Od demencije češće boluju žene

/ Dementia is More Frequent in Women

Suzana Uzun[1,2], Ivana Todorić Laidlaw[1], Marija Kušan Jukić[3], Oliver Kozumplik[1,2], Dubravka Kalinić[4], Nela Pivac[5], Ninoslav Mimica[1,4]

[1] Klinika za psihijatriju Vrapče, Zagreb, [2]Sveučilište Josipa Jurja Strossmayera, Medicinski fakultet Osijek, Osijek, [3]Nastavni zavod za javno zdravstvo „Dr. Andrija Štampar", [1,4]Centar za mentalno zdravlje i prevenciju ovisnosti, Zagreb, [4]Medicinski fakultet Sveučilišta u Zagrebu, [5]Institut Ruđer Bošković, Zagreb, Hrvatska

/ [1]University Psychiatric Hospital Vrapče, Zagreb, [2]Josip Juraj Strossmayer University, Faculty of Medicine, University of Osijek, Osijek, [3]"Dr. Andrija Štampar" Institute of Public Heath, Centre for Mental Health and the Prevention of Addiction, Zagreb, [4]Faculty of Medicine, University of Zagreb, [5]Ruđer Bošković Institute, Zagreb, Croatia

Demencija je sindrom globalnog i progresivnog oštećenja stečenih kognitivnih sposobnosti pri očuvanoj svijesti prouzročen organskom bolešću središnjeg živčanog sustava u kojem su posebno oštećene sposobnosti pamćenja, učenja, apstraktnog mišljenja, orijentacije te poimanja vidno-prostornih odnosa. Prevalencija i incidencija Alzheimerove bolesti (AB), najčešćeg uzroka demencije, znatno je veća kod žena nego kod muškaraca, a ta se razlika s dobi povećava. Dvostruko veća učestalost AB kod žena u odnosu na muškarce djelomično se može objasniti time što žene imaju očekivano dulji životni vijek. Žene imaju lošiju kognitivnu izvedbu na mnogim neuropsihologijskim testovima u odnosu na muškarce u istom stadiju bolesti, odnosno višestruke kognitivne funkcije kod žena teže su i šire zahvaćene nego kod muškaraca. Mogući razlozi za ovakvu nepovoljnost naspram žena su redukcija estrogena u postmenopauzi, veće kognitivne rezerve muškaraca te utjecaj apolipoproteina E. Određeni biološki čimbenici također bi mogli objasniti različite kliničke manifestacije AB s obzirom na spol. Osim što prema prezentiranim podatcima žene češće obolijevaju od AB, žene su također te koje u bitno većoj mjeri pružaju neformalnu njegu ljudima s demencijom, te su oko dvije trećine neformalnih njegovatelja žene. Zaključno, u daljnjem istraživačkom i kliničkom radu s AB svakako bi trebalo obratiti pozornost na spoznaje o spolnim razlikama u razvoju i progresiji ove bolesti.

/ Dementia is a syndrome of global and progressive impairment of acquired cognitive abilities with preserved consciousness caused by an organic illness of the central nervous system with especially pronounced damage to the ability to memorise, learn, think abstractly, orientate, and perceive spatial relations. The prevalence and incidence of Alzheimer's Disease (AD), the most common cause of dementia, is considerably greater in women than in men, and that difference increases with age. The fact that AD occurs twice as often in women than in men may be partially explained by a longer life expectancy among women. Women show worse cognitive performance on numerous neuropsychological tests in comparison to men during the same stage of the disease, meaning that multiple cognitive functions are more widely and severely impaired in women than in men. Possible reasons for such unfavourable results among women are a reduction of oestrogen during post-menopause, larger cognitive reserves in men, and the influence of apolipoprotein E. Certain biological factors may also explain various clinical manifestations of AD regarding sex. Apart from the fact that, according to presented data, women develop AD more often than men, women are also those who offer informal care to people with dementia in much greater numbers, and almost two thirds of informal caregivers are women. In conclusion, further research and clinical work with AD should certainly pay attention to insights about sex differences in the development and progression of this disease.

ADRESA ZA DOPISIVANJE / *CORRESPONDENCE ADDRESS*:
Doc. dr. sc. Suzana Uzun, prim., dr. med.
Klinika za psihijatriju Vrapče / *Psychiatric Hospital Vrapče*
Bolnička cesta 32
10 000 Zagreb, Hrvatska
E-pošta: suzana.uzun@bolnica-vrapce.hr

KLJUČNE RIJEČI / *KEY WORDS*:
Alzheimerova bolest / *Alzheimer's disease*
Demencija / *Dementia*
Hormoni / *Hormones*
Njegovatelji / *Caregivers*
Spol / *Sex*
Žene / *Women*

TO LINK TO THIS ARTICLE: https://doi.org/10.24869/spsih.2018.57

UVOD

Demencija (lat. *de* – bez, *mens*– um) je sindrom globalnog i progresivnog oštećenja stečenih kognitivnih sposobnosti pri očuvanoj svijesti prouzročen organskom bolešću središnjeg živčanog sustava (SŽS), u kojem su posebno oštećene sposobnosti pamćenja, učenja, apstraktnog mišljenja, orijentacije te poimanja vidno-prostornih odnosa. Demenciju se ne može promatrati kao jedinstvenu dijagnozu, već kao skup simptoma koji rezultiraju nemogućnošću obavljanja osnovnih društvenih, moralnih te radnih obaveza.

Prevalencija demencije u Europi kreće se u rasponu od 6 % do 18 % kod osoba starijih od 65 godina, a kod osoba starijih od 85 godina ona čak doseže 30 % (prema nekim podatcima i 50 %) (1). Ako se uzme u obzir činjenica da je stanovništvo sve starije, tj. da se prosječna životna dob stanovništva stalno produžuje, za očekivati je da će u vrlo skoroj budućnosti demencija postati jedan od vodećih medicinskih, društvenih, ali i ekonomskih problema modernog društva. Svjetska zdravstvena organizacija (*World Health Organization, WHO*) procjenjuje da trenutno na svijetu od demencije boluje oko 35,6 milijuna ljudi, a pretpostavka je da će se taj broj do 2030. godine udvostručiti, a do 2050. godine utrostručiti (2).

Demencija je sindrom s visokom incidencijom i Alzheimerova bolest (AB) je najčešći uzrok

INTRODUCTION

Dementia (lat. *de* – without, *mens* – mind) is a syndrome of global and progressive impairment of acquired cognitive competences in a state of preserved consciousness, caused by an organic disease of the central nervous system with especially pronounced impairment of memory, learning, abstract thinking, orientation, and perception of visuospatial relations. Dementia cannot be viewed as a single diagnosis, but as a collection of symptoms which result in the inability to perform basic social, moral, and workplace duties. The prevalence of dementia in Europe is between 6% and 18% in people older than 65, and in people older than 85 it even reaches as high as 30% (even 50% according to some data) (1). If one considers the fact that the population is becoming older, or in other words that the average age of the population is continually being extended, it is to be expected that dementia will become one of the leading medical, social, and economic problems of modern society in the near future. The World Health Organization (WHO) estimates that there are currently around 35.6 million people suffering from dementia, and it is estimated that the number will double by 2030, and triple by 2050 (2).

Dementia is a syndrome with a high incidence, and Alzheimer's disease (AD) is the most common cause of dementia. New data show that the prevalence of dementia will almost double every 20 years, and it is believed that the cur-

demencije. Novi podatci pokazuju da će se prevalencija demencije gotovo udvostručiti svakih 20 godina i vjeruje se da je sadašnji procijenjeni broj osoba s demencijom u Hrvatskoj veći od 80.000 (3) .

AB danas sve više i više dobiva na značenju kako unutar neurologije i psihijatrije tako i u segmentu obiteljske medicine odnosno javno-zdravstvene problematike. Najnoviji epidemiološki podatci pokazuju da trenutno na svijetu od AB boluje oko 47 milijuna ljudi, te da uz svaku oboljelu osobu još najmanje 3 osobe, najčešće kao neformalni njegovatelji, nose to teško breme. Kratkoročne i srednjoročne prognoze glede pojavnosti AB nažalost nisu nimalo optimistične, pa tako predviđaju pravu epidemiju ove bolesti, tj. do 2050. godine očekuje se da bi globalno na svijetu moglo biti i preko 115 milijuna oboljelih od AB (4). Danas kada demenciju nastojimo dijagnosticirati što ranije, bitno je oboljelima i njihovim obiteljima ponuditi kontinuirani i što kvalitetniji program liječenja i skrbi. AB odnosno demencija je stanje koje ne možemo izliječiti, ali upotrebom standardnog (simptomatskog) farmakološkog liječenja antidementivima i drugim psihofarmacima moguće je usporiti prirodni tijek bolesti, poboljšati kvalitetu života oboljelih i njihovih njegovatelja. U menedžmentu bolesti potrebno je rabiti i nefarmakološke intervencije jer su se i one pokazale učinkovitima. Hrvatska, kao zemlja čije je prosječno stanovništvo jedno od najstarijih u Europi, treba napraviti akcijski plan za borbu s AB, tj. znatno se ozbiljnije pripremati za nadolazeću epidemiju te bolesti u skoroj budućnosti (5).

DIJAGNOZA DEMENCIJE

Demencija je karakterizirana pojavom kognitivnih smetnji i otežanog obavljanja svakodnevnih aktivnosti, ali je ona često popraćena i dodatnim neurološkim ili psihijatrijskim simptomima. Za dijagnozu demencije danas se

rent estimated number of people with dementia in Croatia is greater than 80,000 (3).

Today, AD is gaining more and more prominence within neurology and psychiatry but also within family medicine and public healthcare. The latest epidemiological data show that there are currently 47 million people suffering from AD in the world and that there are at least three people per each patient who carry this heavy burden, most commonly as informal caregivers. Short-term and long-term prognoses regarding the appearance of AD are unfortunately not at all optimistic, and a real epidemic of this disease has been predicted. In other words, over 115 million people in the world are expected to be suffering from AD by 2050 (4). Today, when we attempt to diagnose dementia as soon as possible, it is important to offer patients and their families a continued and high-quality program of treatment and care. AD, or dementia, is a condition we cannot cure, but the use of standard (symptomatic) pharmacological treatment using antidementives and other psychopharmacs can slow down the natural course of the disease and improve the quality of life for patients and their caregivers. Disease management also requires the use of non-pharmacological interventions because they too have shown to be effective. As a country whose population is among the oldest in Europe, Croatia must form an action plan to combat AD and seriously prepare for the upcoming epidemic of this disease in the near future (5).

DIAGNOSING DEMENTIA

Dementia is characterised by the appearance of cognitive interruptions and difficulties in performing everyday activities but is also followed by additional neurological or psychiatric symptoms. In the diagnosis of dementia, the following criteria are used today: a combination of laboratory tests and a neurological examination in order to exclude all other potential causes of dementia; a combination of methods of

koriste: kombinacije laboratorijskih pretraga i neurološkog pregleda kako bi se isključili svi ostali potencijalni uzroci demencije; kombinacije metoda radiološke dijagnostike kao što su računalna tomografija (CT, engl. *Computed Tomography*) i magnetska rezonancija (MRI, engl. *Magnetic Resonance Imaging*), kako bi se detektirala atrofija entorinalnog korteksa ili hipokampusa; kombinacije radionukleidnih metoda kao što su pozitronska emisijska tomografija (PET, engl. *Positron Emission Tomography*) i jedno-fotonska emisijska računalna tomografija (SPECT, engl. *Single-Photon Emission Computed Tomography*), kako bi se mogla pratiti snižena perfuzija ili snižena metabolička aktivnost u pojedinim moždanim regijama.

Za procjenu kognitivnog oštećenja koriste se različiti orijentacijski testovi koji moraju uključivati procjenu pažnje, orijentacije, dugoročne i kratkoročne memorije, govora, prakse, vizualno-prostornih sposobnosti, mogućnost donošenja odluke, itd.

Prema rezultatima istraživanja Mimice i sur. (6) rezultati na ljestvici *Mini Mental State-Examination* (MMSE) kada se upitnik standardizira i validira u nekoj populaciji mogu bolje doprinijeti prepoznavanju osoba pod rizikom koje treba uputiti na ambulantno liječenje u klinike za liječenje demencije (6).

Uz navedene metode koriste se i metode neuropsihologijske dijagnostike, tj. psihometrijski testovi koji su posebno dizajnirani za bolesnike s demencijom jer demenciju često prate i drugi psihijatrijski simptomi (depresija, anksioznost, euforija, apatija, psihotični simptomi i dr.) (7). Depresivni simptomi se pojavljuju kod 50 % osoba oboljelih od demencije. Oštećenje mozga bez obzira na etiologiju demencije je čimbenik rizika za razvoj depresije. U oboljelih od AB depresija je povezana s degeneracijom neurona te povećanom gustoćom amiloidnih plakova i neurofibrilarnih snopića posebno u području jezgara moždanog debla (*locus ceruleus, raphe nuclei*). Diferencijalna dijagnoza između de-

radiological diagnostics such as computed tomography (CT) and magnetic resonance imaging (MRI) in order to detect entorhinal cortex atrophy or hippocampal atrophy; a combination of radionuclide methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) in order to follow lower perfusion or lower metabolic activity in certain regions of the brain.

Various orientation tests are used for the assessment of cognitive impairment, and they must include the assessment of focus, orientation, long-term and short-term memory, speech, practice, visual-spatial abilities, the ability to make decisions, etc.

According to the study conducted by Mimica *et al.* (6), the results of the Mini Mental State-Examination scale (MMSE) may, following the standardization and validation of the questionnaire in a certain population, improve the identification of people at risk who should be sent to receive outpatient treatment at a clinic for the treatment of dementia (6).

Along with the methods listed above, there are also the methods of neuropsychological diagnostics, or psychometric tests designed specifically for patients suffering from dementia, because dementia is often followed by other psychiatric symptoms (depression, anxiety, euphoria, apathy, psychotic symptoms, etc.) (7). Depressive symptoms occur in 50% of people suffering from dementia. Brain damage, regardless of the aetiology of dementia, is a risk factor in the development of depression. In patients with AD, depression relates to neuronal degeneration and an increased thickness of amyloid plaques and neurofibrillary bundles, especially in the area of brain stem nuclei (*locus ceruleus, raphe nuclei*). The differential diagnosis between dementia, depression, and dementia with depression is difficult due to the overlapping symptoms in the aforementioned entities such as apathy, agitation, social isolation, impaired cognitive abilities, loss of bodyweight, and insomnia (8). Research results

mencije, depresije i demencije s depresijom je teška zbog preklapanja simptoma kod navedenih entiteta poput apatije, agitacije, socijalne izolacije, oštećenja kognitivnih sposobnosti, gubitka tjelesne težine i nesanice (8). Rezultati istraživanja upućuju da je neuroticizam u srednjoj životnoj dobi povezan s povećanim rizikom od demencije u AB te da stres posreduje u ovoj povezanosti. Rezultati imaju kliničke implikacije jer je identificirana skupina žena pod rizikom za demenciju u AB (9). Osim kognitivnih sposobnosti vrlo je važno pratiti i promjene ličnosti – od početne anksioznosti i depresije do smanjene kontrole emocionalnih reakcija koja, uz potpunu nemogućnost uvida i nekritičnost, nastaje u krajnjoj fazi ove bolesti. Također je važno istaknuti i emocionalnu potporu obitelji, odnosno osoba koje se skrbe o bolesnicima oboljelima od demencije (10). Brojne studije upućuju da uporaba specifičnih antidementiva dovodi do usporavanja napredovanja AB te odgode institucionalizacije kao i opterećenja skrbnika. Navedeno je od izravnog značenja u ukupnim troškovima liječenja ovih bolesnika. Učinjene farmakoekonomske procjene služe kao podloga te opravdavaju buduću uporabu najčešće korištenih antidementiva (kolinesterazni inhibitori) s kliničk*og*, ali i farmakoekonomskog aspekta, a što će biti od značenja ne samo za bolesnike već i za njihove skrbnike te društvo u cjelini (11). Razvojem neuroznanosti došlo je do novih znanstvenih i kliničkih spoznaja iz područja AB koje su uklopljene u DSM–5. Nova kategorija „Neurokognitivni poremećaji" u DSM–5 zamijenila je DSM-IV kategoriju „Delirij, demencija, amnestički i drugi kognitivni poremećaji". Novi naziv obuhvaća poremećaje kojima je glavna karakteristika stečeni gubitak u kognitivnoj funkciji, a ne obuhvaća poremećaje u kojima je stečeno kognitivno oštećenje prisutno, ali nije glavna karakteristika samog poremećaja (npr. shizofrenija, velika depresivna epizoda). DSM–5 definira tri sindroma: delirij, veliki neurokognitivni poremećaj, blagi neurokognitiv-

suggest that neuroticism in middle age is associated with an increased risk of dementia in AD and that stress modulates this association. The results have clinical implications because a group of women at risk of dementia in AD has been identified (9). Apart from cognitive abilities, it is very important to follow changes in the personality – from initial anxiety and depression to reduced control over emotional reactions which, along with a complete lack of insight and self-reflection, appears in the last stage of this disease. It is also important to emphasise the emotional support of the family or the people who care for patients suffering from dementia (10). Numerous studies have suggested that the use of certain antidepressants leads to a slowdown in the progress of AD and a delay in institutionalisation, as well as an increase in the burden placed on the caregiver. All of the above is of direct importance for the overall cost of treatment of such patients. Performed pharmacoeconomic assessments serve as a basis and justify the use of commonly used antidementives (cholinesterase inhibitors) from both a clinical and pharmacoeconomic perspective, which is of importance not just for patients but also their caregivers and the society as a whole (11). Development of neuroscience has brought new scientific and clinical insights from the area of AD which have been integrated into DSM-5. The new category of DSM-5 called *Neurocognitive disorders* has replaced the DSM-IV category *Delirium, dementia, amnestic, and other cognitive disorders*. The new term encompasses disorders which share the main characteristic of acquired loss of cognitive function and does not encompass disorders in which acquired loss is present, but not the main characteristic of the disorder itself (e.g. schizophrenia, major depressive episodes). DSM-5 defines three syndromes: delirium, major neurocognitive impairment, and mild neurocognitive impairment. Major neurocognitive impairment implies the earlier term dementia, although that does not exclude the use of the term dementia within aetiological subtypes in which that term is the standard one,

ni poremećaj. Veliki neurokognitivni poremećaj podrazumijeva od ranije poznati naziv demencija, iako to ne isključuje korištenje izraza demencija unutar etioloških podtipova u kojih je taj izraz standardan, dok blagi neurokognitivni poremećaj označava manje tešku razinu kognitivnog poremećaja (12).

Uloga lipida u etiologiji i progresiji AB još je uvijek nejasna. Visoke razine lipida mogle bi biti jedan od rizičnih čimbenika za AB, ali također je pronađeno da nema povezanosti ili čak da visoke vrijednosti kolesterola mogu imati protektivni učinak na razvoj AB (13).

ALZHEIMEROVA BOLEST

AB je najčešći oblik demencije i na nju otpada oko 60-70 % slučajeva demencije u Europi (14). Oko 15-20 % demencija otpada na vaskularnu demenciju, a 10-25 % na ostale oblike demencije (14).

Još uvijek nije poznat točan uzrok AB, ali je poznato da postoje određeni čimbenici rizika koji pridonose pojavi bolesti (15,16). Kao potencijalni čimbenici rizika za AB spominju se visoka životna dob, genetička predispozicija, spol, kardiovaskularni čimbenici i prisutnost blagog kognitivnog (spoznajnog) poremećaja (MCI, engl. *Mild Cognitive Impairment*) (17-20). Kao čimbenici rizika spominju se također način života (prehrana, tjelesna aktivnost, pušenje, konzumiranje alkohola, itd.) (21-23). Prema podatcima iz literature ulogu u razvoju AB imaju stres, trauma glave, upalni procesi, dijabetes, depresija te okolišni čimbenici (24-28). Postoji više različitih negenetičkih čimbenika rizika koji su do sada istraživani, a povezani su s povećanim rizikom za AB. Ovi negenetički čimbenici rizika odnose se na: pušenje, konzumaciju alkohola, prekomjernu tjelesnu težinu i pretilost, hipertenziju, hiperkolesterolemiju, lošu prehranu, šećernu bolest, kardiovaskularne i cerebrovaskularne bolesti, razinu edukaci-

while mild neurocognitive impairment signifies a less severe level of cognitive impairment (12).

The role of lipids in the aetiology and progression of AD remains unclear. High levels of lipids may be one of the risk factors of AD, but some results have also found no association or that high values of cholesterol may even have a protective effect on the development of AD (13).

ALZHEIMER'S DISEASE

AD is the most common form of dementia and comprises approximately 60-70% of cases of dementia in Europe (14). Around 15-20% are cases of vascular dementia, and 10-25% of other forms of dementia (14).

The exact cause of AD is yet to be discovered, but it is known that there are certain risk factors which contribute to the onset of the disease (15,16). Such potential risk factors of AD are old age, genetic predisposition, sex, cardiovascular factors, and the presence of mild cognitive impairment (MCI) (17-20). Other risk factors are related to lifestyle (diet, physical activity, smoking, drinking alcohol, etc.) (21-23). According to data from existing literature, the development of AD is affected by stress, head trauma, inflammatory processes, diabetes, depression, and environmental factors (24-28). There are several non-genetic risk factors that have been studied and are connected to a higher risk of AD. Such non-genetic risk factors are: smoking, drinking alcohol, excess weight and obesity, hypertension, hypercholesterolemia, poor diet, diabetes, cardiovascular and cerebrovascular diseases, education level, socioeconomic status, and physical and mental activity (29). Age is considered the best-confirmed and most important risk factor in the development of the sporadic form of AD (7). Lower cardiac index is associated with a higher risk of developing AD (30). Smoking has proved to be a risk factor in the development of AD, especially in

je pojedinaca, socioekonomski status, fizičku i mentalnu aktivnost (29). Dob se smatra najbolje potvrđenim i najvažnijim čimbenikom rizika za razvoj sporadičnog oblika AB (7). Niži kardijalni indeks povezan je s povišenim rizikom za razvoj AB (30). Pušenje se pokazalo kao rizičan čimbenik za razvoj AB, posebice kod osoba koje nisu nositelji E4 alela (31-33), a isti je slučaj i s prekomjernom zloporabom alkohola. Poznata je činjenica da osobe s dijagnozom ovisnosti o alkoholu često pate i od demencije uzrokovane dugogodišnjom zloporabom alkohola. Osobe u srednjoj životnoj dobi, ovisne o alkoholu, imaju oko 3 puta veći rizik od razvoja demencije (34).

Dio studija je povezao povišeni krvni tlak s većim rizikom od razvoja AB kod osoba koje nisu primale adekvatnu terapiju (35,36). Kod osoba kod kojih je hipertenzija držana pod kontrolom pomoću antihipertenziva pokazano je da ovi lijekovi zapravo mogu imati protektivan učinak u slučaju razvoja demencije u kasnijoj životnoj dobi (37,38). Hiperkolesterolemija, tj. povišena razina kolesterola u serumu smatra se također jednim od rizičnih faktora za razvoj AB (39,40).

Od psihosocijalnih čimbenika važnih u razvoju demencije ističe se važnost razine obrazovanja kod pojedinaca. Pokazano je da osobe koje imaju višu razinu obrazovanja rjeđe obolijevaju od demencije (41,42). Također, smatra se da je i uključenost pojedinca u društvene obveze važan čimbenik kod razvoja demencije u kasnijoj dobi, tj. istraživanja pokazuju da osobe koje imaju slabije socijalne kontakte te žive više izoliranim životom imaju i veći rizik za razvoj AB (43,44). Fizička aktivnost mogla bi imati pozitivan učinak na kognitivne sposobnosti pojedinca, tj. redovita fizička aktivnost mogla bi odgoditi pojavu simptoma demencije u starosti (45), a isto vrijedi i za mentalnu aktivnost (46).

Prema rezultatima istraživanja Pivac i sur. (47) muški pacijenti bili su mlađi, imali su kraće trajanje bolesti, blažu demenciju i bolje kognitivne izvedbe nego žene s AB. Varijante gena

people without E4 allele (31-33), and the same is true for alcohol abuse. It is a known fact that people who have been diagnosed with alcohol addiction often suffer from dementia caused by years of alcohol abuse. Middle-aged people addicted to alcohol have an approximately three times greater risk of developing dementia (34).

Some studies have found an association between increased blood pressure and a higher risk of developing AD in people who did not receive appropriate therapy (35,36). It has been shown that in people whose hypertension was controlled using antihypertensives, such medications can have a protective effect in the case of the development of dementia in older age (37,38). Hypercholesterolemia, i.e. increased level of serum cholesterol, is considered as another risk factor in the development of AD (39,40).

Among psychosocial factors important in the development of dementia, the importance of education level stands out. It has been shown that people with higher education levels develop dementia less commonly (41,42). It is also believed that the inclusion of people in social obligations is an important factor in the development of dementia in old age. In other words, research has shown that people who have weaker social contacts and a more isolated lifestyle are also at a higher risk of developing AD (43,44). Physical activity may have a positive effect on the cognitive abilities of an individual, meaning that regular physical activity may postpone the onset of symptoms of dementia in old age (45), and the same is true of mental activity (46).

According to the study conducted by Pivac *et al.* (47), male patients were younger, had a shorter disease duration, milder dementia, and better cognitive performance than women suffering from AD. Gene variation of brain-derived neurotrophic factor (BDNF) and the presence of one or two Met allele with regards to BDFN Val-66Met polymorphism were significantly associated with the presence of psychotic symptoms in men, but not in women suffering from AD (47).

za moždani neurotrofni čimbenik (BDNF) i to prisustvo jednog ili dva Met alela s obzirom na BDNF Val66Met polimorfizam bile su značajno povezane s prisustvom psihotičnih simptoma u muškaraca, ali ne i u žena s AB (47).

ALZHEIMEROVA BOLEST U POPULACIJI ŽENA

Prevalencija i incidencija AB, najčešćeg uzroka demencije, znatno je veća kod žena nego kod muškaraca a ta se razlika s dobi povećava (48). Meta-analiza 13 populacijskih studija diljem SAD-a, Europe i Azije upućuje na to kako žene imaju značajno veći rizik za razvoj AB, ali ne i drugih demencija. Dvostruko veća učestalost AB kod žena u odnosu na muškarce djelomično se može objasniti time što žene imaju očekivano dulji životni vijek. Dokazi na temelju oslikavanja mozga, postmortalna analiza, hormonske terapije i genetika upućuju da AB pogađa različito muškarce i žene. Žene imaju lošiju kognitivnu izvedbu na mnogim neuropsihologijskim testovima u odnosu na muškarce u istom stadiju bolesti, odnosno višestruke kognitivne funkcije kod žena teže su i šire zahvaćene nego kod muškaraca. Muškarci značajno nadmašuju žene u nekoliko kognitivnih domena uključujući jezične i semantičke sposobnosti, vizuospacijalne sposobnosti i epizodičko pamćenje. Ove se razlike ne mogu pripisati godinama, edukaciji ni težini demencije. Mogući razlozi za ovakvu nepovoljnu kognitivnu izvedbu u žena su redukcija estrogena u postmenopauzi kod žena, veće kognitivne rezerve muškaraca te utjecaj apolipoproteina E. Određeni drugi biološki čimbenici također bi mogli objasniti različite kliničke manifestacije AB s obzirom na spol. U odnosu na muškarce, žene imaju manji hipokampalni volumen i pokazuju veću atrofiju mozga i degeneraciju temporalnog režnja, a postmortalne analize pokazale su kako žene imaju više neuritskih plakova i neurofibrilarnih klupka u odnosu na muškarce.

ALZHEIMER'S DISEASE IN WOMEN

The prevalence and incidence of AD, the most frequent cause of dementia, is significantly greater among women than men, and the difference increases with age (48). A meta-analysis of 13 population studies across the US, Europe, and Asia suggests that women are at a significantly higher risk of developing AD, but not other types of dementia. The fact that AD occurs twice as much among women than men can be explained by a longer life expectancy in women. Evidence based on brain imaging, post-mortem analysis, hormonal therapy, and genetics suggests that AD affects men and women differently. Women show worse cognitive performance on numerous neuropsychological tests in comparison with men at the same stage of the disease, meaning that a number of cognitive functions are more severely and widely affected in women than in men. Men are significantly better than women in several cognitive areas, including linguistic and semantic abilities, visual-spatial abilities, and episodic memory. Such differences cannot be ascribed to age, education, or the level of dementia. Possible reasons for such unfavourable cognitive performance in women are the reduction of oestrogen during postmenopause in women, greater cognitive reserves in men, and the influence of apolipoprotein E. Certain other biological factors may also explain different clinical manifestations of AD regarding sex. In comparison with men, women have a lower hippocampal volume and show greater brain atrophy and temporal lobe degeneration, and post-mortem analyses have shown that women have higher levels of neuritic plaques and neurofibrillary bundles in comparison with men. Additionally, sexual steroid hormones following menopause may affect the risk of developing AD in women. Similarly, the reduction of testosterone levels with age may also increase the risk of developing AD in men. Despite the advancements in the understanding of the clinical aspect of sex differences in AD, the

Također, spolni steroidni hormoni nakon menopauze mogu utjecati na rizik za razvoj AB u žena. Slično, smanjenje razina testosterona s dobi također može povećati rizik za razvoj AB kod muškaraca. Usprkos napretku u razumijevanju kliničkog aspekta spolnih razlika u AB, mehanizmi u podlozi AB i pitanje zašto je ženski rod podložniji razvoju AB, zapravo ostaju nejasni (48).

Istraživanja pokazuju kako estrogeni moduliraju protok krvi i aktivnost u ključnim područjima mozga uključujući područje za pažnju te verbalno i prostorno pamćenje. Kako se razina estrogena nakon menopauze smanjuje, slabi i kognitivna funkcija (49). Žene zapažaju promjene u kognitivnoj funkciji osobito u vrijeme menopauze. Brojna istraživanja pokazala su kako estrogeni modeliraju protok krvi i aktivnost u ključnim područjima mozga, uključujući područje za pažnju, te verbalno i prostorno pamćenje. Naime, žene u razdoblju menopauze imaju teškoće s pamćenjem i koncentracijom što naposlijetku može rezultirati svakodnevnim problemima s ponašanjem i sposobnošću nošenja s njima. Stručnjaci su suglasni kako na kognitivnu funkciju mogu utjecati brojni drugi čimbenici, no jasno je da je promjena u razini estrogena važna i značajno utječe na kognitivne čimbenike u žena. Također, istraživanja su ukazala na zaštitnu ulogu estrogena ne samo za kogniciju, već i za pojavu Alzheimerove demencije (50). U istraživanju *Seattle Midlife Women's Health Study* 62 % žena žalilo se na teškoće pamćenja i koncentracije u vrijeme oko menopauze, što je rezultiralo u svakodnevnim problemima s ponašanjem i sposobnošću nošenja s njima.

Istražujući pomoć hormonskog nadomjesnog liječenja (HNL) u borbi protiv smanjenja kognitivnih sposobnosti, u baltimorskoj je longitudinalnoj studiji starenja primijenjen niz ispitivanja u istraživanju učinka HNL na kognitivnu funkciju žena u postmenopauzi u dobi između 50 i 89 godina (51,52). Unatoč sličnostima

mechanisms underlying AD and the question of why women are more susceptible to developing AD remain unclear (48).

Research shows that oestrogens modulate blood flow and activity in key brain regions including the regions of attention and verbal and spatial memory. As the level of oestrogen following menopause decreases, cognitive function is also impaired (49). Women notice changes in cognitive function, especially during menopause. Numerous studies have shown that oestrogens modulate blood flow and activity in key brain regions, including the region of attention and verbal and spatial memory. During menopause women experience difficulties with memory and concentration, which may result in everyday problems with behaviour and the ability to cope with such problems. Experts agree that the cognitive function may be affected by numerous other factors, but it is clear that the change in oestrogen levels is important and significantly affects cognitive factors in women. Studies have also emphasized the protective role of oestrogen not just for cognition, but the onset of Alzheimer's dementia as well (50). In the study entitled *Seattle Midlife Women's Health Study*, 62% of women complained about memorization and concentration problems during menopause, which resulted in everyday problems with behaviour and the ability to cope with such problems.

While researching the benefits of hormone replacement therapy (HRT) in the struggle against impaired cognitive abilities, the *Baltimore Longitudinal Study of Aging* applied several tests in the investigation of the effect of HRT on the cognitive function in women during postmenopause at the age between 50 and 89 (51,52). Despite similarities between groups regarding health and other characteristics, women who received HRT exhibited different blood flow in brain regions responsible for memorization and different brain activity while performing tasks related to memory in comparison to women who received a placebo. Women who received HRT were sig-

skupina u zdravlju i ostalome, žene koje su primjenjivale HNL imale su različit protok krvi kroz područja mozga odgovorna za pamćenje te drukčiju moždanu aktivnost tijekom ispunjavanja zadaća u svezi s pamćenjem u odnosu na žene koje su uzimale placebo. Žene koje su primjenjivale HNL značajno su bolje verbalno učile i izvodile testove pamćenja uključujući i ispitivanje svježeg i kratkotrajnog pamćenja. Uz to, bolje su rezultate imale žene koje su primjenjivale kombinaciju estrogena i progestagena nego žene koje su primjenjivale samo estrogen (50). Jacob i sur. (53) uspoređivali su primjenu estrogena s kognitivnom funkcijom. Skupina koju je sačinjavalo 727 žena u postmenopauzi ispitivana je nakon dvije i nakon tri godine primjene liječenja. Žene koje su trenutno i prethodno primjenjivale HNL imale su mnogo više ishodišne vrijednosti kognitivne funkcije nego žene koje nisu nikada primjenjivale HNL. Također, u žena koje su primjenjivale HNL verbalno se pamćenje s vremenom poboljšalo (53). Yaffe i sur. 1998. proveli su meta-analizu deset studija ispitujući ulogu primjene estrogena u poboljšanju kognitivne funkcije, sprječavanja demencije ili smanjenja njezine težine u žena u postmenopauzi (54). Rezultati pokazuju 29-postotno smanjenje rizika za nastanak demencije u žena koje su primjenjivale estrogensko nadomjesno liječenje (ENL) (54). Prema rezultatima istraživanja Yaffe i sur. žene u postmenopauzi s višim koncentracijama nevezana estrogena manje su sklone padu kognitivne funkcije (54).

Uz pomoć testa MMSE 425 je žena u dobi od 65 godina ili starije ispitivano tijekom šest godina. Mjerene su im koncentracije bioraspoloživa estradiola i testosterona nevezana za bjelančevine u krvi. Usporedba je razine estrogena i kognitivne funkcije ukazala kako unatoč nepostojanju sveze između razine ukupnoga estradiola i kognitivne funkcije postoji sveza između razine slobodnog estradiola i kognitivne funkcije (55). Žene s višim koncentracijama slobodnog estradiola imale su 70

nificantly better at verbal learning and performing memory tests, including tests of fresh and short-term memory. Also, women who received a combination of oestrogen and progestogen showed better results than women who received only oestrogen (50). Jacob *et al.* (53) compared the application of oestrogen to the cognitive function. A group comprised of 727 women in postmenopause was tested after two and three years of receiving therapy. Women who were currently receiving HRT and had previously done so showed a much greater starting value of the cognitive function than women who never received HRT. Additionally, women who received HRT showed an improvement in verbal memory over time (53). In 1998, Yaffe *et al.* conducted a meta-analysis of ten studies researching the role of the application of oestrogen in the improvement of the cognitive function, the prevention of dementia, or the reduction of its severity in women in postmenopause (54). The results showed a 29 percent reduction of risk of developing dementia in women who received oestrogen replacement therapy (ORT) (54). According to the results of the study conducted by Yaffe *et al*, women in postmenopause with higher concentrations of unbound oestrogen are less prone to the impairment of the cognitive function (54).

With the aid of the MMSE test, 425 women at the age of 65 or older were followed over a period of six years. Measurements were taken of their concentrations of biodegradable oestradiol and testosterone not bound to blood proteins. The comparison of the levels of oestrogen and the cognitive function showed that despite the lack of association between the levels of total oestradiol and cognitive function there was an association between the level of free oestradiol and cognitive function (55). Women with higher concentrations of free oestradiol had a 70% lower risk of impaired cognitive function than women with lower concentrations of free oestradiol. This result suggests that oestrogen must be able to cross the blood-brain barrier in order to have a favoura-

posto manji rizik za pad kognitivne funkcije nego žene s niskom koncentracijom slobodnog estradiola. Taj nalaz upućuje kako estrogen mora biti sposoban prijeći krvno-moždanu barijeru da bi imao povoljan učinak. Budući da neki progestageni olakšavaju sposobnost slobodnog estrogena da prođe krvno-moždanu barijeru, neki kombinirani pripravci HNL mogu biti najučinkovitiji u sprječavanju kognitivnoga pada (55). LeBlanc i sur. (56) su na temelju provedenog istraživanja zaključili kako su žene s menopauzalnim simptomima, koje su primjenjivale HNL, imale poboljšanja u verbalnom pamćenju, budnosti, prosuđivanju i motoričkoj brzini. Uz to su imale i manji rizik za demenciju (56). McEwen i sur. (57) u studiji također ukazuju kako HNL može spriječiti pogoršanje kognitivne funkcije u svezi sa starenjem, a nadomjestak estrogena možda štiti hipokampus i druga područja mozga povezana s demencijom (57). Opservacijske su studije pokazale kako estrogeni mogu odgoditi ili spriječiti pojavu AB ako je liječenje započeto u ranome razdoblju postmenopauze (50). Tang i sur. proučavali su 1124 starije žene prosječne životne dobi 74,2 godine tragajući za kognitivnim promjenama tijekom pet godina (58). Zaključili su kako je pojava AB bila značajno kasnija u žena koje su uzimale estrogene nego u onih koje ih nisu uzimale. U žena koje su koristile estrogene dulje od godine dana smanjenje je rizika za bolest bilo najveće (58). Randomizirano i placebom kontrolirano ispitivanje *Alzheimer Disease Cooperative Study* istraživalo je prethodnu primjenu HNL u žena kojima je dijagnosticirana blaga do umjerena AB (59). Prema rezultatima istraživanja liječenje estrogenima nije usporilo napredovanje bolesti. U ispitivanju *Cache County Study* (59) koje je istražilo incidenciju AB u 135 muškaraca prosječne životne dobi 73,5 godina i 1889 žena prosječne životne dobi 73,2 godine tijekom tri godine, istraživači su zaključili kako nadomjestak estrogena može zaustaviti degeneraciju i zaštititi žene od pojave AB, no

ble effect. Since some progestogens help free oestrogen pass the blood-brain barrier, certain combined preparations of HRT may be most effective in the prevention of cognitive impairment (55). Based on conducted research, LeBlanc *et al.* (56) concluded that women with menopausal symptoms who received HRT showed improvement in verbal memorization, alertness, judgement, and rapid motor skills. They also showed a lower risk of dementia (56). In their study, McEwen *et al.* (57) also showed that HRT can prevent cognitive function impairment in connection with aging, and oestrogen replacement may protect the hippocampus and other brain regions tied to dementia (57). Observational studies have shown that oestrogens may delay or prevent the onset of AD if the therapy was started in an early stage of postmenopause (50). Tang *et al.* examined 1124 older women of an average age of 74.2 years in search of cognitive changes over a period of five years (58). They concluded that the onset of AD happened significantly later in women who received oestrogens than in those who did not. The greatest reduction of the risk of developing the disease was noted in women who used oestrogens for more than a year (58). The randomized and placebo-controlled *Alzheimer Disease Cooperative Study* studied prior application of HRT in women diagnosed with mild to moderate AD (59). According to the results of the research, the oestrogen therapy did not slow down the onset of the disease. In the *Cache County Study* (59), which investigated the incidence of AD in 135 men of the average age of 73.5 years and in 1889 women of the average age of 73.2 years over the period of three years, the researchers found that oestrogen replacement may stop the degeneration and protect women from the onset of AD, but that effect depends on the length of the therapy and on how soon the therapy was initiated. The oestrogen therapy did not improve the condition of participants who were already suffering from AD (59). In the third workshop in Pisa in 2003, the International Menopause Society concluded that "oestrogens may provide a better protection from

taj učinak ovisi o duljini trajanja liječenja te o tome kako je rano liječenje započeto. Liječenje estrogenima nije poboljšalo stanje sudionika studije koji su već imali AB (59). Na Trećoj radionici (*Workshop)* u Pizi 2003. godine Internacionalno društvo za menopauzu ustvrdilo je kako „estrogeni mogu pružiti bolju zaštitu od AB mlađim ženama u postmenopauzi, a podatci novih opservacijskih studija upućuju kako najveću zaštitu od AB u tih žena može pružiti dulja primjena estrogena“ (50). Epidemiološki dokazi pokazuju smanjenje rizika za AB uz liječenje estrogenima, dok su kontrolirana ispitivanja pokazala izostanak bilo kojega pozitivnog učinka u žena s razvijenom AB (60). Barbara Sherwin zaključuje da s obzirom na prikupljene dokaze može postojati kritični „prozor“ u vremenu za započinjanje liječenja estrogenima, odmah nakon nastupa postmenopauze, koja može najviše povećati njegov potencijal protiv pada kognicije, kao i u smanjenju rizika za AB (60). Ranim započinjanjem i najmanjom učinkovitom dozom žene mogu računati na zaštitni učinak estrogena uz vrlo nizak rizik liječenja (50). Daljnja istraživanja potrebna su kako bi se objasnile razlike prema spolu, a i klinička istraživanja bi trebala rutinski pratiti razlike prema spolu (61). Hormonske promjene povezane s menopauzom i postmenopauzom imaju potencijal da utječu na procese povezane sa simptomima i patogenezom AB, ali učinci menopauze na rizik za AB mogu se povezati samo indirektno. Devet randomiziranih kliničkih ispitivanja terapije koja uključuje hormon estrogen u pacijenata s AB pronađeno je sistemskim pretraživanjem literature. Rezultati upućuju da hormonska terapija ne poboljšava kognitivne simptome žena s AB. Ni jedno kliničko ispitivanje hormonske terapije ne odnosi se na prevenciju AB, ali jedno kliničko ispitivanje daje umjerene dokaze da kontinuirana, kombinirana terapija estrogenom i progestogenom započeta u dobi od 65 godina ili starijoj povećava rizik za demenciju. Hipoteza kritičnog razdoblja ukazuje

AD to younger women in postmenopause, and the data from new observational studies suggest that in those women the best form of protection from AD is provided by prolonged application of oestrogen" (50). Epidemiological evidence has shown a reduction of risk of developing AD while receiving oestrogen therapy, while controlled tests have shown a lack of any positive effects in women with developed AD (60). Barbara Sherwin has concluded that collected data shows there may be a critical "window" in time for starting oestrogen therapy immediately after the onset of postmenopause, which can significantly increase its potential in fighting against cognition impairment, as well as in the reduction of risk of developing AD (60). With an early start and the lowest effective dosage, women can count on the protective effect of oestrogen with a very low treatment risk (50). Further research is needed to explain the differences between sexes, and clinical research should routinely follow the differences between sexes (61). Hormonal changes tied to menopause and postmenopause have the potential of affecting processes associated with the symptoms and pathogenesis of AD, but the effects of menopause on the risk of developing AD can be associated only indirectly. A systematic search of literature uncovered nine randomized clinical studies of a therapy that included the hormone oestrogen in patients with AD. The results suggest that hormonal therapy does not improve cognitive symptoms in women with AD. None of the clinical studies of hormonal therapy refer to the prevention of AD, but one clinical study gives moderate evidence suggesting that continued, combined oestrogen and progesterone therapy begun at the age of 65 or later increases the risk of dementia. The hypothesis of a critical period suggests that a hormonal therapy started at a younger age closer to menopause may reduce the risk of developing AD (62).

Cardiac disease is an independent risk factor for mild neurocognitive impairment. The comparison between sexes has shown a stronger association with the female sex. The prevention

da hormonska terapija započeta u mlađoj dobi vremenski bliže menopauzi može reducirati rizik od AB (62).

Kardijalna bolest je neovisni rizični čimbenik za blagi neurokognitivni poremećaj. Usporedba prema spolu pokazala je jaču povezanost sa ženskim spolom. Prevencija i liječenje kardijalnih bolesti i čimbenika vaskularnog rizika može sniziti rizik za blagi neurokognitivni poremećaj (63). Hormonska terapija estrogenom započeta tijekom kasne postmenopauze ne poboljšava epizodično pamćenje (važan rani simptom AB) i povećava rizik za demenciju (64).

Kod žena koje razviju demenciju, prihvaćanje promjene uloge i identiteta može biti vrlo teško za njih same i za druge. Promjena iz uloge primarnog njegovatelja u obitelji u osobu kojoj treba njega je vrlo velika i često joj se oboljela žena opire. Oboljele žene najviše muči pitanje identiteta te zadržavanje kontrole pri donošenju odluka kao i prelazak iz uloge pružatelja njege i stupa obitelji u status njegovane osobe. Istaknuta je važnost „ručne torbice“ i njenog nošenja kao znaka očuvanosti dostojanstva i identiteta (65). Gubitak neovisnosti u oboljelih žena rađa „zahvalnu krivnju“. Žene koje njeguju kćeri često ne iznose iskreno sve smetnje da bi što duže zadržale neovisnost. U tim bi slučajevima parcijalno uključivanje socijalne skrbi pomoglo premostiti ovaj problem. Žene oboljele od demencije zbog bolesti moraju napuštati svoje uloge njegovatelja, skrbitelja u obitelji te ih to dodatno hendikepira i tjera u naučenu bespomoćnost (66).

Diljem čitavog svijeta demencija neproporcionalno utječe na žene. Iako su istraživanja pokazala veću pojavnost demencije kod žena, nema puno razrađenih strategija i provođenja adekvatnih mjera kao odgovor na te rezultate (67).

Osim što prema prezentiranim podatcima žene češće obolijevaju od Alzheimerove demencije, žene su također te koje u bitno većoj mjeri pružaju neformalnu njegu ljudima s demencijom,

and treatment of cardiac diseases and factors of vascular risk may reduce the risk of mild neurocognitive impairment (63). Hormonal oestrogen therapy begun during late postmenopause does not improve episodic memory (an important early symptom of AD) and increases the risk of dementia (64).

In women who develop dementia, the acceptance of a change in role and identity may be very difficult for themselves and others. The shift of role from primary caregiver in the family to the person who requires care is significant, and women suffering from this disease often struggle against it. Such women are greatly troubled by the question of identity and maintaining control while making decisions, as well as the change from the role of the caregiver and pillar of the family to the person requiring care. There is great significance in the “purse” and carrying it as a symbol of maintained dignity and identity (65). The loss of independence in women suffering from the disease creates “gratitude guilt”. Women who are cared for by their daughters often do not express all their problems honestly in order to maintain their independence for as long as possible. In such cases, partial involvement of social care may help solve the problem. Women suffering from dementia are forced to leave their role of the caregiver in the family, and that additionally handicaps them, forcing them into learned helplessness (66).

Across the world, dementia affects women disproportionately. Although research has shown that dementia is more frequent in women, there are few developed strategies and adequate measures being put into action as a response to those results (67).

Apart from the fact that presented data shows that women develop Alzheimer’s disease more frequently, most people offering informal care to those suffering from dementia are women, and approximately two thirds of informal caregivers are women. The proportion is much greater in countries with low and medium income, so

te su oko dvije trećine neformalnih njegovatelja žene. Taj omjer je puno veći u zemljama s niskim i srednjim prihodima, stoga je učinak pružanja njege na zdravlje i dobrobit, kao i financijski učinak, veći za žene u zemljama s niskim prihodima. Žene čine većinu formalne njegovateljske radne snage, posebice u njezi osoba s demencijom te su one te koje pružaju većinu zdravstvene i socijalne skrbi u zajednici, bolnicama i domovima (67).

U neformalnoj skrbi se razlozi odabira uloge njegovatelja razlikuju i ovdje navodimo četiri glavna razloga. Često je ta uloga njegovatelja nametnuta zbog kulturoloških razloga i tradicije. Na primjer, na Cipru se smatra prirodnom ulogom žene, a sličnog su stava u obiteljima Latinoamerikanaca u SAD-u i domicilnoj Španjolskoj (68-70). Zatim, uloga njegovatelja je kulturološka i tradicijska u multigeneracijskim kućanstvima (Sri Lanka, azijske zemlje). Takva uloga je neupitna i altruistična. Kćeri i snahe su emotivna potpora, podrška u svakodnevnim aktivnostima, sinovi su financijska potpora (70,71). U Sjedinjenim Američkim Državama, u latinoameričkim obiteljima 78 % njegovatelja su kćeri i nevjeste, u kineskim obiteljima 63 %, a ostalim obiteljima 49 % (72). U Nizozemskoj, u turskim i marokanskim obiteljima najstarija kćer ili supruga najstarijeg sina, tradicionalno je njegovatelj (73). Proširena bračna uloga također je razlogom zašto žena preuzima ulogu njegovatelja te na kraju, žena će preuzeti ulogu njegovatelja zbog osjećaja ponosa i zadovoljstva.

Njegovatelji-članovi obitelji razvijaju psihičke tegobe poput velikog depresivnog poremećaja i anksioznih poremećaja (67,74). Žene njegovatelji se žale na osjećaj tereta, stres i depresivne simptome više od muških njegovatelja, i izvještaji su slični iz svih kultura i društava. Supruge-njegovateljice puno teže podnose ulogu njegovatelja. Taj teret je osobito vidljiv nakon dvije godine brige za oboljelog člana; javljaju se teži osjećaj stresa, gubitak bliskosti, anksiozni

the effect of caregiving on health and wellbeing, as well as finances, is greater for women in countries with low income. Women make up the greater part of the caregiving workforce, especially in care for people with dementia, and women also offer most medical and social care in communities, hospitals, and homes (67).

In informal care, the reasons for choosing the role of the caregiver vary, and the four main reasons are listed here. Very often the role of the caregiver is enforced by culture and tradition. For example, caregiving is considered the natural role for women on Cyprus, and a similar attitude is shared among Latino-American families in the US and in their domicile, Spain (68-70). The role of the caregiver is also part of culture and tradition in multigenerational households (Sri Lanka, Asian countries). Such a role is unquestionable and altruistic. Daughters and daughters-in-law provide emotional support and support in everyday activities, while sons are a financial support (70,71). In the United States of America, in Latino-American families 78% of caregivers are daughters and brides, while in Chinese families they make up 63%, and 49% in other families (72). In the Netherlands, in Turkish and Moroccan families the oldest daughter or the wife of the oldest son is traditionally the caregiver (73). The extended marital role is another reason why women take over the role of the caregiver, but also because of a sense of pride and pleasure.

Caregiving family members develop psychological problems such as major depressive disorder and anxiety disorders (67,74). Female caregivers complain of a sense of burden, stress, and symptoms of depression more than male caregivers, and reports from all cultures and societies are similar. Caregiving wives have a more difficult time coping with the role of the caregiver. The burden is especially visible after two years of caring for a sick member of the family; there is a greater feeling of stress, a loss of closeness, symptoms of anxiety and depression, and decreased family support (67,75). First, they

i depresivni simptomi, i manja je podrška okoline (67,75). Susreću se prvo s gubitkom kontrole, zbunjeno prihvaćaju novu ulogu, kvaliteta braka i bliskost stradava te se moraju naviknuti na nove uloge u kućanstvu. Muškarci supružnici njegovatelji se žale na gubitak kvalitetne komunikacije, kognitivne i bihevioralne simptome, gubitak društva i financijski teret (76). Kćeri njegovatelji bolje podnose stres njegovanja, imaju također vlastitu ulogu majke, ali više puše, smanjene su tjelesne aktivnosti, više dobivaju na tjelesnoj težini, razvijaju hipertenziju i češće obolijevaju od kronične bolesti pluća od majki njegovateljica. Latinoamerikanke bolje podnose stres u odnosu na kineske imigrante te bijelu populaciju SAD-a (77).

Žene su najveći udio profesionalne njegovateljske radne snage u skrbi za demenciju te u pružanju formalne zdravstvene i socijalne skrbi i potpore osobi s demencijom i njenom ili njegovom njegovatelju. Mnoge žene koje rade kao njegovateljice skrbe i za svoju djecu i starije roditelje. To djeluje na njihovu sposobnost pružanja obiteljske skrbi i utječe na kvalitetu života cijele obitelji, uključujući i osobu koja živi s demencijom.

Žene čine 42 % radnog pučanstva, a u zdravstvenom sektoru u mnogim zemljama čine 75 % radne snage. Većina ih je zaposlena u skrbi za oboljele od demencije, kako u primarnoj, kućnoj njezi, socijalnoj skrbi, dobrotvornim organizacijama i udruženjima. U Velikoj Britaniji 87 % osoba koje rade u formalnoj skrbi su žene, ¾ su izravno uključene, a ¼ su zaposlene kod privatnih poslodavaca (78).

Sve zemlje moraju shvatiti trenutnu i predviđenu pojavnost i prepoznati da demencija neproporcionalno utječe na žene. Učinak na žene mora biti utvrđen u svakoj pojedinoj zemlji, kao i pregled trenutno dostupne potpore i što je potrebno da bi se zadovoljilo buduće potrebe. Žene treba upoznati s pomoći koja im je dostupna, putem podizanja svijesti i boljeg obavještavanja od strane organizacija zdravstvene

experience loss of control, confusion in accepting the new role, decreased quality of marriage and closeness, and the need to adjust to the new roles in the household. Caregiving husbands complain of a loss of quality communication, cognitive and behavioural symptoms, a loss of companionship, and financial burden (76). Caregiving daughters who are also mothers themselves, cope with the stress of caregiving better, but smoke more, show reduced physical activity, gain more weight, develop hypertension, and develop chronic lung disease more often than caregiving mothers. Latino-American women cope with stress better than Chinese immigrants and the white population of the US (77).

Women make up the largest segment of professional caregivers providing care for those suffering from dementia and the largest part of those offering formal medical and social care and support to people with dementia and their caregivers. Many women who work as caregivers also provide care to their own children and elderly parents. This affects their ability to provide family care and the quality of life of the entire family, including the person living with dementia.

Women make up 42% of the workforce, and in in many countries they make up 75% of the workforce in the health sector. Most are employed as caregivers to people with dementia in primary care, home care, social care, and charities. In Great Britain, 87% of people employed in formal care are women, three-quarters are directly involved, and one quarter is employed in private practice (78).

All countries must understand the current and predicted incidence of dementia, and recognize the fact that dementia affects women disproportionately. Every country must identify the effect on women, as well as review currently available support and what is necessary to satisfy future demands. Women should be informed about the aid that is available to them by raising awareness and improving the way organizations providing health and social care

i socijalne skrbi o formalnim i neformalnim uslugama koje postoje i kako ih ostvariti.

Sve zdravstvene radnike koji rade u zajednici treba obučiti o demenciji kako bi se povećalo njihovo samopouzdanje u shvaćanju ponašanja ljudi s demencijom.

Nizak ekonomski status, financijske nagrade i nedostatna obuka i podrška za rad u njegovateljskoj struci utječu na žene, njihove obitelji i na ljude koji žive s demencijom. Postoji potreba za stručnim kompetencijama zdravstvenih i njegovateljskih radnika koji rade s ljudima koji žive s demencijom s kompleksnim potrebama i komorbiditetima.

Palijativna skrb je fokusirana na ublažavanje i olakšavanje simptoma koje ima osoba s AB pa iako postoje određene zakonitosti i faze kod AB karakteristične za većinu bolesnika, važno je osvijestiti postojanje velikih interindividualnih razlika. Stoga je od iznimne važnosti pristup usmjeren osobi, a naglasak u palijativnoj skrbi treba ležati na fleksibilnosti kako bi se udovoljilo jedinstvenim potrebama svakog bolesnika i njegove obitelji (5,79).

Komunikacija je medij kroz koji se odvija interpersonalna interakcija koja je od iznimne važnosti u palijativnoj skrbi za bolesnika s AB i članovima njegove obitelji (79,80).

ZAKLJUČAK

Spol utječe na tri specifične skupine: žene koje žive s demencijom; žene koje skrbe za ljude s demencijom u ulozi profesionalnog njegovatelja; žene koje preuzimaju ulogu neformalnog njegovatelja osobe oboljele od demencije. Potrebno je napraviti ili poboljšati postojeće nacionalne programe za liječenje demencije te naglasiti jasnije ulogu žena i njihovu specifičnost povezanu s ovim entitetom. Istraživanja treba usredotočiti na pitanja što ljudima pomaže graditi izdržljivost kako bi se prilagodili i dugoročno nosili s problemom demencije.

share information on available formal and informal services and how to use them.

All medical workers working in the community should be educated about dementia in order to increase their confidence in understanding the behaviour of people with dementia.

Low economic status, financial rewards, and a lacking education and support for working in the caregiving profession affect women, their families, and people living with dementia. There is a need for professional competencies in medical and caregiving workers working with people with dementia with complex needs and comorbidities.

Palliative care is focused on mitigating and alleviating symptoms in people with AD, and although there are certain regularities and phases in AD which are characteristic for most patients, it is important to raise awareness about significant interindividual differences. Therefore, an approach focused on the individual person is very important, and the emphasis in palliative care should be on flexibility in order to satisfy the unique needs of every patient and their family (5,79).

Communication is a medium for developing interpersonal interaction, which is of great importance in palliative care for a patient with AD and the members of their family (79,80).

CONCLUSION

Sex affects three specific groups: women living with dementia; women providing care for people with dementia in the role of a professional caregiver; women who are taking over the role of an informal caregiver for a person suffering from dementia. It is necessary to create or improve existing national programs for the treatment of dementia and emphasize the role of women and their specific connection to this entity. Studies should focus on the question what helps people build their resilience in order to adjust to the problem of dementia and cope with it in the long term.

U daljnjim translacijskim istraživanjima i kliničkom radu s osobama oboljelima od AB nužno je obratiti pozornost na spoznaje o spolnim razlikama u razvoju i progresiji ove bolesti, tj. na uočene značajne nepovoljnosti koje nosi ženski spol, a shodno tome prilagoditi i sam tretman bolesti ovisno o spolu.

Further translational research and clinical work with people suffering from AD must pay attention to insights about sex differences in the development and progression of this disease, i.e. in the observed disadvantages related to female sex, and therefore adjust the treatment itself according to the sex of the patient.

LITERATURA/REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 2013; 9: 63-75.
2. World Health Organization. International statistical classification of diseases and related health problems, 10th revision (ICD-10). Geneva: World health organization, 2010.
3. Mimica N, Presečki P. How do we treat people with dementia in Croatia. Psych Danub 2010; 22: 363-6.
4. Mimica N. Alzheimerova bolest – što nam je činiti. Neurol Croat 2014; 63: 61.
5. Mimica N. Demencija i palijativna skrb. Neurol Croat 2011; 60: 119-23.
6. Boban M, Malojčić B, Mimica N i sur. The reliability and validity of the mini-mental state examination in the elderly Croatian population. Dement Geriatr Cogn Disord 2012; 33: 385-92.
7. Nikolac Perković M. Uloga moždanog neurotrofnog čimbenika u demenciji. Doktorska disertacija. Osijek: Sveučilište Josipa Jurja Strossmayera u Osijeku, 2015.
8. Presečki P, Mihanović M, Mimica N. Depresivnost kod oboljelih od demencije. Neurol Croat 2012; 61: 42.
9. Johansson L, Guo X, Duberstein PR i sur. Midlife personality and risk of Alzheimer disease and distress: a 38-year follow-up. Neurology 2014; 83: 1538-44.
10. Pačić-Turk Lj. Utjecaj demencije na mentalne sposobnosti i svakodnevne aktivnosti. Zbornik sažetaka Prve edukativne konferencije o Alzheimerovoj bolesti (EdukAl). Zagreb: Hrvatska udruga za Alzheimerovu bolest, 2015, str. 21.
11. Vitezić D, Mimica N. Lijekovi za liječenje Alzheimerove bolesti – farmakoekonomski aspekti i smjernice. Neurol Croat 2012; 61: 46.
12. Presečki P, Mimica N. Dijagnosticiranje Alzheimerove bolesti u DSM-5. Neurol Croat 2014; 63: 48.
13. Presečki P, Mück-Šeler D, Mimica N i sur. Serum lipid levels in patients with Alzheimer's disease. Coll Antropol 2011; 35: 115-20.
14. Fratiglioni L, Launer LJ, Andersen K i sur. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic diseases in the elderly research group. Neurology 2000; 54: S10-5.
15. Forero DA, Casadesus G, Perry G, Arboleda H. Synaptic dysfunction and oxidative stress in Alzheimer's disease: emerging mechanisms. J Cell Mol Med 2006; 10: 796-805.
16. Fratiglioni L, Ahlbom A, Viitanen M, Winblad B. Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. Ann Neurol 1993; 33: 258-66.
17. Kivipelto M, Ngandu T, Fratiglioni L i sur. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005; 62: 1556-60.
18. Lee AY. Vascular dementia. Chonnam Med J 2011; 47: 66-71.
19. Musicco M. Gender differences in the occurrence of Alzheimer's disease. Funct Neurol 2009; 24: 89-92.
20. Serretti A, Olgiati P, De Ronchi D. Genetics of Alzheimer's disease. A rapidly evolving field. J Alzheimers Dis 2007; 12: 73-92.
21. Kroner Z. The relationship between Alzheimer's disease and diabetes: Type 3 diabetes? Altern Med Rev 2009; 14: 373-9.
22. Sleegers K, Roks G, Theuns J i sur. Familial clustering and genetic risk for dementia in a genetically isolated Dutch population. Brain 2004; 127: 1641-9.
23. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. Int J Biochem Cell Biol 2005; 37: 289-305.
24. Gao Y, Huang C, Zhao K i sur. Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Int J Geriatr Psychiatry 2013; 28: 441-9.
25. Grant WB, Campbell A, Itzhaki RF, Savory J. The significance of environmental factors in the etiology of Alzheimer's disease. J Alzheimers Dis 2002; 4: 179-89.
26. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009; 8: 1006-18.
27. Van Den Heuvel C, Thornton E, Vink R. Traumatic brain injury and Alzheimer's disease: a review. Prog Brain Res 2007; 161: 303-16.
28. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology 2008; 71: 1057-64.

29. Povova J, Ambroz P, Bar M i sur. Epidemiological of and risk factors for Alzheimer's disease: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2012; 156: 108-14.
30. Jefferson AL, Beiser AS, Himali JJ i sur. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham heart study. Circulation 2015; 131: 1333-9.
31. Aggarwal NT, Bienias JL, Bennett DA i sur. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. Neuroepidemiology 2006; 26: 140-6.
32. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. Neurology 1999; 52: 1408-12.
33. Ott A, Slooter AJ, Hofman A i sur. Smoking and risk of dementia and Alzheimer's disease in a population based cohort study: the Rotterdam study. Lancet, 1998; 351: 1840-3.
34. Anttila T, Helkala EL, Viitanen M i sur. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. BMJ 2004; 329: 539.
35. Kivipelto M, Ngandu T, Fratiglioni L i sur. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005; 62: 1556-60.
36. Launer LJ, Ross GW, Petrovitch H i sur. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000; 21: 49-55.
37. Khachaturian AS, Zandi P, Lyketsos CG i sur. Antihypertensive medication use and incident Alzheimer disease: The Cache county study. Arch Neurol 2006; 63: 686-92.
38. Yasar S, Corrada M, Brookmeyer R, Kawas C. Calcium channel blockers and risk of AD: The Baltimore longitudinal study of aging. Neurobiol Aging 2005; 26: 157-63.
39. Kivipelto M, Laakso MP, Tuomilehto J, Nissinen A, Soininen H. Hypertension and hypercholesterolaemia as risk factors for Alzheimer's disease: potential for pharmacological intervention. CNS drugs 2002; 16: 435-44.
40. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005; 330: 1360.
41. Ngandu T, von Strauss E, Helkala EL i sur. Education and dementia: what lies behind the association? Neurology 2007; 69: 1442-50.
42. Qiu C, Backman L, Winblad B, Aguero-Torres H, Fratiglioni L. The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen project. Arch Neurol 2001; 58: 2034-39.
43. Saczynski JS, Pfeifer LA, Masaki K i sur. The effect of social engagement on incident dementia: the Honolulu-Asia aging study. Am J Epidemiol 2006; 163: 433-40.
44. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002; 155: 1081-7.
45. Larson EB, Wang L, Bowen JD i sur. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006; 144: 73-81.
46. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. J Gerontol B Psychol Sci Soc Sci 2003; 58: P249-55.
47. Pivac N, Nikolac M, Nedic G i sur. Brain derived neurotrophic factor Val66Met polymorphism and psychotic symptoms in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35: 356-62.
48. Klepac N, Maljković L. Alzheimerova demencija kod žena. Neurol Croat 2016; 65: 33.
49. Shaywitz SE, Shaywitz BA, Pugh KR i sur. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. JAMA 1999; 281: 1197-202.
50. Demarin V. Kognitivna funkcija u menopauzi: HNL – benefit ili rizik? Medix 2003; 9: 48-9.
51. Resnick SM, Maki PM. Effects of hormone replacement therapy on cognitive and brain aging. Ann NY Acad Sci 2001; 949: 203-14.
52. Maki PM, Zonderman AB, Resnick SM i sur. Enhanced verbal memory in nondemented elderly women receiving hormone replacement therapy. Am J Psychiatry 2001; 159: 227-33.
53. Jacobs DM, Tang MX, Stern Y i sur. Cognitive function in nondemented older women who took estrogen after menopause. Neurology 1998; 50: 368-73.
54. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effect on cognitive function and dementia. JAMA 1998; 279: 668-95.
55. Notelovitz M. E2 and CEE Σ different oestrogens, different effects. Proceedings of HRT in the post-WHI era expert meeting. Madeira, Portugal, 2003.
56. LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001; 285: 1489-99.
57. McEwen BS, Alves SE, Bulloch K, Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. Neurology 1997; 48: S8-15.
58. Tang MX, Jacobs D, Stern Y *et al*. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996; 348: 429-32.
59. Zandi PP, Carlson MC, Plassman BL i sur. Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache county study. JAMA 2002; 288: 2123-9.
60. Sherwin BB. Estrogen and cognitive functioning in women. Endocr Rev 2003; 24: 133-51.

61. Baron S, Ulstein I, Werheid K. Psychosocial interventions in Alzheimer's disease and amnestic mild cognitive impairment: evidence for gender bias in clinical trials. Aging Ment Health 2015; 19: 290-305.
62. Henderson VW. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. J Steroid Biochem Mol Biol 2014; 142: 99-106.
63. Roberts RO, Geda YE, Knopman DS i sur. Cardiac disease associated with increased risk of nonamnestic cognitive. JAMA Neurol 2013; 70: 374-82.
64. Henderson VW. Estrogens, episodic memory, and Alzheimer's disease: a critical update. Semin Reprod Med 2009; 27: 283-93.
65. Buse C, Twigg J. Women with dementia and their handbags: Negotiating identity, privacy and 'home' through material culture. J Aging Stud 2014; 30: 14-22.
66. Calasanti T, Bowen ME. Spousal caregiving and crossing gender boundaries: Maintaining gendered identities. J Aging Stud 2006; 20: 253–63.
67. Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimers Dement 2014; 10: e47-92.
68. Flores YG, Hinton L, Barker JC, Franz CE, Velasquez A. Beyond familism: a case study of the ethics of care of a Latina caregiver of an elderly parent with dementia. Health Care Women Int 2009; 30: 1055–72.
69. Romero-Moreno R, Losada A, Marquez M *et al*. Leisure, gender, and kinship in dementia caregiving: psychological vulnerability of caregiving daughters with feelings of guilt. J Gerontol B Psychol Sci Soc Sci 2014; 69: 502–13.
70. SEARO. Promoting ageing and health – the Sri Lankan experience. Ministries of social services and health. WHO Regional Health Forum 2012; 16 (1).
71. Watt MH, Perera B, Ostbye T, Ranabahu S, Rajapakse H, Maselko J. Care-giving expectations and challenges among elders and their adult children in Southern Sri Lanka. Ageing Soc 2014; 34: 838-58.
72. Gray HL, Jimenez DE, Cucciare MA, Tong HQ, Gallagher-Thompson D. Ethnic differences in beliefs regarding Alzheimer disease among dementia family caregivers. Am J Geriatr Psychiatry 2009; 17: 925-33.
73. Wezel N, Francke AL, Devillé WL, Blom MM, van Grondelle NJ, Kayan-Acun E. Family care for immigrants with dementia: The perspectives of female family carers living in the Netherlands. Dementia 2016; 15: 69–84.
74. Godfrey JR, Warshaw GA. Toward optimal health: considering the enhanced healthcare needs of women caregivers. J Womens Health 2009; 18: 1739-42.
75. Zvěřová M. Frequency of some psychosomatic symptoms in informal caregivers of Alzheimer's disease individuals. Prague's experience. Neuro Endocrinol Lett 2012; 33: 565-7.
76. Pretorius C, Walker S, Heyns PM. Sense of coherence amongst male caregivers in dementia: A South African perspective. Dementia 2009; 8: 79–94.
77. Gusi N, Prieto J, Madruga M, García JM, Gonzalez Guerrero JL. Health-related quality of life and fitness of the caregiver of patient with dementia. Med Sci Sports Exerc 2009; 41: 1182-7.
78. World Health Organization. Gender and health workforce statistics WHO Spotlight on statistics issue 2, 2008. http:// www.who.int/hrh/statistics/spotlight_2.pdf (pristupljeno 9. travnja 2015.).
79. Đorđević V, Braš M, Vučevac V. Izazovi u komunikaciji u radu s oboljelima od Alzheimerove demencije i članovima njihovih obitelji. Neur Croat 2016; 65: 53.
80. Mimica N. Komunikacija s osobom oboljelom od demencije. Medix 2011; 17 (92 - Suppl 1): 56-8.