aβ1-42), t-tau, and p-tau) in cerebrospinal fluid	Hamilton ljestvica depresije (HMD);>7 bodova, kao kontinuirana i dihotomizirana varijabla / Hamilton Depression Rating Scale, HMD;>7 points, as continuous and dichotomous variable	Smjernice Američkog nacionalnog instituta za starenje i Elzhemerovu bolest (NIA-AA) kognitivni pad u odnosu na prvo mjerenje na CDR i neuropsihologijskim testovima / Guidelines of the National Institute on Aging and the Alzheimer's Association (NIA-AA), cognitive decline compared to the first measurement on the Clinical Dementia Rating scale (CDR) and neuropsychological tests	Interakcija depresivnih simptoma i markera AD patologije: depresija je povezana s vremenom javljanja BKP-a kod pojedinaca s nisko zastupljenom AD patologijom (HR= 0,64; 95 %, 0,43–0,95; P= .026). / Interaction of depressive symptoms and AD pathology markers: Depression is associated with the time of onset of MCI in individuals with low burden of AD pathology (HR= 0.64 ; 95% CI 0.43–0.95; P= .026).	✓	X	
Chan et al. (2019), (86).	Populacijsko istraživanje, podaci derivirani iz *BIOCARD studije;* N(KF)=300 M dobi= 57,4 godina / Population study, BIOCARD study data; N(NCF)=300 M age= 57.4 y	20 godina, M= 2,5 godina A / 20 years, M= 2.5 y A	HMD>7 bodova, kao kontinuirana i dihotomizirana varijabla / HMD>7 points, as continuous and dichotomous variable	NIA-AA (Albert i sur., 2011), Klinička ljestvica za procjenu demencije (CDR). / NIA-AA (Albert i sur., 2011), Clinical Dementia Rating (CDR) Scale	23 % sudionika razvilo je BKP. Blagi depresivni simptomi prediktivni su za BKP unutar 7 godina (p = 0.043). Depresivni simptomi ne povećavaju rizik od BKP-a nakon 7 godina. Depresivni simptomi u srednjoj i starijoj dobi rizičan su čimbenik za BKP zbog AD patologije. / 23% of participants developed MCI. Mild depressive symptoms are predictive of MCI within 7 years (p = 0.043). Depressive symptoms do not increase the risk of MCI after 7 years. Depressive symptoms in middle and older age are a risk factor for MCI due to AD pathology.	✓	✓	
Dean et al. (2014), (77)	Populacijsko prospektivno istraživanje *The Oxford Project to Investigate Memory and Ageing (OPTIMA)* N(UKF)=126 / Population prospective study*The Oxford Project to Investigate Memory and Ageing (OPTIMA)* N(NCF)=126	20 godina; A / 20 years A	GDS 0-10 nema depresije; 11-20, blaga depresija; 21-30 teška depresija / GDS 0-10 no depression, 11-20 mild depression; 21-30 severe depression	Petersenovi kriteriji, Cambridgeova procjena poremećaja starijih (CAMDEX): Cambridgeova kognitivna procjena (CAMCOG, <13 bodova), MMSE > ili = 24 ; uredno adaptivno funkcioniranje / Petersen criteria, the Cambridge Examination for Disorders of the Elderly (CAMDEX): the Cambridge Cognitive Examination (CAMCOG, <13 points), MMSE > or = 24; normal adaptive functioning	39,7 % (N=50) razvilo BKP tijekom praćenja; Depresivni simptomi predvidjeli su vrijeme potrebno za BKP kod nenositelja APOE ε4; 1 SD porast depresivnih simptoma smanjuje vrijeme do BKP za 25,4 % (p = .0024, z = -5.6). / 39.7% (N=50) developed MCI during the follow-up period; Depressive symptoms predicted the time required for MCI in non-carriers of APOE ε4: A 1-standard deviation increase in depressive symptoms reduces the period to MCI by 25.4% (p = .0024, z = -5.6)	✓	X	

Dotson, Beydoun, i Zonderman, (2010), (76).	Prospektivno istraživanje, dio *the Baltimore Longitudinal Study of Aging (BLSA)*, N(UKF)= 1,239 (M dobi=55,5+- 18,8 g); / Prospective study, part of *the Baltimore Longitudinal Study of Aging (BLSA)*, N(NCF)= 1.239 (M age=55.5+- 18.8 y);	M= 23,0 godina, maksimalno 51 godina B / M= 23.0 years, max 51 y B	CES-D, >16 bodova. Upitnik broja i ozbiljnosti depresivnih epizoda u posljednjem tjednu / CES-D, >16 points. Questionnaire about the number and severity of depressive episodes in the last week.	Petersenovi kriteriji (Petersen, 2014); kognitivni pad u odnosu na prvo mjerenje na CDR / Petersen criteria (Petersen, 2014); Cognitive decline compared to the first measurement on CDR	7, 1 % (N=88) sudionika je razvilo BKP. Svaka depresivna epizoda povezana je s 14 % porasta rizika od demencije, ali ne i od BKP-a, HR (95 % CI) 1,02 (0,85–1,23) p=.811 / 7.1% (N=88) of participants developed MCI. Each depressive episode is associated with a 14% increase in the risk of dementia, but not of MCI, HR (95% CI) 1.02 (0.85–1.23), p=.811.					✓
Feng et al. (2017), (78).	Dio epidemiološkog istraživanja *the Singapore Longitudinal Aging Study (SLAS)* N=889, starost >55 godina / Part of epidemiological study - *the Singapore Longitudinal Aging Study (SLAS)* N=889, age >55 y	M = 45, 36 mjeseci (SD = 5.52). A (APOE genotip) B / M = 45.36 months (SD = 5.52). A (APOE genotype) B	GDS-15, >5 bodova / GDS-15, >5 points	Mini mental status test (MMSE), Montrealova ljestvica kognitivne procjene (MoCA); CDR = 0.5 / Mini mental status Exam (MME), the Montreal Cognitive Assessment (MoCA); CDR = 0.5	6,6 % sudionika je razvilo BKP. Depresivni simptomi povećali su vjerojatnost razvoja BKP-a neovisno o drugim poznatim rizičnim čimbenicima (dobi, stupnju obrazovanja, rodu, hipertenziji, DM, APOE genotipu): OR=2,56, 95 %, CI 1,17-5,60 / 6,6% developed MCI. Depressive symptoms increased the likelihood of developing MCI independently of other known risk factors (age, education level, gender, hypertension, diabetes mellitus, APOE genotype): OR=2.56, 95% CI 1.17-5.60.		✓	X	X	
Freire, Pondé, Liu, i Caron, (2017), (53).	Populacijsko prospektivno istraživanje , dio *the Montreal PopulationBased Epidemiological Study on Mental Health*. N= 352; M=60 + 3.16 godina / Population prospective study, part of *the Montreal Population Based Epidemiological Study on Mental Health*. N= 352; M=60 + 3.16 y	2 godine / 2 years	Kompozitni dijagnostički intervju (CIDI); Kesslerova ljestvica psihološkog distresa (K10) >9 ; Ljestvica Upravljanja stresom (CCHS 1.2). / Composite diagnostic interview (CIDI); the Kessler psychological distress scale (K10) >9 ; Stress menagement scale (CCHS 1.2).	MOCA	Nije pronađena povezanost depresije i kognitivnog oštećenja. / No connection was found between depression and cognitive impairment.					✓
Geda et al. (2014), (79).	N(UKF)= 1587 M dobi = 79.3 g(70.5-91) / N(NCF)= 1587 M age = 79.3 y (70.5-91)	Longitudinalni nacrt, praćeni do pojave BKP, M=5 g / Longitudinal design, monitored until the occurrence of MCI, M=5 years	NPI	Petersen i sur. (2004), tim stručnjaka / Petersen et al. (2004), team of experts	8,86 % razvilo BKP. Depresija je značajno povezana s incidencijom amnestičkog BKP-a (HR=1,63; 95 % CI=1,23–2,16), pri čemu je značajno povezana s incidencijom amnestičkog BKP (HR=1,74; 95 % CI=1,22–,.47), ali i drugi neuropsihijatrijski simptomi imaju jednaku ili i veću povezanost s incidencijom BKP: agitacija (HR=3,06; 95 % CI=1,89–4,93), apatija (HR=2,26; 95 % CI=1,49–3,41) , anksioznost (HR=1,87; 9 5% CI=1,28–2,73), iritabilnost (HR=1,84; 95 % CI=1.31–2,58). Euforija, dizinhibicija i smetnje spavanja povezani ss s incidencijom neamnestičkog BKP-a, a nisu povezani s incidencijom amnestičkog BKP-a. / 8.86% developed MCI. Depression is significantly associated with the incidence of amnestic MCI (HR=1.63; 95% CI=1.23–2.16), while it is also significantly associated with the incidence of amnestic MCI (HR=1.74; 95% CI=1.22–2.47). However, other neuropsychiatric symptoms have equal or greater connection with the incidence of MCI: agitation (HR=3.06; 95% CI=1.89–4.93), apathy (HR=2.26; 95% CI=1.49–3.41), anxiety (HR=1.87; 95% CI=1.28–2.73), irritability (HR=1.84; 95% CI=1.31–2.58). Euphoria, disinhibition, and sleep disturbances are associated with the incidence of non-amnestic MCI but not with the incidence of amnestic MCI.	?	?	?	?	

Goveas et al. (2011), (32)	prospektivno kohortno istraživanje (WHIMS); N(UKF)=6376 žena u menopauzi / Prospective cohort study (WHIMS); N(NCF)=6376 women in menopause	M= 5.4 godine (SD=1.6) B / M= 5.4 y (SD=1.6) B	Burnamov algoritam, CES-D Dijagnostički interviju nacionalnog instituta mentalnog zdravlja (DIS)- 2 čestice / Burnam algorithm, CES-D Diagnostic interview of NIMH (DIS) – 2 items	Petersenovi kriteriji (1992), Konzorcij za uspostavu registra za Alzheimerovu demenciju (CERAD) Modificirani MMSE (3 MS) / Petersen criteria (1992). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) The Modified Mini-Mental State Exam (MMSE) 3MS	Depresivni simptomi povezani su s povećanim rizikom od BKP (HR, 1,98; 95 %, 1,33–2,94). Depresivne sudionice imaju približno dvostruko veći rizik razvoja BKP ili demencije u odnosu na nedepresivne. Nedepresivne žene s depresijom u ranoj anamnezi imaju povećan rizik od demencije (HR=2,08; 95 % CI 1,15–3,78, p=0,02), ali ne i BKP (HR=1,03; 95 % CI 0,66–1,63, p=0,89). / Depressive symptoms are associated with an increased risk of MCI (HR, 1,98; 95%, 1,33–2,94). Depressive participants have approximately twice the risk of developing MCI or dementia compared to non-depressive participants. Non-depressive women with an early history of depression have an increased risk of dementia (HR=2,08; 95% CI 1,15–3,78, p=.02) but not of MCI (HR=1.03; 95% CI 0,66–1.63, p=.89).	?	X	?
Goveas, et al. (2012), (93).	prospektivno istraživanje (WHIMS); N=6998 žena u postmenopauzi raspoređenih po slučaju u eksperimentalnu skupinu hormonalne terapije i placebo skupinu, 65–79 g / Prospective study (WHIMS); N=6998 postmenopausal women randomly assigned to experimental group of hormonal therapy and placebo group 65–79 y	M= 7.5 godina / M= 7.5 y	Burnam algoritam CES-D (6 čestica) (DIS)- 2 čestice / Burnam algorithm CES-D (6 items), (DIS) – 2 items	Petersenovi kriteriji (1992) loš uspjeh na CERAD bateriji, uz očuvano svakodnevno funkcioniranje; Modificirani MMSE (3 MS) / Petersen criteria (1992) low performance on CERAD battery, with preserved everyday functioning; The Modified Mini-Mental State Exam (MMSE) 3MS	4,7 % žena (N=331) je razvilo BKP Uzimanje antidepresiva (SIPPS-i i triciklički antidepresivi) povezano je sa 70 % povećanog rizika od BKP-a (SIPPS;(HR), 1,78 [95 % CI, 1,01–3,13]; TCA: HR, 1,78 [95 % CI, 0,99–3,21]). Depresivni na antidepresivima (HR, 2,44 [95 % CI, 1,24–4,80]), nedepresivni na antidepresivima (HR, 1,79 (95 % CI, 1,13–2,85]) i depresivni koji ne uzimaju antidepresive (HR, 1.62 [95 % CI, 1,13–2,32]) imaju povećani rizik od BKP-a. / 4.7% of women (N=331) developed MCI. Taking antidepressants (SSRIs and tricyclic antidepressants) is associated with a 70% increased risk of MCI (SSRIs: HR 1.78 [95% CI, 1.01–3.13]; TCAs: HR 1.78 [95% CI, 0.99–3.21]). Depressive individuals on antidepressants (HR 2.44 [95 % CI, 1.24–4.80]), non-depressive individuals on antidepressants (HR 1.79 [95% CI, 1.13–2.85]), and depressive individuals not taking antidepressants (HR 1.62 [95% CI, 1.13–2.32]) have an increased risk of MCI.	✓		
Köhler, Thomas, Barnett, i O'Brien (2010), (73)	klinička skupina N(UKF)=67 sudionika s dg. velikog depresivnog poremećaja pacijenata dnevne psihijatrijske bolnice N(kontrolna)= 36; > 60 godina / Clinical group N(NCF)=67 participants of the day psychiatric hospital diagnosed with major depressive disorder N(control)= 36; > 60 y	Mjerenja 6 mjeseci, 18 mjeseci i 4 godine nakon prvog: bez somatskog komorbiditeta / Controls 6 months, 18 months and 4 years after first trial: without somatic comorbidities	DSM-IV (APA, 1994); Montgomeryjeva ljestvica za procjenu depresije (MADRS). / DSM-IV (APA, 1994); the Montgomery-Asberg Depression Rating Scale (MADRS)	Petersen i sur., 1999) > 1,5 SD na CAMCOG-u; <75 bodova (klinička) ili <80 (kontrolna). / Petersen et al., 1999) > 1.5 SD on CAMCOG <75 points (patients) or <80 points (control group).	Polovica sudionika razvila je BKP. Kognitivni deficiti persistiraju barem 4 godine nakon liječenja depresije. Početak depresije u starijoj životnoj dobi povezan je s izraženijim deficitima pamćenja i izvršnih funkcija. / Half of the participants developed MCI. Cognitive deficits persist for at least 4 years after the treatment of depression. Onset of depression in older age is associated with more pronounced memory and executive function deficits.	✓		
Köhler et al. (2010), (74)	Prospektivno kohortno istraživanje, dio *The Maastricht Ageing Study (MAAS)*; N(UKF)= 412 M (dob)= 69,4 (60,0–82,7) / Prospective cohort study, part of *The Maastricht Ageing Study (MAAS)*; N(NCF)= 412 M (age)= 69.4 (60.0–82.7)	6 godina A (APOE) / 6 years A (APOE)	Revidirana forma upitnika za depresivne simptome (SCL-90) 16-80 bodova; 4 kategorije sudionika po intenzitetu / Revised questionnaire for depressive symptoms (Symptom Checklist- SCL-90) 16-80 points, 4 categories of participants according to severity	CIND: rezultat <1,5 SD ispod norme testovima, rezultat 24 ili više na MMSE Neuropsihologijska procjena / CIND: result <1.5 SD below test norm, score 24 or higher at MMSE Neuropsychological assessment	Povezanost depresivnih simptoma i CIND (kognitivnog oštećenja, bez demencije) najvećaa je za one s perzistirajućim depresivnim simptomima (definiranim kao prisutni u inicijalnom mjerenju i barem jednom novom mjerenju). OR 1,00, 0,87, 0,69, i 2,98 za 4 grupe depresivnih simptoma (P=.05). Depresija i genotip APOE neovisno povećavaju rizik kognitivnog oštećenja. /The connection between depressive symptoms and CIND (Cognitive Impairment, No Dementia) is the highest for those with persistent depressive symptoms (defined as present at the initial assessment and at least one subsequent assessment). The odds ratios (OR) are 1.00, 0.87, 0.69, and 2.98 for the four groups of depressive symptoms (P=.05). Depression and APOE genotype independently increase the risk of cognitive impairment.	✓	X	

Krell-Roesch et al. (2021), (85)	Prospektivno kohortno istraživanje, dio *Mayo Clinic Study of Aging (MCSA)*; N(UKF)=3083 , M= 72,41 godina (SD= 9,72) / Prospective cohort study, part of *Mayo Clinic Study of Aging (MCSA)*; N(NCF)=3083 , M= 72.41 y (SD= 9.72)	M= 6,3 godine , A (apolipoprotein E (APOE) ε4 genotip) / M= 6.3 y A (apolipoprotein E (APOE) ε4 genotype)	NPI-Q Beckov inventar depresije (BDI–II) / NPI-Q Beck's Depression Inventory (BDI–II)	Revidirani kriteriji Mayo Clinic (Petersen, 2004; Winblad et al., 2004) Neuropsihologijska procjena / Mayo Clinic revised criteria (Petersen, 2004; Winblad et al., 2004) Neuropsychological assessment	19,4 % je razvilo BKP. Sinergistička aditivna interakcija nedostatka tjelesne aktivnosti i poteškoća spavanja (HR [95 % CI], 1,61 [1,07, 2,43]; p = .021), kliničke depresije (1,98 [1,34, 2,92]; p < .001) i klinički značajne anksioznosti (1,63 [1,11, 2,41]; p = .013), povezana je s povećanim rizikom od BKP-a. / 19.4% developed MCI. A synergistic additive interaction between lack of physical activity and sleep difficulties (HR [95% CI], 1.61 [1.07, 2.43]; p = .021), clinical depression (1.98 [1.34, 2.92]; p < .001), and clinically significant anxiety (1.63 [1.11, 2.41]; p = .013) is associated with an increased risk of MCI.	?	?	?		
Li, Meyer, i Thornby, (2001), (131).	Prospektivno istraživanje, N=250; N(UKF) =146 n (BKP)=19 n(demencija Alzheimerovog tipa DAT)=42 N(demencija vaskularnog tipa,VAD)=32 / Prospective study N=250; N(NCF) =146 n (MCI)=19 n(Dementia of the Alzheimer type DAT)=42 N(Vascular dementia, VAD)=32	M= 3,5 godina, / M= 3.5 y	HAM-D, >7 klinički značajni depresivni simptomi, grupirani u probleme sa spavanjem, i u depresivne probleme koji su povezani s motivacijom. / HAM-D, >7 Clinically significant depressive symptoms grouped into issues with sleep and depressive problems associated with motivation.	Petersen kriteriji, DSM-III / Petersen criteria, DSM-III	57,1 % je razvilo BKP VAD imaju najveću incidenciju javljanja novih depresivnih epizoda, a slijede ih osobe s DAT i BKP. Depresivni simptomi kod osoba s VAD-om i BKP-om su više perzistirajući i refraktorniji na antidepresive od pacijenata s DAT-om. Depresivni simptomi kod osoba s DAT-om su imali više spontanih remisija, bez potrebe za intenzivnim psihofarmacima. / 57,1% developed MCI. Individuals with VAD have the highest incidence of new depressive episodes, followed by individuals with DAT and MCI. Depressive symptoms in individuals with VAD and MCI are more persistent and refractory to antidepressants compared to patients with DAT. Depressive symptoms in individuals with DAT had more spontaneous remissions, without the need for intensive psychopharmacological treatment.		✓	✓		
Panza, et al. (2009), (84).	Podaci iz *the Italian Longitudinal Study on Aging*, N(UKF)= 2963 M (dob) = 71,9 (5,1) g / Data from *the Italian Longitudinal Study on Aging*, N(NCF)= 2963 M (age) = 71.9 (5.1) y	3,5g A / 3.5g A	GDS-30, 10-19 blaga depresija; 20-30 teška depresija / GDS-30, 10-19 mild depression; 20-30 severe depression	Modificirani Petersenovi kriteriji (subjektivne mnestičke smetnje nisu kriterij), MMSE; Epizodičko pamćenje: IADL / Modified Petersen criteria (subjective mnestic complaints are not a criterion) MMSE; Episodic memory: IADL	Depresivni simptomi u prvoj točki mjerenja su povezani s ubrzanim padom globalnog kognitivnog funkcioniranja i ubrzanim padom epizodičkog pamćenja, ali porast intenziteta depresivnih simptoma tijekom praćenja nije povezan s kognitivnim funkcioniranjem. Depresivni simptomi na početku predviđaju kognitivno oštećenje; dok kognitivno funkcioniranje na početku nije prediktivno za tijek depresivnih simptoma. Depresija s visokom razinom amiloida β (Aβ) 40:Aβ42, je povezana svećim oštećenjem pamćenjam, vizuospacijalnih sposobnosti i izvršnih funkcija, i moguća prodromalna manifestacija AD-a. / Depressive symptoms at the first measurement point are associated with a rapid decline in global cognitive functioning and a rapid decline in episodic memory, but an increase in the intensity of depressive symptoms during follow-up is not linked to cognitive functioning. Depressive symptoms at the beginning predict cognitive impairment, while cognitive functioning at the beginning is not predictive of the course of depressive symptoms. Depression with a high level of amyloid β (Aβ) 40:Aβ42 is associated with more significant impairment in memory, visuospatial abilities, and executive functions, and it may be a possible prodromal manifestation of Alzheimer's disease (AD).			✓		
Panza, et al. (2008), (90).	Prospektivno kohortno istraživanje, dio *the Italian Longitudinal Study on Aging*, N=2963, dob 65,84 g / Prospective cohort study, part of *the Italian Longitudinal Study on Aging*, N=2963, age 65.84 y	3,5 godine, B / 3.5 y, B	GDS-30, 10-19 blaga depresija; 20-30 teška depresija, dihotomizirana 10-30 bodova značajni depresivni simptomi, <10 bez značajnih depresivnih simptoma / GDS-30, 10-19 mild depression, 20-30 severe depression, dichotomised 10-30 points significant depressive symptoms, <10 no significant depressive symptoms	Modificirani Petersenovi kriteriji (subjektivne mnestičke smetnje nisu kriterij te su uključeni oni s nekognitivnih funkcionalnim oštećenjima), MMSE; Epizodičko pamćenje, IADL / Modified Petersen criteria (subjective mnestic complaints are not a criterion, and individuals with non-cognitive functional impairments are included), MMSE, episodic memory, IADL	8,23 % je razvilo BKP. Depresivni simptomi nisu povezani s incidencijom BKP-a. Sociodemografski i vaskularni čimbenici nisu modificirali odnos BKP-a i depresivnih simptoma. / 8.23% developed MCI. Depressive symptoms are not associated with the incidence of MCI. Sociodemographic and vascular factors did not modify the connection between MCI and depressive symptoms.		X		✓	

Pink et al. (2021), (54)	Prospektivno kohortno istraživanje, dio *Mayo Clinic Study of Aging (MCSA)*, N(UKF)=1440 M= 72,41 godina (SD= 9,72) / Prospective cohort study, part of *Mayo Clinic Study of Aging (MCSA)*, N(NCF)=1440 M= 72.41 y (SD= 9.72)	M= 5,5 godina A / M= 5.5 y A	BDI-II (≥13 klinička depresija) / BDI-II (≥13 clinical depression)	Revidirani kriteriji Mayo Clinic: (1) kognitivne smetnje (2) oštećenje 1 li više kognitivnih funkcija (3) uredno svakodnevno funkcioniranje 4) odsutnost demencije, CDR,Neuropsihologijska procjena / Mayo Clinic revised criteria: (1) cognitive complaints (2) damage to 1 or more cognitive functions (3) regular everyday functioning (4) absence of dementia, CDR,Neuropsychological assesssment	Kortikalno taloženje Aβ (PiB+) neovisno o depresiji je povećalo rizik od BKP-a. Postoji aditivna interakcija (PiB+) i anksioznosti, ali ne i depresivnosti. / Cortical Aβ deposition (PiB+) independent of depression increased the risk of MCI. There is an additive interaction of (PiB+) and anxiety, but not depression.			X	✓
Potvin et al. (2011), (89)	Prospektivno kohortno istraživanje, podaci iz *Enquˆete sur la santeˆ des aiˆne´s (ESA Study on Older Adults' Health), N(UKF)=1942 (MMSE >22), 65-96g* / Prospective cohort study, data from *Enquˆete sur la santeˆ des aiˆne´s (ESA Study on Older Adults' Health), N(NCF)=1942 (MMSE >22), 65-96y*	12 mjeseci (M= 12.5; SD= 1,4). B / 12 months (M= 12.5; SD= 1.4). B	Računalni upitnik (ESA-Q): pitanja bazirana na DSM-IV / Computerized questionnaire,(ESA-Q): questions based on DSM-IV	MMSE barem 2 boda ispod inicijalnog rezultata i 15. percentila ispod norme:a) amnestički BKP ukoliko je zbroj bodova na zadatku dosjećanja 3 riječi 0 ili 1; b) neamnestički: deficit izvan zadatka dosjećanja 3 riječi / MMSE: at least 2 points below the initial score and 15th percentile below the norm:a) Amnestic MCI if the sum of points on the three-words recall task is 0 or 1; b) Non-amnestic: Deficit outside the three- words recall task.	Incidencija BKP-a je neovisno o depresiji povezana s anksioznim poremećajem tijekom inicijalne procjene u muškaraca i anksioznih simptoma u žena. Depresivni poremećaji u muškaraca (OR=8,87, 95 %=2,13-36,96) i anksiozni simptomi u žena povezani su s incidencijom amnestičkog BKP, dok su anksiozni poremećaji u muškaraca povezani s incidencijom neamnestičkog BKP-a. / The incidence of MCI, independent of depression, is associated with anxiety disorder during the initial assessment in men and with anxiety symptoms in women. Depressive disorders in men (OR=8.87, 95% CI=2.13-36.96) and anxiety symptoms in women are associated with the incidence of amnestic MCI, while anxiety disorders in men are associated with the incidence of non-amnestic MCI	?	?	?	?	
Richard et al. (2013), (103)	Prospektivno populacijsko kohortno, dio *theWashington Heights– Inwood Columbia Aging Project (WHICAP)*, N= 1156, 65-74 g / Prospective population cohort study, part of *the Washington Heights– Inwood Columbia Aging Project (WHICAP)*, N= 1156, 65-74 y	M=5.4 godine, 1,1-10,1 godine / M=5.4 y, 1.1-10.1 y	CES-D – 10, ≥ 4	Petersenovi kriteriji / Petersen criteria	26,2 % razvilo BKP, 49,7 % (N=151) sudionika razvilo je amnestički BKP, i 50,3 % (N=153). Depresija nije povezana s incidencijom BKP-a niti podtipova BKP-a. / 26.2% developed MCI, 49.7% (N=151) of participants developed amnestic MCI, and 50.3% (N=153). Depression was not associated with the incidence of MCI or MCI subtypes.				✓
Spira et al. (2012), (83)	Prospektivno istraživanje, *the Study of Osteoporotic Fractures (SOF)*, N(UKF)=302, M dobi = 86,9 ± 2,1 / Prospective study, *the Study of Osteoporotic Fractures (SOF)*, N(NCF)=302, M age = 86.9 ± 2.1	5 godina / 5 y	GDS; >6 bodova / GDS; >6 points	Modificirani Petersenovi kriteriji; MMSE, neuropsihologijska procjena / Modified Petersen criteria; MMSE, neuropsychological assessment	70 % depresivnih razvilo BKP, u usporedbi s 37 % nedepresivnih Izraženi depresivni simptomi, su povezani s 3,7 puta većom vjerojatnošću od razvoja BKP-a tijekom naredni pet godina (odnosno više od 70 % smanjene vjerojatnosti urednog kognitivnog funkcioniranja u idućih 5 g). / 70% of those with depression developed MCI, compared to 37% of those without depression Significant depressive symptoms are associated with a 3.7 times higher likelihood of developing MCI over the next five years (i.e., more than a 70% reduction in the likelihood of normal cognitive functioning over the next 5 years).		?	?	

Stepaniuk, Ritchie, i Tuokko (2008), (82).	Populacijsko istraživanje, dio *the Canadian Study of Health and Aging (CSHA sudionici odabrani po slučaju), N=10263, <65 godina* / Population study, part of *the Canadian Study of Health and Aging (CSHA participants randomly selected), N=10263, <65 y*	5 godina / 5 y	Mjere NI, H iz Cambridgeove procjene mentalnih poremećaja starijih (CAMDEX) / Mesures of NI, section H of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX)	Pad u generalnom kogn. f., ili oštećenje pamćenja u H/ Cambridgeovoj procjeni mentalnih poremećaja starijih (CAMDEX) / Decline in general cognitive functioning or memory impairment on H/ Cambridge Mental Disorders of the Elderly Examination (CAMDEX)	Depresija je (p=.041 OR 16,16 1,12-232,94) značajno doprinijela predikciji BKP (p= .013 OR 2,01 95 % CI 1,16-3,48). Oni s gubitkom interesa će gotovo 3 puta vjerojatnije imati BKP [OR] = 2,76. Promjene u ličnosti raspoloženju više od dvostruko češće kod BKP nego onih UKF (OR = 2,18 i 2,26). Depresija je dvostruko vjerojatnija u BKP skupini nego u UKF(OR = 2,01). / Depression (p=.041 OR 16.16 1.12-232.94) significantly contributed to the prediction of MCI (p= .013 OR 2.01 95% CI 1.16-3.48), with those experiencing a loss of interest being nearly three times more likely to have MCI [OR] =2.76. Changes in mood and personality were more than twice as common in the MCI group compared to those with normal cognitive functioning (OR=2.18 and OR=2.26). Depression was twice as likely in the MCI group compared to the normal cognitive functioning group (OR=2.01).			✓	
Sugarman, et al. (2018), (80).	Populacijsko istraživanje, dio *the NACCUD* N(UKF)=6763 / Population study, part of *the NACCUD* N(NCF)=6763	M = 5,71 godina, SD = 2,31), isključeni oni s neurološkim dijagnozama, A – APOE varijabla ISKLJUČENA IZ ANALIZE zbog 13% bez podatka / M = 5.71 y , SD = 2.31), those with neurological diagnosis excluded, A – APOE variable EXCLUDED FROM ANALYSIS due to 13% with no data	NPI-Q GDS-15	Kriteriji Winblad i sur. / Winblad et al. criteria	1,121 je razvilo BKP. Izraženiji depresivni simptomi su povezani s povećanim rizikom od incidencije BKP (B 0,17, 95 % CI [0,15,0,20] Wald Z 180,73 p< .001 Exp (B) 1,19). Smanjenje depresivnih simptoma je zašt. čimbenik za reverziju u uredno kognitivno funkcioniranje. / 1.121 individuals developed MCI. More pronounced depressive symptoms are associated with an increased risk of MCI incidence (B=0.17, 95% CI [0.15, 0.20], Wald Z=180.73, p<.001, Exp (B)=1.19). Reduction in depressive symptoms is a protective factor for reversion to normal cognitive functioning.	?			
Zeki Al Hazzouri, et al. (2014), (75).	Prospektivno kohortno istraživanje, dio *the Study of Osteoporotic Fractures (SOF),* N= 1293 M dobi =73 g / Prospective cohort study, part of *the Study of Osteoporotic Fractures (SOF),* N= 1293 M age=73 y	M= 12,2 godina B, upotreba antidepresiva / M= 12.2 y B, use of antidepressants	GDS–15; raspoređeni u kvartile. / GDS–15; assigned to quartils	Modificirani Petersenovi kriteriji MMSE Neuropsihologijska procjena / Modified Petersen criteria MMSE Neuropsychological assessment	23 % je razvilo BKP. Kumulativni depresivni simptomi tijekom 20 godina povezani su s većim rizikom od razvoja BKP. / 23% developed MCI. Cumulative depressive symptoms over 20 years are associated with a higher risk of developing MCI.	✓		
Rej et al. (2015), (55)	N=104, ≥ 65 godina u remisiji velike depresivne epizode po slučaju raspoređenih na donepezil i placebo; n = 36, kontrolna skupina / N=104, ≥ 65 y, in remission of major depressive episode randomly assigned to donepezil and placebo; n = 36, control group	2 godine / 2 y	Cjeloživotno trajanje depresije SCID/DSM-IV; akutni simptomi: HAM-D / Lifetime duration of depression SCID/DSM-IV; acute symptoms: Hamilton Depression Rating Scale (HAM-D)	MMSE; Neuropsihologijska baterija / MMSE; Neuropsychological battery	10 % je razvilo BKP. Niti SES niti psihosocijalni čimbenici nisu neovisni prediktori BKP-a (p > .05) / 10% developed MCI. Neither SES (Socioeconomic Status) nor psychosocial factors are independent predictors of MCI (p > .05).				✓

Gallagher, Kiss, Lanctot, i Herrmann, (2018) (64),	Podaci iz *the National Alzheimer's Coordinating Centre*; N(UKF) = 2655 >= 50 g / Data from *the National Alzheimer's Coordinating Centre*; N (NCF) = 2655 >= 50 y	M= 41,8 mjeseci / M= 41.8 months	Anamnestički podatak od depresiji unatrag dvije godine; DSM kriteriji, GDS / Anamnestic data of depression in the past two years; DSM criteria, GDS	MMSE CDR (>0,5), i deficit na kognitivnim testovima / MMSE CDR (>0,5), and deficit on cognitive tests	19,2 % razvilo BKP. Rizični čimbenici u depresivnih za razvoj BKP su starija dob, muški rod, niži stupanj formalnog obrazovanja, depresija unatrag 2 godine (HR 95% CI 1.41 (1,15 – 1,74), izraženiji depresivni simptomi1.05 (1,02 – 1,09). Za svaki bod na GDS, povećava se 5-10% vjerojatnost incidencije BKP. / 19.2% developed MCI. Risk factors for the development of MCI in individuals with depression include older age, male gender, lower level of formal education, depression in the past 2 years (HR 95% CI 1.41 (1.15 – 1.74), and more pronounced depressive symptoms 1.05 (1.02 – 1.09). For each point on the GDS (Geriatric Depression Scale), the likelihood of MCI incidence increases by 5-10%.	✓	✓	
Han et al. (2020), (95)	Podaci iz the *National Alzheimer's Coordinating Center (NACC)*, N(UKF)= 716 u dobi od 60 i više godina / Data from the *National Alzheimer's Coordinating Center (NACC)*, N (NCF)= 716 at the age of 60 years and older	M= 5 g , A Prisutnost alela e4 u APOE genotipu; Lijekovi unatrag 2 tjedna / M= 5 y , A The presence of the e4 allele in the APOE genotype; Medication taken in the past 2 weeks.	1) depresija unutar 2 godine 2) (NPI-Q) 3) GDS-15 , >6 bodova 4) klinički intervju; ili 5) klinička dijagnoza depresije / 1) depression within 2 years 2) (NPI-Q) 3) GDS-15, >6 points 4) clinical interview; ili 5) clinical diagnosis of depression	Petersen kriteriji (Petersen, 2004) / Petersen criteria	Od 464 sudionika koji su ikada uzimali antidepresive, 98 (21,2 %) je razvilo BKP nasuprot 105 (41,7 %) od 252 koji nikada nisu uzimali antidepresive. Podjednaki udio onih koji su ikada koristili i nikada koristili antidepresiv obole od demencije. Nekorisnici, unatoč dvostruko češćem BKP od korisnika, obole jednako često od demencije. / Out of 464 participants who had ever taken antidepressants, 98 (21.2%) developed MCI, compared to 105 (41.7%) out of 252 who had never taken antidepressants. An almost equal proportion of those who had at a point used antidepressants and those who had never used them develop dementia. Non-users, despite having twice the incidence of MCI compared to users, develop dementia just as frequently.			?
Sundermann, Katz, i Lipton, (2017) (81).	Kohortno istraživanje, dio the Einstein Aging Study, N= 572 žene (M dobi =78) and 345 muškaraca (M dobi =77) / Cohort study, part of the Einstein Aging Study, N= 572 women (M age =78) and 345 men (M age =77)	4.2 godine (1,0–14,6), Kontrolirano uzimanje antidepresiva / 4.2 y (1.0–14.6), Controlled use of antidepressants	GDS-15 0–2 niski 3-5 blagi simptomi 5–15 umjereni/teški / GDS-15 0–2 low 3-5 mild symptoms 5–15 moderate/severe	Petersen kriteriji: Objektivni deficit : ≤24 na the FCSRT-FR i/ili ≤5 na LOG WMS-R / Petersen criteria: Objective deficit: ≤24 on the FCSRT-FR and/or ≤5 on LOG WMS-R	99 žena i 64 muškaraca razvilo je amnestički BKP tijekom praćenja. Blagi depresivni simptomi, u usporedbi s niskima, povezani s dva puta većim rizikom od razvoja amnestičkog BKP u muškaraca, ali ne i žena. Umjereni/teški depresivni simptomi povezani su s dva puta većim rizikom od razvoja amnestičkog BKP-a u žena. / 99 women and 64 men developed amnestic MCI during the follow-up. Mild depressive symptoms, compared to low, were associated with a two-fold increased risk of developing amnestic MCI in men, but not in women. Moderate/severe depressive symptoms were associated with a two-fold increased risk of developing amnestic MCI in women.	?	?	
Leng, Diem, Stone, i Yaffe (2018), (94)	Istraživanje, dio *the Study of Osteoporotic Fractures*. N(UKF)= 1,234, M dobi (83,2 ± 2,9 godine), od kojih je 11 % uzimalo AD / Part of *the Study of Osteoporotic Fractures*. N(NCF)= 1.234, M age (83.2 ± 2.9 y), of which 11% have taken antidepressants	M=4.7 godina, Kontrolirano uzimanje antidepresiva / M=4.7 y Controlled use of antidepressants	GDS-15, teški depresivni simptomi >6 bodova / GDS-15, severe depressive symptoms >6 points	Modificirani Petersenevi kriteriji 3 MS neuropsihologijska baterija / Modified Petersen criteria Modified Mini-Mental State (3MS) examination Neuropsychological battery	38 % razvile su BKP ili demenciju. Korištenje (SIPPS) i trazodona, povezano je s najviše povećanim rizikom od javljanja BKP-a nakon 5 godina kod žena u poznoj zreloj dobi. Korisnici SIPPS-a imaju više nego dvostruku, a korisnici trazodona više nego trostruko veću vjerojatnost razvoja BKP-a ili demencije u usporedbi s nekorisnicima. Uzimanje tricikličkih i drugi antidepresva nije značajno povezano s kogn. funkcioniranjem. / 38% developed MCI or dementia. The use of SSRIs and trazodone is associated with the highest increased risk of developing MCI after five years in women in late middle age. SSRI users have more than a two-fold increased likelihood, while trazodone users have more than a three-fold increased likelihood of developing MCI or dementia compared to non-users. Taking tricyclics and other ADs is not significantly associated with cognitive functioning.			

Od 33 istraživanja koja su ispitala povezanost depresije i incidencije BKP, 8 ih nije pronašlo. Neka istraživanja ističu druge varijable povezane s incidencijom BKP, apatiju (52), visoku razinu psihološkog distresa i percepciju nesigurnosti u susjedstvu (53), kortikalno taloženje amiloida i anksioznost (54), opterećenost somatskim komorbiditetom kod osoba od ≥ 65 godina u remisiji velike depresivne epizode (55).

Mehanizmi putem kojih depresija sudjeluje u razvoju BKP-a

1. Depresija može koegzistirati s BKP-om koji će posredstvom patologije AD-a uvjetovati ponavljajuća oštećenja i atrofiju hipokampusa te progredirati u AD.
2. Depresija može biti i rizični čimbenik za BKP-a. Mlađa dob početka klinički značajne depresije i dulje trajanje neliječene depresije, odnosno rekurentne depresivne epizode djeluju kao kronični stres, povećavaju razinu kortizola, aktiviraju hipotalamus-hipofizno-nadbubrežnu os koja mijenja imunološki odgovor, te narušava kogniciju i raspoloženje. Nastaje poremećaj na molekularnoj razini, ekscitotoksičnost glutamata i povećana proizvodnja beta-amiloida Aß (56), što dovodi do atrofije hipokampusa (57). Depresija povećava pojedinčevu vulnerabilnost na neuralne gubitke, tzv. kognitivnu/moždanu rezervu (58,59) i pospješuje razvoj BKP-a. Osobe s produljenim ili ponavljanim depresivnim epizodama imaju manji volumen hipokampusa, frontalnih režnjeva, prefrontalnog orbitralnog korteksa i amigdale.
3. Nalazi nekih istraživanja ukazuju na moguću etiološku ulogu dubokih lezija bijele tvari u patogenezi depresije u zreloj životnoj dobi (60,61). Termin vaskularna depresija odnosi se na oblik depresije u

examined the connection between depression and the incidence of MCI, in 8 studies such a link was not found. Some studies highlighted other variables associated with MCI incidence, such as apathy (52), high levels of psychological distress and perceptions of neighborhood insecurity (53), cortical amyloid deposition and anxiety (54), the burden of somatic comorbidity in persons aged ≥ 65 years who were in remission from a major depressive episode (55).

Mechanisms through which depression is involved in MCI development

1. Depression can coexist with MCI, which through AD pathology leads to repeated hippocampal damage and atrophy, progressing to AD.
2. Depression can also be a risk factor for MCI. Younger age at the onset of clinically significant depression and longer untreated depression, i.e. recurrent depressive episodes, act as chronic stressors, increase cortisol levels, activate the hypothalamic-pituitary-adrenal axis which alters the immune response and impairs cognition and mood. This leads to molecular-level disturbances, excitotoxicity of glutamate and increased production of beta-amyloid Aß (56), resulting in hippocampal atrophy (57). Depression increases an individual's vulnerability to neural losses, the so-called cognitive/brain reserve (58, 59) and promotes the development of MCI. Individuals with prolonged or repeated depressive episodes have smaller volumes of the hippocampus, frontal lobes, prefrontal orbital cortex and amygdala.
3. Findings reported in some studies suggest a possible etiological role of deep white matter lesions in the pathogenesis of late-life depression (60, 61). The term "vascular depression" refers to a form of depression

starijoj životnoj dobi, nakon 65 godina, a dovodi se u vezu sa subkortikalnom bilateralnom ishemičnom bolesti malih krvnih žila bijele moždane tvari (62). Depresivni simptomi mogu biti klinička manifestacija vaskularnih lezija (patološke promjene bijele tvari i lezije bazalnih ganglija), koje ujedno dovode i do BKP s deficitima izvršnih funkcija (63), ali i povećati rizik za vaskularne bolesti povećavajući sklonost negativnim zdravstvenim ponašanjima (64,65). Brojna su istraživanja izvijestila o koegzistiranju depresivnih simptoma i vaskularnih bolesti (66), kao i da su osobe s komorbidnim vaskularnim bolestima i depresijom u većem riziku od pojavljivanja BKP-a (67).

4. Neuronski kompromis mogu dodatno pogoršati s depresijom povezane fiziološke promjene poput upale, hiperkortizolemije, povećanog oksidativnog stresa. Vaskularna depresija doprinosom patologiji hiperintenziteta bijele tvari u mozgu može umanjiti učinak kognitivne rezerve i uvjetovati brže javljanje BKP-a i demencije (68-70).
5. Uklazuje se na zajednički genetski uzrok depresije i BKP. Određene varijante presenilina povezane su s većom incidencijom kliničke depresije, a ujedno induciraju i patološke promjene koje rezultiraju BKP-om (71,72).

U tablici 1 navedeno je kojem od potencijalnih mehanizama pojedino istraživanje ide u prilog. Od istraživanja metodološki osmišljenih sa ciljem da ispitaju mehanizme najviše su empirijskog potkrepljenja dobili depresija kao rizični čimbenik BKP-a, značajan dio ide u prilog depresiji koja koegzistira s BKP-om pri čemu su oboje uvjetovani patologijom AD-a. Značajan dio ukazuje da su aktualni depresivni simptomi povezani, a klinički značajni depresivni simptomi u anamnezi nisu povezani s povećanim rizikom od BKP-a.

occurring in older age, after 65 years of age, and is associated with subcortical bilateral ischemic disease of small blood vessels of the cerebral white matter (62). Depressive symptoms can be a clinical manifestation of vascular lesions (pathological changes in white matter and basal ganglia lesions), which also lead to MCI with executive function deficits (63), and can increase the risk of vascular diseases by increasing the tendency towards negative health behaviors (64, 65). The results of numerous studies have shown that there is a coexistence of depressive symptoms and vascular diseases (66), as well as that people with comorbid vascular diseases and depression are at a higher risk of developing MCI (67).

4. Physiological changes associated with depression, such as inflammation, hypercortisolemia and increased oxidative stress, can further exacerbate the neuronal compromise. Vascular depression, through the pathology of white matter hyperintensities in the brain, may reduce the effect of cognitive reserve and lead to the faster onset of MCI and dementia (68-70).
5. A common genetic cause for both depression and MCI has been suggested. Certain presenilin variants are associated with a higher incidence of clinical depression, and at the same time induce pathological changes resulting in MCI (71,72).

Table 1 shows which potential mechanisms are supported in which respective study. In the studies methodologically designed to examine the mechanisms, depression as a risk factor for MCI received the most empirical support, with a significant portion supporting depression coexisting with MCI, whereby they are conditioned by AD pathology. A significant portion suggests that current depressive symptoms are associated with MCI, while clinically significant depressive symptoms in the medical history are not associated with an increased risk of MCI.

Rizični i zaštitni čimbenici u podlozi povezanosti depresije i BKP-a

Rizični čimbenici za incidenciju BKP-a u depresivnih osoba su starija životna dob (66, 73), kumulativni depresivni simptomi, dulje trajanje neliječene depresije (74,75), veći intenzitet depresivnih simptoma (27,32,66,73,75, 77-85), visoka (86), ali i niska zastupljenost patologije AD-a (77,87), sinergistička aditivna interakcija nedostatka tjelesne aktivnosti i poteškoća spavanja, kliničke depresije i klinički značajne anksioznosti (85), muški rod (66, 88,89), niži stupanj formalnog obrazovanja (32,66,84), aktualno posjedovanje recepta za korištenje antidepresiva (80,93,94). Istovremeno, korištenje antidepresiva definirano na temelju ikada prijavljene upotrebe pokazuje se zaštitnim čimbenikom smanjujući vjerojatnost BKP-a (95).

Zaštitni čimbenici koji utječu na povećanu vjerojatnost reverzije BKP-a u uredno kognitivno funkcioniranje u depresivnih osoba su mlađa dob, neamnestički podtip BKP-a, manji intenzitet depresivnih simptoma ili pak smanjenje depresivnih simptoma između mjerenja.

RASPRAVA

1. Od 33 istraživanja koja su ispitala povezanost depresije i incidencije BKP-a, 8 ih nije pronašlo tu povezanost. Kao moguća metodološka ograničenja navode se kratak interval između dviju točki mjerenja (53,78,89,96), niska specifičnost odabrane definicije depresivnih simptoma (28), ograničena procjena neuropsihijatrijskih simptoma, ograničene informacije o psihijatrijskoj povijesti i psihotropnim lijekovima, te nizak intenzitet neuropsihijatrijskih simptoma koji je mogao dovesti do nedostatka statističke snage za otkrivanje značajnih

Risk and protective factors underlying the connection between depression and MCI

Risk factors for the incidence of MCI in depressed individuals include older age (66, 73), cumulative depressive symptoms, longer duration of untreated depression (74, 75), higher severity of depressive symptoms (27, 32, 66, 73, 75, 77-85), high (86), but also low burden of AD pathology (77, 87), synergistic additive interaction of physical inactivity and sleep difficulties, clinical depression and clinically significant anxiety (85), male gender (66, 88, 89), lower level of formal education (32, 66, 84) and current prescriptions for antidepressant use (80, 93, 94). Simultaneously, the use of antidepressants defined on the basis of ever-reported use has shown to be a protective factor reducing the likelihood of MCI (95).

Protective factors influencing the increased likelihood of reversing MCI to normal cognitive functioning in depressed individuals include younger age, non-amnestic subtype of MCI, lower severity of depressive symptoms, or a reduction in depressive symptoms between measurements.

DISCUSSION

1. Out of the 33 studies that examined the connection between depression and the incidence of MCI, 8 of them did not find such a link. Possible methodological limitations cited include a short interval between two measurement points (53, 78, 89, 96), low specificity of the chosen definition of depressive symptoms (28), limited assessment of neuropsychiatric symptoms, limited information on psychiatric medical history and psychotropic medications, as well as a low severity of neuropsychiatric symptoms that could lead to a lack of statistical power to detect significant effects in the domain of depression (28, 97), exclusion of individuals

učinaka na domenu depresivnosti (28,97), isključivanje hospitalno liječenih osoba s depresijom (29), nedovoljno osjetljiv probirni instrument za procjenu BKP-a (28), isključivanje onih koji su tijekom praćenja razvili demenciju (76), osipanje sudionika i pristranost zdravog uzorka koji su u longitudinalnom istraživanju mogli smanjiti snagu detektiranja buduće povezanosti s depresijom (29).

Istraživanja koriste različite granične vrijednosti za značajno kognitivno oštećenje, što može dovesti do velikih razlika u procjeni prevalencije (98). Jak, Bondi i sur. (98) predlažu nove kriterije BKP-a, od najmanje dva rezultata 1 SD ispod normativnog očekivanja unutar kognitivne domene, koji su se dosad u istraživanjima pokazali slično prediktivni za incidenciju demencije kao Petersenovi kriteriji (1), ali uz manju sklonost lažno pozitivnim dijagnozama (99). Dok neka istraživanja izostavljaju kriterij subjektivnog oštećenja pamćenja, s obzirom na sugeriranu upitnu dodatnu prediktivnu vrijednost za konverziju u demenciju (99), nalazi drugih istraživanja ističu da subjektivne smetnje pamćenja djelomično posreduju u odnosu između depresije i kognicije (100). Leng, Diem, Storm i Yaffe (90) upozoravaju da je važno razlikovati kognitivne i nekognitivne (povezane sa somatskim komorbiditetom) teškoće u funkcioniranju. Kao dodatni kriterij za BKP uvjetovan patologijom AD-a predloženo je korištenje biomarkera (101).

Velik dio istraživanja prate kohorte s niskim razinama (sub)depresivnih simptoma, što umanjuje generalizaciju rezultata na teža depresivna stanja. Ipak, praćenjem i subkliničke razine depresivnosti povećava se vjerojatnost uočavanja mogućih uzročnih veza između subkliničke depresije i BKP (27,86,102). Depresija je povezana

hospitalized with depression (29), insufficiently sensitive screening instrument for MCI assessment (28), exclusion of those who developed dementia during the follow-ups (76), participant attrition and selection bias in the healthy sample that could have reduced the power to detect future associations with depression in longitudinal studies (29).

Studies use different cutoff values for significant cognitive impairment, which can lead to significant differences in prevalence estimates (98). Jak, Bondi et al. (98) propose new criteria for MCI, with at least two scores 1 standard deviation below normative expectations within a cognitive domain, which have been shown in research to be similarly predictive of dementia incidence as Petersen's criteria (1), but with a lower risk of false-positive diagnoses (99). While some studies omit the criterion of subjective memory impairment due to its suggested questionable additional predictive value for conversion to dementia (99), findings from other studies emphasize that subjective memory complaints partially mediate the conection between depression and cognition (100). Leng, Diem, Storm and Yaffe (90) warn that it is important to distinguish between cognitive and non-cognitive (associated with somatic comorbidities) difficulties in functioning. Using biomarkers has been proposed as an additional criterion for MCI conditioned by AD pathology (101).

A large portion of the research is followed by cohorts with low levels of (sub)depressive symptoms, which limits the generalization of results to more severe depressive conditions. However, monitoring the subclinical levels of depression as well increases the likelihood of detecting possible causal relationships between subclinical depression and MCI (27, 86, 102). Depression is associated with the prevalence of MCI and progression to dementia, but not with

s prevalencijom BKP i progresijom do demencije, ali ne i s incidencijom BKP-a, što ukazuje da prati BKP, ali mu ne prethodi i ide u prilog depresiji kao prodromalnom simptomu demencije koja ujedno uvjetuje i BKP (103). Prepoznata uloga anksioznosti u razvoju BKP-a (79,85), nadilazi okvire ovog rada.

2. Depresija može biti rizični čimbenik za razvoj BKP-a (27,66,73,75,77-85,93). Uzrokuje atrofiju hipokampusa, smanjuje kognitivnu/moždanu rezervu i pospješuje razvoj BKP-a. Kognitivna rezerva objašnjava individualne razlike u vulnerabilnosti na neuralne gubitke razlikama u neuralnoj redundantnosti (56). Dok je u kognitivnoj rezervi naglasak na efikasnosti i stilu procesuiranja informacija, s njom usko vezana moždana rezerva naglašava razlike u veličini mozga ili broju neurona (57). Kognitivne, društvene i tjelesne aktivnosti, uz veći volumen mozga i veću veličinu glave mogu povećati redundantnost i djelovati kao zaštitni kognitivni čimbenik. Depresija i BKP ujedno mogu imati zajednički uzrok, AD, vaskularne lezije ili genetski uzrok. Iako najveći broj istraživanja ide u prilog depresiji kao rizičnom čimbeniku BKP-a, nacrti većine istraživanja nisu omogućili ispitivanje mehanizma u podlozi povezanosti depresije i BKP-a. Broj istraživanja koja su potvrdila određene mehanizme ne treba promatrati u odnosu na ukupan broj postojećih istraživanja, jer nisu sva istraživanja uključila kontrolu istih kovarijabli. Od 8 istraživanja koja su kontrolirala pokazatelje patologije AD-a, trećina ide u prilog depresiji koja koegzistira s BKP-om pri čemu su oni uvjetovani patologijom AD-a, dok većina navodi da su depresija i patologija AD neovisni rizični čimbenici incidencije BKP-a. Sva su 4 istraživanja koja su kontrolirala vaskularne rizične čimbenike pokazala da su depresija i vaskularni rizični čimbenici međusobno neovisni prediktori incidencije

the incidence of MCI. This suggests that depression follows MCI, but does not precede it, supporting the idea that depression is a prodromal symptom of dementia which also conditions MCI (103). The recognized role of anxiety in the development of MCI (79, 85) goes beyond the scope of this work.

2. Depression can be a risk factor for the development of MCI (27, 66, 73, 75, 77-85, 93). It causes hippocampal atrophy, reduces cognitive/brain reserve and promotes the development of MCI. Cognitive reserve explains the individual differences in vulnerability to neural losses through differences in neural redundancy (56). While with cognitive reserve the emphasis is on efficiency and the information processing style, the closely related brain reserve highlights the differences in brain size or the number of neurons (57). Cognitive, social and physical activities, along with a larger brain volume and head size, can increase redundancy and act as protective cognitive factors. Depression and MCI may also share a common cause, such as AD, vascular lesions or genetic factors. Although most studies support the notion of depression being a risk factor for MCI, the designs of most studies did not allow for an examination of the underlying mechanism in the connection between depression and MCI. The number of studies confirming certain mechanisms should not be viewed in relation to the total number of existing studies, since not all studies included the control of the same covariables. Of the eight studies that controlled for indicators of AD pathology, one-third supported depression coexisting with MCI, with both being conditioned by AD pathology, while most stated that depression and AD pathology are independent risk factors for MCI incidence. All four studies that controlled for vascular risk factors have shown that depression and vascular risk factors are mutually independent predictors of MCI incidence. None of the exist-

BKP-a. Nijedno od postojećih istraživanja nije ispitalo mehanizam povezanosti depresije i BKP-a putem gena. Od manjeg broja istraživanja koji je to metodološki omogućio, značajan dio ukazuje da su aktualni klinički značajni depresivni simptomi, ali ne depresivni simptomi u anamnezi, povezani s povećanim rizikom od BKP-a, što ide u prilog depresiji kao prodromalnom simptomu demencije.

3. Depresivne osobe koje razviju BKP u odnosu na depresivne urednog kognitivnog funkcioniranja starije su životne dobi (66,73). Istraživanja koja su pratila kogniciju depresivnih do razvoja BKP-a uključila su u prosjeku osobe iznad 55 godina. Sa starenjem su povezane strukturne abnormalnosti poput lezija bijele tvari i subkortikalne volumerijske promjene (64), koje nisu mnogo istraživane u mlađim skupinama, a postojeća istraživanja dala su nekonzistentne rezultate (104). Tek je nekoliko istraživanja ispitalo kogniciju isključivo mlađih odraslih s dijagnozom velikog depresivnog poremećaja, u dobnom rasponu od 19 do 45 godina, od kojih je većina u toj skupini pronašla deficit izvršnih funkcija (105). Dok je dio istraživanja izvijestilo o oštećenjima verbalnog pamćenja, neka istraživanja nisu pronašla navedene deficite (106) navodeći da uzorak čine oni s blagim i umjereno teškim depresivnim simptomima. Smith i sur. (107) navode da deficiti izvršnih funkcija i verbalnog pamćenja perzistiraju i nakon remisije depresije kod mlađih odraslih. Mlađi odrasli s psihotičnom depresijom imaju veća oštećenja kognitivnih funkcija od onih s velikim depresivnim poremećajem (108) i obilježja neuropsihologijskih deficita sličnija osobama sa shizofrenijom (109). Težina depresije značajno je povezana s kognitivnim deficitima u mlađih odraslih (109), iako neki autori opovrgavaju tu povezanost (110).

ing studies examined the connection mechanism between depression and MCI through genes. Of the smaller number of studies that methodologically allowed for this, a significant portion indicates that current clinically significant depressive symptoms, but not depressive symptoms in the medical history, are associated with an increased risk of MCI, thus supporting depression as a prodromal symptom of dementia.

3. Depressed individuals who develop MCI, compared to depressed individuals with normal cognitive functioning, are of older age (66, 73). Studies that monitored the cognition of depressed individuals until the development of MCI typically included individuals above 55 years of age. Aging is associated with structural abnormalities such as white matter lesions and subcortical volumetric changes (64), which have not been extensively studied in younger groups, and existing research has yielded inconsistent results (104). Only a few studies have examined the cognition exclusively of younger adults diagnosed with major depressive disorder, ranging from 19 to 45 years of age, most of which found deficits in executive functions in this group (105). While some studies have reported impairments in verbal memory, others have not found these deficits (106), stating that the sample included those with mild to moderately severe depressive symptoms. Smith et al. (107) suggest that deficits in executive functions and verbal memory persist even after remission from depression in younger adults. Younger adults with psychotic depression have greater cognitive impairments than those with major depressive disorder (108), as well as signs of neuropsychological deficits similar to individuals with schizophrenia (109). The severity of depression is significantly associated with cognitive deficits in younger adults (109), although some authors dispute this association (110).

Dio istraživanja pokazuje da je povezanost depresivnih simptoma i BKP-a veća u skupini osoba visoke zastupljenosti patologije AD-a (86), a dok dio u skupini osoba niske zastupljenosti patologije AD-a (77, 87), što je sukladno zaključcima da je depresija ujedno pretkliničk biljeg AD-a, ali i rizični čimbenik za BKP. Tzv. *depresija povezana s amiloidom*, definirana prisutnošću depresivnih simptoma i visokim omjerom amiloid-β (Aβ) Aβ42 u plazmi, potencijalan je prodromalni simptom AD-a, koji ujedno uvjetuje amnestički BKP (111-114).

Često obilježje depresije je poremećena regulacija serotonina, važnog za uredno kognitivno funkcioniranje i za sintezu melatonina (115). Većina depresivnih osoba ima poremećaje cirkadijarnog ritma (116). Najrjeđe smetnje spavanja imaju depresivni (12,5 %), češće osobe s BKP-om (39,1 %), a najčešće osobe s komorbiditetom depresije i BKP-a (43,5 %), (91).

Većina istraživanja koja su ispitivala rod kao moderator povezanosti depresije i BKP navodi da će depresivni muškarci razviti BKP vjerojatnije od depresivnih žena (66,88,89). Niz je mogućih bioloških objašnjenja od kojih se ističu neuroprotektivan učinak estrogena u životinjskim modelima (117,118), vaskularna patologija u podlozi depresija muškaraca (119), iako su druga istraživanja navedeno opovrgnula (120), razlike u endokrinim i neurotransmiterskim sustavima (121), razlike u reaktivnosti hipotalamusno-hipofizno-nadbubrežne osi (122). Subklinička depresija povezana je s manjim medijalnim volumenom frontalnog režnja kod starijih muškaraca, ali ne i kod žena (123), što ukazuje da bi muškarci mogli biti osjetljiviji na moždane promjene povezane s blažom depresijom nego žene. Ističu se i sociološka objašnjenja. Muškarci su zbog društvenih očekivanja i rodne uloge manje od žena skloni priznati depresivne smetnje (119,124) što može rezultirati podcjenjivanjem njihovih simptoma (119).

Some studies show that the connection between depressive symptoms and MCI is stronger in the group of individuals with a high burden of AD pathology (86), while some other studies indicate that it is stronger in the group with a low burden of AD pathology (77, 87), which is consistent with the conclusion that depression is both a preclinical marker of AD and a risk factor for MCI. The so-called amyloid-associated depression, defined by the presence of depressive symptoms and a high ratio of amyloid-β (Aβ) Aβ42 in plasma, is a potential prodromal symptom of AD, which also conditions amnestic MCI (111-114).

A common feature of depression is a disrupted regulation of serotonin, which is important for normal cognitive functioning and melatonin synthesis (115). Most depressive individuals suffer from circadian rhythm disturbances (116). Depressive individuals have the least sleep disturbances (12.5%), followed by those with CI (39.1%), while the highest prevalence is among individuals with comorbid depression and MCI (43.5%), (91).

Most studies which examined gender as a moderator in the connection between depression and MCI suggest that depressed men are more likely to develop MCI than depressed women (66, 88, 89). There is a series of possible biological explanations, the most prominent of which are the neuroprotective effect of estrogen in animal models (117,118), vascular pathology underlying depression in men (119) - although other studies have refuted this (120), differences in endocrine and neurotransmitter systems (121), and differences in the reactivity of the hypothalamic-pituitary-adrenal axis (122). Subclinical depression is associated with smaller medial frontal lobe volume in older men, but not in women (123), suggesting that men may be more susceptible to brain changes associated with milder depression than women. Sociological explanations are also highlighted. Due to social expectations and gender roles, men are less likely than women to admit to depres-

Niži stupanj formalnog obrazovanja rizičan je čimbenik za razvoj BKP-a u depresivnih (66,84,93), moguće zbog manje stimulirajućih kognitivnih aktivnosti i manje kognitivne rezerve.

Women's Health Initiative Memory Study, najveće prospektivno istraživanje koje ispituje odnos između pijenja antidepresiva i specifičnih antidepresiva na kognitivno funkcioniranje zdravih žena u postmenopauzi, otkrilo je povećani rizik od BKP kod žena koje su uzimale selektivne inhibitore ponovne pohrane serotonina (SIPPS) ili tricikličke antidepresive (TCA) (93), a istraživanje Lenga i sur. (94) kod žena starije dobi koje su uzimale SIPPS-e ili trazodon, ali ne i TCA-e. Opaženi odnos između pijenja antidepresiva i kognitivnog oštećenja ostao je i nakon prilagodbe za povijest kardiovaskularnih bolesti. Nejasno je je li povećani rizik od razvoja BKP-a povezan s uporabom antidepresiva rezultat same depresije i je li smanjeni rizik od kognitivnog oštećenja posljedica smanjenja simptoma depresije, a ne izravne dobrobiti antidepresiva. Nije poznato mogu li kognitivni učinci antidepresiva biti posljedica depresije u prošlosti. Han i sur. (95) nisu pronašli značajnu povezanost između upotrebe antidepresiva i rizika od incidentnog BKP-a kada je upotreba antidepresiva definirana na temelju aktualne, dok je pronađen zaštitni učinak, značajna povezanost između upotrebe antidepresiva i nižeg rizika od BKP-a kada je korištenje antidepresiva definirano na temelju ikada prijavljene upotrebe, što ukazuje na važnost definiranja uzimanja lijekova kao vremenski promjenjivu kovarijablu u budućim istraživanjima, te ukazuje na mogućnost postojanja mehanizma neovisnog o djelovanju lijeka koji uvjetuje deterioraciju, primjerice neurodegenerativnog procesa. Iako većina istraživanja ukazuje da će pojedinci s receptom za antidepresiv imati veću vjerojatnost razvoja BKP-a, mnoga nisu provjerila i stvarno pridržavanje propisanog uzimanja antidepresiva, niti uzela podatke o indikaciji i trajanju,

sive symptoms (119, 124), which may result in underestimating their symptoms (119).

Lower levels of formal education represent a risk factor for the development of MCI in depressed individuals (66, 84, 93), possibly due to less stimulating cognitive activities and lower cognitive reserve.

The results of the *Women's Health Initiative Memory Study*, the largest prospective study examining the connection between the use of antidepressants and specific antidepressants on the cognitive functioning of healthy postmenopausal women, found an increased risk of MCI in women who took selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) (93), while a study conducted by Lenga et al. (94) showed these results among older women who took SSRIs or trazodone, but not TCAs. The observed connection between the use of antidepressants and cognitive impairment remained even after adjusting for the history of cardiovascular disease. It is unclear whether the increased risk of developing MCI is associated with the use of antidepressants as a result of depression itself, and whether the reduced risk of cognitive impairment is a result of reducing depressive symptoms, rather than a direct benefit of antidepressants. It is unclear whether the cognitive effects of antidepressants are a result of past depression. In their study, Han et al. (95) did not find a significant association between the use of antidepressants and the risk of incident MCI when antidepressant use was defined based on current use, but they found a protective effect, a significant association between antidepressant use and a lower risk of MCI when antidepressant use was defined based on ever-reported use, indicating the importance of defining medication use as a time-varying covariable in future research, and suggesting the possibility of the existence of a mechanism independent of the effect of medication that conditions deterioration, such as a neurodegenerative process. Although most studies suggest

točne doze pijenja lijekova. Antidepresivi imaju korisne učinke u akutnom liječenju i liječenju održavanja depresije u starijoj životnoj dobi (125). Moguće su sinergističke nuspojave i interakcije antidepresiva i nepsihotropnih i psihotropnih lijekova koje stariji odrasli uzimaju zbog vjerojatnijih komorbiditeta (126). Depresivne žene koje nisu uzimale antidepresive nisu imale manji rizik od kognitivnog oštećenja, što upućuje na složeni odnos između depresije i kognitivnog funkcioniranja uvjetovan različitim patofiziološkim mehanizmima (medijalnog temporalnog režnja, frontalne regionalne atrofije, povećanog hiperintenziteta bijele tvari, opterećenja patologijom AD-a, vaskularnih bolesti) (60). Antidepresivi sami dovode do potpune remisije u manje od 50 % starijih pacijenata s depresijom, a uz farmakološke važno je uvođenje nefarmakoloških intervencija (80,125).

U malom se broju istraživanja ispitalo zaštitne čimbenike reverzije iz BKP-a u uredno kognitivno funkcioniranje u depresivnih. Osobe koje su tijekom praćenja iz BKP-a postigle remisiju u uredno kognitivno funkcioniranje su mlađe dobi, vjerojatnije imaju neamnestički BKP, te niži ukupni rezultati na gerijatrijskoj ljestvici depresije (GDS-15) ili smanjenje depresivnih simptoma između mjerenja (80). Neamnestički BKP, vjerojatno uvjetovan vaskularnom patologijom, zaštitni je čimbenik reverzije BKP-a u uredno kognitivno funkcioniranje, što ukazuje na potencijalnu reverzibilnost nepovoljnog sinergističkog učinka depresije i vaskularnih rizičnih čimbenika. Smanjenjem depresije smanjuje se patologija hiperintenziteta bijele tvari u mozgu i nepovoljan učinak na kognitivnu rezervu, što smanjuje vjerojatnost javljanja BKP-a (68-70). Potencijalan učinak psihoterapije i kognitivno stimulirajućih aktivnosti na prevenciju i liječenje BKP-a (126-128) zasada je nedovoljno ispitan.

Odabir radova učinio je jedan autor. Istraživanja koja koriste isključivo „nepsihologijske metode“ (neuroslikovne i neurofiziološke me-

that individuals with a prescription for antidepressants are more likely to develop MCI, many have not verified the actual adherence to the prescribed antidepressant use, nor have they collected data on indication and duration, the accurate dosing of medication. Antidepressants have beneficial effects in acute treatment and maintenance treatment of depression in older age (125). There may be synergistic side effects and interactions between antidepressants and non-psychotropic and psychotropic medications taken by older adults due to more likely comorbidities (126). Depressive women who did not take antidepressants did not have a lower risk of cognitive impairment, suggesting a complex relationship between depression and cognitive functioning conditioned by different pathophysiological mechanisms (medial temporal lobe, frontal regional atrophy, increased white matter hyperintensity, AD pathology burden, vascular diseases) (60). Antidepressants alone lead to complete remission in less than 50% of older patients with depression, and it is important to introduce non-pharmacological interventions alongside the pharmacological ones (80, 125).

A small number of studies have examined the protective factors for the reversal of MCI to normal cognitive functioning in depressed individuals. Individuals who achieved remission to normal cognitive functioning from MCI during follow-ups are of younger age, they are more likely to have non-amnestic MCI, and have lower overall scores on the Geriatric Depression Scale (GDS-15) or reduced depressive symptoms between measurements (80). Non-amnestic MCI, likely caused by vascular pathology, is a protective factor for the reversal of MCI to normal cognitive functioning, suggesting a potential reversibility of the unfavorable synergistic effect of depression and vascular risk factors. Reducing depression reduces white matter hyperintensity pathology in the brain and the adverse effect on cognitive reserve, reducing the likelihood of MCI (68-70). The potential effect of psychotherapy and

tode, genske analize, određivanja biomarkera iz cerebrospinalnog likvora) su isključena, jer nadilaze okvire rada, a zasigurno su neizostavna za razumijevanje područja. Tako je primjerice nedavno istraživanje koristeći magnetsku rezonanciju mozga ukazalo na strukturne i funkcionalne razlike mozga depresivnih i nedepresivnih osoba s BKP te na njihovu povezanost s obrascima atrofije mozga i kognitivnog funkcioniranja u AD (129). Prednosti budućih istraživanja su longitudinalno praćeni sudionici iz opće, ali i kliničke populacije, s dijagnozama temeljenima na procjeni stručnjaka i formalnim kriterijima (uz korištenje podklasifikacije BKP-a). Važno je prikupiti podatke o dobi javljanja prve depresivne epizode, trajanju depresije, indikaciji za propisivanje, dozi, i stvarnom pijenju lijeka.

ZAKLJUČCI

Većina istraživanja koja su ispitivala depresivne osobe urednog kognitivnog funkcioniranja do pojave BKP-a pokazala su da je depresija povezana s većim rizikom od razvoja BKP-a.

Depresija može biti rizični čimbenik za razvoj BKP-a. Blagi depresivni simptomi mogu biti rana manifestacija BKP-a koji vodi do AD-a. Depresivni simptomi mogu biti klinička manifestacija vaskularnih lezija koje ujedno dovode i do BKP-a, ali i povećati rizik za vaskularne bolesti. Vaskularna depresija doprinosom patologiji hiperintenziteta bijele tvari u mozgu može umanjiti učinak kognitivne rezerve i uvjetovati brže javljanje BKP-a. Određene varijante presenilina povezane su s većom incidencijom kliničke depresije, a ujedno induciraju i patološke promjene koje rezultiraju BKP-om. Od istraživanja koja su metodološki osmišljena sa ciljem da ispitaju mehanizme najviše je potkrepljenja dobila depresija kao rizični čimbenik BKP-a, značajan dio ide u prilog depresiji koja koegzistira s BKP-om pri čemu su oni uvjetovani patologijom AD-a.

cognitive stimulating activities on the prevention and treatment of MCI (126-128) has so far been insufficiently studied.

The selection of works was made by a single author. Studies that exclusively use "non-psychological methods" (neuroimaging and neurophysiological methods, genetic analyses, cerebrospinal fluid biomarker determinations) were excluded as they go beyond the scope of this paper, and are certainly indispensable for understanding the field. For example, a recent study using magnetic resonance imaging of the brain pointed to structural and functional differences in the brains of depressed and non-depressed individuals with MCI, and their association with the patterns of brain atrophy and cognitive functioning in AD (129). The advantages of future research lie in longitudinal monitoring of participants from the general and clinical populations, with diagnoses based on expert assessments and formal criteria (with the use of MCI subclassifications). It is important to gather data regarding the age of onset of the first depressive episode, the duration of depression, indications for prescriptions, dosage, and actual medication use.

CONCLUSIONS

Most studies which examined individuals with depression and normal cognitive functioning prior to the onset of MCI have shown that depression is associated with a higher risk of MCI.

Depression can be a risk factor for the development of MCI. Mild depressive symptoms can be an early manifestation of MCI leading to AD. Depressive symptoms can be a clinical manifestation of vascular lesions that also lead to MCI, and can increase the risk of vascular diseases. Vascular depression, through the pathology of white matter hyperintensities in the brain, can diminish the effect of cognitive reserve and lead to an earlier onset of MCI. Certain presenilin variants are associated with a higher incidence of clinical depression and also

Rizični čimbenici za incidenciju BKP-a u depresivnih osoba su starija dob, dulje trajanje depresije, veći intenzitet depresivnih simptoma, niska, ali i visoka zastupljenost patologije AD-a, sinergistička aditivna interakcija nedostatka tjelesne aktivnosti i poteškoća spavanja, kliničke depresije i klinički značajne anksioznosti, muški rod, niži stupanj formalnog obrazovanja, aktualno posjedovanje recepta za korištenje antidepresiva. Istovremeno, korištenje antidepresiva definirano na temelju ikada prijavljene upotrebe pokazuje se zaštitnim čimbenikom smanjujući vjerojatnost BKP-a. Zaštitni čimbenici reverzije BKP-a u uredno kognitivno funkcioniranje u depresivnih osoba su mlađa dob, neamnestički BKP, manji intenzitet depresivnih simptoma, smanjenje depresivnih simptoma između mjerenja.

Identificiranje rizičnih za BKP u skupini depresivnih je važno, jer su oni potencijalni kandidati za pružanje intervencija, što postaje sve važnije sa starenjem stanovništva, porastom svijesti o demenciji i broja upućenih na specijalističke preglede zbog subjektivnih smetnji pamćenja. Liječenje treba biti usmjereno na smanjenje rizičnih čimbenika: trajanje neliječenih simptoma, intenzitet depresivnih simptoma odnosno težina depresije, smetnje spavanja. Liječenje može reducirati ruminacije, brige, ili poremećaje spavanja i izravno pozitivno djelovati na kognitivno funkcioniranje, ali i ograničiti neurobiološke promjene povezane s BKP-om. Opravdana su daljnja istraživanja o smanjenju rizika od BKP-a u depresivnim skupinama upravljanjem rizičnim čimbenicima (npr. intervencijom antidepresivima, psihoterapijom i kognitivno stimulirajućim aktivnostima).

induce pathological changes that result in MCI. Among studies methodologically designed to examine the mechanisms, depression was the most acknowledged as a risk factor for MCI, with a significant portion of evidence favoring depression that coexists with MCI, both of which are conditioned by AD pathology.

Risk factors for the incidence of MCI in individuals with depression include older age, longer duration of depression, higher intensity of depressive symptoms, low, but also high burden of AD pathology, synergistic additive interaction of physical inactivity and sleep difficulties, clinical depression and clinically significant anxiety. Other risk factors include male gender, lower level of formal education and current prescription for antidepressants. Simultaneously, the use of antidepressants, defined based on ever-reported use, is shown to be a protective factor that reduces the likelihood of MCI. Protective factors for the reversal of MCI to normal cognitive functioning in individuals with depression include younger age, non-amnestic MCI, lower severity of depressive symptoms, and a reduction in depressive symptoms between measurements.

Identifying the individuals at risk of MCI in the depressive group is important because they are potential candidates for interventions, which is becoming increasingly important with the aging population, growing awareness of dementia, and the number of referrals for specialist examinations due to subjective memory complaints. Treatment should be focused on reducing risk factors: the duration of untreated symptoms, the intensity of depressive symptoms, i.e. severity of depression, sleep disturbances. Treatment can reduce rumination, worry or sleep disorders, and can have a direct positive impact on cognitive functioning, while also limiting neurobiological changes associated with MCI. Further research on reducing the risk of MCI in depressive groups through risk factor management (e.g. antidepressant intervention, psychotherapy and cognitive stimulating activities) is justified.

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