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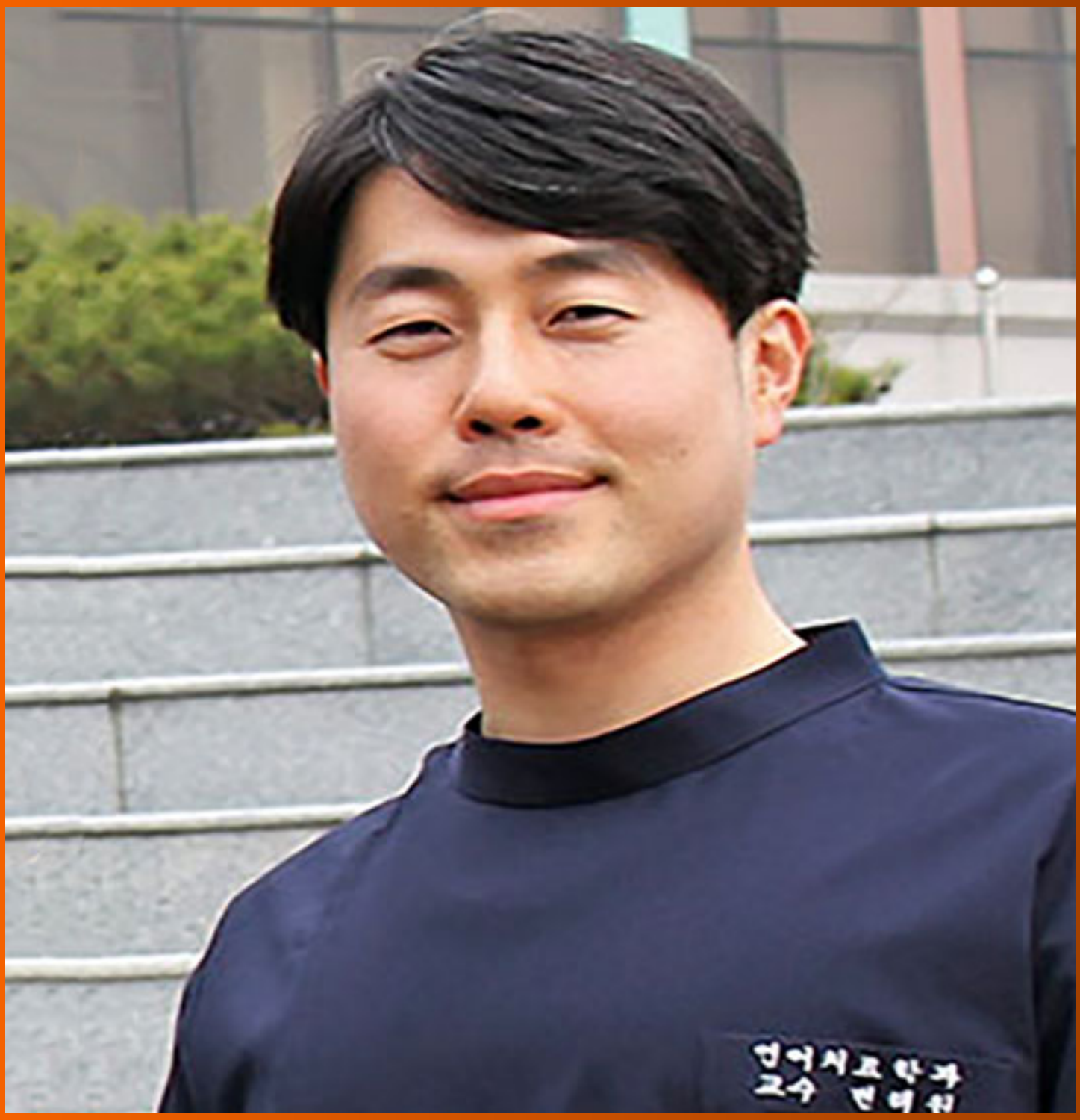

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MINIREVIEWS

Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications

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Abstract

A spectrum of neuropsychiatric disorders is a common complication from stroke. Neuropsychiatric disorders after stroke have negative effects on functional recovery, increasing the rate of mortality and disability of stroke survivors. Given the vital significance of maintaining physical and mental health in stroke patients, neuropsychiatric issues after stroke have raised concerns by clinicians and researchers. This mini-review focuses on the most common non-cognitive functional neuropsychiatric disorders seen after stroke, including depressive disorders, anxiety disorders, post-traumatic stress disorder, psychosis, and psychotic disorders. For each condition, the clinical performance, epidemiology, identification of the therapeutic implication, and strategies are reviewed and discussed; the main opinions and perspectives presented here are based on the latest controlled studies, meta-analysis, or updated systematic reviews. In the absence of data from controlled studies, consensus recommendations were provided accordingly.

Key words: Stroke; Neuropsychiatric disorders; Depression; Anxiety; Post-traumatic stress disorder; Psychosis

Core tip: The purpose of this mini-review is to summarize the research advance of neuropsychiatric disorders including depressive disorders after stroke, anxiety disorders after stroke, post-traumatic stress disorder after stroke, post-stroke psychosis, and psychotic disorders. Recent evidence showed that neuropsychiatric disorders after stroke are associated with worsened outcomes yet are still under-recognized. With the exception of depressive disorders after stroke, the other neuropsychiatric disorders lack

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reliable and high-quality evidence in clinical practice. Further studies should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of neuropsychiatric disorders after stroke.

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INTRODUCTION

With the aging of the global population, stroke has become the second leading cause of death for people over age 60 and the fifth leading cause in people between the ages of 15 and 59 worldwide. Due to brain damage and loss of function, stroke is also a major cause of long-term disability in adults worldwide, which decreases the quality of life for patients and increases the global medical burden[1]. Recently, neuropsychiatric issues appearing after stroke have raised concerns for clinicians and researchers. Psychiatric disorders are common complications post-stroke and are associated with worsened outcomes, including low quality of life, increase in the burden of caregiving, and unfavorable functional status[2,3]. Even early neuropsychiatric disorders after stroke (NDS) may increase the risk of mortality and recurrence in patients with stroke[4,5]. The current management and treatment of the majority of NDS is not satisfactory, except for some antidepressants that show therapeutic benefit[3,6]. Patients with NDS do not even benefit from existing advanced medical intervention. A retrospective study showed patients with stroke and neuropsychiatric co-morbidities were slightly less likely to receive carotid revascularization intervention compared to those who did not have neuropsychiatric co-morbidities[7]. A lack of subjective intervention willingness from patients and inadequate social and family support may be the reason for the difference in intervention.

Neuropsychiatric impairment after stroke encompasses a wide spectrum of diseases, including neurocognitive disorders and non-cognitive disorders[8]. In this review, we will put an emphasis on discussing the most common non-cognitive NDS after stroke or transient ischemic attacks (TIA): Depressive disorders and anxiety disorders, as well as post-traumatic stress disorder (PTSD), psychosis and psychotic disorders after stroke. Uncommon conditions such as apathy, personality disorders, emotional lability, emotional incontinence, fatigue, mania, catastrophic reactions, and some manifestations of NDS will not be included in this review. These conditions were excluded because these disorders and their manifestations do not have widely acknowledged diagnostic criteria at present, have not established definitions, or are not regarded as standard neuropsychiatric diseases in the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5)[9]. Something particularly noteworthy is that some patients may suffer from co-occurring NDS (*i.e.*, depression and anxiety) after stroke. Although there exists substantial overlap of symptoms between these NDS, each issue will be reviewed separately.

This review will address the clinical significance for stroke, screening, and identification of each NDS. We then will focus on therapeutic implications and discuss strategies.

The purpose of this mini-review is to outline the current research in the field of NDS, including clinical presentation, epidemiology, therapeutic implications, and strategies to alleviate neuropsychiatric symptoms, to improve the well-being of patients, and to reinforce physical and mental status for stroke survivors. We focused on clinical significance and therapeutic strategies. Our opinions on management and treatment mainly depend on results from studies of evidence-based medicine and expert consensus.

Risk factors for NDS

Genetic background and family history are considered to be important potential susceptibility factors that can affect NDS. A meta-analysis showed that stroke patients with a family history of psychiatric disorders have an increased risk for developing post-stroke depression[10]. Several studies have also identified a number of potential candidate genes that may underlie susceptibility to depressive and anxiety disorders

after stroke. Serotonin transporter gene is the most common gene associated with depression. A meta-analysis of four studies with 641 individuals indicated that there was a positive association between the homozygous short variation allele genotype of the serotonin transporter-linked promoter region (5-HTTLPR) and post-stroke depression, whereas the homozygous long variation allele genotype of 5-HTTLPR showed a significant negative association with post-stroke depression. The heterozygous short and long allele genotypes for 5-HTTLPR or rs25531 and *STin2 VNTR* gene polymorphisms of the serotonin transporter gene have not been proven to be susceptibility genes for post-stroke depression[11]. Although the 5-HTTLPR polymorphism was found to have a significant association with an antidepressant response and remission in Caucasians[12], the relationship between the 5-HTTLPR polymorphism and the responsiveness of antidepressants for post-stroke depression remained not well-determined.

It was reported that stroke patients with brain-derived neurotrophic factor gene hypermethylation levels and brain-derived neurotrophic factor gene polymorphisms had a higher risk of developing post-stroke depression and post-stroke anxiety (PSA)[13,14]. In addition, polymorphism in the tryptophan hydroxylase 2 gene were also found to be involved in PSA susceptibility[15].

NDS is multifactorial and influenced by many other demographic and external factors. A meta-analysis published in 2017 with 36 studies analyzed the research status and emerging trends in regard to risk factors for post-stroke depression, and suggested that the correlation between a history of psychiatric disorders and post-stroke depression was highest among all factors; other demographic and external risk factors for post-stroke depression were female, age (< 70 years), stroke severity, functional impairments, and lack of social and family support[16]. However, one other meta-analysis also published in 2017 with 18 studies concluded that gender, age, and social factors were not reliable risk factors[17]. Moreover, a recent study confirmed that unmarried status and excessive fatigue were potential negative risk factors for PSA[18].

Medical conditions and socioeconomic status, such as time to access of health services, willingness to seek treatment, health insurance coverage, medical expenditure, and educational level may have a partial effect on NDS[19,20]. However,few prospective studies have focused on the above factors for the development and evolution of NDS. Features of neuropsychiatric disorders after stroke is shown in Table 1.

DEPRESSIVE DISORDERS AFTER STROKE

Screening and identification

Post-stroke depressive (PSD) disorders are the most commonly reported and widely investigated among all types of NDP in the literature. PSD is the most frequent treatable neuropsychiatric complication of stroke at any one time after onset. A prospective study showed PSD can occur from 1 to 18 mo after the onset of stroke, and prevalence of PSD was not found to vary considerably over time (the prevalence at 1, 3, 6, 12, and 18 mo were 24.5%, 27.1%, 28.3%, 19.8%, and 26.3% respectively)[21].

A previous meta-analysis of 61 studies with 25488 patients indicated that the pooled frequency of PSD was 34% in 32 stroke cohorts[22], consistent with a meta-analysis of 32 studies with 8938 patients receiving antidepressant therapy where the pooled frequency was 31%[23].

The proportional frequency of depression reported ranged from 5%[24]-84%[25], which varied considerably across studies because of different PSD identification criteria, threshold time points of assessment during follow-up, and clinical setting. A national register-based cohort study in Denmark consecutively recruited 157243 first-time hospitalized patients with new-onset PSD and 160236 local healthy residents as a reference population during 2 years of follow-up between 2001 and 2011. The total incidence of depressive disorders after stroke was 25.4%, compared with 7.8% in the control population[26].

Compared with orthopedic patients with similar degrees of motor disability[27], myocardial infarction, and similar predisposing factors of cardiovascular disease[23], patients with stroke are more likely to suffer from depressive disorders, suggesting that there is a more complex neurobiological mechanism for the etiology of PSD.

Generally, PSD occurs in the range from 25%-35% of stroke survivors with the frequency estimated to be the highest in the 1st year after onset, with gradually declining prevalence thereafter[28].

Optimal screening for and identification of PSD is vital for following treatment and management; however, there is currently no established diagnostic criterion for PSD. The DSM-5 classifies PSD as a "depressive disorder due to another medical

Table 1 Features of neuropsychiatric disorders after stroke

Disorders	Prevalence/ frequency, %	Main clinical manifestations	Screening tools	Identification	Management and treatment
Depressive disorders after stroke	5-84	Depressed mood; marked reduction in interest or pleasure in activities; decreased/increased appetite/weight; insomnia or hypersomnia; psychomotor agitation/retardation; loss of energy/fatigue; feelings of worthlessness/inappropriate guilt; loss of concentration; appear pessimistic about health issues/recurrent thoughts of death or suicide	Center for epidemiological studies-depression scale; hospital anxiety depression scale; Hamilton depression rating scale; beck depression inventory; geriatric depression scale; PHQ-9	According to the DSM-5 classification, PSD is defined as a depressive disorder due to TIA or stroke.	SSRIs and SNRIs; psychological intervention; mental and physical exercise; neuromodulation
Anxiety disorders after stroke	20-24	Prominent anxiety; excessive fear, worry, and concern about health issues; intense dread or uneasiness; panic attacks, or obsessions or compulsions predominate	Hamilton anxiety scale; hospital anxiety and depression scale-anxiety subscale	According to the DSM-5 classification, PSA is defined as an anxiety disorder due to TIA or stroke.	SSRIs; Tricyclic antidepressant; benzodiazepines; "Z-drugs" (zolpidem, zaleplon and eszopiclone); psychological interventions; mind-body interventions
PTSD after stroke	8.3-29.6	Intrusive memories; alterations in physical reactions and arousal; avoidance; negative alterations in cognition and mood	PTSD checklist for a stressor, TIA or stroke as stressor; clinician administered PTSD scale; impact of events scale-revised; posttraumatic stress diagnostic scale; structured clinical interview for DSM	PTSD is related to TIA or stroke which creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events.	Psychotherapeutic approach procedures; antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs
Psychosis and psychotic disorders after stroke	4.67-5.05	Hallucinations or delusions; disorganized speech; catatonic or inappropriate motor behavior	Neuropsychiatric inventory	According to the DSM-5 classification post-stroke psychotic disorders are defined as psychotic disorders due to TIA or stroke.	Antipsychotic drugs; neuromodulation and psychosocial therapy; psychological intervention

TIA: Transient ischemic attacks; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin-norepinephrine reuptake inhibitors; PSD: Post-stroke depressive; PSA: Post-stroke anxiety; PTSD: Post-traumatic stress disorder; PHQ-9: 9-item patient health questionnaire; DSM-5: Diagnostic and statistical manual of mental disorders.

condition". The identification and diagnosis of PSD is usually based on the combination of detailed clinical assessment and screening scale tools in the clinical practice. For example, clinicians diagnose PSD using a structured clinical interview for DSM-5 combined with a screening scale before initiating PSD treatment. There is no universally accepted screening tool for PSD. The following psychiatric scales are frequently used to measure PSD symptoms in clinical study and practice: The center for epidemiological studies depression scale, hospital anxiety depression scale, Hamilton depression rating scale, beck depression inventory, geriatric depression scale, and nine-item patient health questionnaire (PHQ-9). In 2017, the American Heart Association and American Stroke Association jointly issued the first scientific consensus statement for healthcare, which comprehensively discussed the epidemiology, pathophysiology, screening, management, and prevention of PSD[28]. Based on the results of a meta-analysis with 2907 participants, the center for epidemiological studies depression scale, Hamilton depression rating scale, and PHQ-9 scores have proven to have higher sensitivities for identifying PSD, using the international classification of disease or DSM diagnosis of depression as the reference standard[29]. The PHQ-9 is one of the most commonly used tools for screening for PSD with high validity and reliability in primary care. One individual patient's data meta-

analysis showed that a cutoff of a score of 10 on the PHQ-9 yielded a maximum diagnostic performance[30]. Considering the structured interview for DSM as the reference standard for PSD, the sensitivity and specificity of PHQ-9 were 0.82 and 0.97, respectively. The overall diagnostic performance of the PHQ-9 was better than the hospital anxiety depression scale-D and geriatric depression scale[31]. Another individual participant's data meta-analysis of PHQ-9 reported the existence of selective cutoff reporting bias when estimating sensitivity in most studies[32]. In addition, a systematic review concluded that the results regarding the sensitivity and specificity of the PHQ-9 for PSD screening and identification were uncertain[33].

Remarkably, unlike depressive disorders caused by other diseases, screening for PSD faces many challenges; particular attention should be paid to the actual condition of patients with stroke. Neurological symptoms resulting from stroke such as aphasia, alexia, or agnosia may lead to expressive or receptive dysfunction[34]. Cognitive impairment such as loss of concern, anosognosia, abulia, or lack of insight may develop similar depressive symptoms[35]. The above adverse factors for screening could hinder the identification and diagnosis of PSD. Therefore, screening and identification procedures of PSD should be performed following protocols tailored to the individual.

Management and therapeutic implication

PSD is associated with worsened functional outcomes after stroke. A meta-analysis including 14 studies before May 2018 with 17609 PSD patients evaluating the association between PSD and the mortality of different follow-up times revealed that PSD showed a negative impact on survival rates; the effect of PSD on short-term mortality was slightly higher than its effect on long-term mortality[4]. A recent case-control study showed PSD increased disability severity in ischemic stroke survivors, whose Barthel index and Rivermead mobility index scores were both lower than stroke survivors without PSD at both admission and discharge[36].

In theory, the early and prophylactic use of PSD may reduce the risk of PSD in stroke survivors. A meta-analysis with eight prospective randomized controlled trials published from 1990 to 2011 revealed that antidepressant prophylaxis (mianserin, fluoxetine, nortriptyline, sertraline, escitalopram, milnacipran) reduced the odds of developing PSD, and pooled results uncovered the benefit of early initiation of pharmacotherapy in stroke patients[37]; however, the final conclusion of this review was based on eight studies with four classes of antidepressants [selective serotonin reuptake inhibitor (SSRI), tetracyclic antidepressant, tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor (SNRI)]. Therefore, there may be a high relative heterogeneity among the studies. A systematic review just published in November 2019, which retrieved data from 2009 to 2018, suggested that the use of SSRIs, psychological intervention [*e.g.*, cognitive behavioral therapy (CBT)], as well as mental and physical exercise could relieve most mood symptoms of PSD, but the level of evidence quality of the included studies were low to moderate[38]. A meta-analysis including 20 studies with 1485 patients indicated that both SSRIs and SNRIs had favorable therapeutic effects on PSD, and furthermore that citalopram may improve depressed moods faster than other SSRIs[39].

Fluoxetine for motor recovery after acute ischemic stroke is a randomized placebo-controlled trial conducted in France, which included 118 patients with ischemic stroke and moderate-to-severe motor deficits, found that the early use of fluoxetine with physiotherapy promoted motor recovery after 3 mo[40]. Similar to the conclusion of fluoxetine for motor recovery after acute ischemic stroke, most meta-analyses and systematic reviews published before 2019 supported that, if given early, fluoxetine could alleviate neurological deficits and disability and allow patients to recover independently through rehabilitation after stroke[41-43].

With the release in December 2018 of results on the effect of fluoxetine on functional outcomes after acute stroke (FOCUS), SSRI-modulated neuroplasticity that could enhance neurological recovery began to be questioned. The FOCUS trial is a multicenter randomized double blind and parallel control, collaborative study held at 103 hospitals through the National Health Service, United Kingdom, which focuses on the effect of fluoxetine on neurological functional outcomes after acute stroke.

In FOCUS, from 2 to 15 d after onset, there were 3,127 eligible patients with stroke (not patients with PSD) that were recruited and randomly allocated fluoxetine (20 mg daily) or placebo for 6 mo. After an extended follow-up period of up to 12 mo, only the neuropsychological scale questionnaire showed statistically significant differences between the two groups, although results of the clinical trial indicated that fluoxetine would enable the improvement of depression symptoms rather than clinical outcomes, and even increase the risk of bone fractures. The results from the FOCUS trial do not support the routine use of fluoxetine in prophylactic treatment for PSD or to promote the recovery of neurological function[44]. The TALOS study (the Efficacy of

Citalopram Treatment in Acute Stroke) was a placebo-controlled, randomized, double-blind study with 642 stroke patients in Denmark. Similarly to the FOCUS results, the TALOS study also did not show that citalopram could promote functional recovery, reduce the dependence on activities of daily living, or decrease the risk of recurrent cardiovascular events in acute ischemic stroke[45].

Since the FOCUS study has the largest number of patients among similar studies so far, the results from the FOCUS study undoubtedly carry a higher weight in the present meta-analysis. Both a recent systematic review[46] and a meta-analysis[47] that encompassed FOCUS data did not support the routine prescription of fluoxetine or other SSRIs to reduce and promote function recovery early after stroke without PSD. Instead, they suggested that fluoxetine or other SSRIs might be used to treat depressive disorders in patients with PSD. Nonetheless, the present result may not be the final conclusion, and the therapeutic effect of SSRIs and SNRIs for PSD functional rehabilitation remains controversial. Consequently, the two big ongoing trials, assessment of Fluoxetine in Stroke recovery (participants are being recruited from Australia, New Zealand and Vietnam), and efficacy of fluoxetine, a randomized Controlled Trial in Stroke (participants are being recruited from Sweden) will provide further information regarding fluoxetine for stroke recovery[48]. In addition, a meta-analysis using individual participant data will be needed[47].

SSRIs and antithrombotics are always simultaneously prescribed for patients with PSD in clinical practice. Clopidogrel is one of the commonly used anti-platelet medications that prevent and treat ischemic stroke. Clopidogrel can be metabolized into active products with therapeutic properties by cytochrome P450 (CYP) enzymes. A cohort study and meta-analysis (which included 72020 participants) have shown that CYP2C19-inhibiting SSRIs (fluoxetine and fluvoxamine) can decrease the therapeutic efficacy of clopidogrel. Patients using clopidogrel who were co-prescribed CYP2C19-inhibiting SSRIs had an 11% higher risk of developing ischemic disease than patients using clopidogrel who were treated with non-inhibiting SSRIs[49]. Serotonin could be released from platelets in the blood during the coagulation process. Aspirin is another important prescription medication for treating and preventing ischemic stroke and TIA. In theory, SSRI and SNRI reuptake serotonin in platelets as well as they do in the central nervous system, which reduce platelet serotonin and may be associated with aspirin-related bleeding[50].

Therefore, there are also growing concerns on the relationship of SSRIs with abnormal bleeding events[51]. Mortensen's study demonstrated that prestroke SSRI exposure was significantly associated among the severity and mortality of patients with hemorrhagic stroke[52]. In a large collaborative study, the preadmission use of SSRI alone did not increase the risk of spontaneous intracerebral hemorrhage after intravenous thrombolytic therapy for acute ischemic stroke. While there was a significant interaction between the concurrent preadmission use of SSRIs and oral anticoagulants on the occurrence of intracerebral hemorrhage related to thrombolysis[53], this condition can be seen in PSD patients with recurrent acute ischemic stroke that are treated with SSRIs. Moreover, fluoxetine and fluvoxamine are reported to have potential interactions with warfarin, and inhibit warfarin metabolism by competitively binding plasma protein and interfering with CYP isoenzymes, which are more likely to strengthen the anticoagulant effects of warfarin. Paroxetine also seems to have a low-to-moderate risk of enhancing the pharmacological effects of warfarin; however, other SSRIs and SNRIs do not appear to interact with warfarin[54].

A recent systematic review suggested that there is no high quality evidence to support that SSRIs used alone can increase the risk of spontaneous intracerebral hemorrhage. In addition, the association between SSRIs and intracerebral hemorrhage as previously reported was partly accounted for by biases and methodological limitations[55]. Neurologists and psychiatrists need to be well aware of the pharmacological interaction profiles when co-prescribing antidepressants and antithrombotics to patients with PSD and other NDS, monitor the possible adverse events during follow-up, and provide tailored therapeutic strategies for treating PSD and other NDS.

Psychotherapy is also an important intervention for PSD. CBT may be the most effective psychotherapeutic intervention. A meta-analysis on the efficacy of psychotherapy for PSD concluded that the evidence for the benefit of CBT in PSD remains inconclusive due to the high degree of heterogeneity and low quality across the majority of included studies[56]. Neuromodulation, such as transcranial magnetic stimulation and transcranial direct current stimulation, are promising adjunctive therapies. However, high quality randomized controlled trials using psychotherapy or neuromodulation are limited, and further research is needed[57].

In summary, antidepressant therapy should be used early once the definitive diagnosis of PSD has been made. SSRIs and SNRIs are recommended as a first-line

pharmacotherapy for mitigating depression. Other treatment approaches, *i.e.*, psychotherapy, neuromodulation, and psychosocial interventions, should also be considered. No reliable evidence exists to show that the use of SSRIs and other antidepressants can improve neurological function outcomes for patients with PSD.

ANXIETY DISORDERS AFTER STROKE

Screening and identification

PSA disorders are relatively common psychological problems and are the secondary NDS after depressive disorders. There are several distinct types of anxiety disorders: generalized anxiety disorder, phobias, selective mutism, agoraphobia, social anxiety disorder, and panic disorders. These disorders share similar core psychological symptoms, including feelings of uneasiness, excessive and persistent worry, and fear. Notably, anxiety disorders can also be accompanied by significant physical symptoms, some of which resemble neurological manifestations, such as tense muscles, dizziness, numb or tingling hands or feet, headache, chronic muscle or joint pain, and disturbed sleep[58]. Furthermore, unfavorable physical conditions due to brain damage caused by stroke, such as chronic pain, sleep disturbance, and communication difficulties, posed a high risk of developing PSA[59].

A case-control study conducted in Sweden revealed that the odds of PSA were predominantly higher than in the control population, which cannot be attributed to higher rates of comorbid depression. Remarkably, PSD did not show a significant independent association with PSA[60]. A meta-analysis reported that the frequency of PSA gradually rises over time, which ranged from 20% [95% confidence interval (CI): 13%-27%] within 1 mo, 23% (95%CI: 19%-27%) for one to five-mo after stroke, to 24% (95%CI: 19%-29%) for 6 mo or more after stroke[61]. The DSM-5 classifies PSA as an "anxiety disorder due to another medical condition". The prognosis of patients with PSA was markedly poor, as they likely suffered from persistent dependence with poorer quality of life and restricted social participation at 3 mo after stroke[62]. Similarity, a longitudinal study in South Korea found that PSA occurs within 2 wk after stroke, which may be an independent detrimental factor for long-term functional outcomes and daily life activities[63].

The Hamilton anxiety scale and the hospital anxiety and depression scale-anxiety subscale are the most commonly used to screen and measure the anxiety symptom severity of PSA. The cutoff score of possible and probable diagnosis of hospital anxiety and depression scale-anxiety subscale was the most widely considered identification criterion[59].

Management and therapeutic implication

There are no widely accepted guidelines that have been developed for the treatment of PSA. Several classes of pharmacotherapy were used to treat PSA in clinical practice, including SSRIs, tricyclic antidepressants, benzodiazepines and "Z-drugs"[64]. Likewise, various forms of psychological interventions, such as CBT, were frequently used for PSA, but few high-quality intervention studies have been shown.

In a study by Chun *et al*[62,64,65], meta-analysis including four pharmacotherapy comparisons studies (three studies published in Chinese journals) using paroxetine, imipramine, and buspirone, as well as eight psychotherapy comparisons studies showed an overall favorable pharmacotherapy and psychotherapy effect compared with control; however, the heterogeneity of the included studies of this meta-analysis was high and the quality of literature was relatively low. The positive conclusion may be driven by risk of bias[65]. In line with the study by Chun *et al*[64], a Cochrane review suggested that there was no high-quality clinical evidence to guide PSA management. Large-scale randomized double-blind controlled trials are required to determine the efficacy of pharmaceuticals and psychological therapies[64].

A systematic review revealed that mind-body interventions (*i.e.*, yoga, Tai Chi) may have potential benefits for treating both PSA and PSD by improving the mood and quality of life of stroke survivors[66]. Likewise, self-help mindfulness and relaxation techniques have been reported to be effective self-administered therapies to help alleviate symptoms, especially for patients with communication difficulties[67]. This suggests that PSA subtypes[62] and tailored therapeutic strategies are vital for future interventional studies.

PTSD AFTER STROKE

Screening and identification

PTSD is a mental health condition that develops following a traumatic event, including acute stroke and TIA. Under the DSM-5, PTSD is categorized as a subtype of anxiety disorder. The occurrence of PTSD is related to an event that creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events. PTSD has four main hallmark characteristics: (1) Intrusive memories; (2) Alterations in physical reactions and arousal; (3) Avoidance; and (4) Negative alterations in cognition and mood[68]. As an unexpected "traumatic" event, acute stroke or TIA may be considered to be potentially life-threatening or as severe disability disorders by patients. A growing body of clinical evidence has highlighted PTSD as a common result of neuropsychiatric sequelae of stroke or TIA[69].

Patients with post-stroke PTSD were likely to combine PSD and PSA[70]. A cross-sectional study showed that PSD, PSA, and post-stoke PTSD have a remarkably high degree of co-occurrence (approximately 40% patients with NDS comorbidity have the above three psychiatric disorders)[2]. However, the biological mechanism and clinical significance of overlap and comorbidity among these NDSs have yet to be well elucidated[68]. Studies report that the frequency of poststroke PTSD was varied, which depended on the type of stroke, assessment time-point, and morbidity condition[71,72]. Notably, the incidence rate was even as high as 37% in survivors with spontaneous subarachnoid hemorrhage, which was disadvantageous to patient quality of life and outcome[73]. A retrospective study with 12 mo follow-up showed that the prevalence of probable PTSD was lower within 1-year than that within 3 mo (8.3% compared with 29.6%) after TIA, suggesting that the risk of PTSD declined gradually over time after onset, This improvement could be due to the reversibility and transience of TIA, and the trauma event and psychological distress might therefore be more likely to be temporary unless it progresses into ischemic stroke[74]. A meta-analysis with data collected before January 2013 also suggested that the prevalence of PTSD after stroke and TIA was 23% within 1 year of onset and 11% after 1 year[75]. PTSD after stroke might have a worse effect on the mental health of survivors and an undesirable functional prognosis[76]. Correspondingly, patients with PTSD also had a higher risk of developing stroke than control people without PTSD[77]. A similar association was also seen in veterans with PTSD[78], but whether PTSD treatment offset the risk of developing stroke or TIA is unknown. Additionally, the treatment adherence to medication prescribed by specialists of stroke or TIA survivors with PTSD was reported to be poor[79], which impeded the efficient management of mental and physical health.

In most studies, PTSD after stroke was identified by the combination of diagnostic interviews and self-rating scales and questionnaires. A variety of assessments was used for screening; more frequently used scales included the PTSD checklist for a stressor using the "stroke or TIA" as a stressor[71,76,79], the clinician-administered PTSD scale[80], impact of events scale-revised[72], posttraumatic stress diagnostic scale[70], as well as the structured clinical interview for DSM. As the most widely used scale at present, a cutoff score of 50 on the PTSD checklist for a stressor highly indicated probable PTSD diagnosis after stroke.

Management and therapeutic implications

To our knowledge, there is no high-quality randomized controlled trial evaluating the efficacy of pharmacotherapy or psychotherapy for the intervention of post-stroke PTSD[68,69]. The psychotherapeutic approach procedures, such as CBT, trauma-focused psychotherapies, and exposure therapy are useful for facilitating compliance for developing strategies, which look promising for post-stroke PTSD of which the efficacy needs to be tested in future studies[81]. It remains unclear whether post-stroke PTSD could benefit from pharmacotherapeutic interventions like PSD, such as SSRI antidepressants. Although antidepressants were usually administrated for patients with post-stroke PTSD with comorbid depressive disorders, evidence for the effectiveness of medication (antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs) has still been inconsistent[82].

PSYCHOSIS AND PSYCHOTIC DISORDERS AFTER STROKE

Screening and identification

Under DSM-5 classifications, post-stroke psychotic disorders may be categorized as psychotic disorders due to another medical condition. The main symptoms of post-stroke psychotic disorders are characterized by hallucinations or delusions, which may be accompanied by disorganized speech, catatonic or inappropriate motor behavior, typically followed by acute severe stroke. Post-stroke psychosis refers to a series of symptoms after stroke; psychosis can be a clinical syndrome embedded with

many medical conditions, including schizophrenia, bipolar disorder with psychotic properties, and other psychotic disorders. The most prominent symptoms of psychosis include delusions and hallucinations[83]. Psychosis may manifest within 1 wk after stroke and rapidly develop into psychotic disorders, but psychosis would also be delayed and occur several weeks after onset. Delusions and hallucinations may be permanent as an accompanying sequel, or temporary as a result of functional rehabilitation.

Post-stroke psychosis didn't appear to notably raise many clinical research concerns like PSD or PSA, resulting in the lack of robust consensus supported by evidence-based medicine. Previous studies have suggested that post-stroke psychotic disorders are a rare complication of stroke. A cohort study published in 1991 included 1191 stroke patients with a 9-year follow-up, of whom only five patients were identified to suffer psychosis[84]. Although single psychotic symptoms (psychosis) may not meet the criteria of strict psychotic disorders, delusions and hallucinations seem to be more frequent in stroke survivors. A recent meta-analysis reported that the estimated frequency from the eligible four studies with delusions symptom was 4.67%, and the estimated frequency from the three studies with hallucination symptoms was 5.05%, with a pooled prevalence rate of psychosis after stroke of 4.86%[85]. A retrospective study consecutively included 1,108 stroke survivors in Western Australia from 1990 to 2002, and reported the cumulative incidence of psychosis after stroke to be 6.7%, which is a significantly positive correlation with a 10-year mortality[86]. Structural lesions that were related to delusions were centered on the right frontal, temporal, and parietal lobes, as well as white matter lesions with connectivity to the above areas, in addition to the right caudate nucleus[87,88].

Although different versions of the neuropsychiatric inventory were administered to stroke survivors for detecting delusions and hallucinations in some studies[89-91], unfortunately neuropsychiatric assessment tools for psychosis and psychotic disorders after stroke were presented inconsistently in the current studies. Moreover, there is no structured assessment that is suitable for a quantitative evaluation of psychosis and psychotic disorders respectively. It is thus a challenge to represent standardization studies across different research endeavors about psychosis and psychotic disorders after stroke.

There is no widely acknowledged diagnostic criterion for psychosis and psychotic disorders after stroke, and most studies adopt the DSM and International Classification of Diseases as diagnostic criteria for psychotic disorders. Therefore, it is hard to yield consistent conclusions, or to stand in agreement with these promising study results. Such deficiencies have already been highlighted by the latest systematic reviews or meta-analyses on post-stroke psychosis[85,92]. Validated structured assessment tools of psychosis and acknowledged diagnostic criteria are needed to identify the presentation and estimate the severity of psychosis and psychotic disorders after stroke, which will facilitate the standardization of research in this field.

Management and therapeutic implication

Currently, there is no randomized controlled trial study that systematically investigates the therapeutic efficacy and safety of antipsychotic medication for post-stroke psychosis. Most studies applied the management and treatment for post-stroke psychosis in a similar manner with that used for primary psychotic disorders, indicating that they share the same clinical and etiology properties. In some case reports and case series studies, stroke survivors with psychosis or psychotic disorders were mostly treated with antipsychotic medications. Approximately two thirds of patients who were treated with antipsychotics attained complete or partial recovery[85].

Second-generation antipsychotic drugs, such as risperidone, quetiapine, and olanzapine, were the most commonly used antipsychotic medications for post-stroke psychoses. The safety of antipsychotics for patients with stroke is still highly controversial. Antipsychotic drugs appear to have undesirable side effects on glucose and lipid metabolism. Whereas different antipsychotics exhibited distinctly varying degrees of influence on metabolic side-effects, a meta-analysis suggested that olanzapine and clozapine showed the most unfavorable effects on metabolism[93]. Previous studies have concluded that either first or second generation antipsychotic drugs may increase the risk of stroke, especially for patients with vascular dementia[94,95]. A recent meta-analysis revealed that antipsychotic drug exposure may significantly increase the risk of developing a stroke, but the conclusion remains unproven due to the high heterogeneity of these included studies[96]. A meta-analysis indicated that the risk of developing stroke might be higher in patients who received first-generation antipsychotic drugs than in those who received second-generation antipsychotic drugs[97]. However, a large-scale case control study found that neither first nor second generation antipsychotic drugs increase the risk of stroke in elderly

subjects with non-cognitive decline[98]. Therefore, as an important complementary therapy, non-pharmaceutical approaches such as physical neuromodulation and psychosocial therapy are promising therapeutic options for psychosis and psychotic disorders after stroke. It has been shown that CBT might help mitigate the distress caused by hallucinations or delusional beliefs[99].

CONCLUSION

At present, more and more attention is paid to the screening, diagnosis, and management of NDS. There is still lack of a widely-acknowledged structured scale for screening and assessing each NDS. Pharmacotherapy by modulating neurotransmitters is the mainstay treatment modality for NDS. Except for PSD being studied extensively, large-scale randomized double-blind controlled trials are still required to determine the efficacy of pharmaceuticals and psychological therapies for other NDS. Further aim should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of NSD. Current evidence reveals the limitations of our knowledge about NDS and may change as scientific research reflects that stroke is the pathological basis and cause of NDS.

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ORIGINAL ARTICLE

Observational Study

Visual impairment and depression: Age-specific prevalence, associations with vision loss, and relation to life satisfaction

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Abstract

BACKGROUND

To our knowledge, no study has obtained specific estimates of depression for young and middle-aged adults with visual impairment (VI). As estimates of depression varies across age groups in the general population, it is of interest to examine whether the same applies to adults with low vision or blindness.

AIM

To estimate depression prevalence and its association with VI-related characteristics and life satisfaction in adults with VI.

METHODS

A telephone-based cross-sectional survey was conducted between January and May 2017 in an age-stratified sample of adults who were members of the Norwegian Association of the Blind and Partially Sighted. Participants were asked questions about their sociodemographic characteristics, VI characteristics, and life satisfaction. Depression was measured with the Patient Health Questionnaire. The diagnostic scoring algorithm was used to calculate the point prevalence of depression (*i.e.*, major depression and other depressive disorders) across categories of gender and age (years: 18-35, 36-50, 51-65, ≥ 66). The associations were estimated using regression models.

RESULTS

Overall, 736 adults participated in the study (response rate: 61%). The prevalence estimates of depression varied across different age groups, ranging from 11.1%-22.8% in women and 9.4%-16.5% in men, with the highest rates for the two youngest age groups. Results from the multivariable models including sociodemographic and VI-related variables showed that losing vision late in life [Prevalence ratio (PR), 1.76, 95%CI: 1.11, 2.79] and having other impairments (PR:

given by each participant, the data are to be stored properly and in line with EU Regulation 2017/679 (General Data Protection Regulation (GDPR)). However, anonymized data is available to researchers who provide a methodologically sound proposal in accordance with the informed consent of the participants. Interested researchers can contact project leader Trond Heir (trond.heir@medisin.uio.no) with a request for our study data.

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1.88, 95%CI: 1.32, 2.67) were associated with higher rates of depression, whereas older age was associated with lower rates (PR: 0.83, 95%CI: 0.74, 0.93). Additionally, participants who were depressed had lower life satisfaction than those who were not depressed (adjusted β: -2.36, 95%CI: -2.75, -1.98).

CONCLUSION
Our findings suggest that depression in adults with VI, and especially among young and middle-aged adults, warrants greater attention by user organisations, clinicians, and healthcare authorities.

Key words: Blindness; Depression; Life satisfaction; Major depression; Vision loss; Visual impairment

Core tip: Depression in people with visual impairment (VI) goes often unrecognized and untreated, yet knowledge about its occurrence can help to inform the design of mental health services targeting the specific population. The study's findings of a high rate of depressive disorders in adults with VI, particularly among young and middle-aged adults, should in part be interpreted in the light of the extensive stigma, discrimination, isolation, and loneliness that they experience. For depressed adults with VI, the consequences may be severe in terms of a lower quality of life.

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INTRODUCTION

Visual impairment (VI) refers to a substantial and often irreversible loss in one of the functions of the visual system[1]. About 1.3 billion people are classified with near or distance VI on a global basis[2,3] and the numbers are projected to increase in the future due to an aging population and the greater burden of vision-threatening conditions such as diabetes and stroke[2]. Researchers, clinicians and others often refer to VI as a single entity, but VI is, in fact, a highly heterogeneous condition in terms of the visual function affected, onset age, severity, cause, and prognosis of vision loss. A distinction is often made between congenital and acquired vision loss, and between moderate VI, severe VI and blindness[1].

The literature on depression in people with VI is quite extensive[4-12], with many studies suggesting a link between vision loss and depression[6-8,10,12]. However, the prevalence estimates for depression have been found to vary greatly across studies. A meta-analysis of depression or depressive symptoms in people with vision-related conditions revealed that the prevalence estimates ranged between 5% and 57%, with a mean of 25%[12]. Much of the variation in the reported prevalence estimates is related to the inclusion of small and non-representative samples. In addition, most of the studies have been restricted to specific vision conditions or to older adults. Of studies involving young and middle-aged adults from the VI population[8,11], none have estimated the prevalence of depression for these age groups. As estimates of depression differ across different age groups in the general population[13,14], it is of interest to examine whether the same applies to adults with low vision or blindness.

Most studies of people with VI have relied on symptom rating scales in their screening for depression, while few studies have estimated the prevalence of depressive disorders[12,15,16]. Although clinical interviews are considered the gold standard for diagnostic classification, the impracticability of interviews in large surveys has led to the development of brief screening tools that match the criteria set in official diagnostic systems. One such questionnaire is the nine-item Patient Health Questionnaire (PHQ-9)[17]. The PHQ-9 has been applied in research on people with various health conditions[18]. Furthermore, the operational characteristics of the PHQ-9 are either equal or superior to other depression measures[18], and the results of a recent

meta-analysis, which included 40 studies, have confirmed its validity as a diagnostic measure in primary care settings (sensitivity: 41%-71%; specificity: 88%-97%)[19].

There is little consensus in the literature about whether there are certain subgroups of the VI population at greater risk of developing depression than others. Earlier research has mostly focused on the association between the severity of vision loss and depression[4,7,9,11,16,20-22], often finding no relationships[4,5,7,11,20-22], whereas more inconsistent evidence has been reported for factors such as the duration and cause of vision loss[4,9,22]. Furthermore, we have not identified any publications related to the risk of depression among adults with congenital or childhood vision loss, and more research is therefore needed.

We conducted a cross-sectional study that included a large, age-stratified sample of Norwegian adults with VI. Data were obtained *via* structured telephone interviews, and the PHQ-9 was used to obtain a probable diagnosis of current depression. This study had three main aims: To estimate the point prevalence of depressive disorders in stratified age groups of adults with VI; to examine whether depression was associated with different characteristics of vision loss; and to describe the association between depression and life satisfaction.

MATERIALS AND METHODS

Ethical considerations

The Regional Committee for Medical and Health Research Ethics was sought, and the committee confirmed that the study required no formal ethical approval as it was carried out in accordance with principles of anonymized data (Reference number: 2016/1615A). Prior to the survey, the participants were informed about all aspects of the research project, including potential risks and the voluntary nature of the survey. The participants consented by completing the interviews. No identifying information was collected.

Design and participants

An anonymous cross-sectional survey was conducted in an age-stratified sample of adult members (aged ≥ 18 years) of the Norwegian Association of the Blind and Partially Sighted. For a person to be granted full membership of the organization, he or she needs to enclose in their application form medical documentation of either VI or an untreatable eye condition that will progress towards low vision or blindness. Data were collected between January and May 2017, through structured telephone interviews. The interview guide contained more than 120 questions covering a wide range of topics, including sociodemographic factors, cause and onset of vision loss, serious life events, coping, mental health, and quality of life. Each interview took about 30 min to complete.

Most people with VI are of old age[1]. We therefore used an age-stratified sampling technique to allow for more precise estimations across all age groups in the adult VI population. First, the study population was divided into four age groups (years: 18-35, 36-50, 51-65, ≥ 66) and then we surveyed an equal number of members across the different age groups. The sample size calculations showed that it was desirable to enrol about 200 participants to estimate a prevalence with a precision of ± 5%, at a 95% confidence interval (CI), within each age group[23]. The calculations were founded on the assumption that the prevalence for different mental health outcomes would not exceed 15% in the study population. We almost reached our target, ending up with 156-200 participants per age group. A flow chart of the sample selection is provided elsewhere[24].

Assessment and evaluation

Depression: Depression was assessed by the nine-item PHQ depression module (PHQ-9), with one item anchored to each of the nine symptoms required to establish a probable diagnosis of depression (*i.e.*, major depression and other depressive disorder) based on the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[18]. The PHQ-9 also matches the new DSM-V criteria[25]. The participants were presented a list of nine symptoms, and instructed to indicate how often they have experienced each symptom during the past two weeks. The response alternatives were: (0) "not at all"; (1) "several days"; (2) "more than half of the days"; and (3) "nearly every day". In the study, the PHQ-9 had a Cronbach's alpha of 0.84.

We categorized depressive disorders using the DSM-based diagnostic algorithm created by Spitzer *et al*[17]. To be classified with major depression, the algorithm requires that at least five symptoms are scored as 2 ("more than half of the days") (1,

"several days" for the suicidal ideation item), in which one of the symptoms is anhedonia or depressed mood. For other depressive disorders, two to four symptoms, including anhedonia or depressed mood, are endorsed with a score of at least 2 ("more than half of the days") ("several days" for suicidal ideation). A final item assesses functional limitations caused by the depressive symptoms, and in our study, it included the following four response alternatives: "No difficulties", "somewhat difficult", "very difficult", and "extremely difficult". We categorized the item into a dichotomous variable ("no difficulties", "difficulties").

Life satisfaction: Cantril's Ladder of Life Satisfaction was employed in the questionnaire to measure current life satisfaction[26]. The participants were asked to imagine a ladder with 10 steps, with the bottom step representing the worst possible life (a score of 1) and the top step representing the best possible life (a score of 10). The scale was treated as an untransformed continuous variable in the main analyses.

Referral to psychologist: During the study it became apparent that the need for professional help was large and unmet in the sample population. Based on early feedback we received from the participants, we decided to offer referrals for psychological counselling for the subsequent participants (421 of 736 participants). Patients were referred to psychological counselling for subjectively experienced mental disorder with the desire for professional help. The psychologist recorded the number of participants who met for counselling and the main themes of the consultations.

Independent variables: The participants were asked questions about their age (years: 18-35, 36-50, 51-65, ≥ 66), gender, education (years: < 11, 11-13, ≥ 14), native origin (Norwegian, non-Norwegian), place of residence (village/town, small or large city), the current status of their vision loss (stable, progressive), and whether they had other impairments (no, yes). Moreover, the severity of vision loss was assessed by asking the following question: "How good is your current vision (better-seeing eye, with glasses or contact lenses)". The question had the following response alternatives: "blind", "severely impaired", "moderately impaired", and "unspecified". As only 42 participants reported unspecified VI, we chose to merge the unspecified VI category with the category moderately impaired because we considered those participants to have a lower degree of vision loss than those who reported severe impairment and blindness. Lastly, we created an "age of VI onset" variable by subtracting the participant's age with the number of years since VI onset. The variable was categorized into the following three categories: "Congenital", "childhood/adolescence (2-24 years)", and "adulthood (≥ 25 years)".

Statistical analysis

All statistical analyses were performed using Stata Version 15 (Stata Corp., Texas, United States). The significance level was set at $P = 0.05$. Descriptive statistics included frequencies and percentages, and differences in frequency counts were assessed by Pearson's chi-squared or Fisher's exact tests. To account for the age-stratified sampling method, we tested in all analyses whether the estimates varied across the different age groups (years: 18-35, 36-50, 51-65, ≥ 66) by performing statistical analyses of cross-tabulated data or by including a product term between age and each independent variable in a regression model.

Depressive disorders involved major depression and other depressive disorders. We estimated the point prevalence and corresponding 95% exact CIs for all depressive disorders separately for women and men and for each of the four age groups. Next, to explore differences between classification methods, we performed supplementary analysis by using the sum score method of the PHQ-9 dichotomized into no or mild depression (a sum score < 10) and moderate to severe depression (a sum score ≥ 10)[18]. A sum score of 10 or higher has been recommended as the most optimal cut-off in screening for major depression[18,19].

Binomial generalized linear models with log-link function were used to derive unadjusted and adjusted estimates of associations between the independent variables (sociodemographic factors and VI characteristics) and depression[27]. The results were presented in terms of prevalence ratios (PRs) and 95%CIs. We did not include national origin and municipality size in the adjusted models because the full model resulted in less accurate estimates of the independent variables[28]. To reduce the risk of sparse data bias, we decided to model age (10-year intervals) and education as continuous variables. This decision had minor impact on the model fit.

The association between depression and life satisfaction was estimated using linear regression. The models were either unadjusted or adjusted for all indicated covariates. Our data m*et all* assumptions relating to linear regression, and we did not find any impact from outliers or multi-collinearity on the main results.

Statistical review

The statistical methods of the study were reviewed by Ragnhild Sørum Falk, PhD, Oslo University Hospital (e-mail: Rs@ous-hf.no).

RESULTS

A total of 1216 members were contacted, of which 736 participated (response rate: 61%). We had no additional sources of missing data; all participants answered all questions and none of the participants chose to withdraw from the study after completing the interviews. The characteristics of the VI population for women and men are listed in Table 1. Women were more likely than men to be of non-Norwegian origin and to have self-reported moderate VI. There were no gender differences in age, education, native origin, place of residence, onset-age or current status of vision loss, or whether the participants had any other impairments.

Point prevalence of depressive disorders

The results presented in Table 2 show the prevalence of depressive disorders in the VI population according to participants' age and gender. The point prevalence varied in different age groups between 4.2% and 15.6% for major depression (women: 5.6%-17.8%, men: 2.4%-12.9%), 4.0% and 6.2% for other depression (women: 3.8%-5.6%, men: 3.5%-7.1%), and 10.3% and 19.9% for any depression (women: 11.1%-22.8%, men: 9.4%-16.5%). Overall, the estimates were highest in the age group 36-50 years and lowest in the age group 66 years or above. There were no statistically significant differences between women and men (results not shown).

We then performed a supplementary analysis by estimating the proportion of the study population with moderate to severe levels of depression. Although this type of categorization resulted in higher rates of depression, the results from the analysis supported our main findings of severe depression being most prevalent among the youngest participants (Online Supplementary Table 1).

Associated factors of depression

The unadjusted and adjusted PRs for depressive disorders across different characteristics of the VI population are listed in Table 3. Having addition impairments, losing vision in adulthood, and having progressive vision loss were associated with a higher prevalence of depression in the unadjusted models. In contrast, lower rates of depression were found with older age. In the fully adjusted models, the PRs did not change much after adjusting for age, gender, education, and all indicated VI characteristics, except that the VI stability variable turned out to be non-significant. Depression was not related to gender, education or the severity of VI. There were no statistical interactions between age and any of the other independent variables ($P > 0.05$).

Functional limitations

Eighty-seven percent of depressed participants reported functional limitations in daily life, against 47% in those without depression. There was also a somewhat higher rate of functional limitations among depressed participants in the two youngest age groups (18-35 years and 36-50 years) than found among the older participants ($P = 0.10$).

Life satisfaction

The life satisfaction of participants with any depressive disorder was considerably lower than that of participants without depression (mean: 4.64 *vs* 7.18, β -2.54, 95%CI: -2.93, -2.16). The strength of the association remained similar after adjusting for age, gender, education, national origin, municipality size, and each of the four VI variables (β -2.36, 95%CI: -2.75, -1.98). None of the interactions involving age and the other independent variables reached statistical significance ($P > 0.05$).

Referral to a psychologist

Among the 421 participants that were offered mental health care, 45 (10.7%) participants had a consultation with a psychologist, with similar rates across the different age groups ($P = 0.91$). Of the 45 referred to counselling, 30 (8.4%) had no depression, 13 (28.9%) had major depression, and 2 (10.0%) had other depression ($P < 0.001$). The main themes of the consultations were related to minority stress and struggles in handling stigma that had been internalized in many cases. Other important themes were feelings of marginalization and the violation of basic human rights. Some participants described that having VI involved feelings of anxiety.

Table 1 Characteristics of the sample by gender

Characteristics	Total (*n* = 736), *n* (%)	Women (*n* = 403), *n* (%)	Men (*n* = 333), *n* (%)	*P* value[1]
Age[2]				0.93
18-35 yr	157 (21.3)	88 (21.8)	69 (20.7)	
36-50 yr	186 (25.3)	101 (25.1)	85 (25.5)	
51-65 yr	200 (27.2)	106 (26.3)	94 (28.2)	
≥ 66 yr	193 (26.2)	108 (26.8)	85 (25.5)	
Education				0.20
< 11 yr	115 (15.6)	69 (17.1)	46 (13.8)	
11-13 yr	286 (38.9)	162 (40.2)	124 (37.2)	
≥ 14 yr	335 (45.5)	172 (42.7)	163 (49.0)	
Native origin				0.006[b]
Norwegian	645 (87.6)	341 (84.6)	304 (91.3)	
Non-Norwegian	91 (12.4)	62 (15.4)	29 (8.7)	
Place of residence				0.21
Village/town	399 (54.2)	227 (56.3)	172 (51.7)	
Small or large city	337 (45.8)	176 (43.7)	161 (48.3)	
VI severity				0.05[a]
Moderate	254 (34.5)	155 (38.5)	99 (29.7)	
Severe	296 (40.2)	152 (37.7)	144 (43.2)	
Blindness	186 (25.3)	96 (23.8)	90 (27.0)	
Age of VI onset				0.24
Congenital	330 (44.8)	118 (46.7)	142 (42.6)	
Childhood/adolescence	142 (19.3)	69 (17.1)	73 (21.9)	
Adulthood	264 (35.9)	146 (36.2)	118 (35.4)	
Current VI status				0.06
Stable	523 (74.5)	275 (68.2)	248 (74.5)	
Progressive	213 (25.5)	128 (31.8)	85 (25.5)	
Other impairments				0.46
No	478 (64.9)	257 (63.8)	221 (66.4)	
Yes	258 (35.1)	146 (36.2)	112 (33.6)	

[a]$P < 0.05$.
[b]$P < 0.01$.
[1]*P*-value derived from Pearson's Chi-squared test.
[2]The sample had a mean age of 51.4 years (SD: 17.2), 51.7 for women and 51.1 for men. VI: Visual impairment.

DISCUSSION

Key findings

In our cross-sectional study we found that the prevalence of having any depressive disorder varied considerably across the four age groups, with 11%-23% in women and 9%-17% in men, and with highest rates for the youngest participants. Losing vision in adulthood and having addition impairments were found to be independently associated with increased rates of depression, whereas older age was associated with decreased rates. Furthermore, participants who were depressed had considerably lower life satisfaction compared with those who were not depressed.

Strengths and limitations

Our study is the largest study to date to address the prevalence of depression in VI populations across the entire adult age range, and the first to report estimates of other depressive disorder. The stratified sampling procedure made it possible to obtain robust depression estimates in all four age groups. The use of telephone interviews, the good response rate, and the lack of missing data increased the validity of the study findings.

Our study had also some limitations. First, it relied on cross-sectional data, which restricted our ability to make causal inferences about the observed associations. Second, the rates of PHQ-defined depressive disorders were not validated by a clinical interview and therefore the estimates reflected a probable diagnosis instead of

Table 2 The point prevalence of depressive disorders in the visual impairment population by age and gender

Disorders	Cases/total	Total (*n* = 736) (95%CI)	Women (*n* = 403) (95%CI)	Men (*n* = 333) (95%CI)
Major depression				
18-35 yr	18/157	11.5 (6.9, 17.5)	12.5 (6.4, 21.3)	10.1 (4.2, 19.8)
36-50 yr	29/186	15.6 (10.7, 21.6)	17.8 (10.9, 26.7)	12.9 (6.6, 22.0)
51-65 yr	14/200	7.0 (3.9, 11.5)	7.6 (3.3, 14.3)	6.4 (2.4, 13.4)
≥ 66 yr	8/193	4.2 (1.8, 8.0)	5.6 (2.1, 11.7)	2.4 (0.3, 8.2)
P value		0.003[b]	0.05[a]	0.08
Other depression				
18-35 yr	7/157	4.5 (1.8, 9.0)	4.6 (1.3, 11.2)	4.4 (0.9, 12.2)
36-50 yr	8/186	4.3 (1.9, 8.3)	5.0 (1.6, 11.2)	3.5 (0.7, 10.0)
51-65 yr	8/200	4.0 (1.7, 7.7)	3.8 (1.0, 9.4)	4.3 (1.2, 10.5)
≥ 66 yr	12/193	6.2 (3.3, 10.6)	5.6 (2.1, 11.7)	7.1 (2.6, 14.7)
P value		0.76	0.95	0.75
Any depression				
18-35 yr	25/157	15.9 (10.6, 22.6)	17.1 (9.9, 26.6)	14.5 (7.2, 25.0)
36-50 yr	37/186	19.9 (14.4, 26.4)	22.8 (15.0, 32.2)	16.5 (9.3, 26.1)
51-65 yr	22/200	11.0 (7.0, 16.2)	11.3 (6.0, 18.9)	10.6 (5.2, 18.7)
≥ 66 yr	20/193	10.3 (6.5, 15.6)	11.1 (5.9, 18.6)	9.4 (4.2, 17.7)
P value		0.07	0.59	0.16

[a]$P < 0.05$.
[b]$P < 0.01$.

diagnosed depression. Researchers have been concerned about the possibility that standard rating scales could overestimate the prevalence of depression in VI populations, given that certain depressive symptoms and especially somatic symptoms bear resemblance to complications of vision loss[4,7]. However, the PHQ algorithm method used in our study may produce fewer false positives than continuous cut-off scores, as it puts more weight on the core symptoms of depression (*i.e.*, depressed mood and anhedonia) and thus downplays the importance of somatic symptoms. Third, there was a potential risk of misclassification of the VI characteristics because some of the participants might not have known or been able to recall specific details about their condition. We expect non-differential misclassification, and in studies like ours, which include high-prevalent outcomes, the magnitude of the bias is likely to be low and drawn towards the null value[29]. Fourth, and lastly, because our sample was recruited from a member organization for the blind and partially sighted, it may be questioned whether it was representative of the broader VI population. However, the demographics of our sample were comparable with the 2015 census data of people with self-rated vision loss provided by Statistics Norway[30], except that our sample had a higher level of education. Since high levels of education may protect against the development of depression, we assume that the depression rates in our study were underestimated.

Comparison with the literature

To our knowledge, this is the first study of its kind to estimate the prevalence of depressive disorders in young and middle-aged adults with VI. The 16% and 20% rates in the respective age groups 18-35 years and 36-50 years were almost twice as high as those obtained in similar age groups in a survey of the general United States population in which depression was classified using the PHQ algorithm[28]. Furthermore, the prevalence rates of major depression in the same age groups were two to three times higher than the age-specific estimates for the general Western European population[13,14]. We also found that the youngest adults had worse outcomes than the older adults in terms of functional limitations. Our results illustrate that visually impaired adults of young or middle age are at particular risk of developing depressive disorders and that the demand for mental health care in these age groups is substantial.

The prevalence rates of depressive disorders or major depression in our two oldest age groups with VI were similar to those reported in earlier studies[4,5,7] or lower[9,10]. Furthermore, our depression rates did not differ from those reported elsewhere for older adults in the general Western European population[13,14]. These findings reflect

Table 3 Prevalence ratios for depressive disorders with sociodemographic factors and characteristics of visual impairment estimated using regression analysis (*n* = 736)

Variables	Any depressive disorder			
	Cases/total	%	Unadjusted PR (95%CI)	Adjusted PR (95%CI)
Age (continuous)[2]	-	-	0.89 (0.81, 0.99)[1]	0.83 (0.74, 0.93)[1]
Gender				
Men	42/333	12.6	1 [Reference]	1 [Reference]
Women	62/403	15.4	1.22 (0.85, 1.76)	1.17 (0.82, 1.68)
Education (continuous)	-	-	0.85 (0.72, 1.01)	0.86 (0.72, 1.02)
VI severity				
Moderate	40/254	15.8	1 [Reference]	1 [Reference]
Severe	44/296	14.9	0.94 (0.64, 1.40)	0.87 (0.60, 1.32)
Blind	20/186	10.8	0.68 (0.41, 1.13)	0.82 (0.49, 1.36)
Age of VI onset				
Congenital	35/330	10.6	1 [Reference]	1 [Reference]
Childhood/adolescence	26/142	18.3	1.73 (1.08, 2.76)[1]	1.63 (1.03, 2.58)[1]
Adulthood	43/264	16.3	1.54 (1.01, 2.33)[1]	1.76 (1.11, 2.79)[1]
Current VI status				
Stable	65/523	12.4	1 [Reference]	1 [Reference]
Progressive	39/213	18.3	1.47 (1.02, 2.12)[1]	1.43 (0.99, 2.06)
Other impairments				
No	50/478	10.5	1 [Reference]	1 [Reference]
Yes	54/258	20.9	2.00 (1.41, 2.85)[1]	1.88 (1.32, 2.67)[1]

[1]Results indicate statistical significance.
[2]Rescaled into 10-year age intervals. VI: Visual impairment; CI: Confidence interval; PR: Prevalence ratio.

the mixed results of previous studies of elderly adults in which the aim was to compare differences in estimates for visually impaired people and non-impaired people[5,7,10].

We found that adults who acquired VI late in life and adults with other impairments in addition to their vision loss had particularly high rates of depression. Vision loss may result in dramatic changes to people's lives and have implications for daily life activities, such as driving and travelling outside the home. Depression may develop as people struggle to cope with vision loss and its consequences for daily life[15,16]. Such challenges may be even greater for those with additional impairments. When people experience vision loss or receive a VI diagnosis, significant changes in self-esteem, self-efficacy, identity, social relations, and well-being may occur[31]. Many experience stress reactions such as shock, fear, frustration, helplessness, and grief[31], and their future life prospects become distorted. By contrast, those who have lost their vision earlier in life might have adapted to their vision loss during this period and accepted their life situation.

The high rates of depression in people with vision loss should be discussed also in the light of discrimination, stigmatization, alienation, and social isolation. Social interaction is considered an integral part of a fully-fledged life, and unmet needs could make life less pleasurable and less meaningful[32]. Loneliness and isolation are common in VI populations[33]. Also, those populations are more likely than their sighted peers to experience discrimination[34]. Exposure to negative social events may induce feelings of alienation, persistent negative thoughts and mood, distorted blaming of oneself and others, and loss of trust and faith in oneself and others[24]. Once people experience negative social events or social exclusion, they may become socially inactive or avoid certain situations in which they might experience further adverse events. This could become part of a downward spiral, resulting in isolation, loneliness, and depression[35].

We did not find any evidence of a relationship between self-reported VI severity and depression, which is consistent with the literature on this subject[7,9,11,20-22]. For example, in a survey of 1232 elderly outpatients from low vision rehabilitation services, van der Aa *et al*[7] did not find any differences in depression rates across the participants' degree of visual acuity loss. Direct or self-reported measures of visual functions may not capture the overall impact of a condition on people's daily lives[1],

and moderate vision loss may be as challenging to manage as a more severe one[31].

Our finding of a strong association between depression and lower life satisfaction is in accordance with documented findings relating to the general population[36,37]. Although causality may be reversed in that people who are less satisfied with life may be more likely be depressed, our findings probably point to the negative impact of depression on several life domains.

Implications

Our findings suggest that the risk of depressive disorders is high among young and middle-aged adults with VI. Vision loss can occur abruptly, resulting in a sudden loss of function, or it may develop gradually over a longer period, accompanied by the uncertainty about what the further development will cause. The high risk of depression should receive greater public attention, and special attention should be paid to adults of young age, the loss of vision in adulthood or those who have other impairments in addition to their vision loss. Preventive strategies, such as improved access to education, work, social services, and de-stigmatization programs, is also warranted. Ophthalmologists and other professionals who face people with vision loss should be aware of the high risk of depression and consider the need for referral to mental health care.

Quite unintentionally, our survey revealed an unmet need for consultations with a psychologist. People with vision loss may have a higher threshold when it comes to seeking help due to personal concerns such as a desire for self-reliance or avoidance of being labelled a "victim". More importantly, there is a lack of knowledge among health personal about the mental health adversities associated with VI[38], and to date, special mental health care services for people who are blind or have low vision is lacking in countries such as Norway. Thus, these issues should be addressed by both health care authorities and user organizations in cooperation.

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ARTICLE HIGHLIGHTS

Research background

People with visual impairment (VI) may be at risk of depression, but previous studies have demonstrated inconsistent results and have either reported extremely low rates or reported rates that ranged as high as 60%. Furthermore, previous studies of depression have mainly been restricted to older people or to specific subgroups of the population.

Research motivation

Depression in this population goes often unrecognized and untreated. We have yet to fully understand the magnitude of the problem and who is at particular risk of developing depression. By obtaining more precise knowledge about the age-specific prevalence and associated factors of depression, this information can be valuable in the design of preventive efforts and to anticipate service needs.

Research objectives

We conducted a large, age-stratified study in the adult population of people with low vision or blindness, with the following three main aims: (1) To estimate the point prevalence of depressive disorders in stratified age groups of adults with VI; (2) To examine whether depression was associated with different characteristics of vision loss; and (3) And to describe the association between depression and life satisfaction. By doing so, we hoped to examine and better understand the age-specific risk of depression among people with VI, as well as its associated factors and potential consequences on people's quality of life.

Research methods

The study was conducted as a cross-sectional interview-based survey between January and May 2017 and included an age-stratified sample of adults with VI. All participants were recruited through the members list of the Norwegian Association of the Blind and Partially Sighted. A total of 736 (61%) adults participated by completing the interview.

Research results

The prevalence of depression in different age groups varied from 11.1%-22.8% in women to 9.4%-16.5% in men. The estimates were highest in the two youngest age groups, and these rates were two times higher than those presented in previous studies of Westernized populations. Additionally, we found that depression was independently associated with having other impairments and loss of vision late in life, indicating that having difficulties in adapting to a new situation of being visually impaired or blind may put people at increased risk of developing depression. Lastly, depressed people in our study sample had considerably lower life satisfaction and were more likely to be referred for psychological counselling than were people without depression. The themes most often brought up by the participants during their consultations with the psychologist were related to problems with minority stress and handling stigma. We therefore argue that the high rates of depression in people with VI should be viewed in terms of stigma, discrimination, loneliness, and isolation.

Research conclusions

To our knowledge, our study is the first to provide estimates of depression for the youngest part of the adult VI population. We have identified some subgroups of the population at greater risk of depression than others. Because of the high depression rates and their strong associations with quality of life, we recommend the initiation of efforts that would improve access to professionals trained in the needs and challenges of people with VI.

Research perspectives

Our research findings should be supported by future studies that include a large probability sample of the entire adult VI population and that diagnose depression through clinical interviews. Moreover, future research should involve measures of modifiable risk factors of depression so that effective interventions can be designed to reduce the burden of depression for this population.

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