ADDRESSING COMORBIDITY BETWEEN MENTAL DISORDERS AND NEUROLOGICAL CONDITIONS IN THE ELDERLY

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REVIEW
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Impulse Control Disorders in Parkinson's Disease: Epidemiology, Pathogenesis and Therapeutic Strategies

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Impulse control disorders (ICDs) in Parkinson's disease (PD) are aberrant behavior such as pathological gambling, hypersexuality, binge eating, and compulsive buying, which typically occur as a result of dopaminergic therapy. Numerous studies have focused on the broad spectrum of ICDs-related behaviors and their tremendous impact on patients and their family members. Recent advances have improved our understanding of ICDs. In this review, we discuss the epidemiology, pathogenesis and treatment of ICDs in the setting of PD.

Keywords: Parkinson's disease, impulse control disorders, dopaminergic drugs, pathological gambling, hypersexuality, binge eating, compulsive buying

HIGHLIGHTS

- Impulse control disorders are increasingly recognized as highly impactful features in patients with Parkinson's disease.
- Dopamine receptor agonists are the strongest risk factors.
- The mechanism of impulse control disorders is still not well-understood but the dopamine reward system and inhibition systems are clearly involved.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder (1). Chronic use of dopaminergic medications in PD is associated with motor and non-motor side effects such as dyskinesias, and impulse control disorders (ICDs) (2). Motor symptoms of PD have traditionally been the major focus of research, but non-motor symptoms, especially ICDs have gradually attracted great attention because of their tremendous impact on patients and their family (3–5). In general, ICDs refer to pathological gambling (PG), hypersexuality, binge eating, and compulsive buying. The core features of ICDs include repetitive or compulsive behavior, reduced control over these behavior, and pleasurable feeling while carrying out the behavior (4).

PG is defined as persistent and recurrent problematic gambling behavior as indicated by features such as increasing amounts of money, restlessness or irritability when cutting down, failing to control the behavior, preoccupation with gambling, lying to others, and so on (at least four criteria required). However, based on neuropsychiatric and possibly pathophysiological features, PG is currently considered as typical example of behavioral addiction and included in the diagnostic category of "substance-related and addictive disorders" according to DSM-5 (6, 7). Hypersexuality means increasing preoccupation with sexual thought, excessive sexual needs, increased use of pornography and self-stimulatory behavior, seeking out prostitutes, engaging in exhibitionism and paraphilia (8). Binge eating involves uncontrollable consumption of a large amount of food, which results in harmful gain of weight (9). Compulsive buying or shopping can be defined as irresistible excessive buying that can lead to psychological consequences and financial debt (10).

In addition to the ICD, there are also some ICD-related disorders (ICRDs), such as Dopamine dysregulation syndrome (DDS) and punding. DDS implies repeated, unnecessary, or sometimes deleterious daily intake of dopaminergic agents far more than the dosage required for treatment of objective motor impairment, leading to severe dyskinesia, euphoria, aggressivity, hallucination, confusion, or frank psychosis (11). Punding is a term that was coined originally to describe complex prolonged, purposeless, and stereotyped behavior in chronic amphetamine users (12). It shares similarities with addictive behavior and involves psychiatric symptoms relating to dopamine system (13).

Besides the classic ICDs symptoms there are many other ICDs-related behavioral problems including reckless driving (14), impulsive smoking (15), compulsive singing (11), tattooing (16), stealing (17), pet killing (18), and zoophilia (19) (**Table 1**). The wide clinical spectrum of ICDs symptoms necessitates careful monitoring of behavior when patients are taking dopaminergic drugs. As the researches indicated, dopamine, have been known to have a strong association with ICDs (20).

This review mainly focuses on the ICDs in PD patients from the point of epidemiology, pathogenesis and therapeutic strategies.

THE EPIDEMIOLOGY OF ICDs

The prevalence of ICDs in PD patients using dopamine replacement therapy (DRT) varied from 3.5 to 43% (21–23). Dopamine receptor agonist (DA) treatment in PD is associated with 2–3.5-fold increased odds of having ICDs compared with patients without DA treatment (24). Estimated incidence of ICDs in PD patients increases with time especially in those on DRT (23). In one longitudinal study, the 5-year cumulative incidence of ICDs was about 46% (25). A study showed that 17.5% PD subjects resulted positive with ICDs before starting treatment, indicating the need for a detailed behavioral assessment before dopaminergic therapy (26).

ICD is probably much more frequent in PD than previously reported as patients often underestimate the presence and severity of ICD symptoms (27). This is in part due to lack of insight, but also as a defense mechanism with denial and minimization of symptoms on a background of feelings of shame or guilt. Some patients with ICDs may have a relative lack of empathy and do not perceive any stress from their aberrant behavior, despite marked concerns by family members and friends (28).

THE RISK FACTORS OF ICDs

Dopaminergic Drugs and ICDs

Although the frequency of impulsivity and compulsive behavior in PD patients before initiation of dopamine receptor agonists is similar to the frequency in healthy control, it is conceivable that dopamine receptor agonists may turn impulsive personality traits into clinically disorders (26). Specifically, affinity of pramipexole and ropinirole for the D3 receptors is much greater than the D2 receptor (100 and 25 times, respectively) as well as for D1 receptor (>1,000 and 300 times, respectively) (29, 30). Other dopamine agonists commercially available in only some countries such as piribedil may also lead to ICDs (31). At the same time, the oral dopamine agonists (pramipexole and ropinirole) have been found to have a greater risk for causing ICDs than the transdermal dopamine agonist rotigotine (29), which might be partially explained by the theory that transdermal delivery bypasses erratic gastric emptying and it may avoid other changes in gastrointestinal motility, leading to the stability of plasma level (29). In a *post-hoc* analysis about PD treated with rotigotine, although no definite conclusion can be reached on any dose-response relationship between rotigotine and ICDs, the incidence of ICDs appeared to increase with the dosage increase (25), as increased with longer exposure to rotigotine and recommend active surveillance with increased duration of treatment and dose reduction when ICDs are present (32).

In addition to dopamine agonists, levodopa, particularly in high dosages, has been also associated with ICDs (24). In patients taking dopamine agonist, concurrent levodopa usage is reported to increase the odds of ICDs by ∼50% (24). This multi-center study indicated that there is no association with higher dopamine agonists dose but a link with higher levodopa dose with ICDs, suggesting an intrinsic role for levodopa (33). And also, patients with PD treated by levodopa show ICDs more frequently and more severely than patients without levodopa, thereby suggesting the levodopa's significance in a way (34).

Antidepressants and sleep inducers are also significant predictors for individual ICD (35). Aripiprazole, an antipsychotic drug with partial dopamine agonist properties, has been reported to be associated with ICDs especially pathological gambling (36). It has high affinity for the D3 receptor besides regarded as a D2 agonist. The ICD symptoms resolved completely with its cessation according to reports (36).

Abbreviations: ICDs, Impulse control disorders; PD, Parkinson's disease; PG, Pathological gambling; DDS, Dopamine dysregulation syndrome; DRT, Dopamine replacement therapy; DAs, Dopamine agonists; ACC, anterior cingulate cortices; OFC, orbitofrontal cortex; VTA, ventral tegmental area; DAT, Dopamine transporter; RBD, Rapid eyes movement sleep behavior disorder; STN, Subthalamic nucleus; DBS, Deep brain stimulation; TMS, Transcranial magnetic stimulation.

TABLE 1 | Rare ICD symptoms in Parkinson's disease.

Symptoms	Age (yr) and sex	Course of PD (yr)	Describes	Medicine (peak dose)	Source
Reckless driving	65, male; 70, male	9; 20	Impairment in driving performance associated with risk-seeking, including reckless high-speed driving.	L-dopa(-)	(14)
Impulsive smoking	63, male	7	Urge to smoke. Pramipexol was discontinued and the abnormal symptoms disappeared. However, with switching to ropinirole, impulsive smoking developed again.	Pramipexol(6 mg/d)/Ropinirole extended release (12 mg/d)	(15)
Compulsive singing	70, Female; 71, Male	9; 5	Urge to sing repeatedly the same song.	L-dopa(1,268LEU); L-dopa(634 LEU)	(11)
Tattooing	50, Male	–	Got tattooed seven times in 6 months and planned to make five others.	Pramipexol extended release 1.05 mg/d and rasagiline 1 mg/d	(16)
Stealing	48, Female	–	Impulsive stealing.	Pramipexol (-)	(17)
Pet killing	33, Male	–	Compulsive behavior of adopting and killing cats.	Pramipexol (4.5 mg/d)	(18)
Zoophilia	58, Male	20	Attempting to have sexual intercourse with a female family dog.	Pramipexol(8 mg/d)	(19)

PD indicates parkinson's disease. LEU indicates L-dopa equivalent units.

In addition to that, studies have failed to find correlation between ICDs and severity of levodopa-related motor fluctuations (37, 38). There were no differences between PD with ICD and PD without ICDs in terms of LID exhibited by DA dose or scores on UPDRS part IV, mania, impulsive choice, alcohol use, or current or former smoking (39).

Non-Medication Related Risk Factors

Demographic Risk Factors

According to current research, many demographic factors participate in the development of ICDs in PD. For example, age, gender, and personality traits. Young age at PD onset is one of most established independent risk factors for ICDs in PD (40). Compared to patients without ICDs, ICDs patients were much younger (21, 24, 25, 29, 41, 42), which can be partly explained by that younger patients are more likely to be prescribed taking dopamine agonists. However, the age effect remains after controlling dopamine agonists exposure (24, 43). Gender difference may contribute to the different subtypes of ICDs. Overall, ICDs increased over time in a more pronounced way in men compared to women (25). Hypersexuality is more prevalent in males while binge eating and buying are more common in women (24, 42, 43). Moreover, male, unmarried, personal or family history of smoking, gambling, drug or alcohol addiction, pre-existent or current symptoms of depression or anxiety and personality traits such as impulsiveness and novelty seeking behaviors are also risk factors of ICDs (4, 37, 41, 42, 44–46). These findings suggest that multiple elements including neurobiological, environmental, genetic factors all contribute to the development of ICDs (24). Furthermore, there are many other personal risk factors, such as depression, anxiety, aggression, irritability, obsessive-compulsive traits, impulsivity traits, novelty seeking traits, and alexithymia (41, 47–50). The inclusion of these factors in the neuropsychiatric assessment of patients with PD may help identify patients at risk for ICDs.

Symptomatically Related Risk Factors

The duration of disease or medicine was correlated with ICDs in PD (40). Then the rapid eye movement sleep behavior disorder (RBD) in PD with ICDs is also worth of concern. Actually, whether RBD is a risk factor for ICDs in PD is controversial. Baig et al. (51) recruited 921 cases of PD and screened positive for ICDs at each visit. After statistics, they found that RBD is not associated with increased ICD risk. Another clinical trial involved 401 newly diagnosed PD patients, evaluated ICD behaviors annually and finally revealed that probable RBD is not clearly associated with ICDs in early PD (52). However, a meta-analysis included 10 studies involving 2,781 PD patients drew a conclusion that RBD was associated with a more than 2-fold higher risk of developing ICBs (OR 2.12, $P < 0.01$) (53), reminding us that RBD in PD is confirmed to be a risk factor for impulsive-compulsive behaviors. Hence, more research is needed to explore the role RBD played in PD with ICDs.

Genetic Risk Factors

There have been studies focusing on DNA polymorphisms of impulsive and compulsive behavior and additive behaviors in decades. A larger number of SNPs in dopaminergic (DRD1

rs 265981, DDC rs 3837091 and rs 1451375, D3Rp.S9G) glutamatergic, serotonergic and opioid neurotransmitter system have been reported as candidates that improved predictability of ICDs when compared with clinical risk factors (54–56). We here cite certain findings that have strong relationship with ICDs. A study indicated that carriage of either AA genotype of DRD3 or CC genotype of GRIN2B was identified as an independent risk factor for ICDs. Furthermore, variants of DRD3 p.S9G and GRIN2B c.366C>G may be associated with ICDs in PD (57). In another study, besides GRIN2B (rs7301328), DRD1 (rs4532 and rs4867798), and DRD2/ANKK1 (rs1800497) increase risk for developing ICDs (58). Polymorphism of DRD4 7-allele also associated with ICDs (59, 60). In addition, a study supported a possible contribution of genetic variation in the HTR2A (serotonin 2A receptor gene) to the susceptibility of ICDs in PD patients, with the T allele, which is presumably linked to higher receptor expression, increasing the risk by 2.8 and 6.9 times in CT and TT carriers (61). More recently, DRD3 p.Ser9Gly (rs6280) CT genotype was proved to be associated with PD patients in Indian population (62). Moreover, with the suggestive association between the opioid receptor gene (OPRM1) and ICDs in PD, the researchers bring potential new insights to the understanding of molecular mechanisms of ICDs (63).

A multicenter case-control study showed that specific subtypes of ICDs, such as compulsive shopping, binge eating and punding, had high frequency and were more severe in PD patients with Parkin mutation compared with non-Parkin mutation (39). The possible explanation was related to neurodegeneration of frontal-striatal-limbic structures (64). In addition, gray matter volume of caudate nuclei, which is involved in reward and stimulus-reinforcement association learning, decreases in PD patients with Parkin mutation (65).

Comparing with single genetic variants, multiple gene interactions may play a more important role. Using candidate genetic multivariable pane, Kraemmer et al. conducted an interesting study to estimate ICD heritability in PD patients, which included several transmitter systems such as dopamine, serotonin, and norepinephrine genes. They found a substantial 11–16% increase in ICD behavior predictability compared to examining clinical variables alone. In addition, in 13 candidate variants, OPRK1, HTR2A and DDC genotypes were the strongest genetic predictive factors and OPRK1 polymorphism rs702764 significantly predicted incident of ICD behavior. Hence, they suggested the potential for developing clinical-genetic models to identify PD patients at increased risk of developing ICD and further guide treatments (66).

Although polymorphisms of dopaminergic genes are not considered as the strongest risk factor for developing ICDs in PD patients at present, further research in the genetic susceptibility will explain the reason why some patients taking low doses of dopaminergic drugs still develop ICDs. Genetic studies can enlarge the understanding of ICDs from pathogenesis to therapy.

NEUROPSYCHOLOGICAL STUDIES IN ICDs

Various neuropsychological studies have found that ICDs are associated with frontal/executive dysfunctions (67–70). Imbalance of the frontal-striatal circuits which manifested with cognitive dysfunction was considered to be associated with ICDs (71). One study showed that pathological gambling patients performed significantly worse than non-pathological gambling patients in PD on cognitive tasks that evaluated visuo-spatial long-term memory and several frontal lobe functions (68). And PG relates to reward-based decision-making, which is a major topic of behavioral psychology. Clinical neuropsychologists have been using Iowa Gambling Task to evaluate financial risk attitude (72, 73). More straightforward behavioral economics task has been tested. Another study indicated that ICDs patients in PD had poorer working memory performance than either the control or PD patients without ICDs (70). A study found that hypersexuality is associated with prefrontal and memory dysfunctions, whereas pathological gambling and compulsive eating seem to be related to only frontal dysfunction (67).

However, there were several studies considering no difference in frontal executive dysfunction on neuropsychological testing between ICDs and non-ICDs patients in PD (73–78), which suggested that executive dysfunction may contribute to ICD behavior, but is not a necessary component (76). A long-term study investigating the progression of cognitive decline in ICDs patients compared with PD patients without ICDs showed that ICDs patients were not with greater cognitive impairment or executive dysfunction, but rather show relatively lower cognitive decline over time. Drug-induced overstimulation of relatively preserved prefrontal cognitive functions may impair the top-down inhibitory control contributing to ICDs (77). These finding still needs to be verified.

Intertemporal choices, decisions between options available at different times, are commonly applied in impulsivity-related studies. The presence of impulsivity trait in intertemporal choices is usually suggested by a strong preference for small immediate rewards over large delayed ones (79). Temporal discounting is a phenomenon that the subjective valuation of reward declines with delay. In studies using intertemporal choice task, investigators found that dopamine agonist use was associated with greater choice impulsivity in ICDs patients compared to PD. It is suggested that there has been a U-shaped relationship between dopamine activity and temporal discounting (80). Dopamine agonists are associated with a greater discounting of larger delayed rewards, therefore contributing to impulsive choices (69).

THE PATHOGENESIS OF ICDs

The mechanism of ICDs is not well-understood. Yet based on animal and clinical researches, the dopaminergic system has been strongly implicated. There are three main dopaminergic pathways in central nervous systems (CNS): (a)the nigrostriatal

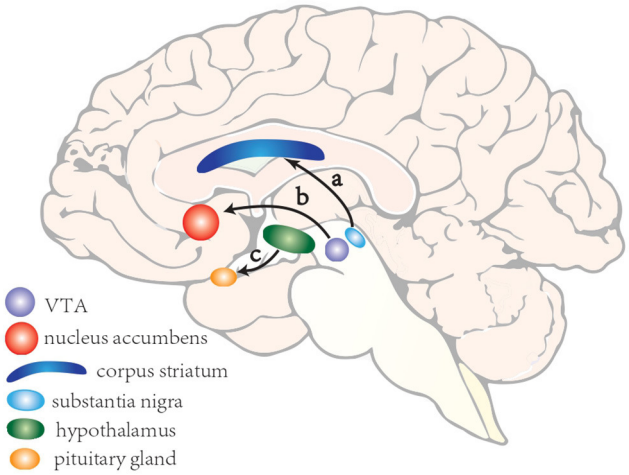

FIGURE 1 | A schematic illustration of three main dopaminergic pathways in central nervous systems. (a) the nigrostriatal pathway consisting of cell bodies in the substantia nigra whose axons terminate in the corpus striatum; (b) the mesocorticolimbic pathway (also known as the reward system), whose cell bodies are situated in the ventral tegmental area and whose axons project to parts of the limbic system; and (c) the tuberoinfundibular pathway, whose cell bodies are found in the ventral hypothalamus and project to the median eminence and pituitary gland.

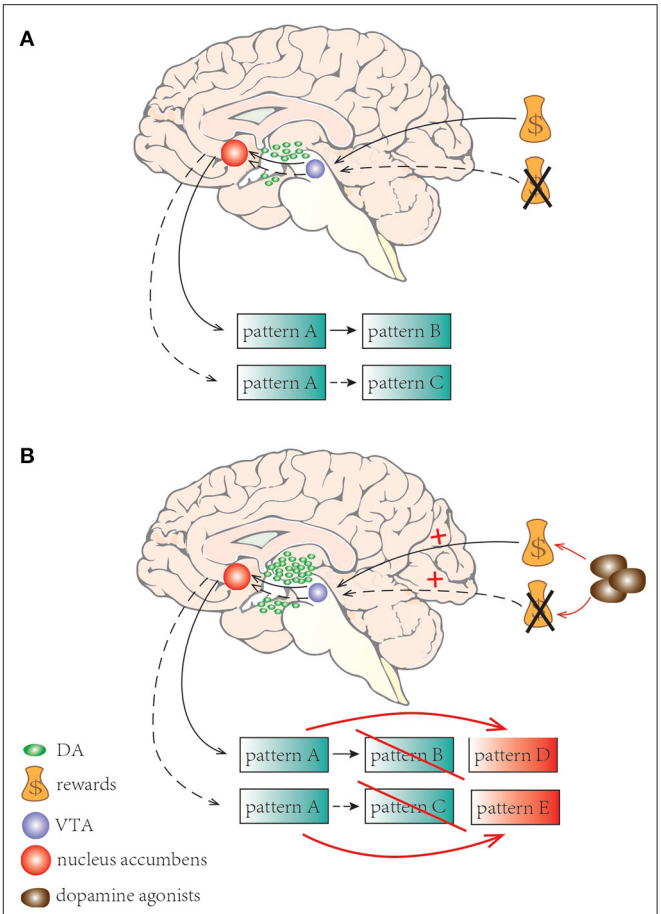

FIGURE 2 | A schematic illustration of learning process and set shifting with dopamine neurotransmission. **(A)** Normally, when expecting a reward or receiving an unexpected reward, phasic release of dopamine from VTA to the nucleus accumbens occurs; phasic suppression of dopamine occurs when an expecting reward is not received. Adaptive behaviors happened shifting from one pattern to a more appropriate one. **(B)** In PD, dopamine agonists may elicit excessive stimulation results in facilitating the appearance of ICDs. ICD patients are less sensitive to negative events but more sensitive to rewarding outcomes.

pathway consisting of cell bodies in the substantia nigra (SN) whose axons terminate in the corpus striatum; (b) the mesocorticolimbic pathway (also known as the reward system), whose cell bodies are situated in the ventral tegmental area and whose axons project to parts of the limbic system; and (c) the tuberoinfundibular pathway, whose cell bodies are found in the ventral hypothalamus and project to the median eminence and pituitary gland (**Figure 1**). Of the three dopaminergic pathways the mesocorticolimbic system seems to play a key role in the reward system, whose main components include nucleus accumbens, amygdala, hippocampus, anterior cingulate and orbitofrontal cortex (81).

Dopamine, as a modulator of risk behavior along the mesocorticolimbic pathway, plays an important role in reinforcement of learning. It signals the difference between predicted and experienced reward, and is also involved in shaping behavior to maximize reward and avoid punishment (82). Normally, in anticipation of a reward or when receiving an unexpected reward, phasic release of dopamine from the ventral tegmental area (VTA) to the nucleus accumbens occurs (83). In contrast, phasic suppression of dopamine occurs when an expected reward is not received (83). Contingencies would result in decreasing activation of the mesocorticolimbic dopaminergic system leading to adaptive behavior and shifting from one pattern to a more appropriate action (84) (**Figure 2A**). In PD, excessive doses of dopamine, dopamine reuptake impairment or stimulation on postsynaptic dopamine receptors by dopaminergic agonists may shift this normal physiologic response and facilitate the appearance of ICDs (57, 82). ICDs patients exhibit reduced ability to learn from negative events and they usually underestimate the adverse consequence of stimuli with punishment, yet they are more sensitive to rewarding outcomes (85) (**Figure 2B**).

There are several observations relevant to reward system and ICDs that are worth highlighting. First, the usual pleasurable stimuli such as food can induce tonic dopamine response in the outer shell of the nucleus accumbens. Second, dopamine auto-receptors in SN provide feedback to regulate synaptic dopamine concentration. Third, the orbitofrontal and anterior cingulate cortices (ACC) are involved in the top-down control, evaluating the reward and directing a suitable reaction, thus making adjustments for optimizing future choices (86). Finally, the prefrontal cortex exerts inhibitory influence to "balance" the system (**Figure 3**). All these components are working together to help individuals adapt to their environment.

PD is associated with a neurodegenerative process that involves mesocorticolimbic network, but there is paucity of data

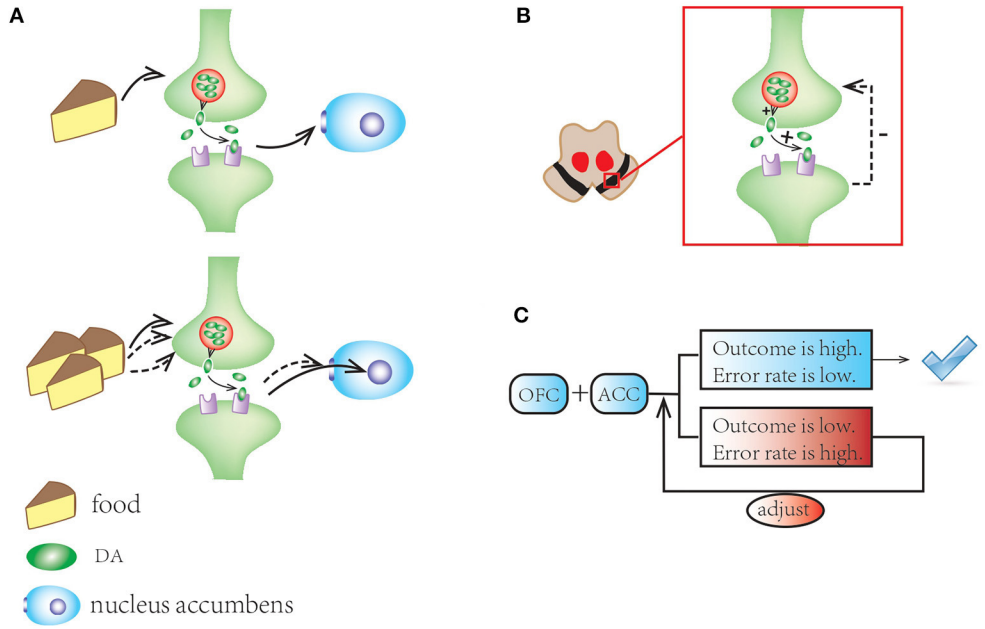

FIGURE 3 | A schematic illustration of mesocorticolimbic network and reward system. **(A)** Standard stimuli (e.g., food) motivate tonic dopamine response in the outer shell of the nucleus accumbens; repeated stimuli induce habitation with the response shifting to its core. **(B)** In substantia nigra, dopamine autoreceptors offer feedback to regulate synaptic dopamine concentrations. **(C)** The OFC and ACC make adjustments for optimizing future choices and balance the system.

linking abnormalities of this network to ICDs. One study, using volumetric magnetic resonance imaging (MRI) technique, found that amygdala volume was greater in PD patients with ICDs than those without ICDs, but similar to health control subjects (64). Since amygdala is important in processing both positive and aversive emotional inputs, relatively preserved amygdala is needed for the expression of ICDs (87, 88). Another study showed that ICDs patients have a thicker cortex in certain limbic regions especially in ACC and orbitofrontal cortex, which may be linked to increased impulsivity and behavioral disinhibition (89). In addition, this study demonstrated positive correlation between the ACC thickening and ICD severity (89). Moreover, a whole-brain diffusion-tensor MRI study found white-matter integrity in the reward system is relatively preserved in ICDs-PD patients compared to PD patients without ICDs (90). A BOLD fMRI study observed that PD patients with ICDs had elevated network connectivity in the mesocorticolimbic network (91).

The mesocorticolimbic reward system plays an important role in the development and maintenance of addictive behavior. The reason for male preponderance in patients exhibiting this behavior is still unclear, but some imaging studies have suggested that males have a stronger functional connectivity in the reward mesocorticolimbic system than females (29, 92). Thus, the relative preservation of neural integrity in mesocorticolimbic network and the intact reward-processing circuits are thought to increase risk for ICDs in PD patients treated with dopaminergic medications (90).

In addition to the reward system, ICDs are also involved in the inhibition system. One fMRI study showed impairment in response-inhibition abilities in ICDs patients (93). The observation found that the rostral portion of the corpus callosum in ICDs patients is thinner compared to healthy control. And it has been interpreted to indicate that there might be some disconnection in the inhibitory system normally mediated by the corpus callosum, leading to behavioral disinhibition and ICDs. The normal inhibitory mechanisms may be further disrupted by treatment with dopaminergic drugs which may explain why some PD patients become vulnerable and experience loss of impulse control (disinhibition) and finally results in the development of ICDs (94). In support of this hypothesis is the finding that pramipexole decreases the interaction between the nucleus accumbens and prefrontal cortex, which might lead to a reduction of normal prefrontal inhibitory control of impulses (95). Thus, dopamine agonists presumably act by suppressing the inhibitory system and elicit a response bias toward impulsive choices (96).

Dopamine agonists improve motor symptoms in PD patients through their effects on the dorsal striatum, but they also activate the ventral striatum and the mesolimbic pathway (97). The brain activity in ventral striatum can be separated spatially and temporally into signals correlated with risk and reward expectation which are both the foundation of decision-making (98). In addition to the involvement of the striatum in ICDs, several studies have implicated the ventral pallidum in the modulation of hedonic responses to rewards (99). Using arterial-spin-labeling MRI, increased cerebral blood flow to ventral striatum in ICDs patients had been substantiated in response to dopamine agonists, which indicated that dopamine agonists can

augment mesocorticolimbic network activity in ICDs patients (100). The function of the orbitofrontal cortex (OFC) is critical in understanding the mechanisms of rewards or punishments (65, 101). The OFC may be activated by stimuli from reward-related memories or environment which then induces a strong sense of urge with or without activation of the nucleus accumbens (102). While the medial OFC engages in reward-based decision-making the lateral OFC is associated with the punishment-based decision-making (101). The role of OFC in ICDs is supported by studies that have found dysfunction of impaired long-term memory and frontal lobe functions in patients exhibiting pathological gambling compared to control (68). Other studies have found evidence that frontal lobe dysfunction facilitates the onset and persistence of pathological gambling in PD (103).

THERAPEUTIC STRATEGIES FOR ICDs

In ICDs patients with PD, caregivers suffer huge burden from mental stress specifically on spousal safety. ICDs are associated with high rate of separation and divorce, child abuse, and neglect (4, 104, 105). It is important to recognize the disease and treat it without delay.

As discussed above, ICDs are considered to have strong relationship with dopamine agonists. Decreasing or even withdrawing dopamine agonists is usually the first choice for clinicians. For PD patients who have developed ICDs on account of dopamine agonist treatment, they will get remission significantly after decreasing dosages. One longitudinal study suggested that ICDs resolved after 1 year in about 50% of the patients who stopped dopamine agonists and continued to improve (25). Patients can increase levodopa dosage instead to avoid worsening in motor symptoms (106). However, treatment is still challenging, as patients may experience dopamine agonist withdrawal syndrome (107–109).

Considering the benefit from reducing dose of dopamine agonists such as pramipexole or ropinirole, it is recommended that temporary replacement of pramipexole by bromocriptine instead may relieve or reverse the ICDs while the D2 stimulation needed for motor symptoms are still maintained (95).

Subthalamic nucleus (STN) deep brain stimulation (DBS) as a treatment for ICDs is considered a controversial method according to reported literature. Compared to patients without ICDs, ICDs patients exhibited increased proportion of subthalamic neurons responsive to prospective reward and decreased proportion to prospective loss in STN but no in GPi (110). STN-DBS and the following tapering of dopaminergic treatment can change personality traits in PD patients (111). A few studies are in favor of DBS surgery as a treatment for ICDs and even suggest that ICDs may be considered as new indication for STN-DBS (112, 113). ICDs patients exhibited a complex outcome after STN-DBS, with a tendency for overall reduction but with several factors affecting its effect (114). It is believed that effective management of medication and correct stimulation parameters may explain these results better than previous literature. Successful surgery allows a marked decrease of total dopaminergic medication. The STN stimulation may also have specific effect on limbic part of the STN (115). In general, fine-tuning of stimulation parameter after DBS surgery, accompanied with drastic reduction of dopaminergic medication are considered as an effective method to give remission to ICDs patients especially advanced subgroup (116, 117). Furthermore, there has been a study indicating that unilateral procedures may be an alternative to bilateral DBS for some patients if they are with asymmetric symptomology (118). Meanwhile, some studies disapprove of using STN-DBS because ICDs may persist or even worsen after DBS surgery (119). Even more, some evidence shows that ICDs may emerge following DBS surgery regardless of unilateral or bilateral DBS (120–122). Stimulation by DBS might sensitize the brain to the impulsive behaviors induced by dopamine agonists, especially in patients with addictive behavior history (121). Besides, stimulation with electrode contacts located mainly within the sensorimotor territory can result in spread of current to limbic and associative area (123). Failed surgery, with misplaced electrodes outside the STN, would result in failure to reduce dopaminergic medication or even causing new onset of dopaminergic treatment (112). Stimulation intensity increased too rapidly will elicit ICDs in the same way as dopaminergic treatment (124). Therefore, we should be careful when choosing DBS treatment in clinical practices.

Amantadine, acting as a dopaminergic and glutamatergic modulator, was reported to have great effect on reversing ICD symptoms without aggravating motor function. Amantadine add-on therapy is considered to reduce hypersensitivity in ICDs patients therefore decrease risky choice (125–127). However, amantadine was associated with an increased risk for ICDs in another multicenter study (128).

As ICDs are thought to be linked to oral dopamine agonists, strategies utilizing intrajejunal levodopa which utilize continuous drug delivery may decrease the risk of developing ICDs. This therapy may become a popular treatment of ICDs not only because its positive effect on behavioral disorders but also motor complications (129, 130).

Clozapine were reported as a potential treatment for refractory ICDs. Clozapine not only has an effect on dopamine-blocking activity in the limbic system but also has weak antagonistic D3 and high antagonistic D4 activity that makes it capable of adjusting the reward circuit. Besides, N-desmethyloclozapine, the major active plasma metabolite of clozapine, may have an important partial agonist activity on dopamine D2/D3 receptors (131). There have been several cases reporting beneficial responses to clozapine in ICDs patients (132, 133).

There has been an emerging method to treat ICDs using transcranial magnetic stimulation (TMS). A study reported that low-frequency repetitive TMS was used to treat four PD patients with punding whose symptoms were reversed magically. TMS deserves more studies to explore the best pattern and more indications (134).

To date, there have been few studies concerning the role of cognitive behavior therapy in ICDs. Okai et al. proved the efficacy of cognitive behavior treatment in ICD patients with PD through a randomized controlled trail. They found the combined treatment of cognitive behavior treatment with medical care was more effective in reducing the severity of ICDs compared

with medical care alone. The severity of symptom (measured on the Clinical Global Impression (CGI) index) significantly reduced 75% of the experimental group compared with only 29% in the control group. The intervention seemed to be also effective in depression and anxiety. Larger and long-term follow up studies are needed to confirm the benefit of cognitive behavior treatment in each subtype of ICDs, and meanwhile assess the cost-effectiveness (135).

In addition to those treatments discussed above, valproate, zonisamide, naloxone, apomorphine, and bromocriptine may also be beneficial in treating ICDs (136, 137). Dopamine agonists with lower D3 selectivity appear to have lower proportion of causing ICDs. Switching to bromocriptine was proposed as a method to mitigate ICDs. More research and clinical trials are needed to explore the best therapeutic strategy.

CONCLUSION

In conclusion, present studies remind us to pay much attention to non-motor symptoms including ICDs. With rapid advance regarding to ICDs, mechanisms of ICDs will become gradually clear and specific individual treatment strategies will be applied in the future. Given that ICDs would have terrible impact and consequence on families, patients and their caregivers should be educated in clinical practice. In addition, ICDs in PD patients may also provide a model for better understanding of the neurobiology of addiction.

AUTHOR CONTRIBUTIONS

Y-CW provided the funding support and designed the project. J-FZ, X-XW, and YF searched for literature and wrote the manuscript. Y-CW, RF, and JJ revised the paper. All authors contributed to the article and approved the submitted version.

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What You Believe Can Affect How You Feel: Anger Among Caregivers of Elderly People With Dementia

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Background and Purpose: Anger has been recognized as a commonly experienced emotion among caregivers of elderly people with dementia. While several cognitive behavioral therapy (CBT)-based intervening methods have been developed, limited research has systematically examined the associations between dementia-related cognition and caregiving anger. Currently, we focused on three representative and well-studied cognitive constructs, *person-centered attitude* (PCA), *dementia representation* (DR), and *empathy*, exploring how they related to caregiving anger.

Methods & Results: In total, 327 caregivers (239 female) participated in the study and finished online questionnaires. Multi-variable regression analyzes showed that PCA ($\beta_{PCA} = -0.22^{**}$) and empathy ($\beta_{empathy} = -0.18^{**}$) could negatively predict caregiving anger. However, all DR dimensions had no influence on caregiving anger except *coherence* ($\beta_{coherence} = -0.24^{**}$) in the current study.

Conclusion: Generally, lower caregiving anger was associated with: (1) being more empathic; (2) having a person-centered attitude; and (3) having a comprehensive understanding of dementia. The results of this study provide detailed suggestions for the development of anger management programs for caregivers of people with dementia.

Keywords: elder, dementia–Alzheimer disease, caregiver, anger, epidemiological

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Dementia, referring to a clinical syndrome characterized by progressive deterioration in cognitive ability and the capacity for independent living (1), affects more than 4% of people aged 60 years or over worldwide (5.21% in China). And due to aging of the population worldwide, the number of patients with dementia is estimated to triple in the next two decades (2). The rapid increase in prevalence of dementia will generate a substantial burden on health care systems and the local economy. Data showed that providing dementia patients with health care costs nearly US $ 30 billion in the UK per year, and this number is projected to rise in the future (3). In China, experts estimated that annual health care costs directly associated with dementia are supposed to reach $ 1 trillion (4). Considering the rising demand for formal health care and relatively limited public health resources, informal care needs to serve as an important supplement. It is reasonable to foresee that more and more patients with dementia will live within the community and receive unpaid care from their relatives (i.e., informal caregivers).

However, many caregivers do not choose their role. Previous research has shown that caregivers could find it difficult to adapt to caregiving due to emotional distress and burnout (5). In fact, caring for patients with chronic disease has long been identified as a resource of stress which could bring about various negative consequences (6). Anxiety and depression are two of such consequences

which have received much research attention (7). However, several studies have shown that anger is also commonly experienced among family caregivers and this emotion response has largely been overlooked (8, 9). This lack of interest could be attributed to caregivers' difficulty in acknowledging their anger (9).

Fortunately, several intervention methods have been designed to help caregivers manage the anger they experience during caregiving. For example, psychoeducation programs in the form of a face-to-face course or video have been developed (10, 11). These programs can be categorized as following: (1) skill training. These courses aim to teach participants cognitive skills in dealing with their feelings, such as relaxing techniques (i.e., distraction techniques) and awareness training (11); (2) cognitive behavioral therapy (CBT)-based methods. These courses provide trainees with cognitive change strategies such as cognition reconstruction (12) and stopping thoughts which commonly precede anger (13).

However, previous meta-analyses indicated that these intervention programs could be less efficacious than researchers have expected. Gallagher and his colleagues (14) reported an averaging effect size of 0.15 based on 19 interventions studies. This indicated relatively low effectiveness for existing intervening methods to alleviate caregivers' psychological dysphoria. The low effectiveness could partly be attributed to the lack of insights on the cognitive bases which may lead to anger (14). According to Beck's cognitive behavior model (15), one's cognitive explanation about an event can influence his or her behavioral and emotional reactions to it. Thus, caregivers' disease-related cognition may determine the feelings (including anger) they experience during caregiving. There has been some initial evidence which could support this assumption. For example, Lo Sterzo's (16) research found that caregivers' comprehensibility of dementia could influence the level of depression they experienced during caregiving. Likewise, Shinan found that caregivers with higher levels of dementia-related knowledge were less likely to experience burnout conditions (17).

Although all the intervention paradigms mentioned above are expected to target caregivers' cognitive systems, the relation between caregivers' cognition about dementia and anger experiences have not been clearly explored. According to the common sense model [CSM, (18)], beliefs, attitudes, and cognitive ability are the three essential constituents of disease-related cognition. Holding together several theoretical threads, we assumed that three representative, well-studied cognitive conceptualizations could be related to anger during caregiving, including (1) dementia representation (DR, beliefs about dementia); (2) person-centered attitudes (PCA, a widely recommended attitude toward patients with dementia); and (3) empathy (an essential cognitive ability when dealing with people with dementia).

First, dementia representation (DR), which reflects how caregivers understand dementia, could be possibly related to caregiving anger. Quinn's (19) research found that the caregivers who described their patients as "being forgetful" and attributed the symptoms to aging were less likely to go through depression than those who regarded the care-receivers as "having an incurable disease." According to REDIX (19), the way caregivers name the disease is referred to as "identity," which is one dimension of DR. Likewise, Lo Sterzo and Colleagues (16) found that coherence, one dimension of DR, was associated with caregivers' general well-being. Thus, it is reasonable to assume that how caregivers perceive dementia-related problems may affect caregiving anger.

Second, person-centered attitudes (PCA) (20), characterized by regarding patients as individuals with *personhood and dignity,* could also be related to anger in caregivers. Previous findings indicated that after the caregivers received training on person-centered care, their care-receivers showed lower levels of psycho-dysphoria (21). Evidence also showed that being cognitively impaired does not necessarily reduces one's perception of the way in which he/she is treated (21). It is reasonable to assume that viewing patients as people with an intact personhood and self-esteem may reduce the conflicts between caregivers and patients, and subsequently lead to lower levels of anger for caregivers.

Finally, empathy is defined as "an ability to place oneself mentally and emotionally in the world of another person, to apprehend another's condition and state of mind, to communicate understanding back to the other and perceive his reaction to it" (22). Previous evidence showed that empathy may also play an essential role in improving caregiving outcomes and alleviating negative feelings (such as depression and anxiety) during caregiving (23). It is reasonable to assume that being empathic may alleviate caregiving anger.

In summary, the aim of the current research is to explore systematically how caregivers' disease-related cognition (DR, empathy, and PCA) may influence their anger experiences during caregiving.

METHODS

Participants

The participants consisted of 327 dementia caregivers, who were recruited from two local dementia/neurological centers using Weixin, a smartphone application used for online communication. One important function of Weixin is "group chat" by which people (<500) can chat with each other simultaneously. In the Chinese medical system, a large amount of physicians utilize such "group chats" to manage and send out information simultaneously to all of their patients (equivalent to online bulletin boards). A total of 10 psychiatrists/physicians participated in the current study, and the recruitment advertisements (including the main conductor's phone number) were sent out in each psychiatrist/physician's Weixin group chat. A total of 340 caregivers joined the study and 327 of them finished the online questionnaire. The main inclusion criteria were: (1) caregivers were identified as family members/friends of patients and the care he/she provided was not paid; (2) patients were diagnosed with dementia according to the International Classification of Disease, Tenth Edition (ICD-10) and lived within the community (not living in or receiving care from professional organizations). And the main exclusion criterion was: caregivers were paid. By this criterion, formal caregivers (care workers) were excluded.

Procedure

The research was approved by the Ethnic Committee of Dalian's Seventh People Hospital (DLS20200812). All the assessments were conducted by trained graduate students. First, participants were read an institutional review board (IRB)-consented script and gave vocal consent before participating in the study. All responses from the participants were recorded carefully and stored safely in an online file.

Measurements

DR was measured by the brief illness presentation questionnaire (Brief IPQ) developed by Lo Sterzo (16). Considering the questionnaire had not been localized using the Chinese population, a double translation method was adopted to make sure the items were suitable for a Chinese sample. Results showed that all items except IPQ-5, "how much do you experience symptoms from your relative's illness" could be double translated appropriately. We further interviewed 10 participants to examine whether the Chinese version of the Brief IPQ made sense to Chinese caregivers. And the results showed that half of them (5) found IPQ-5 weird, for the reason that "usually they don't think in that way." Regarding this, IPQ-5 was deleted in the version we finally adopted. As all items in the Brief IPQ are independent, the deletion of one item cannot affect the others.

PCA was measured by one subscale of the approach to dementia questionnaire [ADQ, (24)], which is widely used to evaluate to what extent caregivers agree with the idea that "people with dementia are unique individuals with the same values as others." Both a previous study and the current study showed good reliability ($\alpha = 0.83$; $\alpha = 0.89$ for the current research).

Empathy was measured by the "perspective-taking" subscale of the interpersonal reactivity index (PT-IRI) (25), which is a widely used instrument to evaluate adults' tendency to adopt the psychological perspective of someone else. In the current study, "others" in the items were re-phrased as "dementia patient" but the response keys were kept unchanged. In the current study, PT-IRI showed good reliability ($\alpha = 0.94$).

Anger related to caregiving was measured with a caregiver anger interview (11), which was developed specifically for measuring caregivers' anger intensity. Participants were asked to write down three most annoying events in the last 2 weeks which were directly or indirectly related to caregiving. And then they were asked to rate the three events across six anger adjectives (aggravated, angry, annoyed, disgusted, frustrated, and resentful). The measurement showed good reliability in the current study ($\alpha = 0.91$).

Data Analysis

Descriptive statistics and multi-variable regression analyses were conducted using SPSS 19.0. Missing values (<5%) were substituted with the average value for the subscale. As more than 95% of caregivers perceived dementia as "lasting forever," the item about *timeline* was deleted from further analyzes.

TABLE 1 | Participants' characteristics.

Demographic information	*N* (%)
Characteristics of caregivers	
Gender	
Female	239 (73.1%)
Marriage	
Married	267 (81.7%)
Unmarried	45 (13.8%)
Divorced	15 (4.6%)
Age	
<65	238 (72.8%)
Kin-relationship	
Spouse/partner	98 (30%)
Adult children	194 (59.3%)
Other	35 (10.7%)
Education	
Middle-school level	242 (71.4%)
College-level and above	85 (28.6%)
Characteristics of care-recipients	
Diagnosis	
Alzheimer's disease	182 (55.7%)
Mixed Alzheimer's and vascular dementia	51 (15.6%)
Vascular dementia	32 (9.8%)
Unspecified/other dementia	31 (19%)
Time since diagnosis	
<1 year	100 (30.6%)
1–2 years	60 (18.3%)
3–5 years	167 (51.1%)

RESULTS

Participants' Characteristics

The majority of the 327 caregivers were female (73.1%), married (81.7%), and middle-school-level educated (71.4%). More than half of the care receivers were diagnosed as having "Alzheimer's disease" (55.7%), and most of them had a long disease course (>3 years). Participants' demographic information is listed in **Table 1**.

Sociodemographic Variables and Caregiving Anger

Subgroup analysis was conducted to evaluate the effects of demographic variables on caregiving anger. *T*-test showed that female caregivers had higher levels of anger ($t = -3.71$, $p < 0.001$). Results from one-way ANOVA found that characteristics of both caregivers (such as education level) and patients (dementia subtypes) had no effect on caregiving anger.

DR and Caregiving Anger

The mean score and deviation of every single dimension of DR are listed in **Table 2**. All seven dimensions of DRs were related to caregiving anger ($r_{\text{consequences}} = -0.55$; $r_{\text{personal control}} = -0.62$; $r_{\text{treatment control}} = -0.53$; $r_{\text{concern}} = -0.57$; $r_{\text{coherence}} = -0.65$; $r_{\text{emotional representation}} = -0.33$). Then, a multiple regression analysis was conducted to evaluate how well the DRs predicted

TABLE 2 | Mean scores and deviations of every dimensions of DR.

Dementia representation	Means	S.D.
Consequences	6.00	1.22
Personal control	3.67	0.76
Treatment control	2.64	2.44
Concern	3.87	1.17
Coherence	4.65	1.13
Emotion representation	3.71	1.05

TABLE 3 | Dementia representation, empathy, and person-centered attitude predicting caregiving anger.

Anger	β	*t*-value
Dementia representation		
Consequences	−0.07	−1.27
Personal control	−0.08	−1.52
Treatment control	−0.08	−1.11
Concern	−0.11	−1.92
Coherence	−0.24**	−3.96
Emotion representation	0.03	0.40
Empathy	−0.18**	−3.98
Person-centered attitude	−0.22**	−4.37

*$P < 0.05$, **$p < 0.01$, ***$p < 0.001$.

caregiving anger, adjusting for the covariate (gender). The results revealed that only *coherence* had a predictive effect on caregiving anger ($\beta = -0.24^{**}$; *t*-value = 4.29).

Empathy, PCA, and Caregiving Anger

The result showed that empathy and PCA were also significantly associated with caregiving anger ($r_{\text{empathy}} = -0.57$; $r_{\text{person-centered attitude}} = -0.60$). A multiple regression analysis was also conducted to how well-empathy and PCA predicted caregiving anger. After adjusting for covariates (age, gender, and time since diagnosis), empathy and person-centered attitude still had a predictive effect on caregiving anger ($\beta_{\text{empathy}} = -0.22^{**}$, *t*-value = 2.09; $\beta_{\text{PCA}} = -0.18^{**}$, *t*-value = 6.09). The results from multivariate regression analysis are shown in **Table 3**.

DISCUSSION

This is the first study to investigate anger among Chinese caregivers of patients with dementia. A total of 66% of caregivers reported having experienced moderate to high levels of anger in caregiving situations. Considering previous research findings (9, 26), more than half of family caregivers reported anger-related problems. This stresses the necessity of developing effective anger management methods for caregivers of people with dementia. Consistent with previous findings (27), female caregivers showed higher anger intensity, which is probably due to their propensity to be "emotionally involved" (28). Highly involved caregivers are more likely to have their emotions affected by patients and thus can more easily burnout. Compared to female caregivers, male caregivers are disassociated from the patients whom they take care of Jutten et al. (23).

The current research is also the first to systematically explore the effects of caregivers' dementia-related cognition (beliefs, attitude, and cognitive ability) on anger they experience during caregiving. Being more empathic did lead to lower caregiver anger intensity as expected. Actually, abundant evidence has shown that cognitive empathy (i.e., perspective taking) is reversely related with anger. Research by Oliver and colleagues (29) indicated that individuals with higher levels of empathy were more aware of others' distress and were more concerned with negative consequences caused by them if they expressed their anger. That is, high-empathy individuals are better at anger control. Besides, Jutten and her colleagues (30) found that empathy may help caregivers recognize dementia symptoms as part of disease presentations rather than intentional acts of the patients. This may possibly reduce caregivers' anger during caregiving. However, research showed that being empathic consumes more cognitive resources (31) and may add to psychological burden (23). For high-empathy caregivers, it is still unclear whether their low anger expression is at the expense of their general psychological well-being. The relation between caregivers' anger, empathy, and psychological well-being need further exploration.

PCA was found to be related to lower levels of caregivers' anger in the current study. In contrast to the traditional belief that people with dementia are mentally disabled, a person-centered attitude implies that caregivers regard patients as people with personhood, strengths, and normal needs (32). In other words, PCA requires caregivers to view patients as a "*whole person with cognitive impairment.*" Research showed that behavioral and psychological symptoms of dementia (BPSD), a main source of caregivers' anger and resentment, are not only the consequence of disease itself, but responses to adverse psycho-social environments (20). Caregivers with PCA are less likely to infantilize, disempower, and objectify their care-recipients, and in consequence the care-recipients showed less agitation and aggression (20). It is reasonable to assume that caregivers with PCA experience lower levels of anger for their care-recipients, and their patients show less BPSD. In addition, according to Kitwood (32), caregivers with person-centered attitudes have higher levels of self-compassion, and thus the emotional strains (such as anger) of being a caregiver are more likely to be recognized, respected, and reasonably expressed.

The current study was also the first to explore the effects of caregivers' dementia-related beliefs (DR) on their angry feelings during caregiving. The results showed that only one of the six dimensions of DR, *coherence* (i.e., "*understanding the disease well*") was associated with lower caregiving anger. A sense of coherence is one of the core conceptions in health psychology (33), which refers to "a global and pervasive feeling that the life events one faces are comprehensible, meaningful, and worthy of engagement." For dementia caregivers, being coherent means that he/she feels the symptoms of dementia are comprehensible and manageable to some extent. Lo Sterzo and colleagues (16) found that caregivers with a sense of coherence

about dementia were prone to lower levels of caregiving-related anxiety and depression. Likewise, Quinn and her colleagues (34) found that even patients who have a general comprehension of the symptoms they experience (i.e., high sense of coherence) can deal with the impact of dementia more effectively. These findings showed that viewing symptoms as comprehensible and manageable render caregivers or patients more self-efficient in dealing with disease consequences (16), including frustration and anger. It should also be noted that items of specific knowledge about dementia (such as cause, timeline, and cure effectiveness) were not associated with lower caregiving anger in the current research. These results may reflect that being coherent requires a "feeling of understanding" rather than specific knowledge about dementia (such as knowledge about causes, disease course, etc.).

In all, in the current study we found that lower caregiving anger was associated with: (1) being more empathic; (2) having a person-centered attitude; and (3) understanding symptoms of dementia more comprehensively (i.e., being more coherent). These findings may inform the designs of anger management lectures that provide participants with the whole picture of dementia and facilitate intuitive understanding of the illness. On the contrary, providing specific disease-related knowledge and explanations may not be helpful like expected. Programs based on virtual reality (VR) technologies may be an ideal choice to help caregivers understand the perspective of people with dementia (35). It may provide a sense of what it is like to live with dementia, and such "subjective knowledge" is essential for caregivers to develop empathy and a general comprehension of dementia (35).

There are also several limitations in the current study which should be noted. First, the convenient sampling methods adopted may undermine the representativeness of the current research. The participants from two major cities of China (Qingdao, Dalian) may not represent caregivers living in other parts of China, and it should be noted when generalizing the findings. Second, a cross-sectional design did not allow the determination of causal relationships, and thus the current study may act as an initial exploration of associations between dementia-related cognition and caregiving anger. Research using longitudinal designs are needed in the future to verify these associations. In conclusion, the current study examined the associations between caregivers' dementia-related cognition (DR, PCA, and empathy) and caregiving anger. Future research is needed to examine the associations between a wider range of dementia-related cognition and caregiving anger, hoping to provide more specific and detailed guidance for designs of anger management programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Dalian NO.7 People's hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CY proposed the research idea. HW collected the data and wrote the paper. HC and MW helped in data collection, revised the manuscript, and provided many constructive suggestions. All authors contributed to the article and approved the submitted version.

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Risk Factors for Delirium Are Different in the Very Old: A Comparative One-Year Prospective Cohort Study of 5,831 Patients

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Background: In an ever-aging society, health care systems will be confronted with an increasing number of patients over 80 years ("the very old"). Currently, knowledge about and recommendations for delirium management are often based on studies in patients aged 60 to 65 years. It is not clear whether these findings apply to patients ≥80 years.

Aim: Comparison of younger and older patients with delirium, especially regarding risk factors.

Methods: In this prospective cohort study, within 1-year, 5,831 patients (18–80 years: $n = 4{,}730$; ≥80: $n = 1{,}101$) with delirium were enrolled. The diagnosis of delirium was based on the Delirium Observation screening scale (DOS), Intensive Care Delirium Screening Checklist (ICDSC) and a DSM (Diagnostic and Statistical Manual)-5 construct of nursing instrument. Sociodemographic trajectories, as well as the relevant predisposing and precipitating factors for delirium, were assessed via a multiple regression analysis.

Results: The very old were more commonly admitted as emergencies (OR 1.42), had a greater mortality risk (OR 1.56) and displayed fewer precipitating risk factors for the development of a delirium, although the number of diagnoses were not different ($p = 0.325$). Predisposing factors were sufficient almost alone for the development of delirium in patients ≥ 80 years of age; in 18–80 years of age, additional precipitating factors had to occur to make a delirium possible.

Conclusion: When relevant predisposing factors for delirium are apparent, patients over 80 years of age require comparatively few or no precipitating factors to develop delirium. This finding should be taken into account at hospitalization and may allow better treatment of delirium in the future.

Keywords: delirium, very old, risk factors, comparison, prospective

INTRODUCTION

Delirium is the most common, acute neuropsychiatric disorder manifesting in abrupt and fluctuating disorders of consciousness, attention or cognition (e.g., concentration and memory) (1). The causes and risk factors for delirium are complex; indisputably, age is one of the major risk factors for the development of a delirium (2, 3).

Despite the rise of life expectancy in industrialized countries, and as a consequence increase in health care demands of aging patients, there is a lack of evidence of the characteristics of delirium in very old patients (≥80 years, also referred to as the "very old" or "very elderly"). It is unclear to what extent the delirium of this increasing number of patients differs from that in "younger" patients (18–80 years). The short and long-term socioeconomic and medical consequences of delirium are vast (4): Delirium is associated with higher health care costs, increased complications, mortality and loss of independence. Since developing delirium is associated with higher age and society in itself is getting older, there is a risk that the health care costs of delirium could exhaust the resources of future health care systems.

In addition to age, further risk factors for developing delirium can be divided into predisposing and precipitating factors (5–8). Predisposing factors exist prior to the development of delirium, e.g., dementia, substance addiction or gender. Precipitating factors, on the other hand, acutely cause delirium, e.g., infections, fever or surgeries. In general, the more predisposing factors exist in a patient, the fewer precipitating factors are necessary for the development of a delirium (9). Since aging in itself is associated with diseases and comorbidities or, predisposing factors, it is plausible that older patients have a higher risk of developing delirium than younger patients. As far as we know, the extent and differences vs. the younger patients have not been investigated. In general, previous studies commonly compared delirious vs. non-delirious patients, but the scope omits characteristics of delirious patients between age groups.

Therefore, in this study we compared very old delirious patients, ≥80 years, with younger delirious patients between 18 and 80 years. The cut-off-value ≥80 years was chosen due to several aspects: Since in the literature a distinction is made between old and very old patients and this cut-off value is repeatedly given at 80 years of age, it seemed reasonable to follow this cut-off value. Furthermore, the rate of multimorbidity (10), frailty (11, 12) and neurocognitive disorders (13) increases significantly from the age of 80 years, making a comparison with younger patients conclusive. The aim was to explore the distinction between these groups and to investigate the contribution of potential factors to inform future management studies or advanced care planning.

METHODS

Study Design, Patients and Procedures

Between January 1st and December 31st 2014, a delirium detection initiative (DelirPath, **D**etect **E**valuate Contro**l** **I**npatient **R**isk factors, **P**revent **A**nd **T**reat **H**ospital Acquired Deliriums, **Figure 1**) at the University Hospital Zurich, a tertiary care center, prospectively assessed 39,442 patients for delirium. Patients were excluded if age was below 18 years, the length of stay (LOS) was below 1 day and missing data, including the electronic patient's assessment, leaving 28,806 eligible patients. Of these eligible patients, 5,984 (20.8%) had delirium. An additional 153 patients were excluded from this analysis due to partial incompleteness of available data. Of the remaining 5,831 patients, 1,101 (18.8%) were > 80 years and 4,730 (81.2%) were between 18 and 80 years old.

Characterization of the Predisposing and Precipitating Factors for Delirium

Previously, several predisposing and precipitating factors for the development of delirium have been described. For the purpose of this study, predisposing and precipitating factors for the development of delirium were based on diagnostic clusters, according to the 10th revision of the International Statistical Classification of Diseases (ICD-10) (14) (**Table 1**), which is used in Switzerland. Furthermore, the ICD 10 provides uniform criteria and since the corresponding diagnoses are made by the respective specialists (e.g., the cardiologist diagnoses the heart disease), a high validity can be assumed.

Measurements and Diagnosis of Delirium

Since different delirium scales were used in normal wards and intensive care units, we used a set of three scales in total to measure delirium:

1) The Delirium Observation Screening Scale (DOS, cut-off ≥3) (15),
2) the Intensive Care Delirium Screening Checklist (ICDSC, cut-off ≥4) (16), and
3) a nursing instrument most recently validated by our group for the diagnosis of delirium, the Ergebnisorientiertes PflegeAssessment Acute-Care (ePA-AC) (17, 18) DSM-5-criteria (1), see also below.

   Given the circumstance that three different scales were used and the ePA-AC was not evaluated for delirium severity or subtype (hypoactive vs. hyperactive), we reduced the scales to whether delirium was present or not.

The DOS is a 13-item scale validated to indicate delirium according to DSM-IV criteria. Items include disturbances of consciousness (1), attention (2–4), thought processes (5 and 6), orientation (7 and 8), memory (9), psychomotor behavior (10, 11, and 13), and affect (12). Symptoms are rated on a scale (0–1) as not existent (0), sometimes to always existent (1), and unable to assess (-). The cut-off score for delirium is ≥3 and values were aggregated throughout recordings. This approach proved to be valid and correctly identified 91% of delirium diagnoses as determined by the consultation-liaison psychiatry service.

The ICDSC is a screening instrument with eight items based on the DSM-IV criteria specifically designed for the intensive care setting with two points: Absent or present. This scale was designed for patients with limited communication abilities such as intubated patients. The items include the assessment of 1 - consciousness (comatose, soporose, awake, or hypervigilant), 2

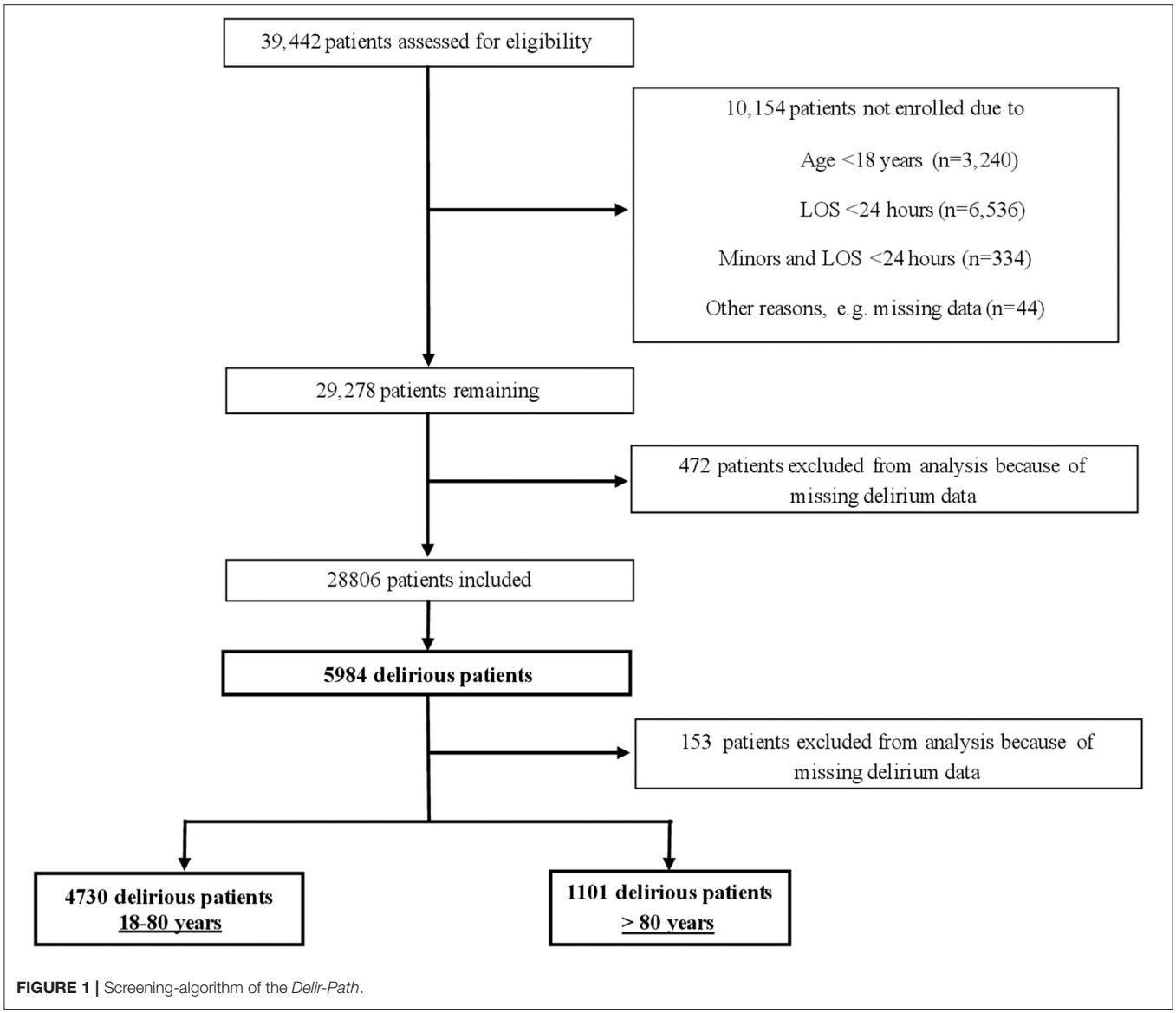

FIGURE 1 | Screening-algorithm of the *Delir-Path*.

- orientation, 3 - hallucinations or delusions, 4 - psychomotor activity, 5 - inappropriate speech or mood, 6 - attentiveness, 7 - sleep-wake cycle disturbances and 8 - fluctuation of symptomatology. The maximum score is eight; scores of more than three indicate the presence of delirium. Each item is rated on the patient's behavior over the previous eight (15, 18).

The ePA-AC is a nursing instrument administered daily assessing mobility, personal care and dressing, feeding, elimination, cognition and alertness, communication and interaction, sleeping, breathing, pain, pressure ulcers and wounds (17).

On regular floors, patients ≥ 80 years were screened daily with DOS and ePA-AC. On intensive care units (ICU), ICDSC was conducted three times per day. Patients below 80 years were not routinely screened for delirium at hospital admission, but the delirium scales were applied in cases of clinical suspicion and a consultation psychiatry service was usually involved. DOS, ICDSC and ePA-AC were conducted by nursing staff and continued until remission of delirium was apparent. Nursing staff had been trained in a 4-h course with tests of achievement; In addition, literature research and eLearning were conducted. Further, the training was completed via case reports, lessons on epidemiology and characteristics of delirium, including the diagnostic criteria and approaches.

The chosen approach implementing the DOS, ICDSC and DSM-construct based on the ePA-AC was validated in the following manner: delirium diagnoses as determined by the gold-standard, the assessment by the consultation-liaison psychiatry service, were detected in 91%. Further, this construct was tested against the DOS and ICDSC and achieved perfect agreement (Cohen's κ 0.83, $p < 0.001$).

DOS, ICDSC and ePA-AC values as well as medical data was obtained from the electronic medical chart (Klinikinformationssystem, KISIM, CisTec AG, Zurich).

TABLE 1 | HDiagnostic clusters with their respective included diagnoses according to the International Statistical Classifications of Diseases and Related Health Problems 10th Revision (1CD-10).

	ICD-10-Chapter
Dementias/degenerative cerebral disorders	F00 Alzheimer's disease F01 Vascular dementias F02 Dementia due to elsewhere defined disorders F03 Neurodegenerative disorder G30 Alzheimer's disease G31-.0 Localized atrophies (frontal temporal dementia) G31-.1–2 Senile and alcohol-induced degenerations G31.8–9 Degenerations ned G32 Degenerations due to elsewhere defined disorders
Epilepsies	G40
Intracerebral hemorrhage	I61–62
Sepsis-related disorders	A40–41 Other sepsis, streptococcal B00.7 Herpetic sepsis R65 Systemic inflammatory response syndrome
Diseases of the genitourinary system	N18 Chronic renal failure
Diseases of the digestive system	K56 Paralytic ileus K65 Peritonitis K74 Liver cirrhosis K72 Liver failure including acute hepatitis
Neoplasm	C00-C69, C73-C97 C70-C72 neoplasm of the brain
Substance-induced	F10-F14
Hydrocephalus	G91
Brain edema	G93.6
Diseseas of the cardiovascular system	I10-I15 Arterial Hypertension I34-I37 Valvular heart disesase I42 Cardiomyopathy I70 Atherosclerosis I95 Arterial Hypotension
Diseases of the pulmonary system	J93 Pneumothorax
Syncope	R55
Malnutrition	E44

This study was approved by the ethics committee of the Canton of Zurich (KEK-ZH-Nr. 2012-0263). A waiver of informed consent was obtained from the committee. Our reporting is in line with the STROBE (strengthening the reporting of observational studies in epidemiology)-statement (19).

Statistical Methods

Data analysis, viewed in a highly simplified manner, involved two steps: (1) a descriptive description of sociodemographics and (2) a logistic regression of risk factors for delirium between the groups delirium 18–80 years vs. delirium ≥80 years. The analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 25 and R statistical software version 3.5.0 for Windows.

Descriptive characteristics were summarized based on parametric properties using means and standard deviations or medians and interquartile ranges for continuous variables, and percentages for categorical variables. The data were tested with Shapiro-Wilk's test for distribution of normality. Inter-group differences for continuous variables were computed based on their parametric properties using Student's *t*-test and Mann-Whitney *U*-test, and Pearson's-χ^2 test for categorical variables.

Then, simple logistic regressions were performed in order to determine the sociodemographic and clinical characteristics of delirium, as well as for the inclusion of medical clusters in the multiple regression analysis, with their respective odds ratios (OR) and corresponding confidence intervals (CIs). The multiple regression model was optimized with Cox-Snell's and Nagelkerke's r^2 by omitting non-contributory cluster.

For all inferential tests, two-tailed tests were chosen and the significance level alpha (α) was set at $p<0.05$. the delirium construct based on DSM-5 was tested on its agreement with the validated approach - with a DOS cut-off ≥3 or ICDSC≥4 - with Cohen's κ as measure of concordance. The agreement was defined as >0.80 as perfect (20).

RESULTS

Comparison of Characteristics of Delirious Patients

The sociodemographic and medical characteristics of the delirious patients as well as the corresponding differences between age groups are displayed in **Table 2** and **Figure 2**. There were group differences in terms of gender distribution, residence prior admission, admission mode, length of stay and residence after hospital. Within the very old (≥80), gender distribution

TABLE 2 | Sociodemographic and medical characteristics of delirious patients.

	Patients ≥*80 years* (n = 1,101)		**Patients *18–80 years*** (n = 4,730)		
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	***p***
Age in years	85 (4.2)	84 (6)	59 (15.2)	63 (21)	<0.001
Length of stay in days	12.4 (10.5)	10 (11)	16 (17.6)	11 (14)	<0.001
Number of Diagnoses	6.6 (5)	5 (6)	6.5(5.1)	5 (6)	0.325
Affected organ systems	3.9 (2.5)	3 (3)	3.8(2.6)	3 (3)	0.076
Operations	7 (10.4)	5 (7)	9.9 (10.4)	6 (10)	<0.001
	Percentage	**Percentage**	***p***	**OR**	**CI**
Gender					
Male	50.2	62.8	<0.001	0.6	0.52–0.67
Female	49.8	37.2	<0.001	1.7	1.49–1.94
Residence prior to admission					
At home, unassisted	68.9	73.6	<0.001	0.82	0.71–0.95
At home, assisted	12.8	3.7	<0.001	3.87	3.08–4.86
Nursing home	16.8	19.4	0.072	0.9	0.72–1.01
Other hospital	1.5	3.3	0.001	0.44	0.26–0.72
Admission					
Emergency	66.5	58.7	<0.001	1.42	1.24–1.63
Elective	33.5	41.3	<0.001	0.76	0.66–0.87
Residence after hospital/delirium					
At home, unassisted	36	48.3	<0.001	0.6	0.53–0.69
At home, assisted	15.6	4	<0.001	4.4	3.55–5.47
Nursing home	13.3	9.8	0.001	1.41	1.16–1.71
Other hospital	3.1	3.6	0.44	0.87	0.59–1.25
Rehabilitation	17.4	24.4	<0.001	0.65	0.55–0.77
Deceased	14.6	9.9	<0.001	1.56	1.29–1.88

SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval.

was balanced, whereas in younger patients more men than women were delirious. Prior to admission, very old patients depended on assistance (OR 3.87) than living independently (OR 0.82), and were more likely to be admitted as emergencies (OR 1.42). Although emergent admissions might be due to greater comorbidity, neither the number of diagnoses nor involved organ systems were different between groups. The hospitalization of the very old was marginally shorter (10 vs. 11 days), however, they were more often transferred to a nursing home (OR 1.41), depended on assistance upon discharge at home (OR 4.4) or deceased (OR 1.56,). Conversely, transfers to rehabilitation were less common (OR 0.65).

Inter-group Differences of Predisposing Factors for Delirium

The differences between groups are listed in **Table 3** and **Figure 2**. Corresponding regression coefficients [Exp (B)] at values >1 indicate higher risks (e.g., dementia) in the very old. Hence, dementia, arterial hypertension as well as hypotension, valvular heart disease, atherosclerosis and chronic renal failure predisposed the very old to develop a delirium. Conversely, in patients <80 years, these factors did less commonly lead to delirium. Predisposing factors such as liver cirrhosis, substance addiction or hydrocephalus increased the risk of delirium in patients <80 years, but comparatively less so in patients ≥80 years.

Inter-group Differences of Precipitating Factors for Delirium

The differences between groups are listed in **Table 3** and **Figures 2**, **3**. Syncope and intracranial hemorrhage were precipitating risk factors for developing delirium at ≥ 80 years, whereas in those <80 years, these factors were not as relevant. In patients <80 years, brain edema, acute hepatitis or liver failure were more common precipitating risk factors than in patients ≥ 80 years.

Only statistically significant results are reported. Factors frequently reported in the literature such as anemia, electrolyte disorder, or diabetes were analyzed, but did not reach the statistical significance level of $p < 0.05$.

DISCUSSION

Summary of Main Findings

By comparing very old patients with younger ones between 18 and 80 years we found that delirium in patients ≥80 years occurs

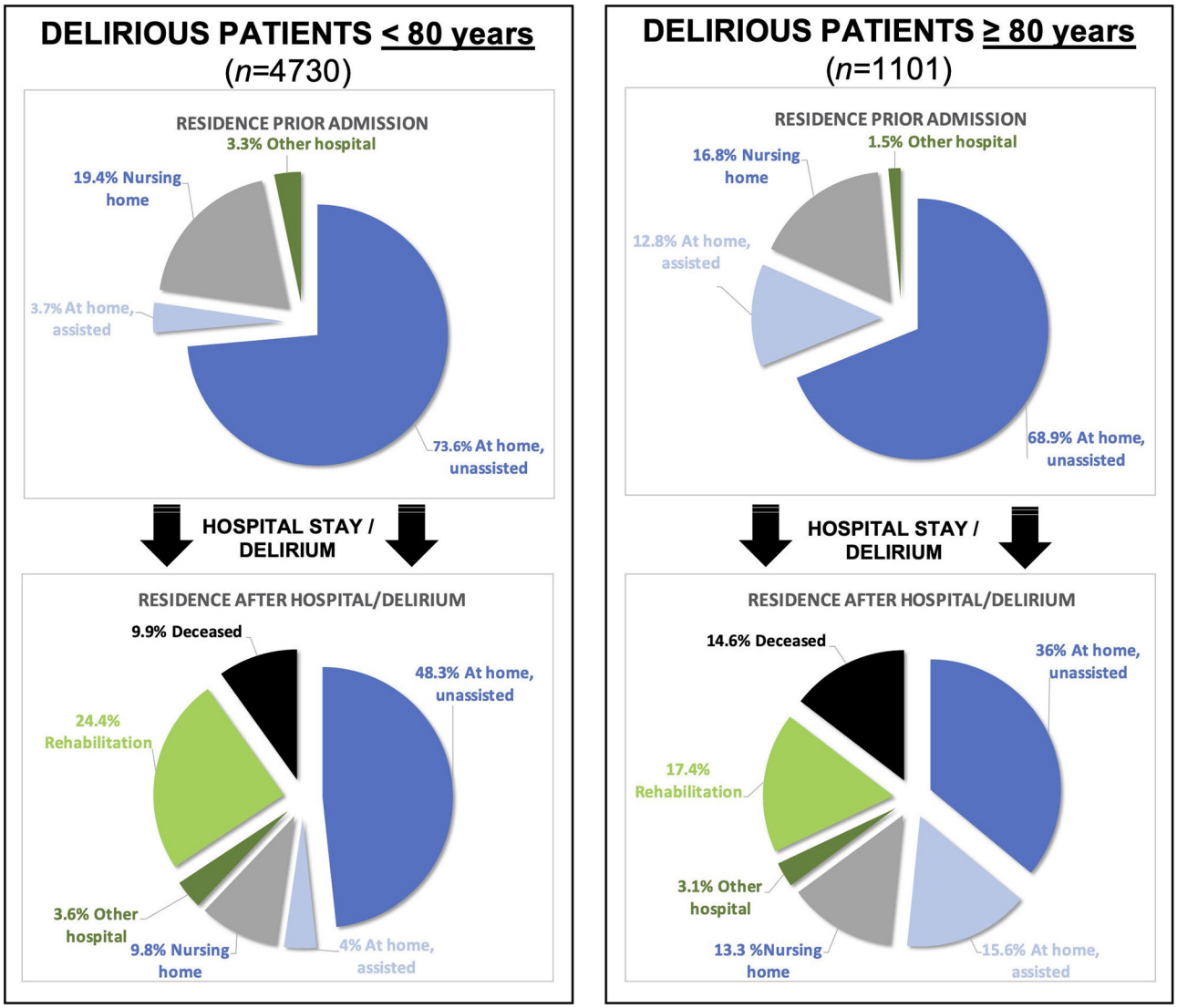

FIGURE 2 | Graphical illustration (pie chart) of the residence before and after the hospital stay/delirium of the two groups. Note that delirious patients ≥ 80 years have a higher mortality and lose more often their independence.

more commonly and is characterized by a complicated course and worse prognosis (e.g., mortality risk is 1.5 times higher). It is novel to compare delirious patients between age groups rather than non-delirious controls; hereby, the age factor can be better determined.

The prevalence of delirium in our sample was 20.8% (5,984 out of 28,806 patients), which concurs with numbers reported in the literature (21–23). Between groups, ≥ 80 vs. 18–80 years, the very old were more commonly admitted as emergencies, developed delirium more frequently and showed increased mortality. Comorbidities as measured with the number diagnoses were the same ($p = 0.325$), which might indicate a healthy survivor effect (24). Consequently, a delirium in patients ≥ 80 seems to have a stronger influence on the course during or after the hospital stay. It is consistent with the literature that delirium in the very old can be triggered by few or no precipitating factors, since apparently the presence of predisposing factors suffices (9, 21). These were dementias, cardiovascular diseases such as atherosclerosis, valvular heart disease or arterial hypertension. Further, the prognosis of delirium in the very old was dire, as they were more commonly transferred to a nursing home, were more commonly dependent on assistance at home, less commonly transferred to rehabilitation, or deceased. Interestingly, their hospitalization was marginally shorter, but this might also reflect earlier transfer and higher mortality rate.

Comparison With the Existing Literature

To our knowledge, there are no studies to date that directly compare different age groups of delirium patients, especially not in patients ≥80 years.

However, there are few comparative studies that have examined how the type and severity of delirium differ between

TABLE 3 | Predisposing and precipitating risk factors.

n= 5,831	B (SE)	Exp (B)	CI	Sig.
Predisposing factors				
Dementia	1.65 (0.13)	5.21	4.06–6.68	<0.001
Arterial hypertension	0.66 (0.07)	1.94	1.68–2.25	<0.001
Valvular heart disease	0.55 (0.1)	1.73	1.41–2.12	<0.001
Arterial hypotension	0.51 (0.25)	1.66	1.03–1.66	0.039
Chronic renal failure	0.61 (0.09)	1.56	1.56–2.19	<0.001
Atherosclerosis	0.4 (0.12)	1.5	1.18–1.89	0.001
Neoplastic disease (brain excluded)	−0.22 (0.09)	0.8	0.68–0.96	0.015
Malnutrition	−0.39 (0.16)	0.68	0.49–0.92	0.013
Cardiomyopathy	−0.52 (0.24)	0.6	0.38–0.94	0.028
Epilepsy	−0.61 (0.15)	0.54	0.4–0.73	<0.001
Neoplastic brain disease	−0.86 (0.44)	0.42	0.18–0.99	0.049
Hydrocephalus	−0.9 (0.29)	0.41	0.23–0.71	0.002
Substance-induced	−1.54 (0.2)	0.22	0.15–0.32	<0.001
Liver cirrhosis	−2.05 (0.72)	0.13	0.03–0.53	0.005
Precipitating factors				
Syncope	0.73 (0.35)	2.1	1.04–4.15	0.039
Intracranial hemorrhage	0.62 (0.18)	1.85	1.3–2.63	0.001
Sepsis/SIRS	−0.37 (0.13)	0.69	0.54–0.88	0.003
Liver failure	−0.71 (0.34)	0.49	0.25–0.96	0.037
Acute hepatitis	−1.05 (0.44)	0.35	0.15–0.82	0.016
Brain edema	−1.92 (0.73)	0.15	0.04–0.61	0.008
Constant	−1.84 (0.07)	0.16		

children (0–17 years), adults (18–65 years) or elderly patients (66–91 years) (25–27). Grover and colleagues (27) described that adults and elderly patients did not differ significantly in severity or type of delirium: 321 delirium patients, 245 adults (18–64 years), and 76 elderly patients ($\geq$ 65 years) were compared regarding the prevalence of underlying etiologies: In the elderly group, decompensations of cardiovascular disease were more common; in contrast, substance abuse or intoxications were more common in adult delirium patients. Consistent with these findings, the logistic regression in our study shows that substance abuse in those <80 years of age and cardiovascular disease in those >80 years of age have a higher risk of developing delirium. In addition, there are studies examining the effect of age in alcohol delirium by forming subgroups in decades (e.g., 20–30 years, 30–40 years), but unfortunately no patient groups >80 years and only in alcohol withdrawal delirium. One meta-analysis compared symptoms in delirious pediatric and adult patients (28), but this study does not reflect the theme of our study in the very elderly.

Furthermore, there are studies comparing delirious patients of different specialties (29), but studies comparing age groups, especially regarding risk factors, do not exist.

Implications

The causes, manifestations and outcomes of delirium vary with age; although this may seem trivial, in this study of the very old, $\geq$ 80 years of age, admission mode, predisposing and precipitating factors for delirium and outcome were very different and not advantageous. The results of this study can be used as possible starting points for future management studies, as well as advanced care planning and, once again, illustrate that delirium is a common and potentially life-threatening condition.

Strengths and Limitations

Clear strengths of this study are the overall (1) large group sizes and (2) prospective data collection and (3) extensive description of sociodemographic, medical and clinical characteristics of delirious patients. A novelty in this study is the comparison between two age groups of delirious patients, which leads to a better determination of the age factor. The differences in group sizes (4,730 vs. 1,101 patients) can be considered problematic, potentially having led to disproportionate power in 18–80-year-olds; however, the different group sizes represent the natural demographic age distribution. In addition, the severity of diseases was not characterized, as this is difficult to statistically represent or operationalize. A major limitation of this study may represent the dichotomization of the variable age, which, while providing good contrast between groups, may also distort the results. Future studies on the variable age are necessary to further investigate this effect. The collected data is from 2014 and may not be fully generalizable due to improved delirium prevention in recent years. The administration of any medication (e.g., benzodiazepines, antipsychotics) was not recorded, as this was not methodologically possible. Our patient population was representative for a tertiary care center, generalizability to other

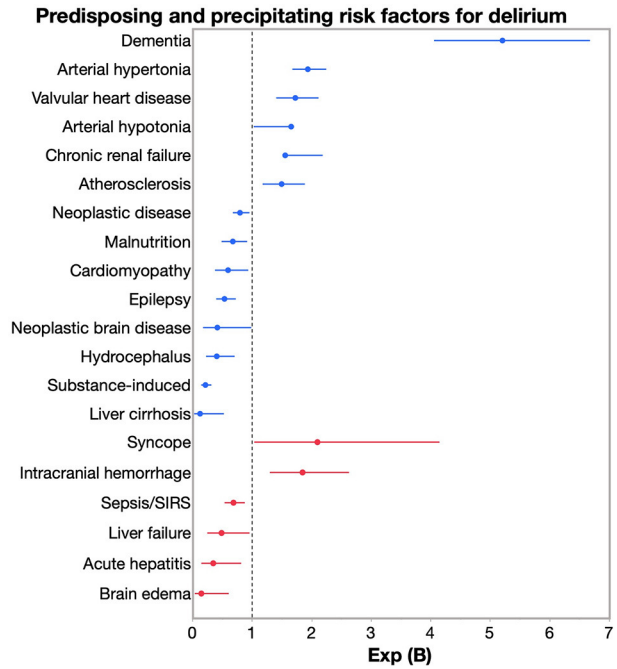

FIGURE 3 | Risk for developing delirium: Exp (B), confidential intervals (CI) for well-known predisposing (blue) and precipitating (red) risk factors. Corresponding regression coefficients [Exp (B)] at values >1 indicate higher risks (e.g., dementia) in the very old.

health care facilities is limited. Since patients > 80 years of age were routinely screened for delirium, but patients <80 years of age were not, there is a possibility that delirium is underdiagnosed in this age group, leading to biased results. Future studies are required to confirm these findings.

CONCLUSIONS

Delirium in very old patients, i.e., those ≥ 80 years, is different from delirium in the general hospital population. The very old are at high risk for developing delirium. When relevant predisposing factors for delirium become apparent, the very old require only few or no precipitating factors for the development of delirium. This should be accounted for on admission and may allow better screening for and management of delirium in this age group in the future.

LOCATION OF CONDUCTION

Between January 1st and December 31st 2014, a delirium detection initiative (DelirPath, **D**etect **E**valuate Contro**l** **I**npatient **R**isk factors, **P**revent **A**nd **T**reat **H**ospital Acquired Deliriums, **Figure 1**) at the University Hospital Zurich, a tertiary care center, prospectively assessed 39,442 patients for delirium.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of the Canton of Zurich (KEK-ZH-Nr. 2012-0263). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

JM analyzed clinical and diagnostic data and drafted and revised the manuscript. LB acquired clinical and diagnostic data and revised the manuscript. SF acquired clinical and diagnostic data and revised the manuscript. FH, JE, and RK analyzed clinical and diagnostic data and revised the manuscript. SB conceptualized the study, acquired and analyzed clinical and diagnostic data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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CORRECTION
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Corrigendum: Risk Factors for Delirium Are Different in the Very Old: A Comparative One-Year Prospective Cohort Study of 5,831 Patients

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Keywords: delirium, very old, risk factors, comparison, prospective

A Corrigendum on

Risk Factors for Delirium Are Different in the Very Old: A Comparative One-Year Prospective Cohort Study of 5,831 Patients

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An author name was incorrectly spelled as "Roland von Kaenel." The correct spelling is "Roland von Känel."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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ORIGINAL RESEARCH
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Emotional Comparison Between Semantic Dementia and Alzheimer's Disease

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Background: Previous studies have suggested that Alzheimer's disease (AD) and semantic dementia (SD) are both associated with emotional processing impairment. However, the degree and type of emotional symptoms between the two types of dementia have not been previously compared.

Method: We used the Apathy Evaluation Scale (AES), the Toronto Empathy Questionnaire (TEQ), the Geriatric Depression Scale (GDS) and the Self-rating Anxiety Scale (SAS) to examine apathy, empathy, depression and anxiety, respectively.

Results: Between mild AD and mild SD, moderate-to-severe AD and moderate-to-severe SD, the total scores of TEQ are significantly different, but the total scores of GDS, SAS and AES have no significant differences. In addition, normal individuals, AD and SD patients got the similar scores in SAS and GDS.

Conclusions: Empathy emotion in SD patients is more severe than that in AD patients. However, apathy, depression and anxiety emotion is similar between the two groups.

Keywords: anxiety, depression, apathy, empathy, alzhaimer's disease, semantic dementia

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INTRODUCTION

Semantic dementia (SD; also known as semantic variant primary progressive aphasia) is one of the clinical variants of frontotemporal dementia (FTD), in which naming problems and single-word comprehension are both severely impaired due to asymmetric atrophy (generally left greater than right) in the anterior temporal lobes (1). In contrast, Alzheimer disease (AD) is clinically characterized by prominent episodic memory disturbance affecting learning and retrieval of newly learnt information, accompanied by deficits in at least one other cognitive domain (ie, visuospatial, language, and executive functions) (2).

Emotional changes such as apathy, empathy, depression and anxiety are the most common symptoms in all-cause dementia and are strongly associated with increased caregiver burden and lower quality of life in people with dementia, but the relationship has yet to be determined. Some studies suggest that emotional changes are accompanying symptoms of dementia, while others consider there is a link between emotional symptoms and dementia. One possible explanation is that emotional illness causes dementia, while another possibility is that dementia triggers a relapse of emotional symptoms (3). In order to determine the relationship, it is first necessary to know the differences of emotional symptoms between normal individuals and patients of dementia. The next step is to determine whether the emotional changes are different in different types and stages

of dementia. This study focuses on the four emotional symptoms (apathy, empathy, depression and anxiety) in AD, SD and normal individuals, in order to provide better care advice to different dementia patients.

Depressive symptoms are very common in dementia. In AD, the prevalence of depression varies from 6 to 42% (4). In SD, the reported prevalence is 44–78%. The proportion seems to be relatively similar across dementia stages and is higher in patients with vascular dementia (VaD) and FTD than in AD (3, 5).

Apathy is a symptom defined as lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress related to daily function (6). It is one of the most prevalent and disabling non-cognitive symptoms of dementia, affecting up to 90% of individuals over the disease course (7). Sixty percent of AD and 84% of behavioral variant frontotemporal dementia (bvFTD) patients had some degree of apathy, and bvFTD patients had more severe and more frequent symptoms than AD (8). Some studies found that the rate of apathy in SD is lower than those seen in disorders involving cortical dysfunction, such as AD and Traumatic Brain Injury (9, 10).

There has been a growing body of research supporting an association between anxiety and dementia. It is more common in people who are cognitively impaired than in those who are not (11). A meta-analysis shows that the overall prevalence of anxiety in people with dementia was 14% (3). In AD, the pooled prevalence of anxiety is reportedly 39% (12). While in SD, the anxiety symptoms are ranging from 41 to 56% (13). Considering the severity of dementia, anxiety symptoms are generally equally prevalent at mild and moderate levels of severity but decrease at the severe and profoundly demented stage (14).

Empathy is the ability to share the emotions and sensations of others. It is often characterized as the ability to "put oneself into another's shoes," or in some way experience another person's emotions within oneself. This is crucial for a higher social functioning, and when impaired, difficulty with social conduct and relationship turmoil is observed. The loss of empathy is an early symptom reported by carers of patients with FTD (15–17). Mendez et al. analyzed empathy in patients with bvFTD and indicated that these patients had decreased empathic behavior with or without emotional blunting (18).

Most studies just reported one or two of these symptoms in AD or SD. Our main objective is to simultaneously describe and compare the above four emotional symptoms of patients presenting with different stages of AD and SD. This study may contribute to a better understanding of the emotional symptoms of these patients, thus providing suggestions to caregivers in taking care of them.

MATERIALS AND METHODS

Participants

Patients with SD or AD and cognitively normal controls (NC) were recruited from the Memory Clinic, Huashan Hospital, during Apr 2012-Feb 2018. In the present study, 165 subjects (105 men, 60 women) were enrolled including 83 AD patients, 43 SD patients and 39 NC. All of the 126 demented patients had finished the laboratory tests and cranial CT/MRI scan and were found to have no clinically significant abnormalities in vitamin B12, folic acid, thyroid function (free triiodothyronine-FT3, free tetraiodothyronine-FT4, thyroid stimulating hormone-TSH), rapid plasma regain (RPR), or treponema pallidum particle agglutination (TPPA).

AD was diagnosed as probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA/NINCDS-AIREN) criteria. SD was diagnosed according to the guidelines proposed in 2011, in which anomia and single-word comprehension deficits are the core features (19). The severity of AD and SD was judged according to Clinical Dementia Rating (CDR) Scale (20) and FTLD-modified Clinical Dementia Rating (FTLD-modified CDR) Scale (21). CDR = 1, 2, or 3 indicated mild, moderate, or severe dementia.

Emotional Scales

The emotional scales were administered by a trained rater who was blind to diagnosis. To determine the general cognitive function, all study subjects completed MMSE(Mini-Mental state examination) (22), MES (memory and executive screening scale) (23), CFT(complex figure test) (24), AVLT(auditory verbal learning test) (25), AFT(animal fluency test) (26), BNT(Boston naming test) (27), SDMT (symbol digit modalities test) and reading (26).

Geriatric Depression Scale

The 15-item short form developed by Sheikh and Yesavage in 1986 (28) was used for the present study. Responses were coded 1 = yes, has symptom; vs. 0 = no, symptom not present. Items were summed and higher scores indicated a greater degree of depressive symptoms.

Self-Rating Anxiety Scale

The SAS (29) is a 20-item measure developed to assess the frequency of anxiety symptoms based on diagnostic conceptualizations. It consists primarily of somatic symptoms. The respondent indicates how often he or she has experienced each symptom on a 4-point Likert scale consisting of "one or a little of the time" (coded as 1), "some of the time" (coded as 2), "good part of the time" (coded as 3), and "most or all of the time" (coded as 4). Items 5, 9, 13, 16, and 19 are reversed scored and total scores on the SAS range from 0 to 80.

Apathy Evaluation Scale

The presence of apathy was established on the Apathy Evaluation Scale. The 18-item informant-rated scale (AES-I) used here was developed by Marin et al. (30). It rated a person's thoughts, actions, and emotions over the previous 4 weeks. A score higher than 20 points is associated with an apathic syndrome. This scale was validated in participants with Alzheimer's disease and other dementias, stroke and major depression.

The Toronto Empathy Questionnaire

The toronto empathy questionnaire (TEQ) developed by Spreng et al. (31) is an uni-dimensional, 16-item, five-point Likert type

scale to assess the empathy levels of individuals. We used the informant-report style. There are 16 items in the questionnaire and the informants are expected to express their opinions in the questionnaire ranging from "Never" to "Always" on 5-point Likert type scale with answer of "Never" been marked as "1," "Always" as "5." The high scores accounts for high empathy.

Validity and reliability of the Chinese versions of these four scales have been assessed.

Ethical Compliance

This study was approved by the ethics committee of Shanghai Huashan Hospital Fudan University. All participants signed a consent form.

Statistical Analysis

Statistical analysis was done using the SPSS package version 13.0. Overall differences among the groups were determined by chi square tests for categorical data and analysis of variance (ANOVA) for continuous variables. To eliminate the confounding factor of education years, an analysis of covariance (ANCOVA) was performed. *Post-hoc* tests for ANOVA or ANCOVA was performed to determine whether there were significant differences between pairs of groups while accounting for multiple comparisons. Correlation was done using the Pearson bivariate correlation analysis. The level of significance for all comparisons was set at $p < 0.05$.

RESULTS

Demographic Features

One hundred and sixty five subjects (105 men, 60 women) were enrolled in the study. Among these, 83 were affected by AD, and 43 were diagnosed with SD. The detailed demographic features are shown in **Table 1**. One-way analysis of variance and chi square tests showed that the patient groups were matched on age and gender; but moderate-to-severe SD patients got significantly less education than NC group and mild AD patients, and moderate-to-severe AD patients were less educated than NC group.

Background Neuropsychology

The subjects underwent a background neuropsychological examination. Their performance was summarized in **Table 2**. Most patients with moderate-to-severe SD did not perform neuropsychological evaluation because they were not able to copy a geometric figure or to read words. Based on the existing data, the results of our analysis were as follows. The difference between mild AD and mild SD, moderate-to-severe AD and moderate-to-severe SD for the MMSE score, did not reach statistical significance. MES showed no significant difference between mild AD and mild SD. For AFT, there was no significant difference between moderate-to-severe AD and mild SD. The score of AVLT-DR was lower in AD and SD than in healthy adults. For CFT-copy, CFT-DR, BNT, SDMT and reading, significant differences existed in any two of the four groups.

In all, AD is characterized by impaired episodic memory, while SD mainly has semantic memory disturbance. The severity of memory impairment is close between mild AD and mild SD, as well as between moderate-to-severe AD and moderate-to-severe SD.

Emotional Comparison Between AD and SD

Analysis of covariance (ANCOVA) was computed to explore differences between NC, AD and SD groups (see **Table 3**). Adjusting for years of education, analysis of covariance revealed significant group differences on AES and TEQ score. Compared to NC, patients with AD and SD got lower scores in AES and TEQ. In TEQ, mild AD performed better than mild SD ($p = 0.030$), and moderate-to-severe AD performed better than moderate-to-severe SD ($p = 0.038$). But in AES, the scores were not significantly different between AD and SD with the same severity. In addition, NC, AD, and SD got the similar scores in SAS and GDS.

Correlations Between Emotional Scales and Other Cognitive Measures

Table 4 presents the correlation coefficients R-value between the four scales and other cognitive measures in dementia patients using correlation analysis. Both AES and TEQ correlated with MMSE, TEQ also correlated with delayed recall of complex figure test (CFT-DR), and correlation between GDS and delayed recall of auditory verbal learning test (AVLT-DR) was significant. There was no significant correlation between other emotional scales and cognitive measures.

DISCUSSION

This study is the first one to simultaneously assess apathy, empathy, depression and anxiety in patients with SD and AD. The results revealed both similarities and differences with past studies in which emotion was investigated in dementia patients. For example, similar to studies of apathy and empathy (7, 8, 16–18), the current study showed AD and SD patients got lower scores than healthy adults in AES and TEQ. Unlike those previous studies (3–5, 11–13), however, anxiety and depressive scores between dementia patients and healthy adults had no significant difference.

Empathy can be broadly defined as the ability to understand what others feel (cognitive empathy) and feel what others feel (emotional empathy). Patients with dementia have primarily cognitive impairments and also emotional deficits that lead to behavioral dysregulation (32), impairments in empathy will be evident in them. In order to compare it between AD and SD patients, it is informative to have two groups of patients who suffer similar cognitive deficits. In our study, the severity of cognitive impairment was close between mild AD and mild SD, as well as between moderate-to-severe AD and moderate-to-severe SD. Moreover, from our study, we found that in TEQ, mild AD performed better than mild SD ($p = 0.030$), and moderate-to-severe AD performed better than moderate-to-severe SD ($p = 0.038$). Therefore, we propose that emotional deficits were different between AD and SD, or a specific deficit

TABLE 1 | Demographic features of the subjects.

	NC ($n = 39$)	Mild AD ($n = 48$)	Moderate-to-severe AD($n = 35$)	Mild SD ($n = 20$)	Moderate-to-severe SD ($n = 23$)	Statistics and *P*-value
Age	62.9 (10.7)	62.4 (11.1)	62.8 (13.3)	62.4 (7.7)	62.6 (8.3)	$F = 0.01$, $p = 1.00$
Years of education	12.3 (3.4)[c,d]	11.4 (3.1)	9.9 (3.9)[a,d]	10.8 (2.9)	8.6 (4.1)[a,b]	$F = 5.04$, $p = 0.00$
Male (*N*%)	25 (64.1%)	35 (72.9%)	25 (71.4%)	10 (50.0%)	10 (43.5%)	$\chi^2 = 8.35$, $p = 0.079$

Continuous variables compared by ANOVA with post-hoc pairwise Bonferroni tests. Gender compared by chi square.
The scores were presented as mean (standard deviation).
[a]*$p < 0.05$ compared to NC group.*
[b]*$p < 0.05$ compared to mild AD group.*
[c]*$p < 0.05$ compared to moderate-to-severe AD group.*
[d]*$p < 0.05$ compared to moderate-to-severe SD group.*

TABLE 2 | General neuropsychology of the five groups.

	Total score	NC ($n = 39$)	Mild AD ($n = 48$)	Moderate-to-severe AD ($n = 35$)	Mild SD ($n = 20$)	Moderate-to-severe SD ($n = 23$)	*F* (*P*)
MMSE	30	27.6 (1.8)[b,c,d,e]	21.1 (2.5)[a,c,e]	10.7 (3.9)[a,b,d]	20.4(4.3)[a,c,e]	9.2 (2.5)[a,b,d]	213.69 (0.00)
MES	100	81.7 (8.9)[b,c,d]	48.5 (12.3)[a,c]	25.8 (13.2)[a,b,d]	51.1 (17.9)[a,c]	-	107.60 (0.00)
AVLT-DR	12	4.6 (1.6)[b,c,d]	0.4 (0.9)[a]	0.1 (0.4)[a]	0.1 (0.5)[a]	-	126.31 (0.00)
CFT-copy	36	32.5 (4.5)[b,c,d]	25.1 (10.0)[a,c,d]	19.9 (10.9)[a,b,d]	31.0 (6.4)[a,b,c]	-	11.54 (0.00)
CFT-DR	36	14.5 (5.3)[b,c,d]	4.5 (3.8)[a,c,d]	3.7 (4.4)[a,b,d]	9.3 (5.1)[a,b,c]	-	26.98 (0.00)
BNT	30	24.1 (3.2)[b,c,d]	18.1 (5.2)[a,c,d]	10.0 (5.5)[a,b,d]	7.1 (4.1)[a,b,c]	-	68.74 (0.00)
AFT	-	16.7 (4.4)[b,c,d]	11.7 (3.8)[a,c,d]	8.4(4.1)[a,b]	6.7 (3.5)[a,b]	-	29.86 (0.00)
SDMT	-	34.5 (11.4)[b,c,d]	19.9 (12.4)[a,c,d]	8.6 (8.4)[a,b,d]	27.3 (8.5)[a,b,c]	-	20.51 (0.00)
Reading	50	42.8 (4.4)[b,c,d]	35.9 (6.5)[a,c,d]	28.1 (10.6)[a,b,d]	16.5 (11.4)[a,b,c]	-	52.84 (0.00)

These variables compared by ANCOVA with post-hoc pairwise LSD tests.
The scores were presented as mean (standard deviation).
[a]*$p < 0.05$ compared to NC group.*
[b]*$p < 0.05$ compared to mild AD group.*
[c]*$p < 0.05$ compared to moderate-to-severe AD group.*
[d]*$p < 0.05$ compared to mild SD group.*
[e]*$p < 0.05$ compared to moderate-to-severe SD group.*
MMSE, total score of Mini-Mental state examination; MES, memory and executive screening scale; AVLT- DR, delayed recall of auditory verbal learning test; CFT-Copy, copy part of complex figure test; CFT-DR, delayed recall of complex figure test; BNT, Boston naming test; AFT, animal fluency test; SDMT, symbol digit modalities test.

may exist in SD patients. The exact mechanism is unclear and should be the topic of future studies. One possibility is that the cognitive and affective empathy may be mediated in different domains. At a neuroanatomical level, a broad network of structures has been implicated for empathy. Lesion studies have indicated that ventromedial frontal lesion result in deficits in cognitive empathy, yet deficits in emotional empathy most prominently arise from disturbances in the medial frontal cortex (such as the ventromedial prefrontal cortex and anterior cingulate gyrus and the anterior insula (33, 34). Besides, A meta-analysis in FTD showed that emotional empathy was also associated with amygdale and right anterior temporal lobe as well as corresponding neural networks (35). Some studies proposed that emotional empathy may arise from disease affecting precentral gyrus (36), orbitofrontal cortex (37), inferior parietal lobule, brainstem, and thalamus (38). Future studies should test the hypothesis.

An unexpected finding of our study was that anxiety and depressive scores between dementia patients and healthy adults had no significant differences. Interestingly, both SAS and GDS score did not correlate with almost all of the cognitive measures we did in our study. Maybe there were other factors that would increase the odds of anxiety and depression in dementia patients. For example, Hynninen et al. found that anxiety was not associated with cognitive test performance, but with depression, higher caregiver stress, and more dementia-related impairment (39). In addition, some researchers suggested that there were several areas where depression and dementia may overlap. Depression in a cognitively healthy older person may indicate early dementia,

TABLE 3 | AS, GDS, AES, and TEQ performance of the groups.

Index	NC ($n = 39$)	AD ($n = 83$)		SD ($n = 43$)		F (P)
		Mild ($n = 48$)	Moderate-to-severe ($n = 35$)	Mild ($n = 20$)	Moderate-to-severe ($n = 23$)	
SAS	35.75 (2.274)	38.82 (2.242)	38.80 (2.529)	33.48 (2.764)	35.38 (3.080)	0.210 (0.932)
		38.81 (2.386)		34.50 (2.922)		0.326 (0.723)
GDS	5.72 (1.040)	7.39 (1.093)	6.99 (1.127)	5.66 (1.281)	6.73 (1.399)	1.114 (0.353)
		7.22 (1.112)		6.23 (1.338)		1.723 (0.183)
AES	34.87 (3.127)[b,c,d,e,f,g]	25.30 (3.104)[a,c,e]	19.13 (3.039)[a,b]	18.087 (3.725)[a]	13.08 (3.765)[a,b]	4.813 (0.001)
		22.70 (3.071)[a]		15.41 (3.744)[a]		4.545 (0.013)
TEQ	43.66 (2.321)[b,c,d,e,f,g]	36.69(2.356)[a,d,e]	33.14(2.322)[a,e]	29.76(2.729)[a,b]	27.19(2.737)[a,b,c]	9.374 (0.000)
		35.19(2.338)[a,g]		28.39(2.734)[a,f]		16.845 (0.000)

These variables compared by ANCOVA with post-hoc pairwise LSD tests.
The scores were presented as mean (standard deviation).
[a]$p < 0.05$ *compared to NC group.*
[b]$p < 0.05$ *compared to mild AD group.*
[c]$p < 0.05$ *compared to moderate to severe AD group.*
[d]$p < 0.05$ *compared to mild SD group.*
[e]$p < 0.05$ *compared to moderate-to-severe SD group.*
[f]$p < 0.05$ *compared to AD group.*
[g]$p < 0.05$ *compared to SD group.*
SAS, Self-rating anxiety scale; GDS, Geriatric depression scale; AES, Apathy Evaluation Scale; TEQ, The toronto empathy questionnaire.

TABLE 4 | Correlations between emotional scales and other cognitive measures in dementia patients.

	MMSE	MES	BNT	AFT	SDMT	reading	AVLT-DR	CFT-copy	CFT-DR
SAS	0.115	0.069	0.011	−0.113	−0.118	0.045	0.182	−0.043	0.162
GDS	0.149	0.021	−0.011	−0.008	0.116	0.002	0.293**	0.095	0.119
AES	0.237**	0.186	0.061	0.222	0.131	−0.001	0.022	−0.151	−0.134
TEQ	0.282**	0.047	0.223	0.159	−0.072	0.218	−0.081	−0.206	0.316*

R-value was presented in this table.
**Correlation is significant at the 0.05 level (two-tailed).*
***Correlation is significant at the 0.01 level (two-tailed).*

and depression may be a risk factor for dementia (40). Common biological and psychosocial risk factors for depression may exist among the cognitively intact as well as cognitively impaired older populations. For example, the interaction between an individual person and his environment is thought to play a role in the expression of depression and other behavioral and psychological symptoms (41). Therefore, an important issue regarding anxiety and depression in dementia is whether they should be considered as a separate clinical entity or as part of a broader syndrome.

One of the biggest strengths of the study is its employment of scales rating. However, this is also the study's biggest weakness: scale rating is highly subjective, solely based on individuals' reaction or opinion. For example in SAS, to the same degree of fatigue, someone choose "1," but others choose "2." This limitation, however, becomes less serious when more participants are tested. Thus, more participants should be recruited in future studies. Moreover, AD was diagnosed as probable AD according to the NINCDS-ADRDA/NINCDS-AIREN criteria, SD was diagnosed on the basis of clinical manifestation, and there were no distinctive biomarkers such as amyloid β (Aβ) or position-emission tomography (PET), so error could not be avoided.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Shanghai Huashan Hospital

Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW, ZH, and QG designed the study and participated in the diagnoses of the diseases. JL and QG performed the data analysis. PW, QZ, and YZ participated in the evaluation of scales and interpretation of data. PW wrote the paper with input from all authors. All authors discussed the results and contributed to the final manuscript, revised the manuscript content, and approved the final version of the manuscript.

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Family Dynamics and Grandparents' Anxiety and Depression in Intergenerational Rearing Families: A Correlational Study

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Background: In China, intergenerational rearing is a ubiquitous phenomenon based on unique national conditions. This study aimed to explore family dynamics in intergenerational rearing families as well as their correlation with older household members' anxiety and depression.

Methods: The elderly from intergenerational ($n = 141$) and non-intergenerational rearing families ($n = 266$) were investigated using the following scales: the general information questionnaire, Self-Rating Scale of Systemic Family Dynamics, Geriatric Depression Scale, and Self-Rating Anxiety Scale.

Results: Scores from the four dimensions (family atmosphere, system logic, individuation, and the concept of disease) of the structure of family dynamics were computed. The comparison of these dimensions scores and the total scores of grandparents' anxiety and depression for the two groups were not statistically significant ($p > 0.05$). In Pearson's correlation analysis, no significant correlation between the family atmosphere dimension and the total score of the grandparents' depression and anxiety scales was observed. The system logic aspect was negatively correlated with depression and anxiety scale scores. The individual dimension was positively correlated with the anxiety scale scores. The disease concept dimension was positively correlated with depression and anxiety scale scores. Hence, the results were statistically significant.

Conclusion: There were no significant differences in terms of family dynamics and risk of anxiety and depression among grandparents between the two family types. The system logic, individuation, and disease concept dimensions were correlated with their anxiety and depression.

Keywords: intergenerational rearing, anxiety, depression, correlation, family dynamics

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INTRODUCTION

In China, intergenerational rearing is a ubiquitous phenomenon based on unique national conditions. The elderly participate in their grandchildren's non-age period. Meanwhile, a large number of new parenting concepts have emerged because of rapid economic development over the last 40 years, since the implementation of China's reform and opening up.

Family dynamics, a model of family categories developed by the Heidelberg Group, describe the domestic relationships and their interactive features completely and systematically. By accepting the opinions of the Milan Systemic Family Therapy Group and performing treatment on mentally ill patients based on systemic family theory, they discovered the family dynamic structural characteristics of schizophrenic, bipolar affective disorder, and psychosomatic patients. These features are related to the recovery of individuals' psychological symptoms (1). In China, Zhao et al. maintain the same outlook that family dynamics are a subject focusing on the interaction between the family's internal (psychology, behavior, and communication) and external environments, in which its members' relations are reflected. Therefore, we speculated that the family dynamic structure of intergenerational rearing families may differ from others, and these variations would have numerous noticeable effects on grandparents' mental health.

In recent years, studies on intergenerational rearing problems have received increasing attention globally, and two contrary views regarding the influence of grandchildren rearing on grandparents exist. Some research has shown that it has a positive effect on the physical and mental health of the elderly (2, 3). However, other studies have demonstrated its negative impact on grandparents; this is because the investment of time, physical strength, and emotions lead to early retirement and psychological pressures such as loneliness and trepidation (4–6).

This study investigated whether intergenerational rearing could produce different family dynamic structures, as well as the relationship between them and the elderly's anxiety and depression.

METHODOLOGY

Participants and Procedure

Screening and evaluation of 957 older people living in Yinhang Street Community, Yangpu District, Shanghai was performed from November 1 to December 4, 2019. In the current research, we adopted random sampling methods to obtain the sample. The survey was conducted during a routine check-up, which is a well-fare provided by the local government. Among all the participants, there are 407 of them completed the questionnaires (141 from intergenerational family and 266 from non-intergenerational family). The participants were required to be over 55 years old, have normal vision (naked eye or redness), and have the ability to communicate. Informed consent was obtained from them prior to their participation in the survey. The exclusion criteria included having a history of major physical illness, particularly those that may be associated with alterations in brain tissues, as well as abnormalities in the nervous system, including major head traumas (loss of consciousness lasting over 5 min), epilepsy, cerebrovascular diseases, brain tumors, and neurodegenerative diseases. The study protocol was approved by the Ethics Committee of the Shanghai Mental Health Center subsequent to the initiation of the research.

Instruments

We used the Self-Rating Scale of Systemic Family Dynamics (SSFD) to explore family dynamics, the Geriatric Depression Scale (GDS) to determine the participants' depressive states, and the Self-Rating Anxiety Scale (SAS) to assess their anxiety states.

The Self-Rating Scale of Systemic Family Dynamics (SSFD)

The SSFD comprises 29 items categorized into four dimensions. First, family atmosphere refers to the emotional aspect of communication within the family system (7). A higher score indicates hostility and oppression, while a lower score reflects pleasantness and comfort. Second, system logic entails the logical characteristics of household members' value judgments. A high score indicates resolution, while a lower one reflects indecisiveness. Third, personalization is the differentiation of their emotions and behaviors. Lower scores indicate that a family member is more independent. Last, disease concept evaluates the amount of responsibility the members consider they ought to shoulder when having a disease. A high score indicates that they believe themselves to be absolute victims, whereas a low score means that they perceive themselves as complete actors. Each item is marked from 1 (completely suitable) to 5 (completely wrong) the Cronbach coefficients of the SSFD are 0.74 for "family atmosphere," 0.79 for "system logic," and 0.81 for "disease cognition," respectively.

The Geriatric Depression Scale (GDS)

The GDS (8), which is aims at depression assessment of elderly people aged over 56 years, was developed in 1982 by Brank et al. It evaluates their most relevant feelings over a 1-week period, and contains 15 columns. The scores reflect the state of depression, with 0–4 points referred to as normal, and 5–8, 9–11, and 12–15 points as mild, moderate, and major depression, respectively. The Cronbach's coefficient is 0.64 for GDS in the current research.

The Self-Rating Anxiety Scale (SAS)

The 20-item SAS is a self-rating measure including 20 items (9). It evaluates the user's subjective feelings during the last week, and the scores are divided into 4 degrees. The first, second, third, and fourth levels refer to no, sometimes yes, frequently yes, and almost yes or yes, respectively. The cut-off score of 41 may indicate an anxiety condition. The Cronbach's coefficient is 0.77 for SAS in the current research.

Survey Method

The survey comprised an on-site questionnaire conducted by several professional evaluators who underwent a standardized training. They briefly explained the questionnaire through standard instructions prior to the survey; it was later completed by the participants independently. The evaluators provided appropriate explanations to those individuals who had any related queries. All the survey forms were collected immediately; the data were checked, and entered using Epidata version 3.1; a logical test was performed in order to exclude invalid questionnaires.

TABLE 1 | Socio-demographic data from the participant grandmothers. *n* (%).

Variable	Intergenerational rearing families ($n = 141$)	Non-intergenerational rearing families ($n = 266$)	t/χ^2	*p-value*
Age	65.35 ± 5.00	65.21 ± 8.36	0.18	0.86
Gender			0.022	0.881
Males	53 (37.59)	102 (38.35)		
Females	88 (62.41)	164 (61.65)		

TABLE 2 | The comparison of dimensions scores of family dynamics, total scores of grandparents' anxiety-depression in such two kinds of families. ($\bar{x} \pm s$).

Scales	Intergenerational rearing families ($n = 141$)	Non-intergenerational rearing families ($n = 266$)	*t*	*p-value*
Family dynamic structure				
Family atmosphere	26.79 ± 6.15	27.41 ± 5.20	−1.08	0.282
The system logic	15.82 ± 4.84	15.85 ± 5.01	−0.05	0.959
Individuation	18.01 ± 4.71	18.02 ± 3.96	−0.02	0.985
The concept of disease	8.41 ± 3.44	8.59 ± 3.29	−0.53	0.600
Depression scale and the anxiety scale				
GDS	3.13 ± 3.00	3.01 ± 2.89	0.38	0.703
SAS	33.30 ± 6.58	33.01 ± 6.86	0.42	0.673

Statistical Analyses

The Statistical Package for the Social Sciences version 17.0 software was used for data analysis, and the measured data were expressed as mean ± standard deviation ($x \pm s$). Comparisons between groups were assessed using *t*-tests. The association of anxiety and depression with the dimensions of family dynamic structure was investigated using Pearson correlation analysis. Statistical significant was set at $p < 0.05$.

RESULTS

The mean ages of the intergenerational and the non-intergenerational rearing group were 65.35 ± 5.00 and 65.21 ± 8.36, respectively. The former comprised 53 males and 88 females, while the latter included 102 males and 164. Neither group showed any significant differences in gender, as shown in **Table 1**.

P-value > 0.05 (see **Table 2**). Scores of family dynamics (family atmosphere, system logic, individuation, and the concept of disease), anxiety and depression were computed. The results from *T*-tests showed that the inter-generational rearing group did not differ significantly from the non-inter-generational group on the aforementioned variables ($p > 0$).

Pearson's correlation analysis revealed no significant correlation between the family atmosphere dimension and the total score of the grandparents' depression and anxiety scales; however, the system logic aspect was negatively correlated with it. The individual dimension had a positive correlation with the anxiety scale score. Furthermore, the disease concept element was positively correlated with the scores on the depression and anxiety measures. Results were listed in **Table 3**.

DISCUSSION

Family is a basic environment that shapes personality, the constituent factors of which influence individual personality performance and psychological health (10). Family intimacy is an index that evaluates the emotional connection between household members, and describes various family categories. Theoretically, a balanced family intimacy is ideal. Overly intimate or distant relationships are harmful to an individual's mental health in several ways. The former entangle family members' lives excessively, while the latter estrange them (11).

Family dynamics provide an effective observational perspective for clinical practice by focusing on emotions, behaviors, negotiations, and their processes within the family, as well as by abstracting the psychological processes and interpersonal interaction patterns of the family (12, 13). Moreover, it is an indicator that can comprehensively assess the family system (14).

This study investigated the family dynamic structural features of intergenerational and non-intergenerational rearing families and their association with the anxiety and depression emotional characteristics of grandparents. The results revealed no significant differences in the family dynamic features and anxiety and depression between the two groups. The systemic logical dimension was inversely related to the total score of the depression and anxiety scales. The disease concept dimension was positively correlated with the total score of the depression and anxiety scales. The lower the score on this dimension, the lower the scores on the two scales. If elderly family members link disease and rehabilitation to self-response and subjective effort instead of regarding themselves as victims of diseases, depression and anxiety are unlikely to occur.

A study conducted in China reported that older people rearing their grandchildren were limited by factors such as age,

TABLE 3 | Pearson's correlation between the dimensions scores of family dynamics and total scores of grandparents' anxiety-depression. (*r*).

	GDS	SAS
Family atmosphere	0.012	0.079
The system logic	−0.162**	−0.155**
Individuation	0.039	0.103*
The concept of disease	0.127*	0.145**

*$P < 0.01$.
**$P < 0.05$.

physical health, education level, economic conditions, urban, and rural environments. The previous findings regarding how inter-genenerational rearing may influence the mental health conditions are mixed (15, 16). Research on the impact of intergenerational rearing on aging individuals found that raising grandchildren can benefit their psychological health, reinforce the intergenerational relationships of the rural elderly, and protect their cognitive functions (17–19). Similarly, a Taiwanese study indicated that intergenerational rearing can decrease the risk of depression and anxiety in aging individuals (20). On the other hand, research holding the opinion that it has a negative impact on older people found that it can cause them various psychological problems. Reliance on grandchildren can influence the grandparents' mental health and result in early retirement (21–23). Neither of the two perspectives has been proven in this research and thus further research efforts are needed.

This research was unable to clarify the differences in the family dynamic structure between intergenerational and non-intergenerational rearing and the impact of the former on the elderly, the current study provided evidence for an association between the family dynamic structure and the elderly's depression and anxiety. The influence of family on the psychological health of the elderly cannot be disregarded because it is the most important living environment for aging individuals. Intergenerational rearing problems need to be considered in different respects In the future, more research effort should focus on the relations between family dynamics and elderly people's mental health conditions. Limitations As the research focused on the elderly, for whom the concepts of family dynamics were relatively abstract, it was challenging to avoid the occurrence of bias in their responses. This resulted in some interference with the findings. The representativeness of this research is limited because the sample comprised elderly individuals belonging to the same community. Therefore, to improve the investigation, the sample needs to be extended to different areas, and the quality of the survey questionnaires should be strictly controlled. Additional targeted research conclusions will be explored after an in-depth analysis of the results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Dalian No. 7 People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL proposed the research idea. CY-Y collected the data and wrote the paper. H-JX, S-SL, Y-JW, YL, H-SL, and Y-PC helped in data collection, revised the manuscript, and provided many constructive suggestions. All authors contributed to the article and approved the submitted version.

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Suicide Attempts, Neurocognitive Dysfunctions and Clinical Correlates in Middle-Aged and Elderly Chinese Schizophrenia Patients

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Background: Suicide is a common and complex symptom of schizophrenia that may be related to clinical variables and neurocognitive function. This study aimed to investigate the associated correlates of suicide attempts in Chinese middle-aged and elderly inpatients with schizophrenia, including demographic and clinical characteristics and cognitive level, which has not yet been reported.

Methods: A total of 426 schizophrenia inpatients were recruited for this study. Clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS). Neurocognitive function was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Results: The prevalence of suicide attempts in middle-aged and elderly Chinese schizophrenia patients was 13.3%. Female patients had a higher suicide rate than male patients. Patients with suicide attempts had significantly higher PANSS-positive subscores, depressive subscores, and RBANS-story recall than non-attempter patients (all $p < 0.05$). Multiple logistic regression showed that gender, positive subscore, depressive subscore and RBANS-story recall (OR = 1.10–2.19, $p < 0.05$) were independently associated with suicide attempts in middle-aged and elderly schizophrenia patients.

Conclusions: Our study showed that the rate of suicide attempts in Chinese middle-aged and elderly schizophrenia patients is high. Compared to non-attempters, there are less cognitive impairments, more clinical symptoms, and more female patients in the suicide attempters.

Keywords: suicide attempts, neurocognitive function, schizophrenia, PANSS, middle-aged and elderly

INTRODUCTION

With the trend of an increased ageing population, the proportion of psychiatric disorders in middle-aged and elderly individuals has significantly increased. Schizophrenia is a serious mental disorder that has cognitive impairment, positive and negative symptoms and a high suicide rate (1). The prevalence of suicide attempts in schizophrenia patients ranges from 10 to 50% (2, 3), which is far more common (∼10–30 times) than in the general population (4, 5). Suicide is considered to be the primary cause of shortening the life expectancy and worsening the prognosis of patients with schizophrenia (6, 7). The stress of caring for those with schizophrenia, especially in late-life schizophrenia (LLS), has become a major public problem (8), and ageing mental health patients are easy to ignore.

Risk factors for suicide attempts in schizophrenia patients are most relevant to demographic variables, clinical characteristics, and some treatment-related variables. A previous study investigated suicidal characteristics in 520 Chinese patients with schizophrenia and revealed that subjects who attempted suicide tended to be younger, single, have more severe depressive symptoms and longer hospital stays (2). Ran et al. (9) also reported that younger age, a higher rate of depressive symptoms, more positive symptoms and a higher level of education were positive factors for suicide attempts in schizophrenia. The age of onset of psychotic symptoms is independently associated with suicidal behaviour (3). Compared to those under the age of 20, young people between the ages of 30 and 39 have the highest risk of suicide (10). Gender is also a potential risk factor for suicidal behaviour in patients with schizophrenia. Uzun et al. (11) reported that the incidence of attempted suicide in men is higher than in women, and a nationwide cohort study with 174,039 patients demonstrated that women have a higher suicide rate due to jumping and drowning than men (10). Suicidal behaviour in the setting of schizophrenia is positively correlated with the presence of symptoms (1). Some studies showed that several clinical variables and sociodemographic factors are associated with suicidal behaviour in schizophrenia, but these results are often inconsistent (12), requiring more research.

Cognitive impairment is considered to be a cardinal feature of schizophrenia (13–15). However, the results on the relationship between suicide risk and cognitive impairment in schizophrenia have been largely mixed. Several studies have reported that higher cognitive functions in terms of verbal fluency, attention and cognitive flexibility may increase the risk of suicide in schizophrenia (16), while others have not identified a correlation between cognition and suicidal behaviours (17). These conflicting results may be related to different research methods, such as different locations of the study and the combination of neuropsychological tests and samples. Similarly, patients with mental disorders without a history of suicide also have cognitive impairment (18, 19), which illustrates the necessity of exploring whether the cognitive changes in patients with schizophrenia are related to suicidal behaviour. In addition, compared to the elderly healthy control group, there was obvious cognitive impairment in elderly patients with schizophrenia (20). At present, most studies have focused on the relationship between suicide attempts and cognition in schizophrenia without age distinction, and there are almost no research on middle-aged and elderly inpatients with schizophrenia.

To date, results of the correlation among suicide attempts and demographic data, clinical symptoms and cognition have been inconsistent, and there is no study on middle-aged and elderly Chinese inpatients with schizophrenia. To address the heterogeneity of suicidal tendencies in these inpatients, we collected detailed clinical characteristics and cognitive function assessed using detailed cognitive tools to determine (1) the incidence of suicide attempts in middle-aged and elderly Chinese schizophrenia inpatients; (2) whether patients with suicide attempts exhibit increased clinical symptoms; and (3) the relationship between neurocognition and suicide attempts in middle-aged and elderly Chinese schizophrenia inpatients.

METHODS

Participants

The Institutional Review Board (IRB) of the Affiliated Brain Hospital of Guangzhou Medical University approved this study, and all participants provided informed consent to participate. Subjects were recruited from inpatients with schizophrenia at the Affiliated Brain Hospital of Guangzhou Medical University. All data were collected from February 2019 to September 2019. The recruitment criteria included those who (1) met DSM-IV diagnostic criteria of schizophrenia; (2) had at least 2 years of illness duration; (3) were aged $\geq$ 45 years, Han Chinese; and (4) received stable doses of antipsychotic drugs for at least 4 weeks before entering the study. The exclusion criteria were as follows: (1) the presence of severe somatic diseases, infectious diseases or immune system diseases; (2) pregnancy or lactation; (3) drug or alcohol abuse/dependence; (4) education level $<$5 years; and (5) ECT treatment within the last 6 months.

Clinical Measurements

All participants completed detailed questionnaires, including general information, sociodemographic characteristics, history of suicide attempts, and psychiatric and medical history. In this study, patients who exhibited suicidal behaviour at least once in their lifetime were classified as suicide attempters, defined as a behavior of intentional self-harm without considering any consequences that did not cause death. Subjects who had not committed suicide in their lifetime were defined as non-attempters. Suicide attempts were assessed by a psychiatrist based on clinical interviews (all subjects were asked the question "did you ever attempt suicide at any time in your life?"), review of medical records, and confirmation with first-degree relatives and therapists if necessary.

All patients were assessed for psychopathological symptoms by two independent psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (21, 22). Psychiatric scoring physicians participated in PANSS consistency training, and the correlation coefficient of the PANSS score was $>$0.8. Based on the five-factor PANSS model proposed by Wallwork et al. (23), clinical symptoms were divided into the following aspects: (1) negative factor: N1, N2, N3, N4, N6, and G7; (2) excited factor: P4, P7,

G8, and G14; (3) positive factor: P1, P3, P5, and G9; (4) cognitive factor: P2, N5, and G11; and (5) depressed factor: G2, G3, and G6.

Cognitive Assessments

The neurocognitive function of each participant was mainly evaluated by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (24) consisting of five domains of cognition. RBANS is made up of 12 subtests: (1) immediate memory: list learning and story memory; (2) language: picture naming and semantic fluency; (3) visuospatial/constructional ability: figure copy and line orientation; (4) delayed memory: list recall, list recognition, story recall, and figure recall; and (5) attention: forward digit span and coding. In this study, the scores of each test and the total RBANS scores were recorded. In addition, PANSS-cognitive factor (including P2: Concept Disorder, N5: Abstract Thinking Disorder and G11: Attention Disorder) in this study also reflect cognitive functions of patients with schizophrenia.

Statistical Analysis

A sample test of Kolmogorov–Smirnov was applied to test for normal distribution. Regarding group differences between suicide attempters and non-attempters, continuous variables were tested by analysis of variance (ANOVA), and classified variables were analysed by the Chi-square test. Furthermore, analysis of covariance (ANCOVA) was performed to control for age, education, age at first hospitalization and sex as covariates. Multivariate logistic regression analysis (forward: conditional model) was conducted to check the risk factors of suicide attempters in middle-aged and elderly schizophrenia patients. Bonferroni correction was used in multiple tests. SPSS version 18.0 was used to perform all analyses, which have a significance level of 0.05 ($p < 0.05$).

RESULTS

Demographic Characteristics

A total of 426 schizophrenic inpatients, including 146 females and 280 males, were recruited for this study. Their average age was 55.34 [standard deviation (SD) = 6.96]. Their duration of education was 9.11 years (SD = 3.15). The average age of onset was 25.34 (SD = 7.75), and the age at first hospitalization was 28.72 (SD = 10.31).

In the entire patient group, the prevalence of suicide attempts in those with schizophrenia was 13.3% (57/426), with rates of 19.18% (28/146) in female patients and 10.35% (29/280) in male patients, which represented a significant gender difference ($X^2 = 6.442$, $p = 0.016$; Bonferroni corrected $p < 0.05$). There was also a significant difference in the age at first hospitalization ($p < 0.05$; Bonferroni corrected $p > 0.05$). All demographic data of patients in the non-attempter and suicide attempter groups are compared in **Table 1**.

Clinical Variables in Suicide Attempters vs. Non-attempters

The suicide attempt patients had significantly higher PANSS-positive subscores, depressive subscores and excited subscores than non-attempter patients (all $p < 0.05$; Bonferroni corrected $p < 0.05$). When gender and age at first hospitalization were added as covariates, there were still significant differences in PANSS-positive subscores ($F_{1,421} = 2.763$, $p < 0.001$, $r^2 = 0.142$) and depressive subscores ($F_{1,421} = 4.083$, $p < 0.001$, $r^2 = 0.142$) between the two groups. There was no significant difference in negative and cognitive factors between suicide attempters and non-attempters (**Table 1**).

Cognitive Function in Suicide Attempters vs. Non-attempters

The RBANS performance between suicide attempters and non-attempters was showed in **Table 2**. Compared to suicide attempters, non-attempters exhibited poorer cognitive performance in RBANS-list learning, semantic fluency and story recall (all $p < 0.05$; Bonferroni corrected $p < 0.05$). However, only RBANS-story recall ($F_{1,421} = 2.245$, $p = 0.009$, $r^2 = 0.090$) showed a significant difference after controlling for covariates, including gender, age, education level, and age at first hospitalization.

Correlation of Suicide Attempts, Clinical Symptoms and Cognitive Performance

A multiple logistic regression model was used to explore relevant factors for suicide attempts in middle-aged and elderly inpatients with schizophrenia, taking suicide attempts as the dependent variable, and the independent variables were statistically significant factors in ANOVA (including gender, age of first hospitalization, PANSS total score, positive subscores, excited subscore, depressive subscores, RBANS-list learning, semantic fluency, and story recall). The results showed that gender (OR = 2.19; 95% CI: 1.19–4.054), positive subscore (OR = 1.12; 95% CI: 1.05–1.20), depressive subscore (OR = 1.24; 95% CI: 1.11–1.38) and RBANS-story recall (OR = 1.10; 95% CI: 1.00–1.21) were independent contributors to suicide attempts in schizophrenia (**Table 3**).

DISCUSSION

To our best knowledge, we first explored the correlation between suicide attempts and clinical symptoms as well as neurocognitive function in middle-aged and elderly Chinese schizophrenia inpatients. Our main findings are as follows: (1) the prevalence of suicide attempts was 13.3% in middle-aged and elderly schizophrenia patients. (2) Patients with suicide attempts performed better on RBANS-list learning, semantic fluency and story recall than those without suicide attempts. (3) Females are more likely to be suicide attempters than males. (4) PANSS-positive symptoms and depressive symptoms are independently associated with suicide attempts.

In our study, the proportion of suicide attempts (13.3%) in middle-aged and elderly schizophrenia patients was similar to the results of the study of chronic schizophrenia patients with a larger age range (such as 18–65 years old, 25–75 years old, etc.) in China (9.2 and 12%) (2, 25). Interestingly, reported suicide rates in patients with schizophrenia vary widely. For

TABLE 1 | Demographic characteristics of attempter and non-attempter patients.

	Non-attempters $N = 369$	Attempters $N = 57$	F/χ^2	*p*-value
Age, years, M ± SD	55.35 ± 7.04	55.26 ± 6.47	0.007	NS
Gender, Male/female, *n*	251/118	29/28	6.442	0.016
Married, *n* (%)	91(24.66%)	13(22.81%)	1.104	NS
Education level, years, M ± SD	9.17 ± 3.14	8.72 ± 3.19	1.009	NS
BMI, kg/m^2, M ± SD	24.41 ± 3.97	24.64 ± 3.79	0.167	NS
History of physical disease, *n* (%)	92 (24.93%)	14 (24.56%)	0.092	NS
Family history, *n* (%)	50 (13.55%)	6 (10.53)	0.395	NS
Smoking, *n* (%)	194 (52.57%)	27 (47.37%)	0.920	NS
Drinking, *n* (%)	108 (29.27%)	25 (43.85%)	7.534	NS
Age of onset, years, M ± SD	25.57 ± 7.89	23.189 ± 6.59	2.305	NS
Age of first hospitalization, M ± SD	29.14 ± 10.48	25.98 ± 8.61	4.67	0.031
Number of hospitalizations, M ± SD	6.65 ± 9.80	6.02 ± 8.05	0.038	NS
Antipsychotic drug dosage (CPZ equivalent mg), M ± SD	329.80 ± 28.77	408.68 ± 74.59	1.011	NS

BMI, body mass index.

TABLE 2 | Clinical variables and cognitive functions between attempters and non-attempters.

	Non-attempters $N = 369$, M ± SD	Attempters $N = 57$, M ± SD	F	*p*-value
PANSS total score	75.62 ± 15.49	80.25 ± 16.16	4.322	0.038
Negative subscore	16.81 ± 5.34	18.33 ± 5.57	1.398	NS
Positive subscore	9.5 ± 3.87	12.35 ± 4.87	22.654	<0.001
Excited subscore	7.66 ± 2.88	8.75 ± 3.02	7.073	0.008
Depressive subscore	6.70 ± 2.43	8.81 ± 3.25	33.678	<0.001
Cognitive subscore	9.14 ± 2.82	9.21 ± 3.32	0.026	NS
RBANS total score	63.78 ± 12.50	66.37 ± 15.15	1.993	NS
Immediate memory	55.81 ± 29.56	60.32 ± 18.26	1.249	NS
List Learning	14.88 ± 6.21	17.23 ± 7.21	6.715	0.010
Story Memory	6.97 ± 4.63	7.96 ± 5.51	2.163	NS
Visuospatial/constructional	78.55 ± 16.71	79.51 ± 20.41	0.153	NS
Figure Copy	15.4 ± 4.72	15.26 ± 5.64	0.040	NS
Line Orientation	12.19 ± 4.43	11.74 ± 5.72	0.482	NS
Language	79.28 ± 12.93	79.04 ± 14.12	0.017	NS
Picture Naming	9.51 ± 4.96	9.21 ± 1.65	0.207	NS
Semantic Fluency	12.71 ± 4.91	14.53 ± 4.21	6.973	0.009
Attention	77.31 ± 14.73	78.60 ± 17.31	0.359	NS
Forward Digit Span	11.42 ± 4.05	11.39 ± 3.06	0.004	NS
Coding	22.28 ± 12.57	25.72 ± 13.12	3.654	NS
Delayed memory	62.94 ± 18.84	64.21 ± 21.10	0.218	NS
List Recall	2.16 ± 2.31	2.81 ± 2.61	3.759	NS
List Recognition	16.66 ± 9.74	16.72 ± 2.78	0.002	NS
Story Recall	3.32 ± 3.09	4.4 ± 3.67	7.747	0.007
Figure Recall	6.96 ± 8.47	6.81 ± 5.70	0.018	NS

PANSS, positive and negative syndrome scale; RBANS, repeatable battery for the assessment of neuropsychological status.

example, a study involving 510 outpatients with schizophrenia found that the incidence of suicide attempts in rural patients was 7.5% (9). Xiang et al. conducted a study of 505 schizophrenia outpatients and found that 26.7% of patients had a history of suicide attempts in their lifetime, with rates of 20% in Hong Kong and 33.6% in Beijing (26). In regard to other countries, a

TABLE 3 | Factors for suicide attempts in middle-aged and elderly schizophrenia patients.

	Odds Ratio (OR)	95% CI		*p*-value
		Lower	Upper	
Gender	2.197	1.19	4.054	0.012
Positive subscore	1.122	1.047	1.203	0.001
Depressive subscore	1.236	1.105	1.381	<0.001
RBANS-Story Recall	1.103	1.005	1.21	0.038

Variables in the model: Gender, Age of first hospitalization, PANSS total score, Positive subscore, Excited subscore, Depressive subscore, RBANS-List Learning, Semantic Fluency and Story Recall.

current review reported that 10–50% of schizophrenia patients reported a history of suicide attempts (3). The reasons for the differences in suicide rates, especially those domestically and abroad, might be due to differences in research samples (including cultural background, treatment environment, ethnic genes, etc.) (2), sampling methods, and the assessment methods used for suicide attempts (25), which requires an epidemiological study with more samples and a broader geographic area in the future to provide stronger evidence.

Our main findings regarding suicide attempts and neurocognitive function supported the results of previous studies (16, 17, 27), which found that better cognitive performance might increase suicide risk. A recent study on cognition and suicide attempts found that cognitive planning ability is independently related to suicide attempts in schizophrenia patients (28). However, differences are presented in the cognitive assessment tools and the methods used to evaluate suicide in these studies. In this study, we used two instruments to evaluate the cognitive function of patients. A preliminary exploration of cognitive function in the PANSS rating scale did not find a significant correlation between cognitive factors and attempted suicide. However, the more comprehensive and popular RBANS cognitive test found that patients with suicide attempts performed better on list learning, semantic fluency and story recall than those without suicidal behaviour, and RBANS-story recall in the delayed memory domain was an independent influencing factor of suicidal behaviour. Delaney et al. (27) found that patients with suicidal ideation and single suicide attempts outperformed patients with no suicidal behaviour or ideation on global cognition (measures of IQ). A study of 333 patients examined by a neurocognitive battery reported an association between better cognitive performance and greater suicidality in schizophrenia (29). These previous studies concluded that there is an association between suicide attempts and different cognitive domains, such as attention, planning ability and execution ability which may be related to differences in research methods, especially the cognitive evaluation tools and the methods used to evaluate suicide (18). However, all of these results suggest that higher cognitive scores may represent a risk factor for suicide. Furthermore, some studies have revealed that suicide attempts are a conscious initiation of goal-oriented behaviour (30). Better executive function (31) and attention skills (16) may enable patients to plan and initiate targeted goals of suicidal behaviours, which may increase the impulse to commit suicide. To date, there was no study on suicide and cognition in middle-aged and elderly schizophrenia patients. We found that there were less cognitive impairments in the suicide attempters than non-attempters. Similar to a study in older depressed adults, Arslanoglou et al. (32) reported that subjects with suicidal ideation had higher memory scores than those without suicidal ideation. In contrast, our results did not replicate those of other previous neurocognitive studies (33–35), which revealed no relationship between suicide and cognition. A recent review indicated that patients with suicidal behaviour have poorer executive function performance than those without suicidal behaviour (35). A cross-sectional study in 316 chronic inpatients with schizophrenia conducted in Beijing, China found that performance on the total and index RBANS test was not significantly associated with lifetime risk of suicide attempts (33). In summary, there may be an internal relationship between suicide attempts and neurocognition in middle-aged and elderly schizophrenia patients, but the results are superficial and inconsistent and need to be confirmed by further prospective studies in larger samples.

Another interesting finding was that female patients with schizophrenia had a higher suicide attempt rate than male patients, which was consistent with previous studies (36, 37). However, other studies have reported that a higher risk of suicidal behavior in men with schizophrenia (38, 39). Chun-Hung et al. (10) even indicated that although the suicide rate in female patients with schizophrenia was lower than that in male patients, their standardized mortality ratio was higher than that in male patients. Therefore, patients with schizophrenia of any gender need to be monitored for suicidal behaviour to strengthen prevention.

More importantly, we identified significantly positive associations between clinical symptoms and suicide attempts, including the clinical symptoms of PANSS positive symptoms and depressive symptoms being risk factors for suicidal behaviour, which confirmed and extended most previous studies on suicide attempts in patients with schizophrenia (1, 11, 25, 28, 40). A review by Avinash et al. that summarized articles from 2015 to 2019 concluded that positive symptoms played an important role in suicide in schizophrenia patients (1). Similar to Yan et al. report of suicides in schizophrenia (25), a study that investigated the clinical characteristics and symptoms of suicide in patients with schizophrenia in Taiwan showed that depressive and psychotic symptoms were contributing factors to suicidal behaviour (41). Xiang et al. also revealed that Chinese schizophrenia patients who attempted suicide tend to have more severe anxiety and positive depressive symptoms (26). Therefore, current studies indicate that the more severe the clinical symptoms, the more obvious the suicidal tendency, which is the same as that observed in middle-aged and elderly schizophrenia patients. Moreover, patients have more positive symptoms, including psychotic symptoms such as auditory delusions and hallucinations, which make patients more motivated to plan and initiate suicidal behaviour. On the other hand, the relationship between suicide and depression

in schizophrenia is complex. Depression may be a symptom group of schizophrenia, which can increase suicide rate in the following year and lifetime suicidal behaviour (42); however, depression can also be diagnosed separately (43). Regardless of the symptom connection, it is necessary to guard against suicidal tendencies in patients with schizophrenia through timely evaluation and intervention.

Several limitations should be noted in this study. First, limited to the current definition of attempted suicide, we only evaluated whether there were suicide attempts, which lacked specific grading assessment of the degree of suicide (such as suicidal ideation) and lacked examination of specific methods to induce suicide. Second, a cross-sectional study did not directly illustrate a causal relationship between suicide attempts and risk factors in middle-aged and elderly Chinese inpatients with schizophrenia. Third, there was no healthy control group in the current study. Fourth, the subjects included in our study were long-term inpatients who had a longer course of disease, more severe symptoms and longer drug treatment than first-episode or outpatient patients, which may affect neurocognitive outcomes. Fifth, the sample size of the suicide attempters group and the non-attempters group appeared uneven, which might have a certain impact on the results. Therefore, our current survey results are only preliminary and need to be confirmed by prospective studies with a larger sample size in the future.

In conclusion, our results extend previous reports and identified a high incidence of suicide attempts in middle-aged and elderly Chinese schizophrenia patients. Female patients were more likely to be suicide attempters than male patients. Compared to non-attempters, there were less cognitive impairments and more clinical symptoms in the suicide attempters. PANSS-positive symptoms, depressive symptoms and RBANS-story recall were associated with suicide attempts in middle-aged and elderly Chinese schizophrenia patients. Although suicide in psychiatric patients is caused by multiple factors and the cross-sectional study cannot explain the causal association between suicide attempts and schizophrenia, timely detection and intervention will greatly reduce the incidence of suicide. Future prospective researches with large sample sizes are required to further explain the potential risk factors for suicide attempts in middle-aged and elderly schizophrenia patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of the Affiliated Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FW and MY: were responsible for management and oversight of the study. YH and KW: were responsible for general omnibus data analyses and were keys contributing authors to the manuscript. XZ, HL, and YF: were responsible for all research interviews and clinical chart reviews associated with this study. TL and YN: provided guidance on the design of primary analyses. RJ and SZ assisted with all data collection, analysis, and writing of the manuscript. All authors contributed to the study design, data interpretation, critically reviewed the manuscript, and gave final approval for its publication.

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frontiers in Psychiatry

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High Prevalence of Post-stroke Anxiety in Elderly Patients Following COVID-19 Outbreak

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Objective: Post-stroke anxiety (PSA) is a common affective disorder in patients with ischemic stroke. The elderly are more susceptible to mental health issues, however, few studies have so far focused on PSA in elderly patients, especially in the context of the COVID-19, causing psychological issues in the general population. The aim of the present study was to assess the prevalence and risk factors of PSA in elderly patients following COVID-19 outbreak.

Methods: We retrospectively analyzed 206 elderly inpatients with newly diagnosed acute ischemic stroke in the First Affiliated Hospital, Sun Yat-sen University, from January 2020 to December 2020. Patients were categorized into the PSA group and the non-PSA group based on Hamilton Anxiety Scale scores at admission (within 1 week after stroke onset). Demographic and clinical data, mental state by Mini-Mental State Examination, depression by Hamilton Depression Scales (HAMD), and stroke severity and outcome by National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale were compared between the two groups. Univariate analysis and binary logistic regression analysis were used to analyze risk factors associated with PSA. We determined the cutoff scores for significant predictors of PSA using the area under the curve (AUC) and receiver operating characteristic.

Results: Of the 206 stroke patients, 62 (30.1%) developed anxiety. Binary logistic regression analysis showed that female gender [adjusted odds ratio (aOR): 2.288, 95% confidence interval (CI):1.021–5.128, $P = 0.044$], high NIHSS scores [aOR: 1.264, 95% CI: 1.074–1.486, $P = 0.005$] and HAMD scores [aOR: 1.345, 95% CI: 1.215–1.490, $P < 0.001$] were independent risk factors for PSA. The cutoff threshold for the NIHSS scores was 3.5 points with an AUC of 0.64 and the cutoff threshold for HAMD scores was 5.5 points with an AUC of 0.89.

Conclusion: Our results showed a high incidence of PSA in elderly patients after the COVID-19 outbreak. Female gender, high NIHSS and HAMD scores were the independent risk factors for PSA.

Keywords: post-stroke anxiety, elderly patients, acute ischemic stroke, risk factors, COVID-19

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INTRODUCTION

Acute ischemic stroke is one of the leading causes of death and disability worldwide and has become a major disease burden for elderly patients in China (1, 2). Many studies have shown that anxiety and depression can affect patient's quality of life (3, 4). Anxiety and depression are both common complications in stroke patients, but post-stroke anxiety (PSA) appears to have a more stable and lasting effect than post-stroke depression (5–7). It has been reported that PSA occurs in 1.8–27% of stroke survivors (5, 8–12), however, the prevalence of PSA in elderly patients remains unclear.

Since December 2019, the COVID-19 pandemic has caused extensive anxiety and psychological issues in the general public and healthcare workers (13, 14). Although COVID-19 has been effectively controlled in China, it is still spreading around the world, and sporadic cases occur in some places in China. With the stricter management in hospitalized patients including limitations on patient visitations from family members, the elderly patients are more prone to feel loneliness and insecurity, leading to emotional issues including anxiety (15, 16). There is no data so far on the prevalence of PSA in elderly inpatients in the context of COVID-19. The present study aimed to fill this knowledge gap and explore independent risk factors for PSA.

PATIENTS AND METHODS

Patients

This study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University. The study was conducted in accordance with the Declaration of Helsinki. Consecutive inpatient paper medical records and electronic medical records from January 2020 to December 2020 were reviewed at the Department of Neurology, the First Affiliated Hospital of Sun Yat-sen University. After a detailed evaluation of the inclusion and exclusion criteria, 206 patients were included in this study. The inclusion criteria were: (1) Patients were diagnosed with ischemic stroke according to the International Classification of Diseases (ICD-10) (17), with infarction sites confirmed by brain CT or MRI. (2) Patients were admitted to the hospital within 1 week after ischemic stroke onset. (3) Patient age was $\geq$ 60 years old. The exclusion criteria were: (1) Previous diagnosis of anxiety, depression, and other mental disorders. (2) Patients with severe aphasia, confusion, or patients unable to complete the relevant scale tests. (3) Presence of other diseases which can cause emotional disturbance, including severe heart failure, thyroid diseases, severe liver or kidney dysfunction.

Measures

At admission, sociodemographic characteristics (gender, age, marital status, and education) and risk factors for cerebrovascular disease (diabetes mellitus, hypertension, smoking, and drinking) were recorded. Patients were etiologically classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system (18).

The Hamilton Anxiety Scale (HAMA) was employed by two experienced neurologists to evaluate the anxiety of patients. Patients with HAMA scores $\geq$7 were considered to experience anxiety and were enrolled in the PSA group (19, 20). Patients with HAMA scores <7 were considered not to exhibit anxiety and therefore classified in the non-PSA group. HAMA can be summarized into two types of factor structure: one is psychological symptoms consisting of anxious mood, tension, fears, insomnia, cognitive changes, depression, and behavior at interview, while the other is somatic symptoms including

TABLE 1 | Sociodemographic and clinical variables between the PSA and non-PSA groups.

	All patients	Post-stroke anxiety		*P*-value
	(*n* = 206)	No (*n* = 144)	Yes (*n* = 62)	
Demographic variable				
Gender (*n*, %)†				0.007*
Male	125 (60.7)	96 (66.7)	29 (46.8)	
Female	81 (39.3)	48 (33.3)	33 (53.2)	
Age(years)#	67 (64,74)	67 (64,73)	68 (63,74)	0.650
Marital status (*n*, %)†				0.014*
Married	183 (88.8)	133 (92.4)	50 (80.7)	
Single (divorced/widowed)	23 (11.2)	11 (7.6)	12 (19.3)	
Level of education (*n*, %)†				0.196
Primary school and below	87 (42.2)	56 (38.9)	31 (50.0)	
Secondary school	83 (40.3)	59 (41.0)	24 (38.7)	
University and above	36 (17.5)	29 (20.1)	7 (11.3)	
Vascular risk factors				
Diabetes mellitus (*n*, %)†	84 (59.2)	55 (38.2)	29 (46.8)	0.250
Hypertension (*n*, %)†	151 (73.3)	105 (72.9)	46 (74.2)	0.849
Smoking (*n*, %)†	91 (44.2)	67 (46.5)	24 (38.7)	0.300
Drinking (*n*, %)†	54 (26.2)	37 (25.4)	17 (27.4)	0.796
TOAST classification (*n*, %)				
Large-artery atherosclerosis	127 (61.6)	90 (70.9)	37 (29.1)	0.318
Cardio embolism	14 (6.8)	10 (71.4)	4 (28.6)	
Small-vessel occlusion	56 (27.2)	36 (64.3)	20 (35.7)	
Other determined etiology	2 (1.0)	1 (50.0)	1 (50.0)	
Undetermined etiology	7 (3.4)	7 (100.0)	0 (0)	
Lesion location (*n*, %)				
Left hemisphere	66 (32.0)	49 (74.2)	17 (25.8)	0.145
Right hemisphere	77 (37.4)	51 (66.2)	26 (33.8)	
Bilateral hemisphere	21 (10.2)	14 (14.7)	7 (6.3)	
Brainstem	32 (15.5)	20 (62.5)	12 (37.5)	
Cerebellum	10 (1.9)	10 (100)	0 (0)	
Neurophysiological test scores				
NIHSS#	4 (2,5)	3 (2,5)	4 (3,7)	0.001*
mRS#	2 (1,3)	2 (1,3)	2 (1,4)	0.002*
MMSE#	20 (15,24)	25 (21,28)	23 (17,26)	0.001*
HAMD#	4 (1,8)	3 (1,5)	10 (6,15)	0.000*

PSA, post-stroke anxiety; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale; MMSE, Mini-Mental State Examination; HAMD, Hamilton Depression Scale.
*† n(%), Pearson's Chi-square test; n(%), Fisher's exact test; # median(25%Q, 75%Q), Mann–Whitney U-tests; * P < 0.05.*

muscular, sensory, gastrointestinal, genitourinary, respiratory, cardiovascular and autonomic symptoms (21). Depression was assessed using the Hamilton Depression Scales (HAMD). Meanwhile, the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) were used to evaluate stroke severity and outcome while the Mini-Mental State Examination (MMSE) to assess cognitive functions.

Statistical Analysis

All statistical analyses were performed using SPSS 24.0 (IBM Corp, Armonk, NY). Quantitative data with normal distribution were described as mean ± standard deviation ($x \pm s$), while non-normally distributed quantitative data were expressed as median with 25 percentile and 75 percentiles. Qualitative data were described using frequencies and percentages. Univariate analysis of quantitative data were compared with the independent two-sample *t*-tests or Mann–Whitney *U*-tests. Pearson's Chi-square test or Fisher's exact test were used to compare different categories of qualitative variables. Significant features in univariate analysis were selected for multivariate binary logistic regression analysis. To determine the cutoff scores for independent predictors of PSA vs. non-PSA groups, we used the receiver operating characteristic (ROC) curve. The accuracy of significant predictors was determined with the area under the ROC curve (AUC). *P*-values lower than 0.05 were considered statistically significant.

RESULTS

Sociodemographic and Clinical Characteristic

Two hundred and six eligible patients were included in this study. The median age of the patients was 67 (range 60–90), of which 60.7% were male. Twenty-three patients (11.2%) were divorced or widowed. Seventeen percent (17.5%) had received university education or above (**Table 1**). Eighty-four patients (59.2%) had a history of diabetes mellitus and 151 (73.3%) had hypertension. The rates of individuals reporting smoking and drinking were 44.2% and 26.2%, respectively. According to the TOAST etiology classification, 61.6% of patients were classified as large-artery atherosclerosis. In 37.4% of patients, the lesion site was in the right hemisphere.

Sixty-two (30.1%) of the 206 elderly patients were diagnosed with PSA. According to official information released by the National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/xcs/yqtb/list_gzbd.shtml), the COVID-19 pandemic in China has been effectively controlled by the end of the first quarter in 2020. We analyzed the incidence of PSA quarterly in 2020, and found that the incidence of PSA showed a downward trend after the COVID-19 pandemic was controlled (**Figures 1**, **2**). Psychological symptoms of PSA were higher than somatic symptoms by HAMA scores. Psychological symptoms mainly manifested as cognitive changes (88%), insomnia (74.2%), anxious mood (72.6%) and tension (66.1%), while somatic symptoms as muscular symptoms (51.6%), sensory symptoms (58.1%), cardiovascular symptoms (40.3%) and autonomic symptoms (40.3%). **Table 1** demonstrated a higher proportion of female gender and single status patients (divorced or widowed) in the PSA group. Patients with PSA were also more likely to exhibit higher mRS scores, higher scores of mRS, NIHSS and HAMD than patients without PSA.

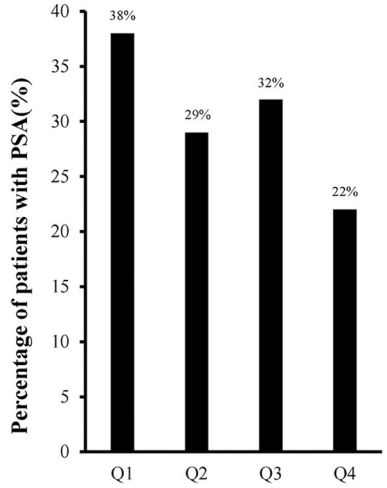

FIGURE 1 | The incidence of PSA each quarter in 2020. Q1, the first quarter; Q2, the second quarter; Q3, the third quarter; Q4, the fourth quarter.

Factors Associated With PSA Among Patients

The following factors were assessed in this study: gender, age, marital status, level of education, vascular risk factors, stroke type, stroke lesion location, neurophysiological test scores. Results from the mono-factorial analysis showed that female gender ($P = 0.007$), single status (including being divorced or widowed) ($P = 0.014$), MMSE scores ($P = 0.001$), mRS scores ($P = 0.002$), NIHSS scores ($P = 0.001$), and HAMD scores ($P < 0.001$) were significantly associated with PSA. There were no statistically significant differences for any of the other examined factors (**Table 1**).

All risk factors with significant associations found in the univariate analysis were then included as predictive indicators in binary logistic regression. Multivariable analysis indicated that female gender (adjusted odds ratio (aOR): 2.288, 95% confidence interval (CI): 1.021–5.128; $P = 0.044$), NIHSS scores (aOR: 1.264 per one-point increase in NIHSS scores; 95% CI: 1.074–1.486; $P = 0.005$) and HAMD scores (aOR: 1.345 per one point increased in HAMD score; 95% CI: 1.215–1.490; $P < 0.001$) were independent predictors of PSA (**Table 2**).

Considering that NIHSS and HAMD scores were independent risk factors of the PSA, we next determined the predictive cutoff threshold for NIHSS scores and HAMD scores using ROC curve analysis. A NIHSS cutoff score of 3.5 was able to differentiate patients with PSA from those without PSA, with a sensitivity of 66% and a specificity of 55%, resulting in an AUC of 0.642. By contrast, a HAMD cutoff score of 5.5 was able to differentiate patients

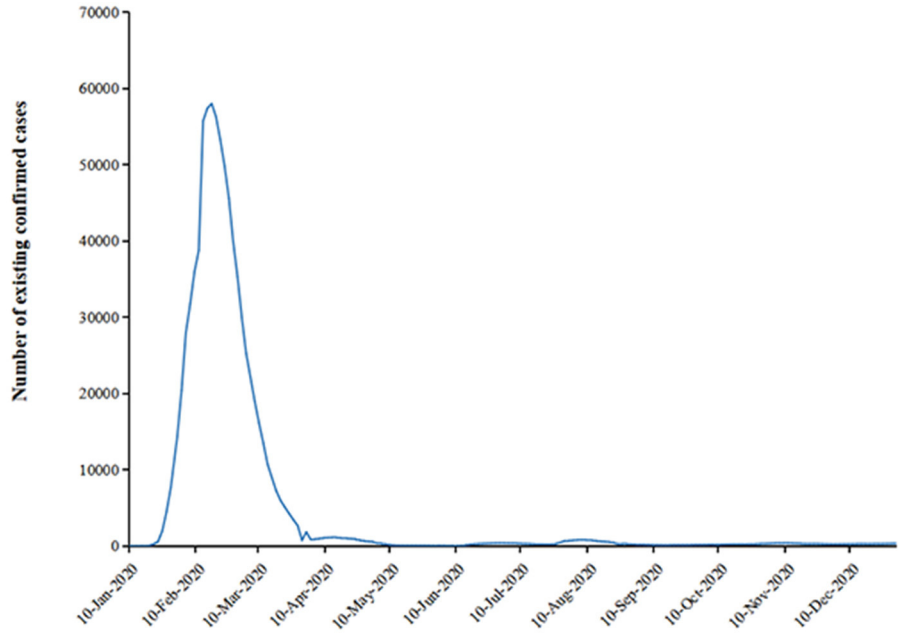

FIGURE 2 | Trends in the number of existing patients with COVID-19 in China in 2020.

TABLE 2 | Multivariate logistic regression analysis for identification of factors associated with PSA in elderly patients.

Variable	B	SE	Wald	aOR	95%CI	*P*
Gender (female vs. male)	0.828	0.412	4.038	2.288	1.021–5.128	0.044*
Marital status (single vs. married)	0.301	0.647	0.217	1.351	0.381–4.800	0.641
NIHSS score	0.234	0.083	7.991	1.264	1.074–1.486	0.005*
mRs score	−0.205	0.210	0.953	0.815	0.540–1.229	0.329
MMSE score	−0.048	0.035	1.913	0.167	0.890–1.020	0.167
HAMD score	0.297	0.052	32.34	1.345	1.215–1.490	0.000*

PSA, post-stroke anxiety; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale; MMSE, National Institute of Health Stroke Scale; HAMD, Hamilton Depression Scales.

*B, regression coefficient; SE, standard error; aOR, adjusted odds ratio; CI, confidence interval; *P< 0.05.*

with PSA from those without PSA, with a sensitivity of 79% and a specificity of 83%. AUC for PSA vs. non-PSA discrimination was 0.897 (95% CI 0.847–0.948, $P < 0.001$) (**Figure 3**).

DISCUSSION

The present study explored the incidence and predictors of PSA in elderly patients admitted to hospital following the COVID-19 outbreak and revealed a prevalence of 30.1% for PSA among elderly patients. We then compared epidemiological factors in 62 patients with PSA and 144 patients without PSA, and found that female gender, high NIHSS and HAMD scores were the independent factors for PSA by binary logistic regression.

PSA is a common neurological disorder that hinder patient rehabilitation (5). The COVID-19 outbreak has harmed psychosocial health, causing anxiety in the general population (22) and physicians (23). Compared to the 13.3% incidence of public anxiety in China during the COVID-19 outbreak (24), the prevalence of PSA with all ages in southern China has been reported between 1.2% and 27% before the COVID-19 pandemic (10, 12, 25). Our study found that 62/206 (30.1%) elderly patients developed PSA, which was higher than that prior to the COVID-19 outbreak but consistent with a recent report of 32% during the pandemic (26). We also identified fewer hospitalizations of elderly patients with ischemic stroke during the COVID-19 pandemic; this is likely a result of an unwillingness of patients to visit hospitals due to a fear of COVID-19 infection. Since the emergence of COVID-19, there has also been a stricter management of hospitalized patients including limitations on patient visitations from family members. Family members are unable to provide social support or emotional comfort directly to patients. Inpatients could therefore have also been

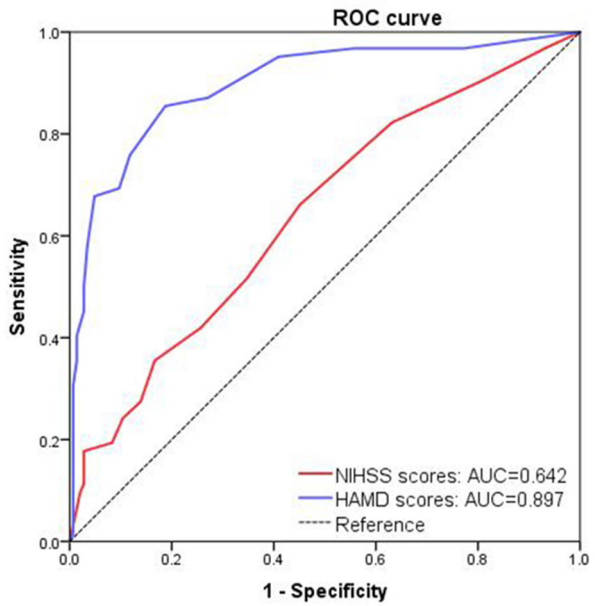

FIGURE 3 | Receiver operating characteristic (ROC) curve analysis of National Institutes of Health Stroke Scale (NIHSS) scores and Hamilton Depression Scales (HAMD) to indicate post-stroke anxiety.

psychologically impacted by these restrictive measures adopted by governments and societies.

We found that the incidence of PSA was higher in females than in males, probably due to the characteristic that female patients are more susceptible to social stress and other psychological factors (8, 27). A previous study assessing the symptoms of depression and anxiety in a neurology clinic also founded that female patients were more susceptible to anxiety than male (28). The single marital status (divorced or widowed) was not found as an independent risk factor for PSA, nonetheless, such patients were more prone to develop PSA by univariate analysis in the present study. It has been reported that lacking of companionship could reduce social support and guidance to patients, resulting in much severe anxiety and stroke mortality (29–31). We also found that more severe neurophysiological dysfunction at admission by the scores of NIHSS, mRS, MMSE, and HAMD in the PSA group than in the non-PSA group. However, after adjusting for confounding factors of gender, marital status, stroke severity and depression, the difference in the scores of mRS and MMSE between the two groups was no longer statistically significant, and only the scores of NIHSS and HAMD were associated with PSA by multivariate logistic regression analysis, in line with previous reports (32, 33). Furthermore, the cutoff threshold of NIHSS scores and HAMD scores were determined for independent predictors of PSA, with the result of 3.5 points (AUC of 0.64) and 5.5 points (AUC of 0.89), respectively. These insights may be helpful for clinicians to recognize PSA and provide more attention and support to such patients.

There were several limitations in the present study. First, this was a single-center retrospective study including inpatient data only. Second, the sample size was relatively small and no long-term follow-up of PSA was performed, possibly causing bias to some extent. Large-scale prospective studies are wanted to clarify these issues in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This retrospective study involving human participants was reviewed and approved by the local clinical trial committee of the First Affiliated Hospital of Sun Yat-Sen the identity University. All patient data were anonymized so that of the patients could not be ascertained in any way.

AUTHOR CONTRIBUTIONS

MY collected the data and wrote the paper. HL and YL conducted the data collection and undertook the statistical analysis. LL undertook the statistical analysis and provided revised suggestions. JY designed the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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The Effect of Chinese Square Dance Exercise on Cognitive Function in Older Women With Mild Cognitive Impairment: The Mediating Effect of Mood Status and Quality of Life

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The present study aimed to assess the effects of square dance exercise on the cognitive function and quality of life in older women with mild cognitive impairment and to investigate the mediating role of a depressed mood and reduced quality of life in the relationship between square dance exercise and cognition. The study design was a single-blind whole-group controlled trial. A total of 136 eligible participants were divided according to their nursing home into either an experimental or control group. The nursing home grouping was determined by the drawing of lots. The Montreal Cognitive Assessment (MoCA), Quality of Life (SF-12) and Geriatric Depression Scale (GDS-15) were used to assess participants at baseline, week 9, and week 18, respectively. Generalized estimating equations (GEE) were used to compare the results at baseline with mid-test and post-test changes in cognitive function and quality of life. Maximum likelihood estimation (ML) and robust standard errors were used to perform the mediation model. The study results indicated that the experimental group (compared to the control group) had a significant improvement in cognitive function, quality of life, and mood state at baseline in the mid-test and post-test results. The results of this 18-week experiment showed that the exercise–cognition relationship was significantly mediated by a reduction in depressive symptoms (indirect effect: $\beta = -0.375$; 95% CI $= -0.864$ to -0.069) and an improvement in quality of life (indirect effect: $\beta = -0.678$; 95% CI $= -1.222$ to -0.290). This study revealed the effects of moderate-intensity square dance exercise on cognitive function and quality of life in older Chinese women with mild cognitive impairment and explored the potential mediating mechanisms. These findings can be used to inform the development of public health policies to promote brain health in older adults with mild cognitive impairment.

Keywords: cognition, depression, mild cognitive impairment, Chinese square dance, mediation model

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INTRODUCTION

Global aging has led to an increased focus on the aging process in the field of public health. There is a transition zone in which people move from normal aging to dementia, described by the term mild cognitive impairment (MCI) (1). Individuals with mild cognitive impairment are at a high risk of developing dementia (2). Whereas, the annual conversion rate from mild cognitive impairment to dementia is estimated to be 10–15% (3), the annual prevalence of dementia in the entire elderly population is estimated to be 1–3% (4). Current global estimates of the prevalence of mild cognitive impairment range from 9.6–21.6% (5–7). The high prevalence of mild cognitive impairment leading to dementia emphasizes the need to implement effective therapeutic approaches at this stage, and preventive interventions for this disorder have been widely explored.

Non-pharmacological interventions are still considered to be the main form of treatment for older adults with mild cognitive impairment (2). Among the various non-pharmacological interventions, physical activity has been widely explored as a low-cost, low-risk, and easily accessible lifestyle intervention, and its effectiveness in promoting brain health in elderly care is well known (8). A recent systematic review of randomized controlled trials showed that physical activity, including aerobic and resistance training, is low to moderately effective in promoting cognitive function in older adults with MCI. Sensitivity analyses showed that moderate-intensity aerobic exercise interventions had the best cognitive function effects compared to other exercise interventions (9, 10). The cognitive benefits of physical activity among older adults with mild cognitive impairment in China are still being explored. A 12-week study of a square dance intervention for older adults in one nursing home in northeastern China showed that square dancing is a promising strategy for older adults with mild cognitive impairment and that long-term adherence to square dancing may be beneficial (11). Furthermore, despite the considerable challenges that mild cognitive impairment poses to patients' daily lives, the impact of physical activity on quality of life in this patient population has rarely been studied. The limited evidence related to this phenomenon reports negative results (12, 13), raising questions about whether the cognitive benefits of exercise interventions are transferable to the overall well-being of patients with mild cognitive impairment.

A recently conducted 16-week moderate-intensity aerobic stepping intervention program in Hangzhou, China, reported positive results and identified reduced depressive symptoms and improved sleep quality as part of a potential possible mechanism involved in the exercise–cognition relationship (14). Despite the considerable evidence supporting the role of physical activity in enhancing cognitive function, studies examining the mediating mechanisms behind the exercise–cognition relationship remain scarce. Song et al. (14) identified depressive symptoms and sleep as possible mediating variables in the exercise–cognition relationship. Considering that depressive symptoms are a significant risk factor for predicting cognitive decline (15), and depressive symptoms are strongly associated with quality of life (16). This study will select square dancing as an aerobic exercise intervention to further investigate the role of improving the mood (depression) and quality of life (spiritual) of elderly adults in the exercise–cognition relationship. Since square dancing is popular among older Chinese women, with only a small number of middle-aged and older men taking part in this activity, older women were selected as the participants in this study.

This study aimed to assess the effects of square dance exercise on cognitive function and quality of life in older women with mild cognitive impairment and to investigate the mediating role of depressed mood and reduced quality of life in the relationship between square dance exercise and cognition. The hypothetical mediator model is presented in **Figure 1**. The following study hypotheses were tested in older women with mild cognitive impairment.

H1: An 18-week moderate-intensity square dance exercise program will be more effective for improving cognitive function and quality of life in the experimental group than in the control group (i.e., the daily life group).

H2: An 18-week exercise program will be better than a 9-week exercise intervention program in terms of improving cognitive function and quality of life.

H3: An 18-week square dance exercise program will have an effect on cognitive function, improving depressive symptoms and quality of life.

METHODS

Study Design

This study was a single-blind whole-group randomized controlled trial. According to their nursing home, the eligible participants were randomly enrolled in either the Chinese square dance exercise program or the normal life group. The random sequence was generated by the drawing of lots. Two nursing homes served as the experimental group (EG), and two other nursing homes served as the control group (CG). Data collection was completed by two research assistants who were not involved in the square dance training. Outcomes and mediating variables were measured by face-to-face interviews at baseline before randomization grouping, at the mid-study intervention (week 9), and at one week after completion (week 18). Single blinding was maintained because the research assistants involved in the post-test data collection did not have any information on the subgroup assignment.

Participants

The sample size required for the experiment was calculated using G*Power software. Independent sample *t*-tests were used to analyze the results of the baseline and post-experimental changes. Based on the effect size (Cohen's d = 0.58), 80% power, and a 5% level I error, we estimated that a minimum of 48 participants were required per group. We recruited 10% more subjects than required to account for potential participant dropouts; therefore, a minimum of 53 participants per group were recruited. Participants were recruited from four nursing homes in Chongqing as long as they met the following criteria: (1) at least 60 years old; (2) presented with a subjective cognitive decline in the previous year; (3) obtained

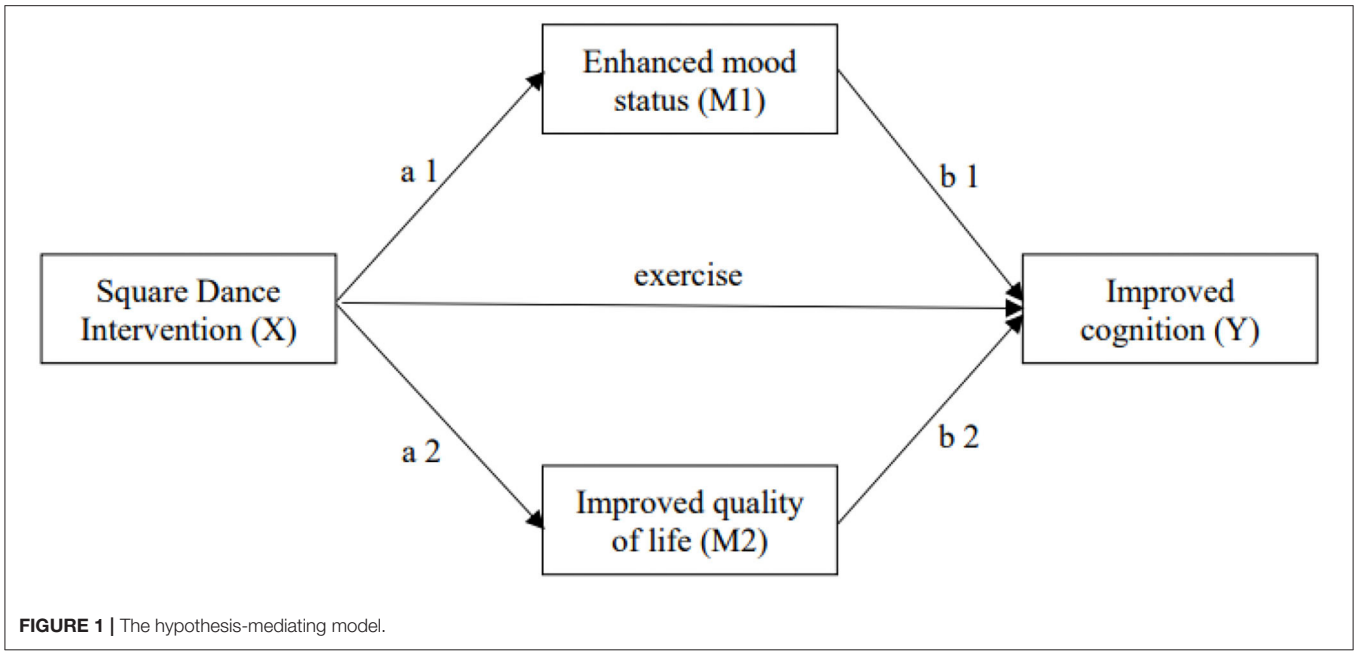

FIGURE 1 | The hypothesis-mediating model.

a score of <26 on the Montreal Cognitive Assessment (MoCA) scale (plus an extra 1 point if they had achieved 12 years of schooling); (4) attained a score of <26 on the Ability for Daily Living (ADL) assessment. Participants were excluded if they were: (1) taking medication for cognitive impairment; (2) had a neurological disorder (e.g., Parkinson's disease, stroke, multiple sclerosis); (3) had an acute or chronic condition that prevented exercise; (4) performed regular exercise (≥30 min/day, ≥3 days/week) within the past 6 months or had sustained exercise experience for more than 5 years (16). All participants signed a written informed consent form before the study began.

Intervention

Chinese square dance is a popular form of aerobic exercise for middle-aged and older women. The dance has a simple, easy-to-learn structure and is suitable for older individuals to use as a form of exercise. We chose Chinese square dance as the exercise approach for the experimental group. Square dance music has a simple melody, low movement activity is required, and the central movement structures are handclapping, high-fiving, chest expansion, arm extension, and leg kicking (https://www.youtube.com/watch?v=AYEasAhzHI0) (16).

One week before starting the experiment, two national social sports instructors with professional dance training gave three lessons in two nursing homes to ensure that each participant had mastered the basic movements. After 1 week of study, we provided square dance instructional videos for the experimental group to review. During the teaching process, one instructor demonstrates in front of the participants, and another instructor assists in teaching and correcting incorrect movements. For the formal experiment, an instructor is responsible for leading the practice, and the nursing home arranges a staff member to assist with teaching and to ensure the safety of participants.

The intervention group performed the square dance exercise program outdoors three times a week for 30 min each (during periods of inclement weather, square dance exercise was held indoors). The exercise was led by a professional national social sports instructor on Monday, Wednesday, and Friday evenings from 7:00 p.m. There was a 5-min warm-up exercise (joint finger movement, etc.) before the official start, followed by a 30-min square dance exercise and a 5-min relaxation exercise (i.e., deep breathing and stretching) at the end of the session. During the square dance exercise, participants were required to wear a sports watch to monitor their heart rate. Participants' heart rates during exercise were controlled at 100–140 beats per minute. The control group was not scheduled for specialized physical activity, but did not restrict their voluntary physical activity.

Measurements

All outcomes were assessed at baseline, midterm (week 9), and within 1 week of the completion of the trial (week 18) by trained assessors whose group assignments to participants were confidential. The primary outcome measures included participants' demographic characteristics, cognitive function, quality of life, and mood state. All scales used were in the Chinese language, and all test tools were supported by proven reliability and evidence of validity.

The Montreal Cognitive Assessment (MoCA) was used for MCI screening in older adults. The MoCA test includes attention and concentration, executive function, memory, language, visual–structural skills, abstract thinking, and computational and orientational skills, with a total scale score of 30, with a normal result considered to be any score ≥26 (17). Similarly,

the scale had a retest reliability of 0.85 (18) and an internal consistency (Cronbach's alpha) of 0.84 (19), as well as good content, concurrent, and construct validity ($p < 0.01$) (19). In addition, the MoCA is relatively brief compared to other complex neuropsychological combinations and was, therefore, more appropriate for older adults with mild cognitive impairment.

The Short-Form 12 Health Survey (SF-12) is a self-reported outcome measure that assesses the effect of health on an individual's daily life. It was used to assess quality of life in this study. The SF-12 is a shortened version of the SF-36, which itself evolved from the Medical Outcomes Study. The SF-12 uses the same eight domains as the SF-36, and the correlation coefficient between both is high (20). The SF-12 includes the assessment of vitality, social functioning, emotions, mental health, general health, physical functioning, role physical, and bodily pain. The first four indicators are used to assess the mental component summary (MCS), while the last four are used to assess the physical component summary (PCS). The SF-12 has good internal consistency, with a Cronbach's coefficient of 0.78. It also has good criterion validity ($p < 0.001$). Higher SF-12 scores indicate a better quality of life (21).

The Geriatric Depression Scale (GDS-15) was used to assess participants' depressive symptoms. GDS-15 comprises 15 items. Participants complete the test by answering "yes" or "no". The GDS has a total score of 15, with higher scores indicating more depressive symptoms. The Chinese version of the GDS-15 has a retest reliability of 0.728 and a Cronbach's alpha of 0.793. In addition, the scale has good discriminant validity ($p < 0.001$) (22).

Statistical Analysis

Statistical analyses were performed using SPSS 24.0 (SPSS Inc., USA) and Mplus8.3 software. Descriptive statistics were used to analyze the basic characteristics of the participants. Skewness and kurtosis statistics were conducted to screen for the normal distribution of all continuous variables. The x^2 test and t-test were used to examine whether demographic and outcome variables were significantly different between the two study groups at baseline. Generalized estimating equation (GEE) models were performed to investigate changes in outcome variables for the two study groups at pre-and post-test (i.e., group*time interaction effects). The data analysis was based on the final number of participants completing the experiment. Effect size estimates were calculated for all mean differences using Cohen's d, which relates mean score differences to the combined standard deviation (23).

The maximum likelihood estimation (ML) and bias-corrected bootstrap methods were used to examine the mediating role of depressed mood and quality of life between participation in the square dance intervention and cognitive change. The number of replication samples was set to 1,000. As suggested by Shrout and Bolger (24), a mediating effect was considered significant at the 0.05 level if the 95% confidence interval (CI) (which did not include zero) indicated significant mediation. The mediational model was performed using MPlus 8.3 software (25).

RESULTS

Baseline Participant Characteristics

A total of 225 potential participants were screened for eligibility, of which 136 were enrolled in the study. **Figure 2** shows the Consolidated Criteria for Reporting Trials (CONSORT) flowchart, which outlines the participant flow and reasons for dropout throughout the study. By the end of the trial, 27 participants dropped out, resulting in a dropout rate of 19.9%. Ten participants dropped out of the experimental group, with two dropping out before the start, five dropping out before 9 weeks, and three dropping out before 18 weeks. Seventeen participants dropped out of the control group, of which 2 dropped out before the start, 6 dropped out before 9 weeks, and 9 dropped out before 18 weeks. Out of all participants who dropped out, 4 dropped due to disagreement with the subgroup protocol, 11 dropped out for physical reasons, and 12 for personal reasons. The mean age of the participants was 76.29 ± 3.60 and the mean years of education were 8.53 ± 2.06. There were no significant differences in participant demographic characteristics between the experimental and control groups at baseline (**Table 1**).

Experimental Outcome Comparisons

Table 2 lists the baseline, 9-week, and 18-week post-experimental MoCA, GDS, and QLS scores. The MoCA scores showed better improvement in the experimental group than the control group after the 9-week experiment compared to the baseline ($\beta = -0.574$; 95% CI $= -0.948$ to -0.200; $p = 0.003$). The effect size was estimated at a moderate level (Cohen's d $= 0.59$). The MoCA scores showed a significant improvement in the experimental group compared to the control group after the 18-week experiment vs. the baseline ($\beta = -0.501$; 95% CI $= -0.748$ to -0.254; $p < 0.001$). The effect size was estimated at a high level (Cohen's d $= 0.71$).

Participants in the experimental group showed a better improvement in depressed mood state scores after 9 weeks and at baseline compared to the control group ($\beta = 0.526$; 95% CI $=$ 0.170 to 0.881; $p = 0.004$). The effect size for the change in the overall GDS score was estimated to be moderate, with Cohen's d $= -0.56$. Participants in the experimental group were found to have significantly improved depressed mood state scores after 18 weeks and at baseline compared to the control group ($\beta = 0.416$; 95% CI $= 0.228$ to 0.604; $p < 0.001$). The effect size for the change in the overall GDS score was estimated to be large, with Cohen's d $= -0.88$.

Participants in the experimental group showed significant improvements in quality of life scores at baseline and after 9 weeks compared with controls ($\beta = -2.670$; 95% CI $= -4.160$ to -1.181; $p < 0.001$), with a moderate effect size estimate (Cohen's d $= 0.63$). Participants in the experimental group showed significant improvements in quality of life scores at baseline and after 9 weeks compared with controls ($\beta = -2.283$; 95% CI $= -3.188$ to -1.379; $p < 0.001$), with a large effect size estimate (Cohen's d $= 0.99$).

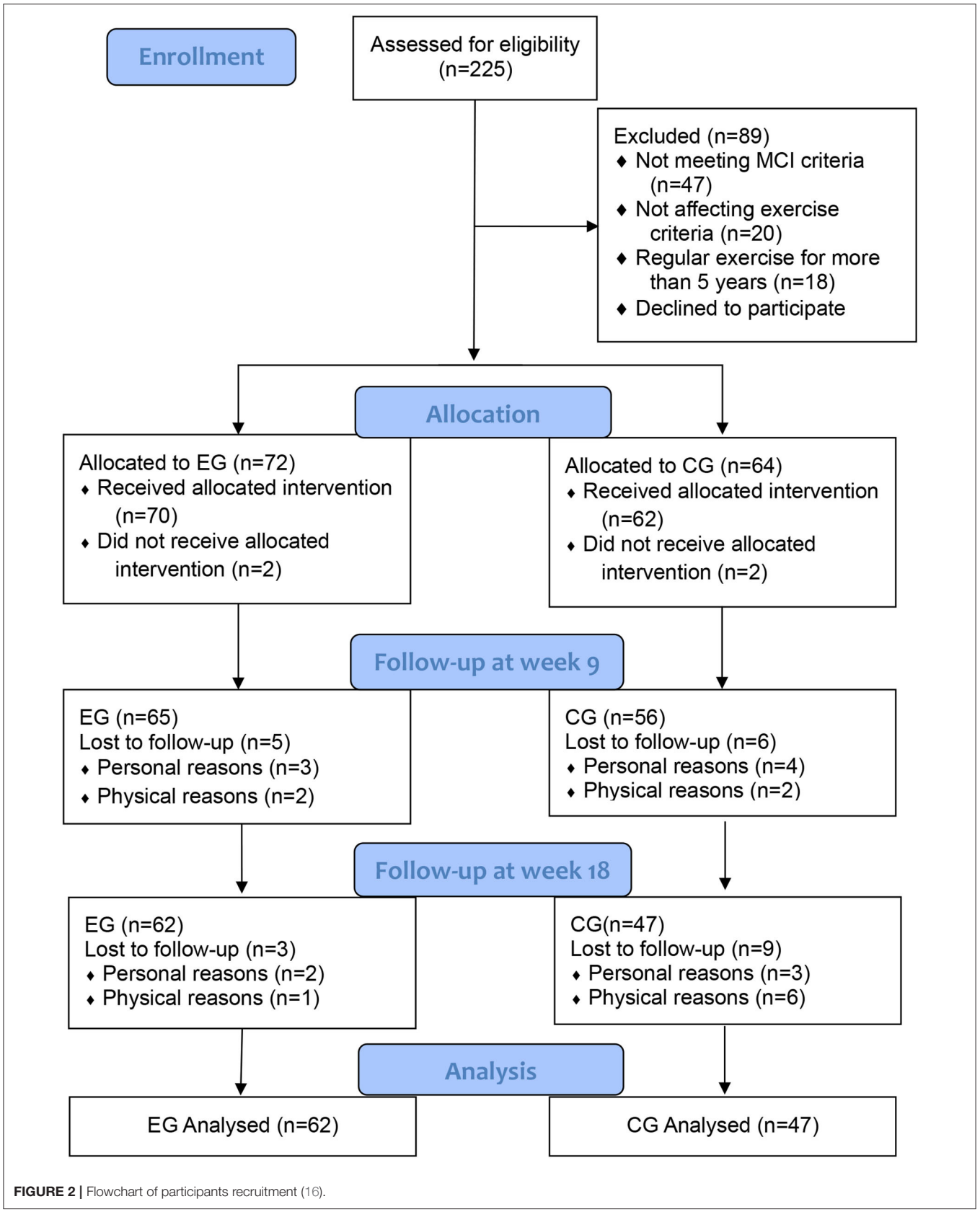

FIGURE 2 | Flowchart of participants recruitment (16).

TABLE 1 | Baseline characteristics of participants.

	Overall ($n = 109$)	EG ($n = 62$)	CG ($n = 47$)	p
Age, years	76.29 ± 3.60	76.56 ± 3.60	75.94 ± 3.61	0.369
Education, years	8.53 ± 2.06	8.73 ± 2.05	8.28 ± 2.06	0.261
BMI, kg/m^2	23.62 ± 2.08	23.63 ± 2.14	23.60 ± 2.03	0.956
MoCA	21.56 ± 2.23	21.61 ± 2.11	21.49 ± 2.39	0.776
GDS	4.92 ± 1.50	4.97 ± 1.41	4.85 ± 1.63	0.690
QLS	90.70 ± 6.74	91.24 ± 6.65	89.98 ± 6.85	0.334
PCS	43.00 ± 6.66	43.09 ± 6.49	42.87 ± 6.95	0.863
MCS	47.70 ± 5.38	48.15 ± 4.97	47.11 ± 5.89	0.320

Continuous variables are presented as the means ± standard deviations (SDs).
BMI, Body mass index; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; QLS, Quality of Life; PCS, Physical Component Summary; MCS, Mental Component Summary.

Results of the Mediating Analysis

The GEE results of the post-test after 9 weeks of the program indicated that the experimental group had significant improvements in depressed mood states ($\beta = 0.526$; 95% CI $= 0.170$ to 0.881) and quality of life ($\beta = -2.670$; 95% CI$=$ -4.160 to -1.181) compared to the control group. The two mediating variables showed differential changes, supporting the further exploration of the mediating effects. **Figure 3** describes the mediation model for the 9-week square dance exercise intervention. The indirect effect of square dance exercise on cognitive function via an improvement in depressed mood ($\beta = -0.294$; 95% CI $= -0.828$ to 0.046) and quality of life ($\beta = -0.073$; 95% CI $= -0.443$ to 0.134) was not significant.

The GEE results of the post-test after 18 weeks of the program indicated that the experimental group had significant improvements in depressed mood states ($\beta = 0.416$; 95% CI $= 0.228$ to 0.604) and quality of life ($\beta = -2.283$; 95% CI $= -3.188$ to -1.379) compared to the control group. The significant differences in the characteristics of the two mediating variables support further exploration of their mediating roles. **Figure 4** depicts the mediation model for the 18-week square dance exercise intervention. The square dance intervention had a significant indirect effect on cognitive function, achieved by an improvement in depressive symptoms ($\beta = -0.375$; 95% CI $= -0.864$ to -0.069) and quality of life ($\beta = -0.678$; 95% CI $= -1.222$ to -0.290).

DISCUSSION

The present study aimed to examine the effects of 18 weeks of moderate-intensity square dance exercise on cognitive function and quality of life in older women with mild cognitive impairment and to investigate the mediating role of a depressed mood and reduced quality of life in the relationship between square dance exercise and cognition. This study found that cognitive function deteriorated over time in the control group, while participants with regular participation in square dance exercise showed significant improvements in the same health parameters. This finding was consistent with the findings of Song et al. (14), which suggested that moderate-intensity aerobic exercise may serve the purpose of preventing disease deterioration in older adults with mild cognitive impairment. The mediation analysis further confirmed that the cognitive benefits of square dance exercise were demonstrated by its positive effects on two cognitive risk factors, which included depressed mood and poor quality of life.

The cognitive benefits of an 18-week period of square dance exercise are consistent with the results of previous studies in older adults with mild cognitive impairment. However, some previous studies have shown that at least 6 months of exercise is required to produce such beneficial effects (12, 26–28), while some studies have shown that 12 or 16 weeks can produce such beneficial effects (11, 14). The present study was conducted using two tests, at 9 and 18 weeks, to test whether both protocols achieved similar effects. The results of the study showed that both 9 and 18 weeks produced positive benefits, but the effect size change was greater for the 18-week intervention than the 9-week intervention. This difference can be explained in terms of the study design protocol. First, ACSM recommends an exercise program of 16 weeks or longer, with regularity. The 18-week, three-times-a-week regular exercise program utilized in this study is consistent with the ACSM guideline recommendations. Previous studies have noted that regular aerobic exercise (i.e., up to twice per week) results in cardiovascular and mood-related changes, which benefit cognitive function (27, 28). Second, the use of a sports watch to monitor participants' exercise heart rates meant that we were able to establish that square dancing provided a moderate level of aerobic exercise intensity. The exercise intensity was therefore controlled and may have been more conducive to achieving positive exercise outcomes. Exercise intensity monitoring has also only been utilized in another recent study (14), despite the fact that it has been rarely addressed in previous studies (27, 28). Third, the use of square dance exercises rather than regular fitness activities such as walking, which provide increased physical movement and musical rhythms, is an arrangement that may require participants to follow instructions successfully throughout the workout, thus inadvertently providing a form of attention and short-term memory training. Moderate results were achieved in terms of cognitive function in older women with mild cognitive impairment after 9 weeks of square dance exercise; however, even better results were achieved in terms of the cognitive function improvement after 18 weeks of exercise. The comparison of the mid-experimental and post-experimental results allows us to better explain the exercise intervention benefits that can be obtained through regular and consistent exercise.

The present study identified the benefits of square dance exercise in mitigating the effects of cognitive decline on quality of life in older adults with mild cognitive impairment. The use of two test design protocols for the current exercise program may explain the different findings compared to previous studies in which similar effects were produced following 12 weeks of square dance exercise (woof) or a 6-month moderate-intensity aerobic walking program (13, 16). Participants in the current study showed significant improvements in PCS. These improvements

TABLE 2 | Comparison of the experimental and control groups across time.

	EG ($n = 62$)	CG ($n = 47$)	Group effect		Time effect		Group*time effect		Effect size (d)
			β(95% CI)	p	β(95% CI)	p	β(95% CI)	p	
MoCA									
Baseline	21.61 ± 2.11	21.49 ± 2.39							
Week 9	22.08 ± 2.03	21.38 ± 2.29	0.451 (−0.584, 1.485)	0.393	1.042 (0.516, 1.568)	<0.001	−0.574 (−0.948, −0.200)	0.003	0.59
Week 18	22.34 ± 1.87	21.21 ± 2.13	0.378 (−0.618, 1.374)	0.457	0.864 (0.428, 1.300)	<0.001	−0.501 (−0.748, −0.254)	<0.001	0.71
GDS									
Baseline	4.97 ± 1.41	4.85 ± 1.63							
Week 9	4.55 ± 1.17	4.96 ± 1.38	−0.642 (−1.470, 0.185)	0.128	−0.945 (−1.468, −0.422)	<0.001	0.526 (0.170, 0.881)	0.004	−0.56
Week 18	4.31 ± 1.14	5.02 ± 1.67	−0.532 (−1.207, 0.142)	0.122	−0.746 (−0.996, −0.497)	<0.001	0.416 (0.228, 0.604)	<0.001	−0.88
QLS									
Baseline	91.24 ± 6.65	89.98 ± 6.85							
Week 9	93.40 ± 6.19	89.46 ± 6.37	1.406 (−2.023, 4.834)	0.422	4.824 (2.530, 7.118)	<0.001	−2.670 (−4.160, −1.181)	<0.001	0.63
Week 18	94.54 ± 5.63	88.71 ± 6.31	1.019 (−2.074, 4.112)	0.519	3.930 (2.470, 5.389)	<0.001	−2.283 (−3.188, −1.379)	<0.001	0.99
PCS									
Baseline	43.09 ± 6.49	42.87 ± 6.95							
Week 9	44.09 ± 6.07	42.88 ± 6.40	0.758 (−2.186, 3.702)	0.614	1.976 (0.735, 3.218)	0.002	−0.982 (−1.800, −0.164)	0.019	0.45
Week 18	44.69 ± 5.35	42.71 ± 6.50	0.654 (−2.205, 3.512)	0.654	1.678 (0.528, 2.828)	0.004	−0.878 (−1.482, −0.274)	0.004	0.43
MCS									
Baseline	48.15 ± 4.97	47.11 ± 5.89							
Week 9	49.31 ± 4.40	46.58 ± 5.34	0.648 (−2.410, 3.706)	0.678	2.847 (0.665, 5.030)	0.011	−1.688 (−3.147, −0.229)	0.023	0.44
Week 18	49.84 ± 4.86	45.99 ± 6.41	0.365 (−2.119, 2.849)	0.773	2.252 (0.910, 3.594)	0.001	−1.405 (−2.245, −0.566)	0.001	0.63

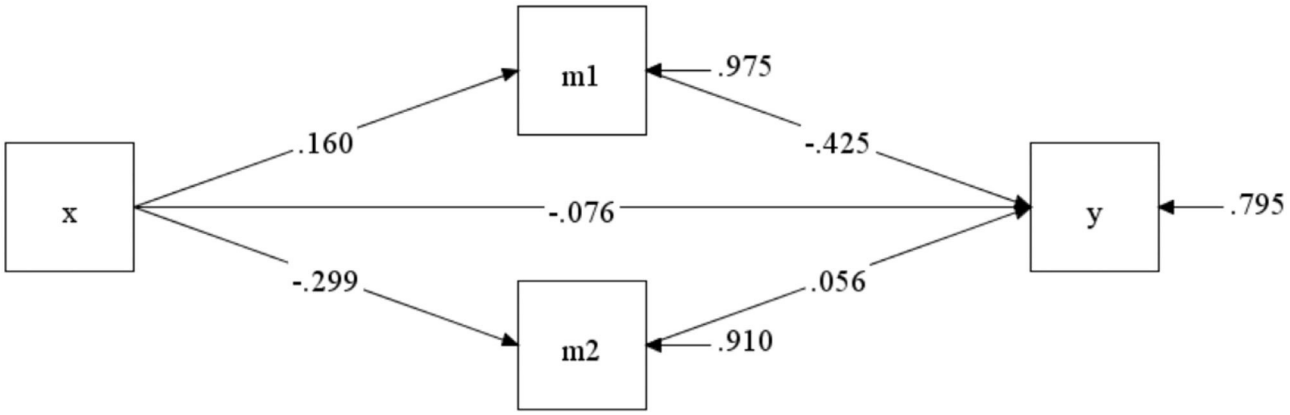

FIGURE 3 | The mediating model after 9-week intervention.

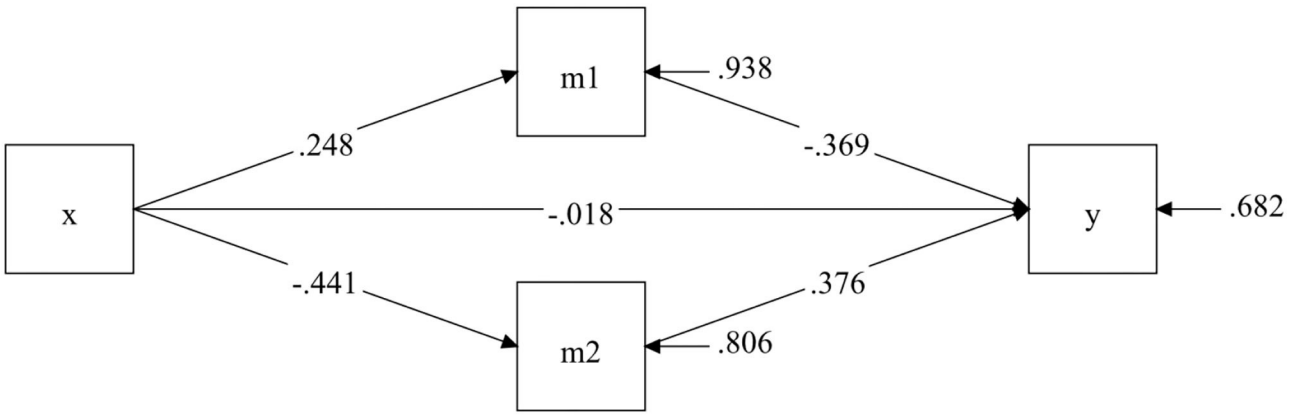

FIGURE 4 | The mediating model after 18-week intervention.

in cognitive function may have a positive impact on a person's perception of health. The present study further validates the previous literature, which suggests that cognitive decline in individuals with mild cognitive impairment disrupts their activity patterns, reduces their social engagement, and leads to clients feeling less empowered and having a poor self-concept (29, 30). The present study suggests that regular square dance exercises may help mitigate such harmful effects in patients.

This trial confirmed that the cognition-enhancing impact of square dance intervention was mediated by a reduction in depressed mood and improved quality of life. The findings illustrate the intervention effects of square dance exercise on cognitive function and propose potentially psychologically relevant mediating pathways to explain the relationship between exercise and cognition. These findings are of substantial value because depression and poor quality of life are highly prevalent in older individuals with mild cognitive impairment. In terms of depressive symptoms, the literature reports a 31.8% prevalence of depressive symptoms in the mild cognitive impairment group compared to 5.5% in cognitively healthy controls. (8). In terms of quality of life, a study by Chandler et al. reported a more significant effect of exercise (e.g., yoga) on memory-related quality of life compared to the support group (effect size = 0.43; 95% CI = 0.13 to 0.72) (31). The Nuzum et al. study also confirmed that this effect was strongly associated with quality of life ($r = -0.38$, $p < 0.01$) (32). As confirmed by large-scale longitudinal studies, both depressed mood and poor quality of life can disrupt the normal lives of older adults with mild cognitive impairment and may further contribute to their cognitive decline (33–35).

The mediating variables in the exercise–cognition relationship—depressed mood and quality of life—can be used to explain how exercise mitigates the adverse effects of these two factors on cognitive function from both functional and physiological perspectives. From a functional perspective, depressed mood and poor mental health due to a reduced quality of life are essentially the same. Both conditions are characterized by physical and mental exhaustion and low motivation. These problems can make it difficult for older adults with mild cognitive impairment to concentrate and

can cause their cognitive performance to suffer (36). At the same time, improving depressed mood and quality of life through exercise will reduce their dysfunctional effects on cognitive function. From a physiological perspective, depressive symptoms and poor mental health-related quality of life are associated with neurophysiological changes. Depression down regulates neurotrophic factor expression in the brain environment, leading to neuronal atrophy and hippocampal atrophy (37). Therefore, depressive symptoms can be alleviated by regular moderate-intensity aerobic exercise, which can restore neurotrophic factor expression and promote hippocampal neurogenesis (38). Thus, square dance exercise can create favorable functional and physiological conditions and improve cognitive performance in older women with a mild cognitive impairment through its positive effects on depressed mood and quality of life.

LIMITATIONS

This study has several limitations. Firstly, the sample population was selected from older women only. There was no male sample, so it is not representative of the characteristics of the entire group of patients who experience mild cognitive impairment. Secondly, the randomized sample was underrepresented due to the fact that nursing homes were used as the group unit, limiting the generalization of the overall results. Thirdly, 19.9% of the participants dropped out of the study, which may undermine the explanatory power of the findings. Fourthly, there was no evidence to suggest that changes in scoring outcomes implied significant differences in clinical treatment; therefore, the results have limited explanatory power in terms of their clinical significance. Lastly, the square dance exercise intervention program in this study was implemented for only 18 weeks. Therefore, we are unable to provide any conclusions regarding the effectiveness of the intervention over a more extended period. Future research will explore the above-described gaps in more detail.

CONCLUSION

This study of 18 weeks of moderate-intensity square dance exercise showed that its effect on improving cognitive function and health-related quality of life in older women with mild cognitive impairment was significant. The mediation model indicated that reducing depressive symptoms and improving quality of life are potential possible mechanisms affecting the square dance exercise and cognition relationship. The evidence of the effectiveness and feasibility of square dance exercise interventions also promotes the need to increase their application in order to prevent further cognitive decline in older adults with mild cognitive impairment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific and Ethics Committee of Institute of Motor Quotient, Southwest University (IRB NO. SWUIMQ20180109). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC, WZ, LY, and MY: data collection. JC, JZ, LY, and JY: data analysis, conception, and design. JC, WZ, JW, and JY: research design and writing the manuscript and revision. All authors contributed to the article and approved the submitted version.

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Stigma and Associated Correlates of Elderly Patients With Parkinson's Disease

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Background: Stigmatizing experiences is common in Parkinson's disease (PD) and appears to provide a negative contribution to the quality of life. Our aim of this study was to investigate the extent of stigma and its predictive factors in patients with PD from our hospital in Shanghai, China.

Methods: In 276 individuals with PD (135 women and 141 men), stigma was measured by the 24-item Stigma Scale for Chronic Illness (SSCI). Multivariate linear regression model was used to assess predictors of stigma including demographics (age and gender), disease duration, stage (Hoehn and Yahr Scale), motor function (Unified Parkinson's Disease Rating Scale Part 3, UPDRS-III), non-motor symptoms (Non-Motor Symptoms Scale, NMSS), cognitive level (Mini-Mental State Examination, MMSE), as well as anxiety (Hamilton Anxiety Rating Scale, HAM-A) and depressive disorders (Hamilton Depression Rating Scale, HAM-D-24).

Results: The total score of SSCI was 49.9 ± 14.3, and 48.5% of the patients checked "rarely" to "sometimes." For the total sample, the full model accounted for 47.8% of the variance in stigma ($P < 0.05$). Higher UPDRS-III scores, longer course of disease, younger age, tremor-dominant subtype, and higher depression scores were significantly associated with stigma among individuals with PD.

Conclusion: Our finding suggested a mild-to-moderate level of stigma in patients with PD. Tremor-dominant subtype, longer course of disease, younger age, severe motor symptoms, and depression are the predictors of stigma in PD.

Keywords: Parkinson's disease, stigma, SSCI, depression, predictor

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting ∼1% of the population over 60 years of age (1). Although PD is traditionally considered to be a motor disorder, the burden of the disease extends far beyond physical impairments. An important issue is the stigma experienced by the individuals with PD (2, 3).

In 1963, Erving Goffman defined stigma as "the situation of the individual who is disqualified from full social acceptance (Preface)," and since then, social scientists have studied the stigma manifested as stereotypes, prejudice, and discrimination (4). The social identity of the stigmatized person may be deeply threatened and damaged (5). The stigma of neuropsychiatric diseases can lead to a variety of adverse consequences, including delays in seeking medical help, diagnosis, and treatment; a low quality of life; failure to adhere to treatment; and increased suicide rates (6–9).

With regard to PD, previous evidence has shown that more than half of the patients with PD are likely to try to conceal their diagnosis (10). Furthermore, there is a high prevalence of stigma in PD patients who attempted to mask their clinical symptoms (11).

There are many reasons and associated factors for the stigma in patients with PD. Stigma may result from motor symptoms such as facial masking, which can increase negative experience in social relationship, even among those trained healthcare providers (12). Meanwhile, invisible stigma is the realization of a self with PD, a form of disability, which attested to the mounting isolation (11). Recently, a few studies revealed that difficulties in activities of daily living, younger age, and higher depression scores were the significant predictors of stigma (13, 14). However, relative studies are limited in China.

Considering the differences between Chinese and Western cultures, the stigma of patients with PD may vary according to different demographic and disease characteristics. The aim of this study was to investigate the extent of stigma and its associated factors in Chinese patients with PD on their early to middle stages of the disease.

MATERIALS AND METHODS

Subjects

The protocol for this study was reviewed and approved by the ethics committee of the First Affiliated Hospital of Naval Medical University. Informed consent was obtained from all participants prior to participation in this study. Patients were recruited from the First Affiliated Hospital of Naval Medical University. Inclusion criteria were as follows: (1) the diagnosis of idiopathic Parkinson's disease according to the UK Brain Bank Criteria; (2) age ≥50 years old; and (3) a modified Hoehn and Yahr stage less than or equal to 4. The exclusion criteria included a diagnosis of other serious physical defects, cognitive impairment, or unable to complete the investigation. A total of 276 patients with idiopathic Parkinson's disease treated in our hospital were enrolled.

Procedures and Measures

Patients were interviewed face to face by neurologists. The Unified Parkinson's Disease Rating Scale (UPDRS III) was applied to assess PD motor symptoms. The disease stage was evaluated by using the Hoehn and Yahr Scale. Motor symptom subtype was calculated by the ratio of mean tremor to mean postural instability and gait difficulty (PIGD) symptoms. For the original UPDRS, a ratio ≥1.5 was classified as tremor dominant (TD), a ratio ≤1.0 was classified as PIGD, and a ratio between 1.0 and 1.5 was classified as indeterminate (IND) (15, 16).

Anxiety and depression symptoms were assessed by using the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D-24), respectively. The cognitive level was evaluated by the Mini-Mental State Examination (MMSE). The severity of non-motor symptoms was assessed by the Non-Motor Symptoms Scale (NMSS).

The 24-item Stigma Scale for Chronic Illness (SSCI) was developed to measure stigma experienced by individuals with chronic neurological disorders including PD. It contains two subscales: felt stigma and enacted stigma (17). The felt stigma subscale (13 items) asks questions about the respondent's feelings (e.g., embarrassment, worry, and self-blame). The enacted stigma subscale (11 items) asks questions about the behavior of others toward the respondent (e.g., avoiding contact, staring, and being unkind). Each item is rated as 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always. A higher score indicates a higher frequency of experiencing stigma. A systematic review suggests that the SSCI has good content validity and enough internal consistency (18). All the assessors were trained before the start of the study. Inter-rater concordance of all assessments was more than 0.8.

Statistical Analysis

The Kolmogorov–Smirnov test was applied to detect the distribution normality of variables. Residual plot was applied for equivalence of variance. Continuous variables were represented as mean and standard deviation. Categorical variables were described as absolute numbers, median, and frequencies. Pearson and Spearman correlations were conducted for continuous variable and categorical ones, respectively, to investigate the association of demographic and clinical characteristics with SSCI score.

Significant correlates were entered as predictors in multivariate linear regression model with SSCI as the dependent variable. The α level of significance was set to $p < 0.05$ (two-tailed). All analyses were performed by IBM SPSS statistics 20 for Windows.

RESULTS

As shown in **Table 1**, the patients recruited in this study had an average age of 62.5 years ($SD = 8.5$) and disease duration of 9.9 years ($SD = 4.9$). Median-modified Hoehn and Yahr (H&Y) stage was 3 (range 1–4). The average motor severity as measured by the UPDRS III was 23.9 ($SD = 11.2$). Motor symptom subtypes consisted of 92 with TD profile (33.3%), 121 characterized by PIGD (43.8%), and 63 IND (22.8%), all as per time of assessment.

TABLE 1 | General characteristics of PD patients.

Variables	Mean ± SD
Gender *n* (%)	
Female	135 (48.7)
Male	141 (50.9)
Age	62.5 ± 8.5
Education (years)	10.8 ± 4.1
Disease duration (years)	9.9 ± 4.9
UPDRS-III	23.9 ± 11.3
Motor symptom subtype, *n* (%)	
TD	92 (33.3)
PIGD	121 (43.8)
IND	63 (22.8)
MMSE	26.7 ± 3.1
NMSS	17.6 ± 5.3
HAM-D-24	16.7 ± 6.4
HAM-A	14.7 ± 3.8
H-Y, *n* (%)	
I	15 (5.4)
II	78 (28.2)
III	140 (50.6)
VI	43 (15.5)
Levodopa equivalent dose (mg/day)	868.6 ± 485.0
SSCI	2.1 ± 1.1
Below rarely (*n*, %)	142, 51.4%
Rarely to below sometimes (*n*, %)	119, 43.1%
Sometimes to below often (*n*, %)	15, 5.4%
Felt stigma	2.3 ± 1.0
Below rarely (*n*, %)	114, 41.3%
Rarely to below sometimes (*n*, %)	125, 45.3%
Sometimes to below often (*n*, %)	34, 12.3%
Often to below always (*n*, %)	5, 1.8%
Enacted stigma	1.9 ± 1.0
Below rarely (*n*, %)	188, 68.1%
Rarely to below sometimes (*n*, %)	58, 21.0%
Sometimes to below often (*n*, %)	29, 10.5%

SCCI, Stigma Scale for Chronic Illness; H-HY; Hoehn and Yahr Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale Part 3; NMSS, Non-Motor Symptoms Scale; MMSE, Mini-Mental State Examination; HAM-A, Hamilton Anxiety Rating Scale; HAM-D-24, Hamilton Depression Rating Scale; PIGD, postural instability and gait difficulty; TD, tremor dominant; IND, indeterminate.

Each participant had a MMSE score more than 24. Up to 80 patients (28.9%) had HAM-D-24 score above 20, suggesting mild to moderate depression. The mean SSCI score was 49.9 (SD = 14.3, range: 24–96). The scores of felt stigma and enacted stigma were 29.4 (SD = 9.5) and 20.6 (SD = 9.7), respectively. For the whole group, the significant correlates of SSCI were age, disease duration, MMSE, NMSS, HAM-D-24, HAM-A, UPDRS III, TD, and PIGD ($P < 0.05$).

Multivariate linear regression model (**Table 2**) showed that SSCI score was significantly associated with UPDRS III, TD, HAM-D-24, disease duration, and age. The full model accounted for 47.8% of the variance in SSCI score ($P < 0.05$). We conducted multicollinearity analysis in the regression model to ensure that the contribution of each aspect was independent. The variance inflation factor was below 2 and the condition index was lower than 30. Felt stigma was significantly associated with UPDRS III, HAM-D-24, and disease duration. This model accounted for 67.3% of the variance. For enacted stigma, the significant correlates were UPDRS III, TD, and age, which together accounted for 23.2% of the variance.

Multivariate linear regression model was also conducted for felt and enacted SSCI according to gender (**Table 3**). Felt stigma was associated in female with higher UPDRS III and HAM-D-24 and in male with higher UPDRS III, longer disease duration, and HAM-D-24. For enacted stigma, the significant correlates in female were higher UPDRS III and younger age, while in male, it included TD and UPDRS III.

DISCUSSION

The main findings of our study were that stigma was at a mild-to-moderate level in patients with PD. Tremor-dominant subtype, longer course of disease, younger age, severe motor symptoms, and depression were the significant correlates of stigma in PD. In addition, female and male PD patients had their own factors. These results suggested that we neurologists could better help elderly PD patients cope with stigma by means of improving their motor symptoms, relieving tremor symptoms, and at the same time paying attention to emotional disorders.

Our study found that the UPDRS III was significantly associated with the score of SSCI. The obvious motor symptoms of Parkinson's disease patients, such as static tremor, bradykinesia, and abnormal posture and gait, could come to light in public places. These changes in body image would lead to patients' sense of shame, embarrassment, and isolation (19, 20). One study suggested that the stigma of Parkinson's disease patients was related to the change of their external image and the gradual loss of their functions (20). At the same time, the language communication barrier and the non-verbal communication barrier caused by "facial masking" also inevitably led to the isolation of the patients (11). Patients may be mistaken for concealing their illness and unwilling to communicate with others, which aggravated the sense of isolation (21). Motor symptoms can directly lead to social isolation and self-discrimination, so motor symptoms can be the main source of stigma in patients with Parkinson's disease.

By separating overall SSCI into felt and enacted stigma, we found that felt stigma, compared to enacted stigma, was experienced to a stronger degree (**Table 1**). Moreover, depression was strongly related to the score of felt SSCI. This finding was in accord with the work by Salazar et al. who recognized that depression was a significant predictor in stigma and depression mediated the relation between stigma and activities of daily living (13). A British study shows that 46% of PD patients stopped working after 5 years of illness, and more than half of them chose to retire early, resulting in economic burden and psychological pressure of patients (22). The change of social role and social interaction exerted a negative impact on the family's quality of life

TABLE 2 | Multivariate linear regression model of factors associated with SSCI.

Variables	*R*	Adjusted R^2	*F*	Coefficient β (95% CI)	*P*-value
SSCI	0.699	0.478	46.04		
UPDRS-III				0.79 (0.66∼0.91)	<0.001
TD				6.61 (3.76∼9.46)	<0.001
HAM-D-24				0.49 (0.24∼0.74)	<0.001
Disease duration				0.42 (0.003∼1.41)	0.003
Age				−0.17 (0.04∼-0.33)	0.043
Felt stigma	0.674	0.447	67.31		
UPDRS-III				0.47 (0.40∼0.55)	<0.001
HAM-D-24				0.39 (0.24∼0.55)	0.001
Disease duration				0.31 (0.13∼0.49)	0.004
Enacted stigma	0.526	0.277	23.18		
UPDRS-III				0.34 (0.25∼0.43)	0.001
TD				5.02 (3.03∼7.01)	0.003
Age				−0.18 (−0.29∼-0.06)	0.035

SCCI, Stigma Scale for Chronic Illness; UPDRS-III, Unified Parkinson's Disease Rating Scale Part 3; HAM-D-24, Hamilton Depression Rating Scale; TD, tremor dominant.

TABLE 3 | Multivariate linear regression model of factors associated with felt and enacted SSCI according to gender.

Variables	*R*	Adjusted R^2	*F*	Coefficient β (95% CI)	*P*-value
Felt stigma					
In female	0.565	0.308	28.77		
UPDRS-III				0.47 (0.33∼0.61)	<0.001
HAM-D-24				0.28 (0.04∼0.53)	0.026
In male	0.780	0.598	60.43		
UPDRS-III				0.48 (0.39∼0.57)	<0.001
Disease duration				0.63 (0.39∼0.87)	<0.001
HAM-D-24				0.55 (0.35∼0.74)	<0.001
Enacted stigma					
In female	0.345	0.105	8.34		
UPDRS-III				0.29 (0.13∼0.45)	<0.001
Age				−0.26 (−0.46∼-0.07)	0.009
In male	0.704	0.487	57.88		
TD				9.12 (6.68∼11.56)	<0.001
UPDRS-III				0.31 (0.22∼0.40)	<0.001

UPDRS-III, Unified Parkinson's Disease Rating Scale Part 3; HAM-D-24, Hamilton Depression Rating Scale; TD, tremor dominant.

and psychology. As stigma is inseparable from the socio-cultural environment, it is important to recognize the social meaning of PD and PD-related symptoms. The association between depression and stigma perception has important implications for conceptualizing stigma in PD and its potential treatment targets.

Inconsistent with other foreign studies, TD subtype, relative to PIGD or IND, was more likely to have higher enacted SSCI score. Hermanns suggested that facial masking was commonly reported by all the PD participants. This can result in isolation of the stigmatized person (11). However, socio-cultural norms about facial expressivity vary according to culture; a study conducted by Tickle-Degnen et al. found that American practitioners' judgments of patient sociability were more negatively biased in response to facial masking than those of Taiwanese practitioners (12). Unfortunately, our study did not separately list "facial mask" as a predictive factor. While communicating with the participants, we were aware of the frequent mention of "tremor," especially in male patients, who still demanded to increase the dosage of drugs when their clinical symptoms have been well-controlled. This kind of care about "other people's attitude" has led to self-cognition bias. Caap-Ahlgren and Lannerheim found that female PD patients felt particularly conspicuous because of involuntary movement of their limbs in social intercourse, and they were mistaken for drunkenness. This misunderstanding further strengthens the public's belittling and discriminatory attitude (23).

Younger age was related to increased perception of stigma in PD. The experience of diagnosis of a neurodegenerative

disease relatively early in life may be qualitatively different than diagnosis in later life, having a greater impact on self-perception and self-expectations in family, social, and occupational roles (24, 25). Meanwhile, the unpredictability and inability to prevent or slow down the progression of Parkinson's disease may bring uncertainty and psychological pressure to patients (26). With the prolongation of the course of disease, the patients were forced to give up their daily work and social life, aggravating social isolation.

There were some limitations in this study. First, this study is not sufficient to infer the causal relationships between independent variables and outcomes. Secondly, this study lacked the assessment of life ability such as PDQ-39 or ADL, which is widely used in other studies. Also, the social status such as household income, marital status, occupation, or type of the medical insurance were not documented. These may also be the influencing factors in stigma. The last but not the least, the sample was only limited to one hospital and did not consist of severely affected patients; therefore, the promotion of the results has certain limitations.

CONCLUSION

This study investigated the stigma in PD patients of different motor subtypes and different stages in our hospital. The results showed that the stigma in PD patients was in the mild-to-moderate level, and the correlated factors were complex, mainly related to the disease progression and emotional disorders. Future research would increase the number of patients from different hospitals and different regions to explore more predictors so that adaptive interventions could be formulated to effectively reduce the stigma and improve the quality of life of PD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics committee of the First Affiliated Hospital of Naval Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KL designed the research. XM and XH examined the patients and collected the data. MH performed the statistical analysis and drafted the manuscript. All authors made contributions to this study, critically reviewed the content, and approved the final version of this article.

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SUPPLEMENTARY MATERIAL

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Evidence of Effect of Aerobic Exercise on Cognitive Intervention in Older Adults With Mild Cognitive Impairment

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This study aimed to evaluate the effectiveness of aerobic exercise as a cognitive intervention for older adults with mild cognitive impairment (MCI). The PubMed, EMBASE (Ovid), Cochrane Library, Web of Science, and Medline databases were searched from their inception until 30 April 2021. Randomized controlled trials (RCTs) examining the effects of aerobic exercise on global cognitive function in older adults with MCI were included. Ten eligible trials with acceptable methodological quality were identified. The meta-analysis results showed that aerobic exercise significantly improved the MMSE ($N = 956$, $MD = 0.60$, 95% CI: 0.28–0.92, $p = 0.0003$, $I^2 = 31\%$, fixed effects model) and MoCA scores ($N = 398$, $MD = 1.67$, 95% CI. 1.18–2.15, $p < 0.0001$, $I^2 = 37\%$, fixed-effects model) and overall cognitive performance in patients with MCI. The results of this study suggest that participation in regular aerobic exercise can improve cognitive function in older adults with MCI. These findings should be used with caution considering the limitations of the study.

Keywords: aerobic exercise, mild cognitive impairment, RCTs, systematic review, meta-analysis

INTRODUCTION

Mild cognitive impairment (MCI) is a typical transitional stage between the normal aging process and the onset of dementia. Mild cognitive impairment includes a group of cognitive impairment conditions presenting in the early stages of dementia (1). According to recent studies involving people over 60 years of age, the prevalence of MCI is about 15% (2, 3), while another cohort study in Beijing, China showed that a prevalence of MCI in older adults of 16.6% (4). In addition, domestic studies have reported conversion rates from MCI to dementia and Alzheimer's disease (AD) of 34 and 28%, respectively (2, 3). There is no positive evidence to support the use of pharmacological interventions to attenuate cognitive decline in MCI patients (5–8). Instead, risk reduction factors (9) and participation in physical activity are widely considered to be effective non-pharmacological interventions. Although studies have investigated the effects of non-pharmacological interventions including diet (10), social relationships (7, 11), and cognitive training (12–14), the advantages of exercise/physical activity are unknown.

A growing number of studies are suggesting that physical activity/exercise may improve cognitive function. However, a meta-analysis of 14 randomized controlled trials (RCTs) reported

that there is no significant evidence that physical activity/exercise improves cognitive function in patients with MCI (15). However, in an intervention involving individuals with MCI, the Hamer prospective study review demonstrated an inverse relationship between physical activity/exercise and the risk of cognitive decline in healthy older adults (14). This evidence is also supported by the results of cross-sectional studies, longitudinal observational studies, and prospective intervention trials (16–21).

Several studies have investigated with beneficial effects of aerobic exercise in older adults with MCI in order to better understand the effects of exercise and how these change depending on the type of exercise performed (8, 15, 16). Although 11 previous aerobic exercise meta-analysis studies found favorable effects on overall cognitive performance and memory in older adults, the effects of beneficial effects on older adults with MCI varied widely depending on the type, frequency, and duration of aerobic exercise performed. Furthermore, it has been suggested that due to differences in measurement instruments used, results regarding the effects of aerobic exercise on cognitive interventions in older adults with MCI have not been uniform (15). Therefore, the purpose of this systematic evaluation and meta-analysis was to investigate the effects of exercise interventions on older adults with MCI based on the measurement tools used and the type of exercise performed and to evaluate the exercise intervention modality recommended in a RCT.

METHODS

Search Strategy

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (22). We searched for relevant studies written in English in PubMed, EMBASE (Ovid), Cochrane Library, Web of Science, Medline, and other databases for aerobics-related subject terms (e.g., aerobic exercise, aerobic dance, Qigong, Tai Chi, Yoga, physical activity) and cognitive impairment-related subject headings (e.g., MCI, memory loss, cognitive impairment). All search terms were grouped together as much as possible to find all relevant studies. In addition, previously cited studies were manually added if they met the inclusion criteria. **Supplementary Materials** used for the search strategy of the articles were available online (See **Appendix 1**. The literature was searched from its inception to April 30, 2021).

Inclusion and Exclusion Criteria

The following inclusion criteria had to be met for exercise intervention trials to be included in this review: (1) Study design: RCTs, including those published by peer review or peer-reviewed journals in print; (2) Participants: older adults (60 years and older) with MCI that met the existing diagnostic criteria. Those with cognitive impairment or other neurological impairments due to AD or dementia were excluded from the study; (3) Intervention: the experimental group performed different types of aerobic exercise (e.g., yoga, tai chi, running, walking, dancing, etc.) for at least 8 weeks and exercised at least once per week; (4) Control: the control group did not perform specific exercise interventions, i.e., the control group only maintained their usual physical activity or performed sham exercises (e.g., stretching and balancing, exercise education, etc.); (5) Outcome: the subjects' overall cognitive abilities or specific cognitive domain abilities such as memory, attention, etc. were measured by any of the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) measurement instruments. Studies without available data were excluded.

Assessing the Risk of Bias

The Cochrane Risk of Bias tool was used to assess the risk of bias in the included trials (23). In addition, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias were assessed, and each study was categorized as high, low, or unclear based on the degree of bias present. This work was done independently by two evaluators (LY and GY). Disagreements between the two reviewers were resolved through discussion with the two corresponding authors (JW and JC).

Statistical Analysis

RevMan version 5.4.1 software (Cochrane) was used for this meta-analysis of the study. The mean difference (MD) or standardized difference (SMD) statistic was used to calculate the combined effect size, and the corresponding 95% CI was used to summarize the data. If the fit heterogeneity of the selected study data was small ($I^2 \leq 50\%$, $p > 0.05$), the analysis model was deemed to be a fixed-effects model. If the data heterogeneity of the selected studies was high ($I^2 > 50\%$, $p < 0.05$), the analytical model was deemed to be a random-effects model. However, when the level of heterogeneity between studies was high ($I^2 > 75\%$), the overall combined analysis was considered inappropriate due to reasons of heterogeneity, including the characteristics of the measurement instruments. Statistical heterogeneity in the included studies was assessed using the χ^2-test and I^2-values, with $I^2 > 75\%$ indicating a high degree of statistical heterogeneity (24).

RESULTS

Study Identification

Following a predetermined search strategy, 5,541 records were initially identified from four major electronic databases. Two reviewers (LY and GY) removed 5,487 irrelevant studies based on their abstracts and titles, leaving a total of 54 potential studies to be further assessed for eligibility. Following assessment, 10 studies were included in a systematic review and meta-analysis involving 1,364 MCI participants. **Figure 1** shows the detailed process used to screen eligible studies.

Characteristics of the Included Studies

Table 1 presents the characteristics of each included study. A total of 10 RCTs involving 1,364 MCI participants (454 men and 910 women, mean age 73.0 ± 6.72 years) were included in the analysis. All studies were published between 2012 and 2021. The study countries and regions included China (26, 31, 34) ($n = 3$), Hong Kong (28, 29) ($n = 2$), Japan (32) ($n = 1$), Pakistan

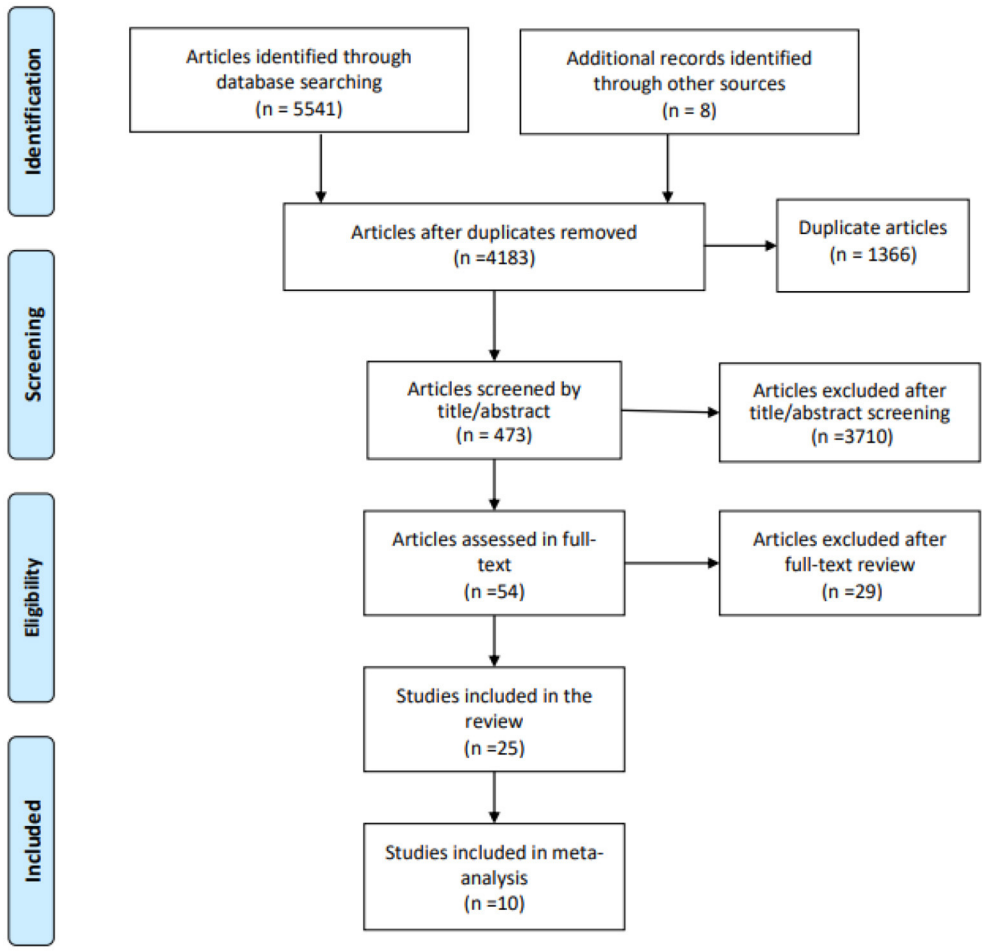

FIGURE 1 | Flowchart of the selected literature.

(25) ($n = 1$), Greece (30) ($n = 1$), Denmark (27) ($n = 1$), and Spain (33) ($n = 1$). All studies were conducted in Asian and European countries, and most of the studies were conducted in developed countries or regions. The majority of the study participants were recruited from the community or from nursing homes. All included studies clearly reported the criteria used for participant enrollment.

The aerobic exercise modalities included in the studies were diverse. There were three dance-based studies (26, 30, 32), two mixed-modality studies (Tai Chi, treadmill, stationary bike, or other) (25, 29), one walking studies (27), one Tai Chi study (28), one aerobic stepping study (31), one cycling study (33), and one handball training study (34). The duration of aerobic exercise interventions was mostly 2–3 times per week for 20–60 min, except for the studies conducted by Lam et al. (28) and Wei et al. (34), which used one and five times, respectively. The intervention duration ranged from 4 months to 1 year, except for one study that used 6 weeks (25). Three of the ten studies compared aerobic exercise with no intervention (i.e., regular physical activity) (26, 27, 30), three studies compared it with stretching activities (25, 28, 29), two studies compared it with educational activities (31, 32), and two studies compared it with recreational activities (33, 34). Even though these studies compared aerobic exercise with stretching activities, educational activities, or recreational activities, these activities were not different from regular physical activity due to their lower level of intensity. They did not change participants' exercise behavior. In the four included studies, during exercise, heart rate was controlled at 40–60% (33, 34) or 60–80% of the participants' maximum (25) or between 100 and 140 (26) to ensure an aerobic level of intensity was maintained. Other heart rates were described as moderate intensity. Two different cognitive assessment tools, MMSE and MoCA, were used to assess the same cognitive domain within or among studies.

Bias Risk of the Included Studies

Figure 2 summarizes the risk of bias for the included studies. All included trials used the random assignment method, with seven of them using the method of random number generation of random sequences. However, there were three studies with unclear random assignment methods. The subject selection bias was unclear in five studies, and it was high risk in one study. Only

TABLE 1 | Characteristics of included trials in this review.

Author, year (Ref.)	N(m/f)	Age	Exercise program	Design	Cognitive test	Cognitive domain	Exercise stimulus	Control condition
Amjad, 2019 (25) (Pakistan)	40(21/19)	CG: 59.56 ± 2.65 EG: 58.23 ± 2.31	EG: treadmill, stationary bicycle, (aerobic exercise) CG: stretch	RCT	MoCA	Global cognitive function	6 weeks, 3 d/wk, 20–40 min/d, 60–80% of maximum heart rate	Stretch
Chang, 2021 (26) (China)	109(0/109)	CG: 75.94 ± 3.61 EG: 75.56 ± 3.60	EG: square dance CG: daily lifestyle	Cluster-RCT	MoCA	Global cognitive function	18 weeks, 3 d/wk, 30 min/d, heart rate 100–140 beats/min	Daily lifestyle
Hoffmann, 2015 (27) (Danmark)	200(113/87)	CG: 71.3 ± 7.3 EG: 69.8 ±7.4	EG: walking CG: received treatment as usual	RCT	MMSE	Global cognitive function Immediate/ Delayed recall	16 weeks, 3 d/wk, 60 min/d	Received treatment as usual
Lam, 2012 (28) (Hong Kong, China)	261(92/169)	CG:78.3±6.6 EG:77.2±6.3	EG: Tai Chi CG: stretching and toning exercise	RCT	MMSE	Global cognitive function Delayed recall, attention, executive function, verbal fluency	1 year, 3 d/wk, 30 min/d, moderate intensity	Stretching and toning exercise
Lam, 2015 (29) (Hong Kong, China)	263(54/206)	CG:75.4±6.1 EG:76.3±6.6	EG: Tai Chi, static bicycle riding and other physical activity CG: social activity	RCT	MMSE	Global cognitive function Delayed recall Verbal fluency	1 year, 1 d/wk, 60 min/d, moderate intensity	Stretching and toning exercise
Lazarou, 2017 (30) (Greece)	129(28/101)	CG:67.92±9.47 EG:65.89±10.76	EG: Dance CG: usual physical activity	RCT	MoCA	Global cognitive function	10 months, 2/wk, 60 min/d	No intervention
Song, 2019 (31) (China)	120(30/90)	CG: 75.33±6.78 EG: 76.22±5.76	EG: aerobic stepping exercise CG: education program	RCT	MoCA	Global cognitive function	16 weeks, 3 d/wk, 60 min exercise/d	8 biweekly 45 min education programs
Doi, 2017 (32) (Japan)	134(52/82)	CG:76±4.9 EG:75.7±4.1	EG: Dance CG: usual physical activity	RCT	MMSE	Global cognitive function	40 weeks, 60 min/wk	40-week 3 health education classes (90 min/class)
Varela, 2012 (33) (Spain)	48(21/27)	EG: 77.88±10.71 CG: 79.40±6.72	EG: cycling CG: recreational activity	RCT	MMSE	Global cognitive function	3 months, 3 d/wk, 30 min/d, 40–60% maximum heart rate	Recreational activities (playing cards, reading newspaper)
Wei, 2014 (34) (China)	60(40/20)	CG:65.27±4.63 EG:66.73±5.48	EG: handball training CG: entertainment	RCT	MMSE	Global cognitive function	6 months, 5 d/wk,30 min/d, 60%Hrmax	Traditional life entertainment (playing cards, etc.)

one study reported the use of specific allocation concealment through envelope preservation (31). The subject selection bias of five studies was unclear, and for one study, it was high risk. In all included studies, the risk of potential performance bias was high because it was difficult to blind participants to the exercise intervention. Only one cluster-randomized trial was consistent with this potentially performance-biased blinded design (26). All included studies blinded the outcome assessors; therefore, their risk of detection bias was judged as low. The risk of completeness bias for two studies was unclear based on the completeness of the study data or the number of studies describing missing data. The risk of selective reporting bias was judged to be low in five studies

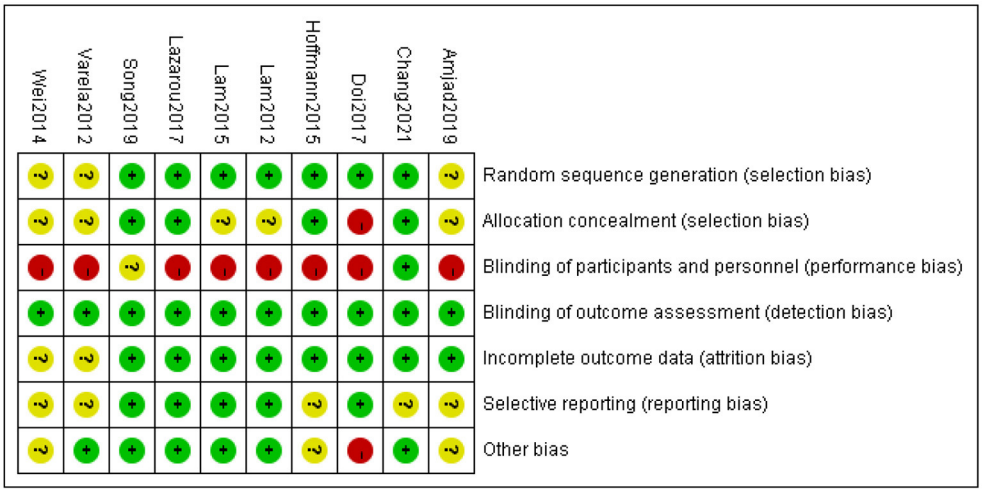

FIGURE 2 | Risk of bias summary of inclusion studies.

after examining the available protocols. The risk of other types of bias was high for one study and unclear for three studies due to their limited sample sizes and unclear comparison with baseline characteristics.

Effect of Intervention

The effect of aerobic exercise on the overall cognitive performance of MCI patients was tested by assessing cognitive function using the MMSE in six of the ten global impact studies and the MoCA in four studies. The combined analysis of the findings obtained by these two measurement tools was inappropriate due to the inconsistent results between studies that used different measurement tools. Therefore, an analysis of subgroups was required. The results of the subgroup analysis showed that aerobic exercise significantly improves the overall cognitive performance of patients with MCI as shown by significant improvements in MMSE ($N = 956$, $MD = 0.60$, 95% CI: 0.28–0.92, $p = 0.0003$, $I^2 = 31\%$, fixed-effects model) and MoCA scores ($N = 398$, $MD = 1.67$, 95% CI: 1.18–2.15, $p < 0.0001$, $I^2 = 37\%$), significantly improved overall cognitive performance in patients with MCI (**Figure 3**).

DISCUSSION

This systematic review and meta-analysis provides positive evidence that aerobic exercise significantly improves cognitive performance in older adults with MCI.

None of the included studies reported adverse events related to aerobic exercise. However, the results of some other studies are inconsistent with ours. The use of different trial periods may have led to inconsistency in results. For example, some reports showed no difference between the experimental and control groups in the area of overall cognitive function following a 3-month intervention (35). In contrast, other trials with longer intervention or follow-up periods identified an improvement in cognitive function (29, 30, 32, 36). In addition, a study using the MoCA measurement tool found no significant improvement after 3 months of intervention (36), while another study showed significant effects after a 10-month intervention (30). Only four of the included studies specified aerobic exercise intensity with target peak levels of 40–60%, 60–80%, 60%, and a heart rate maintained at 100–140 beats per minute (25, 26, 33, 34). This indicates that exercise intensity may be a factor associated with inconsistent results.

A review study proposed that location and gender may affect the impact of an intervention. In this study, three studies were conducted in mainland China, two studies were from Hong Kong, China, and the remaining studies were conducted in Japan, Pakistan, Denmark, Spain, and Greece. Geographically, six studies were conducted in East Asia (26, 28, 29, 31, 32, 34) and four were conducted in Europe and South Asia (25, 27, 30, 33). Geographical concentration may influence the effect of an intervention. In addition, the influence of the gender factor is mainly reflected in the balanced distribution of subjects. For example, in Chang et al.'s study (26, 37), all participants were female, so their study design excluded the interference of gender factors in the experiment. In contrast, in the study designs of Lam et al. (28) and Lazarous et al. (30), the proportion of females was more than 75%, which implies a three-to-one gap.

STRENGTHS AND LIMITATIONS

The strength of this review lies in its systematic approach design. The strength of our design is reflected in three main areas. First, we focused on aerobic exercise. By defining the concept of aerobic exercise, the use of moderate-intensity exercise was identified as an inclusion criterion. In addition, the selection of exercise programs for MCI patients included tai chi, qigong, dance (square dance), yoga, running, walking, and stepping. Second, we focused on the use of measurement tools. Only trials measured by two instruments, MMSE and MoCA, were

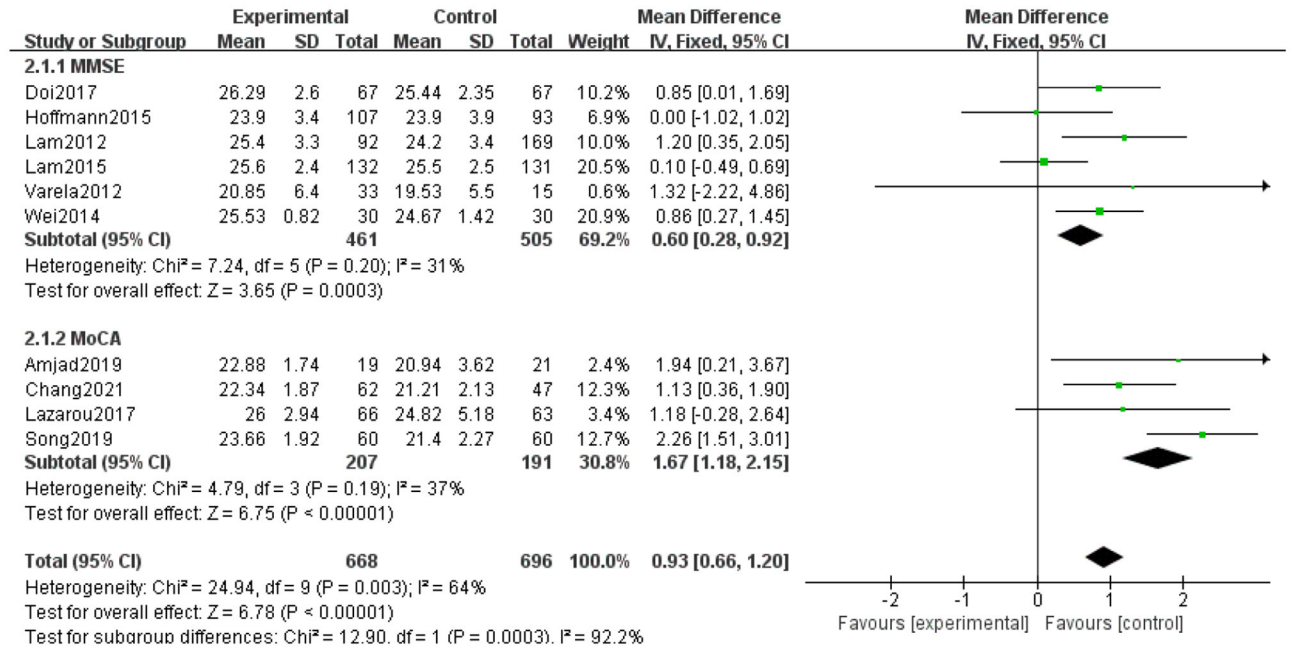

FIGURE 3 | Forest plot for aerobic exercise on global cognition function with MCI older. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

included in the study. This was done to allow us to validate the consistency of the results and to prevent the inclusion of multiple measurement tools from affecting the validity of the analysis. Third, we only discussed the effects of aerobic exercise on global cognitive function in MCI patients and not on specific domains of cognitive function. This allowed us to focus more on the effects of the intervention and thus identify whether aerobic exercise can affect the cognitive performance of patients with MCI.

This study has several limitations. First, the types of aerobic exercise included in the study were diverse, and it is uncertain whether consistent effects were observed due to the different exercise programs used. Second, the frequency and intensity of exercise varied among studies, and the resulting mechanisms of exercise are unclear. Third, although the two measurement tools used have high reliability and validity, their objective measurements need to be further enhanced, for example, through the use of EEG or MRI. Fourth, the standardization of RCTs still needs to be improved. Fifth, insufficient sample size may have seriously limited the interpretability of the results, with three of the 10 studies having sample sizes of <100 individuals. In conclusion, the results of this study confirm the positive effect of aerobic exercise as an intervention for MCI patients. However, the above deficiencies remind us that the effect values provided by the meta-analysis should be interpreted with caution.

CONCLUSION

Participation in aerobic exercise can contribute to the improvement of overall cognitive function in elderly MCI patients. However, the mechanisms by which aerobic exercise influences the overall cognition of MCI patients are unclear due to differences in the type, frequency, and duration of aerobic exercise used in previous studies. Large-scale, rigorous RCTs are needed to explore specific areas of impact and mechanisms of action and determine appropriate intervention programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

LY, GY, and HS: data collection. LY, LL, TD, JC, and MY: data analysis, conception, and design. LY, JW, JC, and MY: research design, writing the manuscript, and revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.713671/full#supplementary-material

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Effect of Square Dance Exercise on Older Women With Mild Mental Disorders

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Many epidemiological studies have demonstrated the therapeutic benefits of exercise (EX) that can be used for adjunctive treatment in mental disorders. Despite several clinical experiments using exercise interventions, controlled studies are sparse in most disorder groups. Square dance is a popular aerobic exercise for older women in China. This study aimed to explore the effect of Chinese square dance exercise on mild mental disorders in older women. Participants included 109 older women with mild cognitive impairment from four large nursing homes. Participants were assigned either to the intervention group ($n = 62$) or the control group ($n = 47$), according to their residential nursing home. The intervention group underwent an 18-week square dance exercise, while the control group maintained their usual lifestyle. The outcomes were tested at baseline and weeks 9 and 18. The results showed that square dance exercise positively affected the results of all evaluations, especially on the participants' depressive symptoms and quality-of-life-related mental health. This study demonstrates that square dance exercise is a safe and effective approach for older women with mild cognitive impairment that benefits their long-term health.

Keywords: cognition, depression, mild cognitive impairment, Chinese square dance, health

INTRODUCTION

Mild cognitive impairment (MCI) is a transitional state between healthy aging and dementia (1, 2). With global aging, the annual prevalence of dementia in the entire elderly population is estimated to be between 1 and 3% (3, 4), and the annual transition rate from mild cognitive impairment to dementia is estimated to be between 10 and 15%; therefore, individuals with mild cognitive impairment are at high risk of developing dementia (1). Some studies have estimated the global prevalence of mild cognitive impairment in older adults to be between 9.6 and 21.6% (5–7). The high prevalence of individuals with mild cognitive impairment and the trend toward dementia suggest that identifying effective treatments to reduce the further decline associated with cognitive abilities is necessary. Non-pharmacological interventions are considered the main approach for treating older adults with mild cognitive impairment (1). Among the various non-pharmacological treatments, physical exercise has been widely studied and promoted as a low-cost, low-risk, and easy-to-use life intervention. Several longitudinal cohort studies have shown that physical activity in midlife can prevent cognitive decline in old age (1, 8). A recent systematic review of 15 cohort

studies (n = 33,816) showed that physical activity protects against cognitive impairment in people who are initially cognitively healthy (9). Another systematic review of prospective epidemiological studies (16 studies, 163,797 cognitively healthy participants) of dementia studies came to similar conclusions (8). Intervention studies of the effects of physical activity on cognitive performance first began in 1990, and this study showed a positive effect of aerobic walking on executive cognitive function in cognitively healthy older adults (10). Randomized controlled trials (RCTs) examining the effects of physical activity on subject cognition in healthy older adults support the claim that exercise promotes cognition in older adults (11–13). Another review study that included 11 RCTs found that aerobic exercise improved cognitive performance on tests measuring attention, delayed recall, and reaction time (14). Two subsequent studies also further confirmed that exercise had the most significant effect on executive function (11, 12). Although there is evidence that the cognitive effects of exercise are relatively consistent in cognitively healthy older adults, the impact of exercise interventions on subjects with mild cognitive impairment (MCI) is less well-understood.

The primary objective of this study was to investigate the effect of Chinese square dancing on the cognitive function of Chinese older adults with mild cognitive impairment, and the secondary purpose was to explore the impact of regular square dance exercise on health-related quality of life in older adults with MCI.

We proposed two research hypotheses. After 18 weeks of intervention, the first hypothesis was that older adult with MCI in the experimental group (i.e., square dance) would significantly improve cognitive functioning than the control group (i.e., daily lifestyle). The second hypothesis was that the experimental group would have considerably fewer depressive symptoms, better balance, and a higher quality of life than the control group.

METHODS

Study Design and Participants

This study was a cluster-randomized controlled trial. The study sites were set in local nursing homes in Chongqing, China. Participants were enrolled in a whole-home approach with two nursing homes serving as the experimental group (EG) and two other nursing homes serving as the control group (CG). Randomization sequences were achieved by drawing lots. The sample size required for the experiment was calculated using G*Power software. The independent samples t-test was used to analyze outcomes in the change between baseline and post-experiment. With effect size (Cohen's $d = 0.58$), 80% power, and 5% Class I error, we estimated that a minimum of 48 participants per group would be required. Taking into consideration the potential dropout of participants, we recruited 10% more subjects than required; thus, each group needed to recruit a minimum of 53 participants.

We recruited participants from four pilot nursing homes recognized by the Chongqing Municipal Health and Family Planning Commission for the integration of medical and health care. These nursing homes possessed similar management patterns and bed sizes. The recruited participants met the following criteria: (1) at least 60 years old, (2) presented subjective cognitive decline in the previous year, (3) obtained a score of <26 on the Montreal Cognitive Assessment (MoCA) (plus an extra 1 point if they had achieved 12 years of schooling), and (4) attained a score of <26 on the Ability for Daily Living (ADL) assessment. Participants were excluded if they were: (1) taking medication for cognitive impairment, (2) had a neurological disorder (e.g., Parkinson's disease, stroke, multiple sclerosis), (3) had an acute or chronic condition that prevented exercise, or (4) performed regular exercise (≥30 min/day, ≥3 day/week) within the past 6 months or had sustained exercise experience for more than 5 years. All participants signed a written informed consent form before the study.

Intervention

Chinese square dance was used for the experimental group exercise. Chinese square dance is a popular form of aerobic exercise for middle-aged and older women. The dance has a simple, easy-to-learn structure and is suitable for older individuals to use as a form of exercise. We chose dance music with simple melodies and low movement activity, and the main movement structures were hand clapping, high-fiving, chest expansion, arm extension, and leg kicking (https://www.youtube.com/watch?v=AYEasAhzHI0).

Two national social sports instructors with professional dance training taught participants Chinese square dancing over three sessions at each of the two nursing homes during the week prior to the start of the experiment. Each session lasted 1 h and was spaced 1 day apart. One of the instructors was responsible for teaching and the other for demonstrating the movements. After learning once, one instructor led the dance, and one instructor was responsible for correcting the actions until all the participants fully mastered the basic moves. Practice videos were provided after the class for everyone to familiarize themselves with the movements. During the experiment, one staff member from each nursing home was responsible for assisting with safety supervision. A sign-in system was implemented for each class during the investigation, and a small gift or daily necessities (towel, soap, toothbrush, etc.) was awarded to those participants who attended each session per week. The attendance rate for the experimental group ranged from 68.5 to 96.3%, with an average of 87.6%. Participants only missed exercise when they were unwell or did not return from an outing.

Square dance workouts were performed outdoors three times a week for 30 min each session, starting at 7 pm on Mondays, Wednesdays, and Fridays (during periods of inclement weather, sessions were held indoors). The square dance workouts at the two nursing homes were conducted in parallel. The square dance exercise was led by two researchers (national social sports instructors) each, with 5 min of warm-up activities (finger joint activities, etc.) before the training, 30 min of dancing, and 5 min of relaxation exercises (i.e., deep breathing and stretching) at the end. During the square dance exercise, it was agreed to wear a sports watch to monitor the participants' heart rate. Exercise intensity was assessed using an exercise heart rate controlled at 100–140 beats per min. The control group did not

participate in the organized physical activity and led a liberal daily lifestyle.

Outcome Measures

This study assessed participants' overall cognition, quality of life, depressive symptoms, and balance at baseline, week 9, and 18. The staff member responsible for the assessment received assessor consistency training. The assessors were blind to the group to which the participant belonged, and the trainers instructed participants not to disclose allocation information while being assessed. The primary outcome was cognitive functioning, and the rest were secondary outcomes. All scales used were in the Chinese version, and all had established evidence of reliability and validity.

The Montreal Cognitive Assessment (MoCA) was used for MCI screening in older adults (sensitivity: 90%, specificity: 83%). The MoCA contains cognitive tasks in a range of domains, including situational memory, visuospatial ability, executive function, attention, language, and orientation, to obtain an overview of a person's cognitive functioning (15). The scale has a maximum score of 30, with higher scores indicating better cognitive abilities. Similarly, the scale had a retest reliability of 0.857, and content validity, concurrent validity, and construct validity were good ($p < 0.01$) (16). The scale showed good internal consistency with a Cronbach's alpha of 0.836 (17) and was more sensitive than the Mini-Mental State Examination in measuring cognitive function in patients with mild cognitive impairment (18). In addition, the Montreal Cognitive Assessment is relatively brief compared to other complex neuropsychological combinations, making it more suitable for older adults with mild cognitive impairment.

The Short-Form 12 health survey (SF-12) was used to assess the quality of life. SF-12 is a simplified version of the SF-36 and shows high correlation with SF-36 (19). The scale includes assessing general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health. The first four indicators are used to assess the physical component summary (PCS), while the last four are used to assess the mental component summary (MCS). Higher scores indicate a better quality of life. For this scale, Cronbach's a was 0.775, and the criterion validity was good ($p < 0.001$) (20).

The Geriatric Depression Scale (GDS-15) was used to assess participants' depressive symptoms. The GDS-15 includes 15 items that require participants to answer "yes" or "no" for a total score of 15. Higher scores indicate more pronounced depressive symptoms, with scores >10 indicating severe depression and those >5 indicating mild depression. For the GDS-15 scale, the test–retest reliability was 0.728, and Cronbach's a was 0.793, with good discriminant validity ($p < 0.001$) (21).

The Berg Balance Scale (BBS) was used to assess participants' balance ability. The scale consists of 14 items, and each item has a score between 0 and 4 for a total score of 56, with higher scores indicating better balance ability. The inter-rater reliability of the scale was 0.992–0.998, and the retest reliability was 0.968–0.985 with good content validity (22).

Statistical Analysis

Statistical analyses were conducted using SPSS 24.0. Tests of normality for all continuous variables were screened by Skewness and Kurtosis statistics. Descriptive statistics were used to analyze the characteristics of the participants. Means and standard deviations (SDs) were used to describe the continuous variables (e.g., age and education level of participants). Independent *t*-tests were used to compare differences between the experimental and control groups on baseline demographics and outcome variables. The paired samples *t*-test was used to compare pre- and post-experimental results within the respective experimental and control groups. To measure intervention effects over time, we used linear mixed-effects models to analyze the effects of time, group, and group-by-group time. A *p*-value of a two-sided test of <0.05 was considered to be statistically significant. Effect size estimates were calculated for all mean differences using Cohen's *d*, which relates mean score differences to pooled standard deviations (23). Data analyses were performed according to the principle of completing all experiments, and missing data were not included in the results.

RESULTS

Baseline Participant Characteristics

A flowchart of participant recruitment and withdrawal is shown in **Figure 1**. The participants were recruited in four nursing homes, two of which were identified as the experimental group and the other two were identified as the control group. Two hundred and twenty-five enrollments were received within 1 week. Eighty-nine individuals were excluded after initial screening, of whom 47 did not meet the MCI criteria, 20 did not meet the criteria for participation in exercise criteria, 18 had more than 5 years of regular exercise experience, and 4 did not agree to participate in the exercise protocol. The participants were grouped according to their nursing homes, with 72 in the experimental group and 64 in the control group. After 9 weeks, seven dropped out of the experimental group, two of whom did not accept the intervention program, three of whom were discharged, and two of whom were physically ill; eight dropped out of the control group, two of whom did not accept the intervention program, four of whom were released or dropped out of participation, and two of whom were physically ill. After 18 weeks, three people withdrew from the experimental group, two of whom were discharged and one who was physically ill; nine people withdrew from the control group, three of whom were discharged or dropped out of participation and six of whom were physically sick. As a result, a total of 109 participants (EG = 62, CG = 47) completed all experimental tests.

The baseline characteristics of the participants are shown in **Table 1**. The mean age of the participants was 76.29 ± 3.60 years, and their education level ranged from 5 to 14 years of schooling. There were no significant differences between the experimental and control groups in the baseline characteristics such as age, education level, body mass index (BMI), MoCA, BBS, PCS, MCS, and GDS scores ($p > 0.05$).

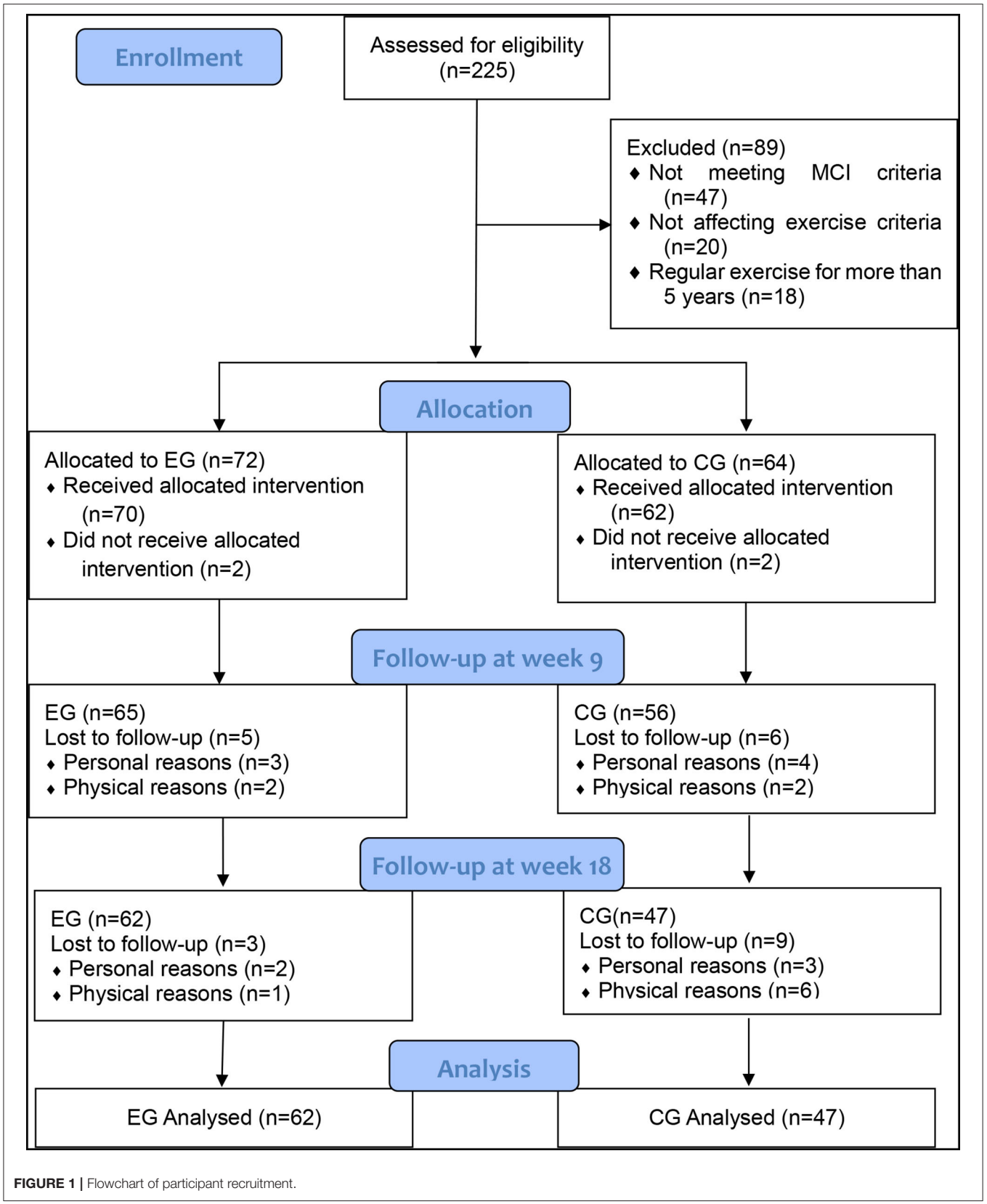

FIGURE 1 | Flowchart of participant recruitment.

Experimental Outcome Comparisons

Table 2 presents comparisons of the results of the experimental and control groups across time. **Figure 2** shows the changing trend in the experimental and control groups across time. The results of the linear mixed-effects model shows that the interaction effects of group and time were highly significant for the MoCA, BBS, and GDS ($p < 0.001$) and significant for PCS and MCS ($p < 0.01$).

Inter-group comparisons at week 9 displayed a significantly higher MCS score in the experimental group (49.31 ± 4.40) than the control group (46.58 ± 5.34; $p = 0.004$). However, MoCA scores (EG: 22.08 ± 2.03; CG: 21.38 ± 2.29; $p = 0.096$), BBS scores (EG: 36.89 ± 5.46; CG: 35.53 ± 4.86; $p = 0.181$), PCS scores (EG: 44.09 ± 6.07; CG: 42.88 ± 6.40; $p = 0.318$), and GDS scores (EG: 4.97 ± 1.41; CG: 4.85 ± 1.63; $p = 0.690$) were not significantly different between the two groups. At week 18, the trend persisted with significantly higher MCS scores in the EG compared to the CG (EG: 49.84 ± 4.86; CG: 45.99 ± 6.41; $p = 0.001$), and there was a significantly lower GDS score in the EG compared to the CG (EG: 4.31 ± 1.14; CG: 5.02 ± 1.67; $p = 0.009$). Unlike week 9, at week 18, MoCA scores (EG: 22.34 ± 1.87; CG: 21.21 ± 2.13; $p = 0.004$) were also significantly higher in the EG than the CG. However, the BBS scores (EG: 37.27 ± 5.40; CG: 35.45 ± 4.72; $p = 0.068$) and PCS scores (EG: 44.69 ± 5.35; CG: 42.71 ± 6.50; $p = 0.084$) remained insignificant between the two groups.

The results of the inter-group comparison in the experimental group showed that the scores of MoCA, BBS, and PCS were significantly higher at week 9 (MoCA: $t = 4.267$, $p < 0.001$, $d = 0.59$; BBS: $t = 5.622$, $p < 0.001$, $d = 0.81$; PCS: $t = 3.583$, $p = 0.001$, $d = 0.45$) as well as at week 18 (MoCA: $t = 3.400$, $p = 0.001$, $d = 0.71$; BBS: $t = 8.361$, $p < 0.001$, $d = 0.84$; PCS: $t = 2.752$, $p = 0.008$, $d = 0.43$) compared to baseline. MCS scores were slightly higher at week 9 compared to baseline ($t = 2.405$, $p = 0.019$, $d = 0.44$) but significantly higher at week 18 ($t = 2.721$, $p = 0.008$, $d = 0.63$). GDS scores were significantly lower at week 9 ($t = -3.681$, $p < 0.001$, $d = -0.56$) and week 18 ($t = -6.789$, $p < 0.001$, $d = -0.88$) compared to baseline. In contrast, the scores of the control group at week 9 and 18 were not statistically significantly different from baseline for all outcomes ($p > 0.05$).

TABLE 1 | Baseline characteristics of participants.

	EG ($n = 62$)	CG ($n = 47$)	p
Age, years	76.56 ± 3.60	75.94 ± 3.61	0.369
Education, years	8.73 ± 2.05	8.28 ± 2.06	0.261
BMI, kg/m^2	23.63 ± 2.14	23.60 ± 2.03	0.956
MoCA	43.09 ± 6.49	42.87 ± 6.95	0.863
BBS	48.15 ± 4.97	47.11 ± 5.89	0.320
PCS	36.15 ± 5.89	35.64 ± 5.46	0.647
MCS	21.61 ± 2.11	21.49 ± 2.39	0.776
GDS	4.97 ± 1.41	4.85 ± 1.63	0.690

Continuous variables are presented as the means ± standard deviations (SDs). BMI, Body mass index; MoCA, Montreal Cognitive Assessment; BBS, Berg Balance Scale; PCS, Physical Component Summary; MCS, Mental Component Summary; GDS, Geriatric Depression Scale.

DISCUSSION

The purpose of this study was to examine the effects of 18 weeks of square dance exercise on cognitive function and health-related quality of life in Chinese older women with mild cognitive

TABLE 2 | Comparison of the experimental and control groups across time.

Scale	Time	EG ($n = 62$)	CG ($n = 47$)	Linear mixed-effects model (p)			Change from baseline (p)		Inter-group comparisons (p)	Effect size (d)
				Group	Time	Group*time	EG	CG		
MoCA	Baseline	21.61 ± 2.11	21.49 ± 2.39	0.400	0.041*	0.776			0.776	
	Week 9	22.08 ± 2.03	21.38 ± 2.29			0.096	<0.001***	0.506	0.096	0.59
	Week 18	22.34 ± 1.87	21.21 ± 2.13			0.004**	0.001**	0.052	0.004**	0.71
BBS	Baseline	36.15 ± 5.89	35.64 ± 5.46	0.867	0.004**	0.647			0.647	
	Week 9	36.89 ± 5.46	35.53 ± 4.86			0.181	<0.001***	0.646	0.181	0.81
	Week 18	37.27 ± 5.40	35.45 ± 4.72			0.068	<0.001***	0.529	0.068	0.84
PCS	Baseline	43.09 ± 6.49	42.87 ± 6.95	0.620	0.011*	0.863			0.863	
	Week 9	44.09 ± 6.07	42.88 ± 6.40			0.318	0.001**	0.969	0.318	0.45
	Week 18	44.69 ± 5.35	42.71 ± 6.50			0.084	0.008**	0.481	0.084	0.43
MCS	Baseline	48.15 ± 4.97	47.11 ± 5.89	0.770	0.446	0.320			0.320	
	Week 9	49.31 ± 4.40	46.58 ± 5.34			0.004**	0.019*	0.364	0.004**	0.44
	Week 18	49.84 ± 4.86	45.99 ± 6.41			0.001**	0.008**	0.069	0.001**	0.63
GDS	Baseline	4.97 ± 1.41	4.85 ± 1.63	0.134	0.013*	0.690			0.690	
	Week 9	4.55 ± 1.17	4.96 ± 1.38			0.097	<0.001***	0.462	0.097	−0.56
	Week 18	4.31 ± 1.14	5.02 ± 1.67			0.009**	<0.001***	0.315	0.009**	−0.88

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

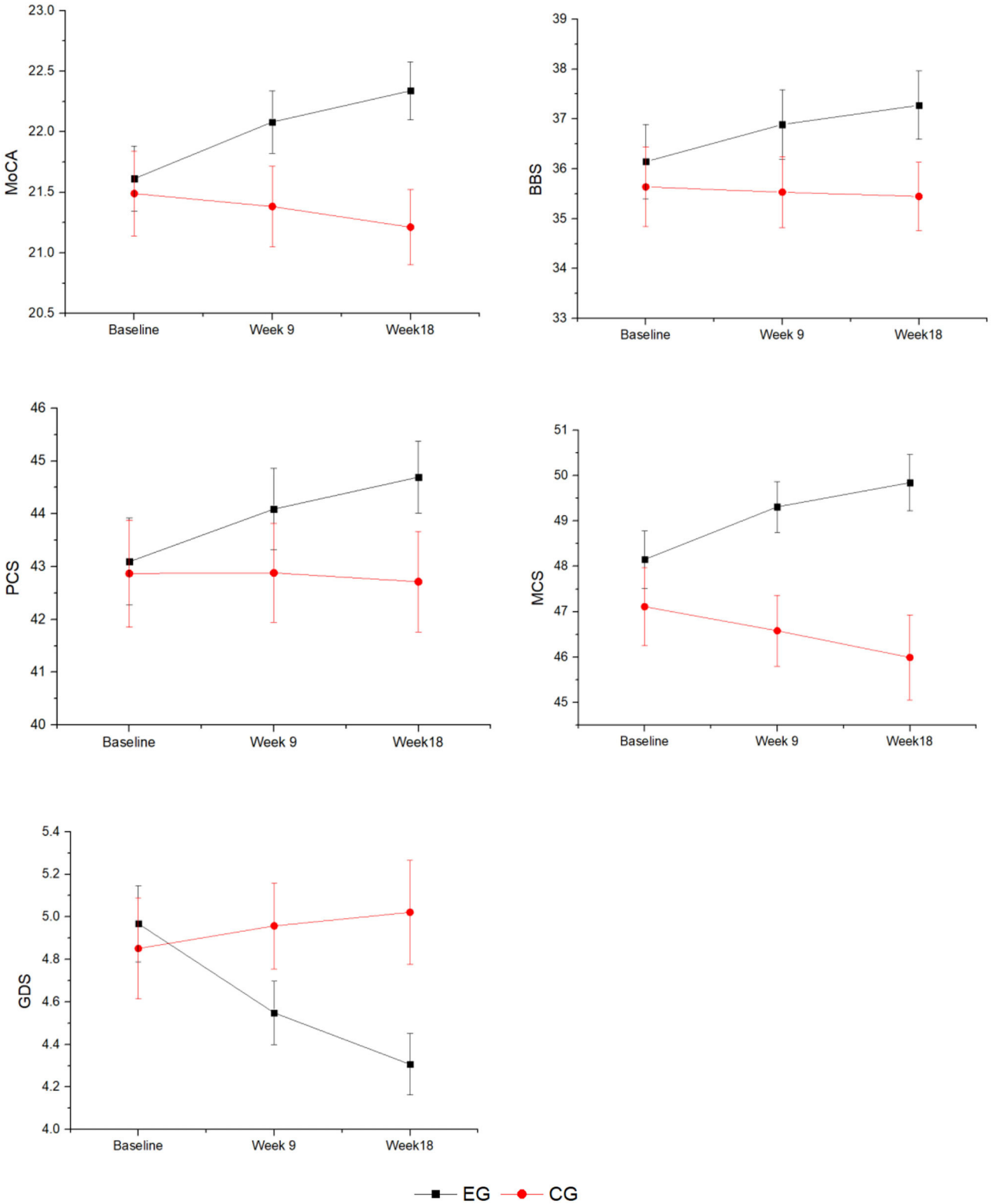

FIGURE 2 | The change trend of the experimental and control groups across time. EG, experimental group; CG, control group; MoCA, Montreal Cognitive Assessment; BBS, Berg Balance Scale; PCS, Physical Component Summary; MCS, Mental Component Summary; GDS, Geriatric Depression Scale.

impairment and to explore its effects. This study provides evidence that Chinese square dancing has a positive impact on overall cognitive improvement, quality of life enhancement, balance enhancement, and depressive symptom regulation in older adults with MCI. To our knowledge, this is the first study in China to examine the effects of Chinese square dancing on people with MCI using southern residents as the subjects (24). We chose square dance because it is easy to learn and because it does not require specialized equipment or venues and is easily accessible, which is particularly beneficial for older participants with MCI. Good attendance and no adverse events support the feasibility of the intervention trial.

This study echoes the benefits of moderate-intensity aerobic exercise on cognitive enhancement in Chinese clinical studies (25). As for the primary outcome, the linear mixed-effects model showed a significant change in the trend of MoCA scores between the two groups. The results of the inter-group comparison showed significant improvement in the scores of the experimental group over 9 and 18 weeks, while there was no significant change in the scores of the control group. This study confirmed that over time, the intervention group exhibited enhanced cognitive function and the control group had worsening cognitive function, indicating that participants who regularly participated in physical activity had significant improvements in the same health parameters. This finding suggests that Chinese square dance as moderate-intensity aerobic exercise can serve the purpose of preventing mild cognitive impairment in older adults.

Currently, this study is consistent with most studies (26–29), although individual studies do not support the idea that aerobic exercise can improve older cognitive function (30). There are two possible reasons for this controversy. First, the small sample size (19 subjects per group) constrains the accuracy of the study results (31); second, the use of the study instrument may lead to problems with the precision of the collected data (29). The positive effects of square dancing as a form of aerobic exercise on cognitive function may be due to the presence of several factors. First, studies have shown that aerobic exercise can improve MCI in older adults (28); second, studies have shown that dance can significantly reduce depressive symptoms in older adults, and depression is an important risk factor for the development of what is known as MCI in older adults (28, 32); third, movement repetition exercises can help older adults improve their memory (33); fourth, the cordial social atmosphere and soothing musical rhythm of square dance have a positive impact on the mood of older adults, and positive mood can reduce depression, thus improving their cognitive function (34).

This study showed that square dancing had a positive effect on all results for the secondary outcomes. At week 9, the experimental group had significantly higher MCS scores than the control group. This may be because, unlike the control group, the intervention group provided more opportunities for socialization, which may have helped eliminate loneliness and improved participants' mood (35). At week 18, there was a significant difference in GDS scores between the two groups. The positive effect of square dancing on the improvement of depressive symptoms is consistent with the results of Wang et al. (23). The positive effect on physical health is supported by the fact that our study found regular, moderate-intensity square dance exercise to be promising in improving the physical condition and mental status of older adults (29).

Overall, square dancing is a promising non-pharmacological intervention strategy for older adults with MCI (36). An 18 weeks daily exercise intervention can improve overall cognition, depressive symptoms, balance, and quality of life in older MCI populations. Additionally, nursing homes and their communities can screen older adults for MCI regularly for early detection and intervention. Square dancing, an affordable form of exercise, is suitable for nursing homes, communities, and other areas where the elderly population is concentrated. Exercising in such an environment improves the mood of the elderly and is equally beneficial to improving cognition. The recommended exercise frequency is 30 min three times a week for 18 weeks; however, beyond is better. It is important to note that nursing homes or communities should provide professional assistance in supervising square dance exercises when organizing them to ensure the safety of participants.

Limitations

This study had several limitations. First, participants were recruited from a single city and were limited by the fact that participants had to have some mild cognitive impairment, and the selected participants were not necessarily fully representative of the characteristics of people with MCI. Second, participants were from four nursing homes, and participants from each nursing home could only be coded as a whole into the experimental or control group, failing to implement a randomized controlled trial. Third, the assessment instrument used only scale measures, which had limitations. Fourth, this study only discussed MCI in older women, and the applicability to men remains to be further explored.

CONCLUSION

This study investigated the effect of square dancing on exercise intervention for older women with MCI. The study supported the positive effects of square dancing in promoting cognition, depression, balance, and quality of life in MCI patients. It is recommended that Chinese square dance be conducted collectively in communities or nursing homes to promote physical and mental health and improve the quality of life of older adults.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific and Ethics Committee of

Institute of Motor Quotient, Southwest University (IRB NO. SWUIMQ20180109). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC, YC, CL, LY, MY, and WZ: data collection. JC, LY, and JY: data analysis, conception, and design. JC, WZ, JY, and JW: research design, writing the manuscript, and revision. All authors contributed to the article and approved the submitted version.

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Prevalence and Clinical Correlation of Decayed, Missing, and Filled Teeth in Elderly Inpatients With Schizophrenia

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Introduction: Schizophrenia is a mental disease with a profound impact on human health. Patients with schizophrenia have poor oral hygiene, increasing their risk of systemic diseases, such as respiratory infections, and declining their quality of life. Therefore, this study aims to assess the oral health status of inpatients with schizophrenia, analyze its related factors, and thus provide scientific evidence for further exploration of corresponding control strategies.

Methods: A total of 425 inpatients older than 50 years with a diagnosis of schizophrenia from two psychiatric hospitals (mean age 58.49 ± 5.72 years) were enrolled. The demographic data of the patients were checked on admission. Two independent dentists examined caries, missing teeth, and fillings. Mini-Mental State Examination (MMSE) and Global Deterioration Scale were performed as cognitive tests. Positive and Negative Syndrome Scale and Repeatable Battery for the Assessment of Neuropsychological Status rating scale were used to determine their mental status.

Results: The average decayed, missing, and filled teeth index was 12.99 ± 8.86. Linear regression analysis showed that the decayed, missing, and filled teeth index had a significantly positive relationship with age ($p < 0.001$) and smoking ($p < 0.001$) and a negative relationship with MMSE ($p = 0.029$). The missing teeth index had a positive relationship with age ($p < 0.001$), smoking ($p < 0.001$), and Global Deterioration Scale ($p = 0.014$) and a negative relationship with MMSE ($p = 0.004$).

Conclusion: The oral health of elderly patients with schizophrenia is poor, which may be related to the cognitive level of patients and affect their quality of life. The focus should be provided to the oral care of patients with schizophrenia, and investment in their specialized oral treatment should be increased.

Keywords: oral health, DMFT, cognitive impairment, schizophrenia, elderly inpatients

INTRODUCTION

The incidence of mental disorders has rapidly increased worldwide, inducing a series of severe family, social, and cultural problems and affecting the development of the economy. Schizophrenia is a complex mental disease with a profound impact on human health; it is a chronic mental disorder affecting 20 million people globally, as revealed by the "Global Burden of Illness, Injury, and Risk Factors study" in 2017 (1). In China, the prevalence of schizophrenia was estimated to range from 0.4 to 0.5% (2), with the elderly accounting for ∼30.0% (3).

Elderly patients with schizophrenia have mental disease *per se* and oral hygiene and health problems resulting from frequent medication and inadequate oral cleaning care (4, 5). Elderly inpatients with schizophrenia present with special diverse disease symptoms, volatile emotional behavior, and decreased intellectual, cognitive level (6). Incomplete oral cleaning and insufficient hygienic management cause poor oral hygiene and significantly increase the incidence of oral diseases. The decayed, missing, and filled teeth (DMFT) index of hospitalized psychiatric patients increases with age (7). Some studies suggested that the oral health of hospitalized elderly patients with mental illness is impaired (8). Oral health problems undoubtedly increase the risk of lung infections, such as aspiration pneumonia (9). A large number of studies have demonstrated that the incidence of nosocomial respiratory tract infection is considerably higher in elderly patients in psychiatric hospitals than in other parts of the human body (10–12), and this incidence is even higher than that in general hospitals.

Recent studies have focused on the interaction between poor oral health and cognitive impairment (13). The incidence of oral health problems in elderly patients with cognitive impairment has increased significantly. Oral pathogenic bacteria, such as *Porphyromonas gingivalis*, and inflammatory factors in the mouth can affect protein regulatory channels and pass through the blood–brain barrier, further aggravating cognitive impairment. Several previous studies investigated the Mini-Mental State Examination (MMSE) scale and the missing teeth (MT) index and concluded that tooth loss is a related factor of cognitive impairment or its deterioration (14–18). Some other studies assessed the effect of positive and negative symptoms on the DMFT index in patients with schizophrenia. They found that the Positive And Negative Syndrome Scale (PANSS) negative subscale (PANSS-N) score is positively correlated with the oral health variables and that the PANSS positive subscale (PANSS-P) score is negatively correlated with MT (19). However, few studies have investigated the relationship between the DMFT index and cognitive impairment. In particular, reports on the correlation between the oral health status and cognitive level using the DMFT index in elderly patients with mental illness are lacking.

Therefore, this study analyzed the oral health status and related factors of elderly patients with schizophrenia from two large-scale psychiatric hospitals. Specifically, we assessed teeth status in patients with schizophrenia and addressed the relationship with cognitive and psychiatric status. Oral health management strategies were proposed to effectively reduce the risk of lower respiratory tract infections and improve the comprehensive medical services of psychiatric hospitals and the quality of life of elderly patients with schizophrenia.

METHODS AND MATERIALS

Sample Selection and Population

We used a cross-sectional study in two psychiatric hospitals on elderly patients with schizophrenia. From 2018 to 2019, 425 hospitalized patients with schizophrenia diagnosed by the International Classification of Diseases, 10th Revision, included 265 from the Guangdong Hospital and 160 from the Wuhan Hospital (**Table 1**). All long-term patients with schizophrenia aged 50 years and older were included in this study. Patients with major basic diseases and acute onset of schizophrenia were excluded. Demographic data included sex, age, education level, marriage, smoking, height, weight, diabetes, hypertension, and use of psychiatric medications. Body mass index (BMI) was calculated from height and weight (BMI = kg/m^2). In accordance with the Chinese reference standard, they were classified as normal ($18.5 \leq BMI < 24$), lean ($BMI < 18.5$), overweight ($24 \leq BMI < 28$), and obese ($BMI \geq 28$). The DMFT index was used to assess oral health, whereas cognitive and mental statuses were measured.

The Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences, approved this study. Ethical approval was conducted in accordance with the latest version of the Helsinki Declaration (lines 96–98). Written informed consent was obtained from all participants.

Dental Examination

Two dentists had been trained before this study. Consistency was assessed by Kappa calibration, and the Kappa value was >0.8. The decayed teeth (DT: number of teeth or surfaces with caries in the mouth), MT (number of teeth lost in the mouth due to caries; dental decay and periodontal disease can no longer be distinguished at age 45 years and older), filled teeth (FT: number of teeth or surfaces that have been filled for caries), and DMFT indices were detected under artificial light in a dental chair.

Measurement of Cognition and Mental States

Cognitive function was evaluated with the MMSE and Global Deterioration Scale (GDSRANK) (20). MMSE is mainly concerned with the ability of orientation, registration, attention, calculation, recall, and language (21). The MMSE score ranges from 0 to 30, and a lower score indicates poorer cognitive ability. Each question has three possible answers: true, false, and unanswerable. We counted the unanswerable as incorrect answers (22). GDSRANK assesses dementia severity over seven grades (23): absence of cognitive changes (first grade), very mild cognitive decline (second grade), mild cognitive decline (third grade), moderate cognitive decline (fourth grade), moderately severe cognitive decline (fifth grade), severe cognitive decline (sixth grade), and very severe cognitive decline (seventh grade). The score was derived from the interview of patients and caregivers.

TABLE 1 | DMFT scores of elderly schizophrenia inpatients in different hospitals.

Hospitals	Number	Percentage (%)	DMFT	SD	*t*	*p*-value
Guangzhou	265	62.4	14.25	8.93	3.855	<0.001
Wuhan	160	37.6	10.89	8.37		
total	425	100.0	12.99	8.86		

Mental status was evaluated with PANSS (24) and Repeatable Battery for the Assessment of Neuropsychological Status rating scale (RBANS) (25). Scores of PANSS-P, PANSS-N, PANSS general psychopathology (PANSS-G), and total were applied separately. The RBANS consists of 12 task tests assessing five aspects of neuropsychological function, namely, immediate memory, visuospatial structure, language, attention, and delayed memory.

Statistical Analysis

IBM SPSS 24.0 was used to analyze the data with *t*-tests. Mann–Whitney *U*-test or Kruskal–Wallis *H*-test was used for variables with non-normality or homogeneity of variance. The Kolmogorov–Smirnov test was used to test normality. Counting variables were analyzed by the chi-squared test or *Fisher's* exact probability test. The relationship between metrological/classification data and DMFT was analyzed using the Pearson or Spearman correlation method. The risk factor analysis for DMFT and MT in elderly hospitalized schizophrenics was performed through linear regression. The statistical significance level was set at 0.05.

RESULTS

The mean DMFT score of the 425 patients was 12.99 ± 8.86, 14.25 ± 8.93 for patients in Guangzhou and 10.89 ± 8.37 for patients in Wuhan (**Table 1**). Patients in the two hospitals showed a significant difference ($t = 3.855$, $p < 0.001$). The total mean DT value was 4.61 ± 5.03, the MT value was 7.82 ± 8.39, and the FT value was 0.56 ± 2.34. The total caries rate, missing rate, and filling rate were 83.1, 83.3, and 14.6%, respectively.

Demography and Decayed, Missing, and Filled Teeth Index

The Kolmogorov–Smirnov test showed that the DMFT and MT indices were not normal ($p = 0.001$). **Table 2** presents the demographic characteristics of elderly inpatients with schizophrenia. Sex ($p = 0.001$), age ($p < 0.001$), education level ($p = 0.038$), and smoking status ($p < 0.001$) significantly influenced the DMFT scores of the patients. High DMFT scores were significantly associated with age and smoking. Female participants and those with high education levels showed significantly lower DMFT scores than their counterparts.

Cognitive and Mental Statuses Against the Decayed, Missing, and Filled Teeth Index

Table 3 shows that the DMFT index was significantly correlated with age ($r = 0.33$, $p < 0.001$), total MMSE score ($r = -0.17$, $p = 0.001$), GDSRANK score ($r = 0.13$, $p = 0.006$), PANSS-N score ($r = 0.11$, $p = 0.024$), and PANSS-G score ($r = 0.11$, $p = 0.031$) but not with PANSS-P score ($r = -0.03$, $p = 0.607$), PANSS total score ($r = 0.09$, $p = 0.06$), or RBANS score ($r = -0.11$, $p = 0.071$).

Cognitive and Mental Statuses Against Missing Teeth Index

Table 3 shows that the MT index was significantly correlated with age ($r = 0.43$, $p < 0.001$), total MMSE score ($r = -0.21$, $p < 0.001$), GDSRANK score ($r = 0.21$, $p < 0.001$), PANSS-N score ($r = 0.12$, $p = 0.014$), PANSS-G score ($r = 0.12$, $p = 0.016$), PANSS total score ($r = 0.11$, $p = 0.025$), and RBANS score ($r = -0.13$, $p = 0.031$) but not with PANSS-P score ($r = -0.00$, $p = 0.120$).

Linear Regression Model of Decayed, Missing, and Filled Teeth

As shown in **Table 4**, age ($\beta = 0.469$, $p < 0.001$), smoking ($\beta = 2.616$, $p < 0.001$), and MMSE score ($\beta = -0.128$, $p = 0.029$) are risk factors for the DMFT index. The DMFT index increased with age and smoking and decreased with MMSE score ascending. The association between MMSE and DMFT scores remained significant after controlling for age and smoking ($p < 0.05$).

Linear Regression Model of Missing Teeth

As shown in **Table 5**, age ($\beta = 0.595$, $p < 0{,}001$), smoking ($\beta = 1.157$, $p < 0.001$), and GDSRANK score ($\beta = 0.661$, $p = 0.014$) are positive risk factors for MT index, whereas total MMSE score ($\beta = -0.156$, $p = 0.004$) is a negative risk factor of MT score. After controlling for age and smoking, total MMSE score and GDSRANK score remained significantly associated with the MT index ($p < 0.05$).

DISCUSSION

Poor oral hygiene in elderly psychiatric inpatients may aggravate cognitive impairment and increase the risk of aspiration pneumonia infection, resulting in a high incidence of hospital infections. The oral health of these patients can be improved by implementing professional oral treatment or nursing during hospitalization (26). Improved oral hygiene can reduce the incidence of respiratory diseases (27) and decrease the incidence of nosocomial infections. The regained mastication function can also improve the cognitive performance of elderly patients (26). Therefore, the oral health of elderly inpatients with schizophrenia needs special attention.

A large number of previous studies examined the relationship between the MT index and cognitive impairment of the elderly in the community or the general population (15, 28, 29), but few

TABLE 2 | DMFT scores of elderly schizophrenia inpatients according to demographic.

Variable		Number	Percentage (%)	DMFT		*U* or *H*	*p*-value
				Mean	SD		
Gender	Male	295	69.4	13.90	9.07	10.532	0.001
	Female	130	30.6	10.91	8.03		
Age	50–54	123	28.9	8.62	7.51	55.329	<0.001
	55–59	121	28.5	13.17	8.84		
	60–64	98	23.1	15.01	8.55		
	≥65	83	19.5	16.81	8.46		
Education	Primary and below	67	15.8	14.55	9.40	8.408	0.038
	Junior high	166	39.0	12.95	9.00		
	Senior high	152	35.8	13.29	8.68		
	University and above	40	9.4	9.38	7.23		
Marital status	Single	233	54.8	13.59	9.09	4.706	0.095
	Married	112	26.4	13.01	8.44		
	Others	80	18.8	11.20	8.63		
Smoking	No	210	49.4	10.64	8.44	37.322	<0.001
	Used to	62	14.6	13.00	7.69		
	Smoking now	153	36.0	16.20	8.91		
BMI	Lean	28	6.6	12.93	9.61	7.531	0.057
	Normal	195	45.9	14.18	9.00		
	Overweight	130	30.6	12.14	8.14		
	Obesity	72	16.9	11.29	9.15		
Diabetes	No	325	76.5	12.93	8.87	0.063	0.803
	Yes	100	23.5	13.18	8.87		
Hypertension	No	315	74.1	12.77	8.87	0.691	0.406
	Yes	110	25.9	13.59	9.10		
Number of Medication	1	242	56.9	13.96	9.23	6.006	0.050
	2	163	38.4	11.91	8.32		
	3	20	4.7	10.00	7.07		

TABLE 3 | Correlations of DMFT and MT with cognition and mental state.

Variable	DMFT		MT	
	r	*p*	*r*	*p*
Age	0.33	<0.001	0.43	<0.001
Total MMSE	−0.17	0.001	−0.21	<0.001
GDSRANK	0.13	0.006	0.21	<0.001
PANSS-N	0.11	0.024	0.12	0.014
PANSS-P	−0.03	0.607	−0.00	0.120
PANSS-G	0.11	0.031	0.12	0.016
PANSS total	0.09	0.060	0.11	0.025
RBANS	−0.11	0.071	−0.13	0.031

analyzed the relationship between the DMFT index and cognitive level. Studies on patients with schizophrenia focused on their oral conditions. Therefore, we investigated the oral health status of elderly inpatients with schizophrenia on the basis of the DMFT index and examined the correlation between DMFT and the cognition or clinical symptoms of mental illness.

Descriptive Analysis of Oral Health

The prevalence rates of dental caries and tooth loss in elderly patients with schizophrenia were 83.1 and 83.3%, respectively, consistent with the previously reported caries rate of ∼80.0% (30, 31) and MT rate of 81.4% (7) in psychiatric patients. Poor oral hygiene indicates a serious lack of oral health care.

TABLE 4 | Linear regression model of DMFT in elderly schizophrenia inpatients.

DMFT	*β*	*t*	95.0% CI		*p*-value
			Lower	Upper	
Age	0.469	6.802	0.333	0.604	<0.001
Smoking	2.616	6.160	1.781	3.450	<0.001
Total MMSE	−0.128	−2.195	−0.242	−0.013	0.029

TABLE 5 | Linear regression model of MT in elderly schizophrenia inpatients.

MT	*β*	*t*	95.0% CI		*p-value*
			Lower	Upper	
Age	0.595	9.173	0.467	0.722	<0.001
Smoking	1.157	2.921	0.379	1.936	<0.001
Total MMSE	−0.156	−2.877	−0.262	−0.049	0.004
GDSRANK	0.661	2.467	0.134	1.187	0.014

Several published studies to date analyzed the oral health of inpatients with mental disorders by using the mean DMFT score, such as 20.6, 15.8, and 16.6 (8, 32, 33), which were higher compared with the 12.99 obtained in the present study. Several possible reasons may explain these inconsistent results. First, ethnic and regional differences existed between studies. The two surveyed areas in China are relatively developed regions. Different countries show large differences in DMFT value (8, 32–34). Second, the present study included only patients with schizophrenia, whereas other studies included patients with other mental disorders, such as substance addiction, mania, bipolar disorder, and depression, which may cause even worse oral health. Third, sample sizes were different. The sample size in this study was relatively larger than those in the other studies (i.e., no more than 200 patients). Among the cases collected, the proportion of Guangzhou hospital was higher than that of Wuhan hospital, and the composition of age and sex was also different.

Demographic Effects of Decayed, Missing, and Filled Teeth Values

The DMFT score of males was higher than that of females ($U = 10.532$, $p = 0.001$), consistent with most previous results (35, 36). This sex difference may relate to the poorer awareness of oral self-management (36) and smoking habits in male patients with schizophrenia. The DMFT score significantly increased with age ($H = 55.329$, $p < 0.001$). The effect of age on oral health was confirmed by a large number of studies (37). As age increases, the functions of chewing and swallowing in the elderly decline, and the incidence of gum atrophy and periodontal disease increases, directly affecting their oral health and nutritional status. The increased education level is significantly related to decreased DMFT ($H = 8.408$, $p = 0.038$), which is in line with the finding of Vano et al. (36). This result may be because people with higher education are more obedient to oral management and willing to require treatment for dental caries. Smoking is also a significant factor influencing dental caries and tooth loss (38, 39). A study on tobacco use and oral conditions showed that chewing tobacco and smoking are important risk factors for dental caries (40). Tobacco affects human gingival health and the morphology and moving ability of periodontal ligament fibroblasts, inducing the development and progression of periodontal disease (31), which can easily cause dental caries and tooth loss.

Relationship Between Decayed, Missing, and Filled Teeth/Missing Teeth and Cognition

Previous studies often used the Montreal Cognitive Assessment (28) and MMSE (17, 18) to conduct the cognitive evaluation of patients. This study enrolled elderly schizophrenia patients with cognitive impairment. Therefore, we chose the MMSE scale, a relatively simple intelligence scale to quantify the cognitive level of patients. DMFT and MT were correlated with MMSE scores, and this correlation remained even after controlling for confounders, including age and smoking. In a Japanese cohort study on community-dwelling older adults, tooth loss was independently associated with the development of cognitive impairment within 4 years, confirming the hypothesis that tooth loss is a predictor or risk factor for cognitive decline (29). Another 13-year longitudinal study showed that tooth loss is associated with a cognitive decrease in older Chinese (15). Several cross-sectional studies demonstrated that DMFT relates to tooth loss and cognition (17, 18, 28). In addition, the nursing group used GDSRANK to assess neurodegeneration of the patients (23), and the results indicated that MT remained associated with GDSRANK score after controlling for age and smoking, whereas DMFT was not. Few studies used GDSRANK as a cognitive scale, but cross-sectional studies identified a weak association between cognitive impairment and MT (41). Therefore, we contend that MT plays an important role in cognitive impairment in elderly patients with schizophrenia.

Tooth loss in adults is mainly attributed to periodontal disease and dental caries (42). Therefore, tooth loss can be regarded as an indicator of severe inflammation caused by oral microorganisms. Periodontal disease caused by *P. gingivalis* may be associated with increased antibody levels (43). A possible reason may be that oral pathogenic bacteria and inflammatory factors enter the blood–brain barrier through influencing protein regulation channels, which further aggravate cognitive dysfunction. Noble et al. (43) showed that patients with high levels of antibodies to *P. gingivalis* have observably greater odds of impaired verbal memory and subtraction test performance than individuals with low levels.

Tooth loss can cause deficiency or decline of chewing function, resulting in changes in brain function (28). Chen et al. (44) found that active chewing can improve thinking ability and memory by promoting heart function and increasing the secretion of related hormones. Meanwhile, chewing can increase the secretion of saliva, and brain areas associated with salivary production are involved in memory and learning. Thus, the more teeth are missing, the worse chewing function is. This condition may indirectly affect cognitive function. Therefore, reconstruction of masticatory function may exert a positive effect on the prevention of cognitive decline in the elderly.

Relationship Between Decayed, Missing, and Filled Teeth/Missing Teeth and the Mental State

Arnaiz et al. (19) showed that the PANSS-N score is associated with poor oral health, suggesting that symptomatology of schizophrenia is a risk factor for poor oral health. The present study showed that PANSS-N and PANSS-G scores were positively correlated with DMFT and MT, whereas PANSS total score was only positively correlated with MT. This correlation disappeared when controlling for age and smoking confounders. Negative symptoms, such as intellectual disability, lack of interest and emotion, and loss of life motivation, may lead to the reduced oral self-cleaning ability of patients with schizophrenia, unable to consciously maintain oral hygiene (45–48). However, elderly inpatients with schizophrenia are often accompanied by difficulties in self-management of life and need to complete daily oral cleaning under the care of others. Delusions and auditory hallucinations associated with positive symptoms may trigger impulsive behavior, resulting in a mixture of traumatic tooth loss factors (46). As a result, no relevance was found between the subscales of symptoms and DMFT or MT when the confounding age and smoking were eliminated.

In conclusion, long-term elderly inpatients with schizophrenia have cognitive impairments themselves. Their limited oral self-maintenance capacity, combined with the potential conflict between respecting patients' autonomy and providing good daily care (49), makes many effective oral care practices difficult to implement, further exacerbating the lack of oral health management in this population. This condition may not only aggravate the cognitive impairment of patients and affect the quality of life but also increase the risk of respiratory nosocomial infection and seriously hamper the improvement of the quality of medical services. Therefore, strengthening the specialized training of oral care skills should be strengthened, and the investment in professional oral treatments must be increased to help these patients obtain good oral health, quality of life, and self-esteem.

LIMITATIONS

Oral health refers to the comprehensive condition of the oral cavity. In this study, only one dimension of the DMFT index was evaluated, and other oral function indexes such as chewing, swallowing, and speech were not included. In determining the mean of caries, an oral curved slice was not used to investigate the root caries alone. In addition, this study was a multicenter cross-sectional study. A regional difference in the dietary habits of patients may also lead to biased results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Institute of Psychology, Chinese Academy of Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MY and QL searched and reviewed the literature, analyzed the data, and wrote the manuscript. CD and GY searched the literature and analyzed the data. XB and XT distributed questionnaires and collected data. XZ negotiated with the hospitals to conduct this study, collected data, and assisted in finding documents, issuing questionnaires, and analyzing the data. All authors contributed to the article and approved the submitted version.

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REVIEW
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Effect of Aerobic Exercise on Mental Health in Older Adults: A Meta-Analysis of Randomized Controlled Trials

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Introduction: The recommendation of exercise programs in the senior population may benefit inactive and sedentary individuals and improve and help to treat specific health conditions. The purpose of this review is to summarize the published evidence from RCT studies of aerobic exercise interventions for mental health in older adults over the last 20 years.

Methods: A literature search was conducted using electronic databases including Web of Science, PubMed/Medline, and ProQuest.

Results: A total of 15 studies met the inclusion criteria. The subjects of these studies were aged 60 years or older and had various physical health statuses. In 15 studies, the mean effect size for the experimental outcome was 0.56 ± 0.39 (95%CI: 0.36–0.76). One-way ANOVA indicated no significant differences in the intervention duration [$F_{(2,15)} = 0.919$, $p = 0.420$], subject category [$F_{(2,15)} = 0.046$, $p = 0.955$], or measurement category [$F_{(3,14)} = 0.967$, $p = 0.436$]. However, there were significant differences in exercise frequencies [$F_{(2,15)} = 6.03$, $p = 0.012$].

Conclusion: The available evidence suggests that aerobic exercise is beneficial for improving the mental health of adults aged 60 years and older. The intervention effect can be achieved regardless of the type of subject and the duration of the intervention. Further, the present study indicates that low-frequency, long-term and regular aerobic exercise is more effective for older adults. Therefore, we recommend that older adults to exercise at a low frequency depending on their physical condition.

Keywords: mental health, aerobic exercise, MCI, dementia, depression, cognition, older adults

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INTRODUCTION

The World Health Organization (WHO) has published several cross-national comparisons of the prevalence, severity, and treatment progression of mental disorders (1–4). Studies have concluded that the 12-month prevalence of any mental disorder is highly variable. However, most countries have no access to timely treatments for mild or moderate mental disorders (5). For example, the median delay in seeking treatment for anxiety disorders is 3 years in Israel and 30 years

in Mexico (5). In addition, seeking treatment for mental illness does not mean that individuals are optimally treated, and the mortality rates are higher for those with chronic or recurrent mental illnesses (6), while the morbidity is higher when depression occurs in combination with physical illnesses such as diabetes or cardiovascular disease (7). Data show that those with mental disorders die 10–15 years earlier than the general population, and major contributing factors include preventable cardiovascular diseases that are caused by poor lifestyle choices, such as a lack of physical activity (8).

Most people know that exercise and physical activity are critical for maintaining physical health; however, what about mental health? According to the U.S. Department of Health and Human Services, exercise can be defined as "physical or mental exertion, especially to train or improve health," while, according to the U.S. Department of Health and Human Services, physical activity is "any physical exercise that exercises muscles and requires more energy than rest." Physical activity is defined by the NIH as "any physical exercise that builds muscle and requires more energy than rest" (9). According to the U.S. DHHS, mental health can be defined as "our emotional, psychological, and social well-being. It helps determine how we handle stress, how we relate to others, and how we make choices" (Mental Health). However, it is still considered taboo to discuss mental health in the public arena. A study of 2,000 people conducted by The Guardian UK found that 30% of people found it "difficult to admit publicly that they have a mental illness" and that "admitting to a mental health condition is harder than admitting to having an alcohol problem, being broke or being gay" (9). People "are four times more likely to break up if their partner is diagnosed with major depression than if they have a physical disability" (10). Mental health has become a major "enemy" of people's health. Especially in the elderly population, the decline of various body functions due to physical decline directly affects their physical and mental health. However, physical activity is a simple and effective form of exercise, so it could play a more prominent role.

Numerous recent epidemiological studies have reviewed the relationship between physical activity and mental health (11). A meta-analysis of prospective studies including nearly 267,000 individuals showed that higher levels of PA were associated with lower odds of developing depression. In another meta-analysis including more than 80,000 people, PA was also associated with elevated odds of experiencing anxiety symptoms but lower odds of anxiety disorders (12). The data showed that, the higher the amount of PA, the lower the risk of mental health problems. There appears to be a dose–response relationship between increased PA and mental health and functioning across exercise modalities (13). Aerobic and resistance exercise proved to be of additional benefit to health (14). In conclusion, the epidemiological evidence supports the idea that more habitual PA is associated with better mental health and functioning (15).

The current research generally agrees that exercise has beneficial effects on a range of mental health outcomes. Some studies have observed that exercise improves mental health in various ways (16–18). For instance, neurobiological theories are used to explain the mechanisms by which aerobic exercise improves mental health in middle-aged and older age groups (18–20). Of these, the conceptual model of neurobiological and behavioral learning mechanisms (NBLMs) and the three overarching mechanistic hypotheses (TOMHs) are widely popular. The NBLM model assumes that exercise improves the neurobiological system of adaptive learning, as well as affective and cognitive control processes, reinforcing a virtuous circle and synergistically improving the regulation of cognitive and affective responses (20). The TOMHs comprise three hypotheses: (a) mental health is associated with the physical effects of exercise, (b) exercise improves mental health through neurobiological mechanisms, and (c) exercise is a vehicle for developing mechanisms of behavioral change (e.g., self-regulatory skills and self-efficacy). Smith et al. confirmed that the TOMHs were useful for constructing hypotheses about treatment improvements (15). However, the evidence for a dose–response effect of exercise is less robust than the observations. Although the frequency of exercise required for therapeutic mental health benefits appears to vary by population and exercise modality (21), interestingly, few studies have linked the degree of improvement to the frequency or duration of exercise (19).

The primary purpose of the current study was to review the randomized controlled trials studying the effects of aerobic exercise on older adults' mental health over the past 20 years and to analyze the effects of aerobic exercise (and their differences) on the effectiveness of mental health interventions in older adults, to provide scientific assurance that older adults should participate in aerobic exercise.

METHODS

Search Strategy

The literature for this study was identified by conducting a comprehensive search in electronic databases, including Web of Science, PubMed/Medline, and ProQuest. The search period ranged from January 2000 to December 2020. The keywords used in our searches were exercise, aerobic exercise, mental health, mental illness, and mental disorders. After removing duplicates, the titles and abstracts of the retrieved references were screened to exclude articles that did not meet the inclusion criteria (22). The full texts of the remaining articles were obtained and fully assessed by the authors (LY and JL). The reference lists of the final included articles were also screened to identify additional studies. The decision to include disputed articles was made jointly with the corresponding author (JC).

Selection Criteria

Studies were considered for inclusion if they met the following criteria (23): (1) the article was written in English; (2) a randomized controlled trial design was used to compare the aerobic exercise intervention group with a control group (either daily life or other forms of exercise); (3) the research question involved cognitive or mental health; (4) the study subjects were 60 years of age or older; and (5) the effect of aerobic exercise on the subjects' mental health was assessed. Studies were excluded if (1) the study subject was completely unable to care for himself/herself (had a severe physical disability); (2) the study

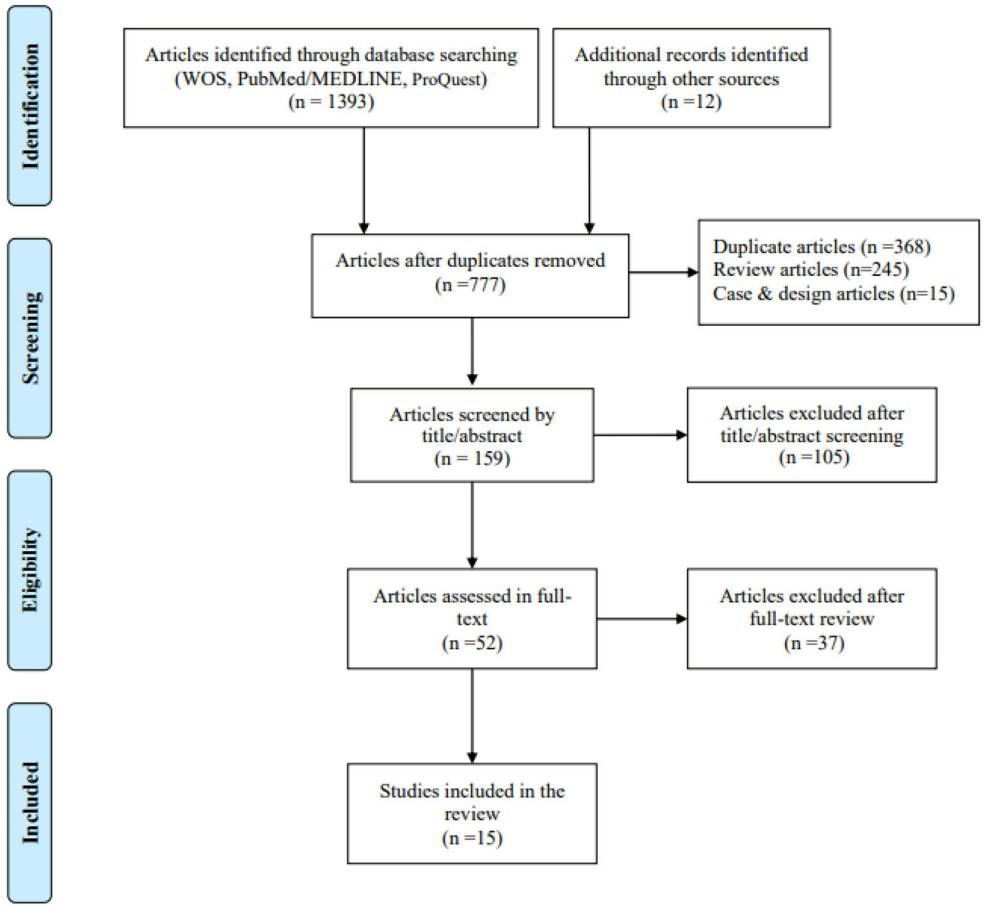

FIGURE 1 | Flow diagram for evidence source search. From: Moher et al. (26).

design included other types of interventions (e.g., intervention diets); or (3) the study results did not include a cognitive or mental health component.

Risk-of-BIAS Assessment

A risk-of-bias assessment was performed to ensure the rigor of the sources of evidence. According to the PRISMA-Scr guidelines, we conducted a partial risk-of-bias assessment based on the Cochrane Guidelines (21). The Cochrane Risk of Bias Tool was used on Review Manager 5.4 (https://community.cochrane.org). Two reviewers independently assessed the sequence generation, allocation concealment, blinding of participants, blinding of assessors, incomplete outcome data, and selective outcome reporting for the included studies (21).

Data Extraction and Analysis

Data were extracted from each article using a pre-designed template according to the study design, sample characteristics, measures, intervention duration, intervention design, and intervention effects (22). The randomized controlled trials (RCTs) had to distinguish between two and three groups in their designs. The specific headings of the summary table included the author (as well as the year of publication and country where the study was conducted), subjects' health characteristics, sample size, mean or age range of the sample, measure/intervention involving aerobic exercise, and intervention effect size (ES). If the study provided values for the intervention effect sizes, the data were extracted directly. If the study did not directly provide values for the effect size, conversion was performed using means, standard deviations (standard errors) and sample sizes; F-values and sample sizes; or *t*-values, *p*-values and sample sizes. Specific conversions were performed using an online program developed by Wilson (24). Additionally, Cohen's d shows a large bias when the sample is small (<20 for the overall sample or <10 for each group). Therefore, Cohen's d calculated based on small samples needs to be corrected using a method proposed by Hedges and Olkin (25). Descriptive statistics and one-way ANOVA were performed on the extracted data using the SPSS 24.0 software.

RESULTS

Selection of Sources of Evidence

A total of 1,393 articles were identified using electronic databases such as Web of Science, PubMed/Medline and ProQuest, as

TABLE 1 | The characteristics of sources of evidence.

ID	Name, country	Time	*N* (f)	Subjects	Age	RCT	Measure	Exercise design	Exercise frequency
1	Anderson-Hanley et al. (11) USA	3 m	111 (73)	MCI	All: 78.1 ± 9.9 EG1: 80.9 ± 12.3 EG2: 75.4 ± 9.83	RCT three groups	Stroop A/C	EG1: exer-tour, low cognitive load, virtual scenic bike tour EG2: exer-score, high cognitive demand, videogame CG: game-only	EG1: 20–45 min, 3–5 tim/wk EG2: 20–45 min, 3–5 tim/wk CG: N/R
2	Awick et al. (27) USA	12 m	179 (N/R)	Low-active non-CI	All: 66.4	RCT	SF12-MCS	EG: walking CG: strengthening and flexibility	EG: first 7 weeks, 50–60% HR; next, 65–75% HR CG: 4 muscle resistance, 2 balance, 1 yoga, and 1 exercise of self-choice in each class
3	Bieler et al. (28) Denmark	4 m	152 (103)	OA	EG1: 69.6 ± 5.4 EG2: 70.0 ± 6.3 CG: 69.3 ± 6.4	RCT three groups observer-blinded	SF36-MCS	EG1: NW, Nordic Walking EG2: ST, strength training CG: HBE, home-based exercise	EG1: NW, 1 h × 3 tim/wk, 12–14 on the Borg scale EG2: ST, 1 h × 3 tim/wk, 75% of 1RM CG: HBE, exercises recommended by the DAA
4	Cancela et al. (29) Spain	15 m	189 (126)	Dementia	EG: 80.63 ± 8.32 CG: 82.90 ± 7.42	RCT blinded	CSDD MEC NPI	EG: aerobic exercise CG: not exercise	EG: daily cycling sessions; 15 min/s, >70% monthly attendance; CG: daily life
5	Cheung et al. (30) USA	8 w	73 (73)	OA	EG1: 68.9 ± 7.1 EG2: 74.4 ± 7.5 CG: 71.8 ± 8.0	RCT three arms blinded	SF12-MCS	EG1: HY, yoga EG2: ASE, aerobic and strengthening CG: education	EG1: HY, (a) 45 min/wk × 8 wk, and (b) 30 min/day, 4 tim/wk of yoga EG2: ASE, (a) 8 tim/wk, (b) aerobic 15–30 min/day, 4 tim/week, and (c) strengthening 30 min/day, 2 tim/wk CG: education brochures, weekly telephone
6	Eggenberger et al. (31) Switzerland	6 m	89 (46)	Non-CI	EG1: 77.3 ± 6.3 EG2: 78.5 ± 5.1 CG: 80.8 ± 4.7	RCT three groups blinded	PACES	EG1: DANCE, virtual reality video game dancing EG2: MEMROY, treadmill walking with simultaneous verbal memory training CG: PHYS, treadmill walking	Each group training: 2 tim/wk, 1 h/tim, vigorous intensity
7	Hall et al. (32) USA	12 w	54 (5)	PTSD	EG: 67.7 ± 3.2 CG: 66.9 ± 4.3	RCT-Pilot blinded	SF36-PCS	EG: exercise CG: wait-list usual care	3 tim/wk, >150 min/wk, moderate intensity
8	Karssemeijer et al. (33) Netherlands	12 w	115 (54)	Dementia	EG1: 80.9 ± 6.1 EG2: 79.0 ± 6.9 CG: 79.8 ± 6.5	RCT: three arms	EFIP	EG1: stationary cycling training EG2: cognitive-aerobic bicycle training CG: relaxation and flexibility	EG1: 30-50 min/tim, 3 tim/wk, 65–75% HR EG2: 30–50 min/tim, 3 tim/wk, 65–75% HR CG: 30 min/tim, 3 tim/wk
9	Langoni et al. (34) Brazil	24 w	52 (40)	MCI	EG: 72.6 ± 7.8 CG: 71.9 ± 7.9	RCT, single-blinded	MMSE	EG: group exercise (aerobic and strength) CG: no exercise	EG: 60 min/tim, 2 tim/wk, 60–75% HR CG: N/R

(Continued)

TABLE 1 | Continued

ID	Name, year, country	Time	*N* (f)	Subjects	Age	RCT	Measure	Exercise design	Exercise frequency
10	Middleton et al. (35) Canada	12 w	126 (82)	cognitive complaints	All: 73.0 ± 6.0 EG: 72.5 ± 5.9 CG: 74.3 ± 5.9	RCT: blinded 2 × 2 factorial design	SF12-MCS	EG: aerobic or stretching/toning, CG: mental activity, computer-based cognitive training or educational DVDs	EG: 3×60 min/wk CG: 3 × 60 min/wk
11	Parvin et al. (36) Iran	12 w	32 (N/R)	AD	All: 67.4 ± 8.8	RCT, single-blinded	MoCA	EG: visual stimulation (muscle endurance, balance, flexibility, and aerobic exercises) CG: daily life	EG: 2 × 40–60 min/wk, warm-up 10 min, exercises 20–40 min, cool down 10 min. CG: daily life
12	Suzuki et al. (37) Japan	12 m	50 (27)	amnestic MCI	EG: 75.3 ± 7.5 CG: 76.8 ± 6.8	RCT	MMSE	EG: aerobic exercises, muscle strength, postural balance CG: education classes	EG: 90 min/d, 2 d/wk CG: 3 d /12 mos
13	Varela et al. (38) Spain	15 m	39 (15)	Non-CI	EG: 83.59 ± 7.05 CG: 77.94 ± 8.79	RCT, single-blinded	MEC NPI	EG: cycling CG: recreational activities	EG: self-selected intensity 15 min/d, >70% completion rate CG: 3 d /12 mos
14	Wanderley et al. (39) Portugal	8 m	105 (27)	Non-CI	EG1: 70.0 ± 5.7 EG2: 67.3 ± 4.9 CG: 67.8 ± 5.5	RCT three-groups blinded	SF36-MCS	EG1: aerobic training EG2: resistance training CG: daily lifestyle	EG1: AT-−70–80% HR reserve, attendance rate >80%; 3 d/wk, 50 min/d; EG2: RT-−80% 1RM, attendance rate >80%; 3 d/wk, 50 min/d; CG: WL— not to change daily lifestyle
15	Zanetidou et al. (40) Italy	24 w	121 (86)	Late-life depression	EG: 74.9 ± 6.2 CG: 75.6 ± 5.6	RCT single-blinded	Anxiety	EG1: AD + NPE (low-intensity, non-progressive exercise), mat work and instrumental exercises EG2: AD + PAE (high-intensity, progressive aerobic exercise), cycling exercise CG: AD (sertraline)	EG1: 3 tim/wk, <70% HR EG2: 3 tim/wk, <70% HR CG: daily lifestyle

N/R, not reported; EG, experimental group; CG, control group; w, week; m, month; tim/wk, times/week; HR, heart rate. MCI, mild cognitive impairment; Non-CI, without cognitive impairment; PTSD, post-traumatic stress disorder; AD: Alzheimer's disease; OA: osteoarthritis. EFIP, Evaluative Frailty Index for Physical activity; SF12/36, SF-12/36 Health related Short Form 12/36; MCS, mental component summary; CSDD, Cornell Scale for Depression in Dementia; MEC, Mini-Examen Cognoscitive; NPI, Neuropsychiatric Inventory; PACES, Physical Activity enjoyment scale; MMSE, the mini-mental state examination; MoCA, Montreal cognitive assessment.

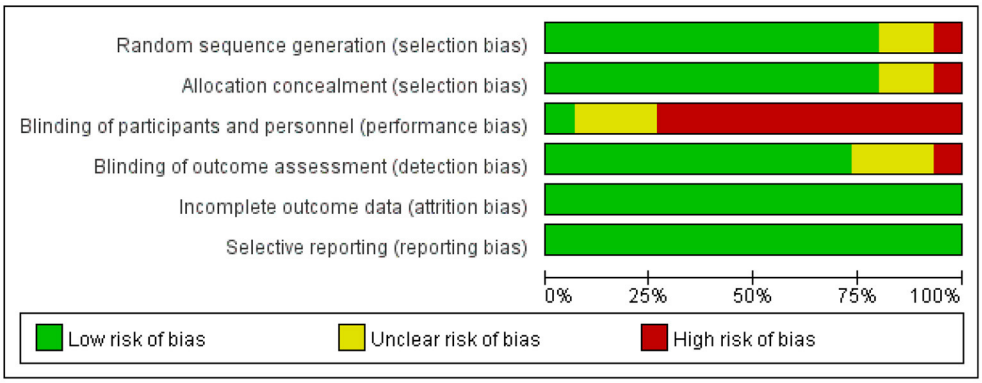

FIGURE 2 | Risk-of-bias chart for studies included in the quantitative analysis.

TABLE 2 | Inclusion of study effect sizes and classification of indicators.

ID	Author, year	ES (Cohen's *d*)	ES level	Measure category	Duration category	Subject category	Frequency category
1	Anderson-Hanley (11)	0.52	M	4	1	1	2
2	Awick (27)	0.44	S	4	3	2	2
3	Bieler (28)	1.13	L	2	2	3	2
4	Cancela (29)	0.35	S	4	3	1	3
5	Cancela (29)	0.48	S	4	3	1	3
6	Cancela (29)	0.42	S	2	3	1	3
7	Cheung (30)	0.16	S	4	1	3	2
8	Eggenberger (31)	1.06	L	2	2	2	1
9	Hall (32)	0.48	S	1	1	1	2
10	Karssemeijer (33)	0.35	S	1	1	1	2
11	Langoni (34)	0.65	M	1	2	1	1
12	Middleton (35)	0.08	S	3	1	1	2
13	Parvin (36)	1.70	L	3	1	1	1
14	Suzuki (37)	0.74	M	1	3	1	1
15	Varela (38)	0.54	M	1	3	2	3
16	Varela (38)	0.22	S	3	3	2	3
17	Wanderley (39)	0.47	S	1	3	2	2
18	Zanetidou (40)	0.30	S	4	2	1	2

ES Level: S, Small; M, Medium; L, Large.
Measure category: 1, SF12/SF36; 2, NPI; 3, Attitude (CSDD/EFIP/PACES/Anxiety); 4, MMSE/MoCA/MEC.
Duration category: 1, ≤3 months or 13 weeks; 2, 3–6 months or 14–26 weeks; 3, >6 months or 26 weeks.
Subject category: 1, MCI/Dementia; 2, Non-CI; 3, OA.
Frequency category: 1. <3 tim/wk; 2, 3–5 tim/wk; 3. >5 tim/wk.

were 12 articles from other systematic reviews. After removing duplicates and reviewing the titles, abstracts and full texts, 15 studies were finally included in the present study (**Figure 1**). Of these studies, two reported two and three measures of testing, respectively. Thus, a total of 18 intervention-effect-size results needed to be extracted.

Characteristics of Sources of Evidence

Data from 1,487 participants from 15 studies were included in the evidence analysis (see **Table 1**). Overall, the mean age of the participants was a minimum of 66.43 years and a maximum of 83.59 ± 7.05 years, with five studies (29, 31, 35, 37, 40) in which the subjects were over 65 years of age, the rest being over 60 years of age. The duration of the exercise interventions was at least 8 weeks (2 months) and at most 15 months. The frequency of the exercise interventions was 2–7 times per week, with the frequency of those in the majority of the studies being 3–5 times per week. In addition, five studies specified maximum loads for exercise, with the load controlled at 50–75% of the maximum heart rate (27, 33, 34, 39, 40); three studies also emphasized that subjects' attendance had to be no <70 or 80% (29, 37, 39).

All the experimental designs included in this study were performed RCTs. Of all the included studies, eight used a three-group experimental design, with two groups for the exercise

TABLE 3 | Outcomes for descriptive statistics and ANOVA.

	N	*M*	SD	95%CI		Min	Max	*F*	*p*
				Lower	Upper				
Subjects									
MCI/dementia	11	0.55	0.42	0.27	0.83	0.08	1.70	0.046	0.955
Non-CI	5	0.55	0.31	0.16	0.93	0.22	1.06		
OA	2	0.65	0.69	−5.52	6.81	0.16	1.13		
Duration (weeks/months)									
≤13/3	6	0.55	0.59	−0.07	1.17	0.08	1.70	0.919	0.420
14–26/3–6	4	0.79	0.39	0.17	1.40	0.30	1.13		
>26/6	8	0.46	0.15	0.33	0.58	0.22	0.74		
Measure									
SF12/36	6	0.46	0.37	0.07	0.85	0.08	1.13	0.967	0.436
NPI	2	0.32	0.14	−0.95	1.59	0.22	0.42		
Attitude	4	0.52	0.36	−0.06	1.09	0.30	1.06		
MMSE/MoCA	6	0.77	0.46	0.28	1.26	0.48	1.70		
Frequency (times/week)									
<3	4	1.04	0.48	0.28	1.79	0.65	1.70	6.030	0.012*
3∼5	9	0.44	0.30	0.21	0.67	0.08	1.13		
>5	5	0.40	0.12	0.25	0.56	0.22	0.54		

*$p < 0.05$.

intervention and one non-exercise control group. For the other seven studies, participants were randomized into two groups for the exercise intervention and control group (41). In the three-group experimental design, except for the aerobic exercise, another exercise intervention group was studied, focusing on resistance training (27), stretching training (30), or a cognitive intervention plus aerobic training (33). The subjects in the study included three categories: no cognitive impairment (27, 31, 38, 39), cognitive impairment [mild (11, 34, 35, 37), dementia (29, 33), depression (32, 40), and Alzheimer's disease (36)] and physical impairment (osteoarthritis, etc.) (28, 30).

Risk-of-Bias Assessment for Sources of Evidence

Figure 2 shows the assessment of the risk of bias for the sequence generation, allocation concealment, participant blinding, assessor blinding, incomplete outcome data, and selective outcome reporting (21). As shown in **Figure 2**, 3 of the 15 studies were unclear in the sequence generation (11, 33, 37), and four, in allocation concealment (32, 37) and the blinding of the assessor (11, 27, 37). Only one study reported blinding of the participants (31). Otherwise, all the studies had a low risk of bias in all domains (for details, see the online **Supplementary Table 1**).

ANOVA of the Intervention Effect Sizes

ANOVA was performed to facilitate the analysis of differences according to the various types of measures, durations, study subjects and exercise frequencies (42). We first categorized the data presented in **Table 1**. The measurements were coded as follows. (1) Measure category: 1 = SF12/SF36; 2 = NPI; 3 = Attitude (CSDD/EFIP/PACES/Anxiety); 4 = MMSE/MoCA/MEC. (2) Duration category: 1 = ≤3 months or 13 weeks; 2 = 3–6 months or 14–26 weeks; 3 = >6 months or 26 weeks. (3) Subject category: 1 = MCI/Dementia; 2 = Non-CI; 3 = OA. (4) Frequency category: 1 = <3 times/week; 2 = 3–5 times/week; 3 = >5 times/week.

Table 2 shows the effect sizes of the included studies and the recoded data. The mean effect size of the 15 included studies was 0.56 ± 0.39 (95%CI: 0.36–0.76). **Table 3** shows the results of the descriptive statistics and one-way ANOVA for the effect sizes of the included studies. The results of the one-way ANOVA show that there were no significant differences in the intervention duration [$F_{(2,15)} = 0.919$, $p = 0.420$], subject category [$F_{(2,15)} = 0.046$, $p = 0.955$], or measure category [$F_{(3,14)} = 0.967$, $p = 0.436$]. However, there was a significant difference in the exercise frequency factor [$F_{(2,15)} = 6.03$, $p = 0.012$].

DISCUSSION

This study focused on the effects of aerobic exercise on the mental health of older adults (43). One-way ANOVA was used to examine four influencing factors across the study subjects, measures, intervention durations, and exercise frequency (44). The results show that only the ANOVA results were significantly different between different exercise frequencies. By contrast, there were no significant differences in the ANOVA results between the subjects, measurement indicators and intervention durations. This may not be in line with traditional studies. Therefore, we need to further analyze the possible reasons for this.

First, the quality of the included literature needs to be analyzed in terms of reliability. All the included studies were RCTs with the highest experimental grade, and all the studies were conducted in strict accordance with the established process for randomized controlled trials (45), except for four experimental designs with unclear random assignment methods and blinding points (11, 27, 33, 37). The included studies were reliable, with more than 70% to ensure a low risk of bias.

Second, was the coding of the impact factor classification scientific? The four impact factors selected for this study were reclassified and coded according to the needs of the study, and this classification was based on conventional experience (46). Therefore, the blind spots in the application of this method are currently unclear.

Finally, was the quality of the intervention effect size data extraction reliable? In addition to the categorical coding, the proposed intervention effect size is also an important factor influencing the results of the ANOVA in this study (47). Only one paper in this study provided effect size values directly (36), and the rest of the data were transformed using effect size calculation formula, which reduced the reliability of the data source. However, two people independently extracted and calculated the effect size separately, ensuring data integrity for the study. Despite all the three issues mentioned above, we followed strict scientific procedures to guarantee the quality of the included literature, coding classification and data extraction. However, the accuracy of the results provided by the original studies and the bias in the publication of the results could have affected the results of this study.

Comparison among the mean effect sizes of different exercise frequency groups (EFGs) showed that the lowest EFG obtained the largest effect size. The finding is similar to the results of a recent meta-analysis study of the cognitive function of older adults. That study suggested, in older adults, high-frequency exercise interventions did not affect cognitive function more than low-frequency ones (48). Similarly, another study of a 6-week exercise intervention showed no significant difference in effect size between the high-frequency and low-frequency groups (49). We reasoned that there might be methodological flaw in using only exercise frequency as an indicator of influencing factor. Yet another study revealed that exercise duration of more than 6 months was more effective than that of <6 months (50). In this study, the duration of the intervention was 6 months or more in 75% of the low-frequency group. Although the current evidence does not directly conclude that duration affects the effect of the intervention, regular and continuous exercise is undoubtedly beneficial for older adults. Thus, considering the benefits of low-frequency exercise with slightly higher or high-frequency exercise, older adults should primarily engage in low-frequency exercise.

In summary, there are several weaknesses in the present study. First, mixing different populations, outcome measures and exercise programs into the study may lead to high heterogeneity of fitting results. Second, one-way ANOVA only investigates the impact of a single factor on the observed variables, and cannot diagnose the interaction effects between factors (51). Third, selecting only effect size indicators ignores the value of sample size, which may produce uncontrollable errors (52). Therefore, future research should focus on seeking methodology breakthroughs while addressing the above issues.

CONCLUSIONS

This retrospective study confirmed the positive effect of aerobic exercise on the mental health of older adults with a moderate overall intervention effect (ES Cohen's $d = 0.56$). The results of the one-way ANOVA revealed that adults over 60 years of age, regardless of whether they have an intellectual disability or not, or are undergoing physical rehabilitation or not (mild motor impairment), can improve their mental health through aerobic exercise. We recommend low-frequency exercise for older adults when the exercise benefits of various modes are compared.

AUTHOR CONTRIBUTIONS

LY, HF, WL, and JL: data collection. LY and JC: data analysis, conception, and design. LY, JL, and JC: research design, writing the manuscript, and revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.748257/full#supplementary-material

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Influencing Factors of Hospital-Acquired Pneumonia Infection in the Middle-Aged and Elderly Patients With Schizophrenia

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Introduction: Pneumonia is an important cause of death in patients with schizophrenia. It is critical to understand the risk factors of hospital-acquired pneumonia (HAP) and determine prevention strategies to reduce HAP. The aim of this study is to elucidate the risk factors for HAP in the middle-aged and elderly hospitalized patients with schizophrenia.

Methods: We retrospectively reviewed the medical records of 2,617 the middle-aged and elderly patients (age $\geq$ 50) with schizophrenia who were admitted for the first time to a large-scale psychiatric hospital between 2016 and 2020. The factors related to the incidence of HAP in patients were analyzed, including personal characteristics, antipsychotics, and non-antipsychotics.

Results: The HAP infection rate of hospitalized the middle-aged and elderly patients with schizophrenia was 7.8%. Chi-square analyses showed that older age, male, and $\geq$60 days of hospitalization were risk factors for HAP infection ($\chi^2 = 94.272$, $p < 0.001$; $\chi^2 = 22.110$, $p < 0.001$; $\chi^2 = 8.402$, $p = 0.004$). Multivariate logistic regression showed that quetiapine, clozapine, and olanzapine significantly increased the incidence of HAP (OR = 1.56, 95% CI = 1.05–2.32, $p = 0.029$; OR = 1.81, 95% CI = 1.26–2.60, $p = 0.001$; OR = 1.68, 95% CI = 1.16–2.42, $p = 0.006$). Antipsychotic drugs combined with aceglutamide had an effect on HAP (OR = 2.19, 95% CI = 1.38–3.47, $p = 0.001$).

Conclusion: The high HAP infection rate in hospitalized the middle-aged and elderly patients with schizophrenia may be related to the increase of age and the use of antipsychotic drugs. The types and dosages of antipsychotic drugs should be minimized while paying attention to the mental symptoms of patients.

Keywords: elder, schizophrenia, hospital-acquired pneumonia, antipsychotics, clozapine

INTRODUCTION

Hospital-acquired infections (HAI) are infections acquired at least 48 h or beyond the average incubation period after admission, not present or incubating at the time of admission (1, 2). Hospital-acquired pneumonia (HAP) is one of the most common nosocomial infections (3, 4), accounting for about 20–40% (5–7) of HAI. Previous evidence has suggested that aspiration pneumonia due to aspiration is an important mechanism for the pathogenesis of pneumonia in elder people (8–10). When aspiration occurs, oropharyngeal or gastric material is usually misdirected into the lower respiratory tract due to dysphagia or ineffective cough (11).

Studies (12, 13) have shown that schizophrenic patients, due to mental consciousness disorder and cognitive status abnormality, has higher risks of other body diseases and more difficulty obtaining better treatment effect (14) than the general population. Elderly patients with severe schizophrenia who need hospitalization are more likely to suffer from HAI, especially respiratory tract infection, due to long-term bedridden, mandatory restraint, decreased immunity, and other factors (15–17). In particular, the incidence of HAP in elderly patients with schizophrenia is higher than that in the general population (OR = 1.7) (18), and HAP is one of the main causes of death in hospitalized patients with schizophrenia (19, 20).

Leischker et al. proposed that the reduced immune function of people aged over 50 is associated with an increased risk of infectious diseases (21). Foppa et al. (22) found that the death rate from influenza increases with age over 50 and is highest in people aged over 65. Merzon's case-control study of 7,807 patients with COVID-19 found that the incidence of COVID-19 is associated with age over 50 years (23). Other studies have reported that the incidence of invasive pneumococcal disease is highest in people under 5 and over 50 years of age (21). Further researches have shown that being older than 50 is a risk factor for death from pneumonia (22, 24).

Therefore, this study analyzes the relationship between multiple indicators of the middle-aged and elderly schizophrenia patients aged 50 or above and HAP in a large-scale psychiatric hospital, in order to assess the risk factors of HAP infection in inpatients and thus formulate corresponding prevention strategies since prevention strategies based on modifiable risk factors are important for reducing HAP-related mortality in elderly patients with schizophrenia (25).

METHODS AND MATERIALS

Sample Selection and Population

The clinical data of consecutive patients admitted to a large-scale psychiatric hospital during a 4-year period from January 2016 to December 2020 were retrospectively reviewed. Patients with schizophrenia hospitalized for 3 days or more during a 5-year period were included. The diagnostic criteria were consistent with the primary diagnosis of schizophrenia (ICD-10). Other inclusion criteria included first admission, age (≥50 years), and use of any antipsychotic medication during hospitalization. The exclusion criterion was that the patient's primary information was incomplete. Subsequently, 2,617 patients with schizophrenia were enrolled. Medications (antipsychotics and non-antipsychotics), epidemic data including age, sex, marriage, hospital stay, diabetes, hypertension, and whether they had HAP were collected. This study was approved by the Institutional Review Committee of the Fourth People's Hospital of Chengdu and was designed retrospectively without written informed consent.

Use of Medicines

The second-generation antipsychotics (SGA) used in this study included clozapine, olanzapine, quetiapine, risperidone, amisulpride, ziprasidone, aripiprazole, and paliperidone. First-generation antipsychotics (FGA) included chlorpromazine, perphenazine, haloperidol, flupentixol, and sulpiride.

The non-antipsychotic drugs used in this study included sedative-hypnotic, antianxiety, antimanic, antidepression, antiepileptic, antiparkinsonian, and other neuron drugs (aceglutamide).

Statistical Analysis

Individual differences between patients with and without HAP were analyzed using Chi-square tests for categorical variables. The *Bonferroni* method was used to adjust the level of α for pairwise comparison. Univariate conditional logistic regression was initially used to compare drug use between patients with and without HAP. Covariates reasonably ($p < 0.05$) associated with HAP infection were then input into the final adjustment model. Multivariate conditional logistic regression was used to adjust the model and assess the impact of individual antipsychotics on the risk of HAP infection. SPSS 24 was used for the analyses. $p < 0.05$ was considered significant.

RESULTS

Personal Characteristics of Schizophrenia Patients

The mean age of the 2,617 the middle-aged and elderly patients with schizophrenia was 59.35 ± 7.85 years. In the patients, 203 cases were infected with HAP. The infection rate was 7.8%. Males accounted for 35.1% and females accounted for 64.9% of the HAP infected patients. The rate of infection significantly increased with age ($\chi^2 = 94.272$, $p < 0.001$) and was higher in males than that in females ($\chi^2 = 22.110$, $p < 0.001$). The rate differed between those hospitalized for less and more than 60 days ($\chi^2 = 8.402$, $p = 0.004$; **Table 1**).

Effect of Antipsychotics on HAP Infection

There were significant differences in HAP infection among patients taking different antipsychotic drugs. Patients taking SGA had a significantly higher incidence of HAP (**Table 2**). The multivariate logistic regression analysis showed that SGA, notably quetiapine, clozapine, and olanzapine, significantly increased the incidence of HAP, and the risk was 1.5–1.8 times higher than it was when these drugs were not used (95% CI = 1.05–2.32, $p = 0.029$; 95% CI = 1.26–2.60, $p = 0.001$; 95% CI = 1.16–2.42, $p = 0.006$).

TABLE 1 | Personal characteristics of HAP infection or not in hospitalized patients with schizophrenia ($N = 2,617$).

Variable		HAP Infections				χ^2	*p*-value
		No (N)	Percentage (%)	Yes (N)	Percentage (%)		
Age	50∼59	1,411	95.7	63	4.3	94.272	0.000
	60∼69	758	90.3	81	9.7		
	70∼79	214	82.3	46	17.7		
	≥80	31	70.5	13	29.5		
Gender	Male	817	88.9	102	11.1	22.110	0.000
	Female	1,597	94.1	101	5.9		
Marital status	Married	1,360	92.8	105	7.2	1.627	0.443
	Single	275	91.4	26	8.6		
	Others	779	91.5	72	8.5		
Diabetes	No	2,067	92.6	164	7.4	3.485	0.062
	Yes	1,120	93.6	77	6.4		
Hypertension	No	1,998	92.5	161	7.5	1.550	0.213
	Yes	416	90.8	42	9.2		
Hospital stay*	3∼6[a]	102	94.4	6	5.6	8.716	0.069
	7∼13[a]	256	92.8	20	7.2		
	14∼29[a]	746	93.1	55	6.9		
	30∼59[a]	691	93.1	51	6.9		
	≥60[b]	619	89.7	71	10.3		
The number of medications	1	844	92.2	71	7.8	0.294	0.863
	2	1,129	92.5	92	7.5		
	3 or more	441	91.7	40	8.3		
Total		2,414	92.2	203	7.8		

[a,b]Indicate that the difference between groups (a and b) was statistically significant after Bonferroni correction.

**Indicate significant differences when patients with hospitalization days < 60 days were combined into one group and compared with ≥60 days ($\chi^2 = 8.402$, $p = 0.004$).*

TABLE 2 | Risk analysis of antipsychotic drug use and HAP infection.

Characteristic *N* (%)	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
FGA						
Chlorpromazine	3.28	0.91–11.84	0.070	2.24	0.59–8.53	0.236
Haloperidol	0.54	0.39–0.75	0.000	0.69	0.49–0.97	0.035
Flupentixol[a]	0.00	0.00	0.999	–	–	–
Perphenazine	1.12	0.34–3.68	0.856	0.94	0.27–3.25	0.926
Sulpiride	0.98	0.60–1.60	0.922	1.02	0.60–1.73	0.936
SGA						
Quetiapine	1.59	1.10–2.29	0.014	1.56	1.05–2.32	0.029
Clozapine	1.28	0.93–1.76	0.133	1.81	1.26–2.60	0.001
Olanzapine	1.65	1.19–2.29	0.003	1.68	1.16–2.42	0.006
Risperidone	1.11	0.82–1.50	0.512	1.39	0.98–1.99	0.066
Aripiprazole	0.58	0.29–1.14	0.114	0.65	0.32–1.33	0.237
Ziprasidone	0.31	0.08–1.26	0.100	0.69	0.16–2.91	0.611
Paliperidone	0.75	0.27–2.08	0.581	0.88	0.31–2.53	0.814
Amisulpride	0.68	0.25–1.89	0.463	0.92	0.32–2.65	0.882

Crude OR (Crude odds ratio): Univariate conditional logistic regression results.

Adjusted OR (Adjusted odds ratio): Multivariate conditional logistic regression results, regression factors include: age, gender, FGA (chlorpromazine, haloperidol, perphenazine, and sulpiride), SGA (quetiapine, clozapine, olanzapine, risperidone, aripiprazole, ziprasidone, paliperidone, and amisulpride) and non-antipsychotic drugs (sedative-hypnotic, antidepression, and aceglutamide).

CI, confidence interval.

[a]The infected number of people using the flupentixol was 0.

Effects of Non-antipsychotics on HAP Infection

Since all patients were on antipsychotics, the analysis of the effect of non-antipsychotics on the occurrence of HAP was in fact an analysis of the effect of the combination of non-antipsychotics and antipsychotics. The results showed that antipsychotic drugs combined with aceglutamide had an effect on HAP (OR = 2.19, 95% CI = 1.38–3.47, $p = 0.001$; **Table 3**).

DISCUSSION

Augmented risks of HAP severely reduces the quality of life and increases the burden of disease and the risk of death in hospitalized psychiatric patients, especially those being over 50 years old (19). Numerous studies (26, 27) have focused on the risk factors for HAP in non-psychotic patients. In contrast, much fewer have address the issue in schizophrenia patients, none of which have concerned HAP risks in elder patients, who are particularly at high risk for HAI and in need of close attention.

Mechanism and Infection Rate of HAP

Our study showed that the HAP incidence in hospitalized the middle-aged and elderly patients with schizophrenia was 7.8%, which is much higher than the overall HAP incidence of 2.33% in a Chinese meta-analysis (28). It is also higher than the HAP rate of 4.17% in schizophrenia patients in Liu et al. (29). Risk factors associated with HAP in this study were age, gender, hospital stay (≥60 days), SGA (quetiapine, clozapine, and olanzapine), and non-antipsychotic drugs (aceglutamide). These findings are basically consistent with the results in previous studies (18, 30, 31).

The ward of mental institutions usually adopts closed-off management, leading to limited space for activities of patients and poor indoor ventilation. Medical staffs specialize in different domains rather than respiratory diseases and patients themselves lack desire for treatment of the diseases, which increases the likelihood to delay the prevention and recognition of respiratory diseases and in turn increases HAP incidence. The patients enrolled in this study were the middle-aged and elderly patients with the age of over 50 years, whose tissues, organs, and immune system function showed a trend of gradual decline (32, 33), leading to a higher possibility of an increasing rate of HAI.

Common Risk Factors for HAP

A significant positive correlation was found between age and HAP ($\chi^2 = 94.272$, $p < 0.001$). This may be due to the age-related changes in patients' body, e.g., the function of respiratory mucosal barrier and cough reflex (32, 33). Although the number of female schizophrenia patients was larger than that of males, the incidence of HAP in male patients was significantly higher than that in females ($\chi^2 = 22.110$, $p < 0.001$), which may be related to smoking and poor oral self-management in men. Patients with a hospital stay of ≥60 days had a higher HAP infection rate ($\chi^2 = 8.402$, $p = 0.004$). This finding is in line with previous evidence showing that long-stay patients are often associated with poorer health and more likely to receive invasive procedures or specific treatments, which may contribute to an increase in HAP (34). It suggests that the middle-aged and elderly male patients with schizophrenia who have been hospitalized for ≥60 days should be regarded as the key population for active HAP prevention.

Antipsychotic Drug Influencing Factors of HAP

The sedation and muscle relaxation effects of antipsychotics inhibit the movement function of respiratory cilia and weakened the ability of the respiratory tract to clear pathogenic bacteria, resulting in increases in pneumonia risk and HAP incidence (35). However, the effect of antipsychotic drug type on pneumonia remains controversial. Some studies (36) have reported that the use of FGA increases the incidence of acute pneumonia in hospitalized patients and leads to an increased risk of death. Others have found that SGA is associated with HAP and clozapine is particularly associated with a higher risk of pneumonia (37). There is also evidence suggesting that the use of either FGA or SGA in elderly patients with mental illness leads to an increased risk of pneumonia (35, 38).

Our study showed that SGA (quetiapine, clozapine, and olanzapine), rather than FGA, was associated with an increased risk of HAP after excluding the interaction between drugs using multivariate conditional logistic regression.

Previous research (37) has suggested that the association between pneumonia and antipsychotics may be mediated by the affinity of the drugs to the muscarinic 1 (M1) and histaminergic 1 (H1) receptor. Antipsychotic drugs competitively bind to the M1 receptor and block the M1 receptor from binding to acetylcholine, bringing about anticholinergic effects. Then, dry mouth, esophagus dilation, reduced paraperistalsis, and reflux of gastric contents eventually lead to aspiration pneumonia (39). Anticholinergic action can also cause bronchial mucus to thicken in the respiratory system, which aggravates bronchitis. Studies (35, 37, 38) have shown that clozapine has the highest affinity with M1 receptor while olanzapine and quetiapine have moderate affinity. In the present study, clozapine had the highest risk ratio for pneumonia (OR = 1.81), followed by olanzapine (OR = 1.68) and quetiapine (OR = 1.56) after adjustment for other interference factors. This also confirms that the affinity of drugs to M1 receptor does have a certain correlation with HAP. Similarly, antipsychotics that antagonize H1 receptors in the central nervous system and lead to oversedation and salivation may also contribute to the development of aspiration pneumonia (40). Drugs (quetiapine, clozapine, and olanzapine) that were strongly associated with HAP (OR > 1.5) here happen to have a high affinity for the H1 receptor, which verifies the previous conclusions about the association between HAP and the H1 receptor (37).

Plenty of studies have shown that clozapine may cause more cases of pneumonia and higher mortality than other antipsychotics (41). The possible mechanisms are as follows: (1) Clozapine is more likely to cause oversedation and salivation than olanzapine and quetiapine, thus leading to a higher risk of aspiration pneumonia (42); (2) Clozapine-induced agranulocytosis/granulocytopenia (CIAG) (43), may

TABLE 3 | Risk analysis of non-antipsychotic drug use and HAP infection.

Characteristic *N* (%)	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Sedative-hypnotic	0.69	0.52–0.93	0.013	0.89	0.64–1.23	0.474
Antianxiety	0.96	0.41–2.24	0.930	–	–	–
Antimanic[a]	0.00	0.00	0.998	–	–	–
Antidepression	1.58	1.06–2.37	0.026	1.53	0.99–2.37	0.057
Antiepileptic	1.39	0.92–2.09	0.115	–	–	–
Antiparkinsonian	0.85	0.62–1.16	0.293	–	–	–
Aceglutamide	2.35	1.53–3.61	0.000	2.19	1.38–3.47	0.001

Crude OR (Crude odds ratio): Univariate conditional logistic regression results.
Adjusted OR (Adjusted odds ratio): Multivariate conditional logistic regression results, regression factors include: age, gender, FGA (chlorpromazine, haloperidol, perphenazine, and sulpiride), SGA (quetiapine, clozapine, olanzapine, risperidone, aripiprazole, ziprasidone, paliperidone, and amisulpride), and non-antipsychotic drugs (sedative-hypnotic, antidepression, and aceglutamide).
CI, confidence interval.
[a] *The infected number of people using the antimanic was 0.*

be contributed by the immune-mediated response against haptenized neutrophils. Within the therapeutic doses range of clozapine, the proliferation of peripheral blood mononuclear cells is stimulated (44). Another potential mechanism is direct toxicity against bone marrowstromal cells (45), as well as immaturity of the neutrophil population (46); (3) Other adverse reactions (ADRs), such as intestinal obstruction caused by severe constipation and myocarditis, may be complicated with pneumonia (47). In addition, some studies have shown a strong bi-directional association between clozapine and pneumonia. When severe inflammation occurs, the metabolism of clozapine is reduced, which enhances serum clozapine concentration and further increases the risk of serum concentration related ADRs, including excessive sedation, salivation, aspiration, and even arrhythmias, resulting in a very dangerous positive feedback (47). de Leon (48) has recommended halving clozapine doses during periods of severe infection, including pneumonia, until a normal clozapine concentration is achieved.

Either olanzapine or quetiapine is an SGA similar to clozapine (49). A systemic review (50) showed that olanzapine, a new generation of antipsychotic drugs derived from clozapine, significantly reduced the side effects of oversedation, seizures, and granulocytopenia. However, olanzapine did not differ from clozapine in cardiac effects, mortality, extrapyramidal reactions (EPS), and weight gain (51). Therefore, olanzapine is also associated with a higher risk of HAP.

Although quetiapine is ideal for the treatment of schizophrenia and has fewer effects on patients' blood lipid, glucose metabolism, and body weight than clozapine or olanzapine (52), there are still side effects such as drowsiness, postural hypotension, palpitations, and dry mouth, which lead to an increased risk of HAP.

In this study, FGA use was not significantly associated with HAP, but the haloperidol group had a lower incidence of HAP. Haloperidol is the main representative of the FGA of butylbenzene. At the same dose, its antagonistic effect on dopamine receptors is 20∼40 times that of chlorpromazine and therefore it is a strong and low-dose antipsychotic drug. It is usually used shortly at the beginning of an acute episode of mental illness and discontinued after rapid control of symptoms. Thus, the most prominent EPS to FGA can be reduced or eliminated with short doses of the drug, reducing the risk of HAP.

Non-antipsychotic Risk Factors for HAP

Our results showed that non-antipsychotic drugs, such as aceglutamide, were associated with HAP, and this association persisted after controlling for other factors. Aceglutamide is used for adjuvant treatment of senile brain function decline. It passes the blood-cerebrospinal fluid barrier and breaks down into glutamate and γ-aminobutyric acid (GABA). GABA binds to GABA receptors and inhibits post-synaptic neuronal excitation. Aceglutamide injection was used in this study. When the infusion is too fast or too large, the blood concentration of the drug increases rapidly, which stimulates the norepinephrine neurons located in the ventral lateral part of the medulla oblongata, thereby inhibiting the neuronal activity of cardiac sympathetic constrictive nerve and leading to vasodilation, drop of blood pressure, and even hypovolemic shock. This may contribute to aspiration pneumonia in patients. Therefore, physicians should carefully choose adjuvant drugs apart from those for the control of patients' specialized diseases in clinical use, so as to prevent new adverse effects on patients.

CONCLUSION

In the retrospective study, we observed 2,617 inpatients aged 50 and older with schizophrenia in a large-scale psychiatric hospital from 2016 to 2020, and drew the following conclusions. Male patients with schizophrenia who are over 50 years old and have been hospitalized for more than 60 days may be at high risk for HAP in psychiatric institutions. While using SGA (quetiapine, clozapine, and olanzapine) drugs with caution, clinicians should also focus on monitoring patients for pulmonary infection. In addition, the use of adjuvant drugs such as aceglutamide should be minimized. However, this conclusion is limited by the lack of data on subjects including comorbidities, combination and dosage of antipsychotic drugs, and symptoms of schizophrenia in the literature.

LIMITATIONS

First of all, this study involves only one mental institution and data from multiple centers of different sizes should be included in the future for a hierarchical analysis. Secondly, there was a lack of interesting data on comorbidities, symptoms, and combination and dosage of antipsychotic drugs in patients with schizophrenia. The collection of the data may help understand the influence of antipsychotics on HAP from all aspects. Finally, this is a retrospective study and a prospective study may need to be designed to validate our results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Committee of the Fourth People's Hospital of Chengdu. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MY and QL searched and reviewed the literature, analyzed the data, and wrote the manuscript. CW, LL, and MX collected and analyzed the data. FY, WC, and YW searched the literature and collected data. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Prevalence of Behavioral and Psychological Symptoms of Dementia in Community-Dwelling Dementia Patients: A Systematic Review

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Background: Identifying the characteristics of behavioral and psychological symptoms of dementia (BPSD) associated with different dementia types may be a promising strategy to effectively deal with BPSD. We aimed to synthesize the prevalence rates of BPSD characteristics in community-dwelling dementia patients.

Methods: We searched Medline, EMBASE, and PsycARTICLES databases for original clinical studies published until December 2020 that enrolled at least 300 community-dwelling dementia patients. The methodological qualities of prevalence studies were assessed using the Joanna Briggs Institute's critical appraisal checklist.

Results: Thirty studies were included. The prevalence of the BPSD characteristic ranged from 4 (elation and mania) to 32% (apathy) in the pooled samples. The prevalence of delusions, anxiety, apathy, irritability, elation and mania, and aberrant motor behavior in Alzheimer's disease patients was 1.72–2.88 times greater than that in vascular dementia (VD) patients, while the prevalence of disinhibition in VD patients was 1.38 times greater. The prevalence of anxiety, irritability, and agitation and aggression, delusion, hallucinations, apathy, disinhibition, and aberrant motor behavior tended to increase as the severity of dementia increased, while that of depression, eating disorder, sleep disorders, and elation and mania tended to stable. In community-dwelling patients with dementia, the pooled prevalence of apathy, depression, anxiety, irritability, agitation and aggression, sleep disorders, and eating disorder was higher than 20%, while that of disinhibition and elation and mania was lower than 10%.

Conclusion: Overall, the pooled prevalence of apathy, depression, anxiety, irritability, agitation and aggression, sleep disorders, and eating disorder was generally high in patients with dementia. Also, the prevalence of some BPSD characteristics differed according to the type and the severity of dementia. The methodological quality of the included studies is not the best, and high heterogeneity may affect the certainty of the findings. However, the results of this review can deepen our understanding of the prevalence of BPSD.

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INTRODUCTION

Dementia is a common neurodegenerative disease in the elderly, causing a worldwide public health burden. Due to the growing aging population worldwide, the prevalence of dementia is increasing exponentially. According to the World Health Organization, the number of patients with dementia is expected to reach 115.4 million by 2050; however, this fact is largely ignored (1). Dementia is a syndrome that can be caused by various diseases, and among those, Alzheimer's disease (AD) and vascular dementia (VD) are the most common. AD is a representative cause of dementia, and once it occurs, there is no known treatment to return it to the pre-morbid state, and the gradual and irreversible decline in cognitive function adversely affects the lives of not only patients but also their caregivers, incurring significant economic and social burdens in our society (2). The clinical manifestations of dementia can generally be classified into three categories: (1) a significant decrease with respect to normative data in cognitive function, (2) the occurrence of peripheral symptoms of dementia, so-called behavioral and psychological symptoms of dementia (BPSD), and (3) the loss of autonomy in activities of daily living (3). BPSD, in particular, is not only related to poor prognosis in dementia patients, but it also increases the care burden for informal caregivers and worsens their quality of life (QoL) (4). In addition, the increased prevalence of BPSD and care burden are related to the worsening of caregivers' mental health (5). Therefore, the evaluation and management of BPSD is an important part of dementia management, along with strategies to delay cognitive decline in dementia patients.

A promising strategy for patients with dementia or patients at risk of AD is an individualized strategy (6, 7). Because BPSD is a combination of various symptoms, therapeutic strategies for patients with dementia can vary depending on each symptom (8). In addition, according to the current clinical evidence, BPSD may differ depending on the type of dementia (9). Therefore, identifying the type of dementia the patient has and the characteristics of BPSD associated with that type may be a promising strategy to effectively deal with BPSD and promote individualized management of dementia patients. However, there has not been any systematic review of the literature comparing the difference in the prevalence of BPSD by type of dementia in community-dwelling settings.

Therefore, the authors tried to synthesize the prevalence rates of BPSD characteristics in patients with dementia based on large-scale community-dwelling populations and determine the difference in the prevalence of each symptom that constitutes BPSD by dementia type. This study was limited to community-dwelling populations because referral and selection biases may exist in environments such as long-term care facilities (10).

Abbreviations: AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; CDR, Clinical Dementia Rating Scale; CI, confidence interval; DLB, dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination; NINCDS/ADRDA, National Institute of Neurological Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; OSF, open science framework; QoL, quality of life; VD, vascular dementia.

MATERIALS AND METHODS

Study Registration

The systematic review protocol was registered in the open science framework (OSF) registries (URL: https://osf.io/dmj7k). We reported this review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (**Supplementary Material 1**) (11).

Data Sources and Search Strategy

One author (CYK) searched Medline *via* PubMed, EMBASE *via* Elsevier, and PsycARTICLES *via* ProQuest, to obtain relevant studies. The search date was December 5, 2020, and all studies published up to this search date were considered. In addition, a manual search was performed on the reference lists of eligible studies and relevant review articles to collect potentially missing literature. There were no language or publication status limitations. The authors were fluent in English, Chinese, Japanese, and Korean, and for papers written in a language other than those mentioned, Google translation or, if needed, a paid service request for translation was made to an academic translation company. The search strategy used for each database is presented in **Supplementary Material 2**.

Inclusion Criteria

Regarding the study type, original clinical studies that enrolled at least 300 community-dwelling participants were included. The cutoff of 300 samples was based on the criteria of a recently published systematic review on the prevalence of dementia in Europe (12). In addition, more than 300 samples are generally considered to provide a reliable estimate of the effect size (13). For longitudinal studies, only baseline data were used. Regarding study populations, people with any type of dementia in community-dwelling settings were included. However, studies on dementia patients with other serious illnesses such as cancer and Down's syndrome, which can affect psychiatric symptoms of dementia patients and studies on patients with psychiatric disorders, which may mimic BPSD in dementia along with delirium, schizophrenia, bipolar disorder, major depressive disorder, post-traumatic stress disorder were excluded. There

were no restrictions on the patient's current treatment status. Studies on dementia patients in nursing homes or hospitals, and studies that were unclear about targeting community-dwelling populations, studies of mixed samples (i.e., including samples other than community-dwelling dementia patients), and studies with unclear sample types and sizes were also excluded. Regarding outcomes, studies that used standardized diagnostic criteria or validated assessment tools for BPSD and studies reporting raw prevalence data on BPSD in community-dwelling dementia patients were included. However, studies that estimated the prevalence of BPSD by the rate of psychotropic drug use and studies that reported only symptom score or prevalence rate without raw prevalence data of BPSD in community-dwelling dementia patients were excluded.

Study Selection

First, the authors (CYK and BL) independently screened the titles and abstracts of all searched articles to find potentially eligible studies. Second, full-texts of potentially eligible studies were retrieved independently by CYK and BL to determine whether those texts meet the inclusion criteria above. Disagreements were resolved through discussion.

Data Extraction

A standardized pilot-tested form was used to extract data from the included studies to assess study quality and evidence synthesis. The extracted information included the first author's name, publication year, country, sample size, dropout rate, dementia type, dementia severity, mean age, disease duration in participants, assessment methods, and raw prevalence data of BPSD. However, for longitudinal studies, the baseline data were collected and analyzed. The authors (CYK and BL) extracted the data independently, and any discrepancies were resolved through discussion. Additional information was requested, the corresponding author was contacted about the included studies *via* e-mail if the data were insufficient or ambiguous.

Quality Assessment

The methodological qualities of prevalence studies were assessed using the Joanna Briggs Institute's critical appraisal checklist (14). This tool assesses the quality of studies reporting prevalence data by assessing the following nine questions: *Was the sample frame appropriate to address the target population? Were study participants sampled appropriately? Was the sample size adequate? Were the study subjects and the setting described in detail? Was the data analysis conducted with sufficient coverage of the identified sample? Were valid methods used for the identification of the condition? Was the condition measured in a standard, reliable way for all participants? Was there appropriate statistical analysis?* Finally, *was the response rate adequate, and if not, was the low response rate managed appropriately?* (14). The authors (CYK and BL) independently assessed the methodological quality of the included studies, and any disagreement was resolved through discussion.

Data Synthesis and Analysis

The prevalence of BPSD characteristics in community-dwelling dementia patients according to dementia type was analyzed. The Neuropsychiatric Inventory (NPI) (15), the most widely used tool for evaluating BPSD, was prioritized. However, other BPSD evaluation tools were also used. The main characteristics of all included studies were descriptively summarized. Regarding meta-analysis, STATA/MP software version 16 (StataCorp LLC, TX, USA) was used with the random-effects model. Specifically, the Metaprop command was used to estimate the prevalence of BPSD characteristics (16). The estimated prevalence of each BPSD symptom and its 95% confidence interval (CI) were calculated by meta-analysis. The overall prevalence rate was reprocessed with the Excel office 365 program (Microsoft, Redmond, WA). The I-squared statistic was used to evaluate the degree of heterogeneity of the studies, and I-squared values >50 and 75% indicated substantial and high heterogeneity, respectively. Using available data, the authors conducted subgroup analyses according to (a) type of dementia, (b) severity of dementia, and (c) mean age of participants. Mild dementia was considered if the Clinical Dementia Rating Scale (CDR) was 0.5 or 1, or the Mini-Mental State Examination (MMSE) score was between 21 and 25. Moderate dementia was considered if CDR was 2 or MMSE was between 11 and 20. Severe dementia was considered if CDR was 3 or more or MMSE was between 0 and 10. Participants up to 75 years of mean age were considered early elderly, and those over 76 years old were considered late elderly. Moreover, sensitivity analysis removing data outliers was performed to investigate the robustness of the meta-analysis results.

Reporting Bias

For each meta-analysis, funnel plot was generated to evaluate the evidence of publication bias. However, it was meaningfully interpreted only when sufficient studies (more than 10 studies in each meta-analysis) were included.

RESULTS

Description of Studies

Among the searched 20,813 documents, titles and abstracts of 16,578 studies were screened after excluding duplicate documents. The initial screening yielded a review of the full-texts of 292 potentially eligible studies, of which 262 studies that did not meet the inclusion criteria were excluded (**Supplementary Material 3**). Finally, 30 studies were included in this review (17–46). Most studies were written in English, except for two in French (23, 24) and one in Chinese (25). Among them, 27 studies (17–33, 35–43, 46) were included in the meta-analysis (**Figure 1**).

Characteristics of the Studies

Of the 30 studies included, 18 (17–21, 23–25, 28, 30, 34, 37–42, 44) were cross-sectional studies, and of the remaining studies, 10 (22, 26, 27, 29, 32, 33, 35, 36, 43, 46) were longitudinal studies, one (31) was a retrospective study, and one (45) was baseline data from two clinical trials. Twenty

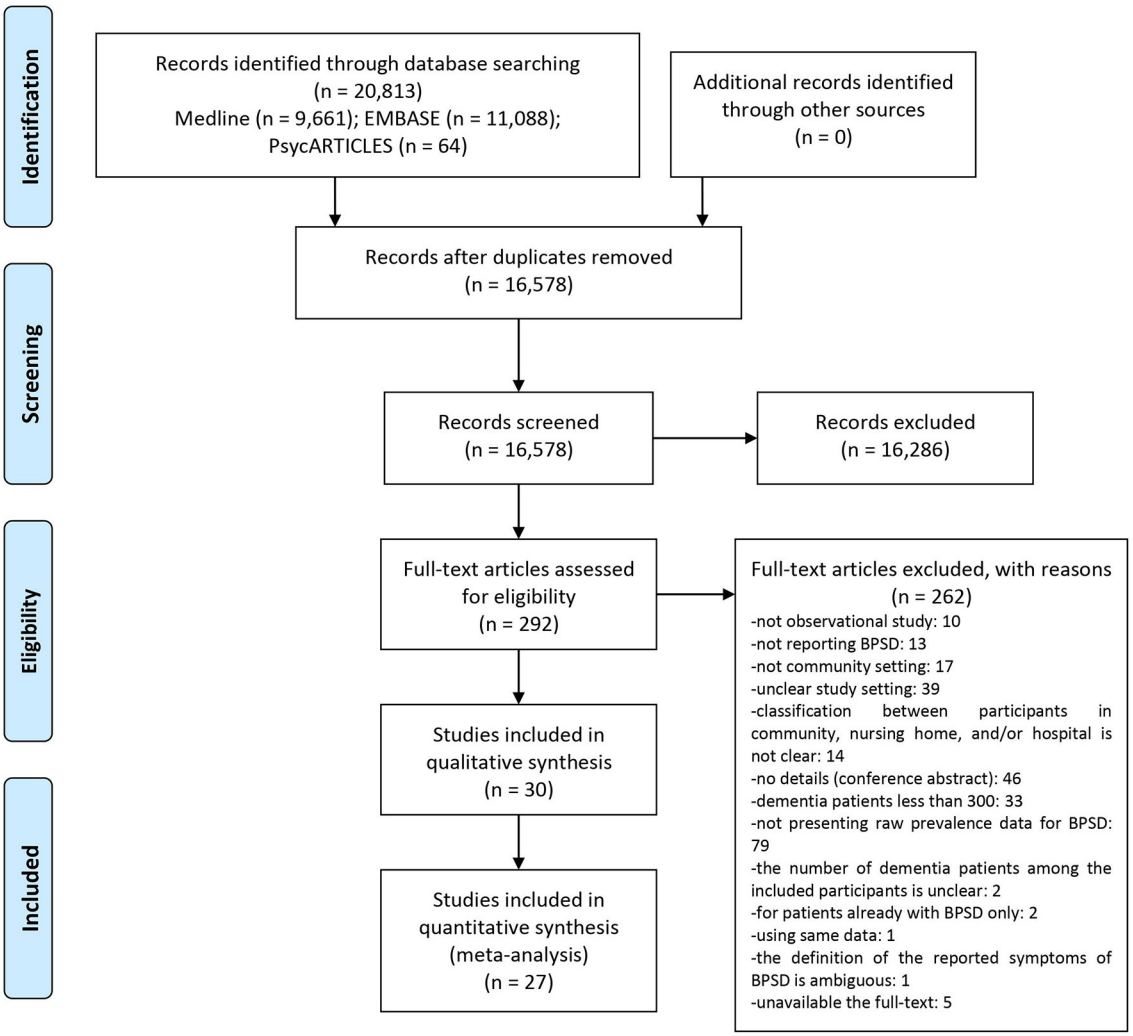

FIGURE 1 | PRISMA flow chart of this review.

studies (18–22, 27, 31–33, 36, 39, 45) were conducted in the United States, six (23, 24, 26, 29, 30, 35) in France, two (25, 37) in China, and one in Sweden (17), Canada (28), Italy (34), Norway (40), Singapore (42), and Australia (43), respectively. The remaining four studies were conducted in several countries: one (41) in Latin America, China, and India, one (38) in Peru, Mexico, Venezuela, Puerto Rico, Cuba, India, China, and the Dominican Republic, and the other two (44) in European countries (including England, Estonia, Finland, France, Germany, Netherlands, Spain, and Sweden). Nineteen studies (17, 21, 23, 24, 26, 28–30, 32–35, 37, 38, 40, 41, 43, 44, 46) did not report the ethnicity of the participants. Otherwise, except for one study (25) involving only Chinese participants, the rest (18–20, 22, 27, 31, 36, 39, 42, 45) were multi-ethnic studies. The sample size (only for community-dwelling people with dementia) ranged from 324 to 3,768. Participants' type of dementia was not specified in 8 studies (17, 25, 28, 37, 40–42, 45), and they were considered mixed samples. Ten studies (18, 21, 22, 31–33, 38, 39, 44, 46) described that they recruited two or more types of dementia patients such as AD, VD, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and/or other types. The remaining 12 studies (19, 20, 23, 24, 26, 27, 29, 30, 34–36, 43) were conducted among AD patients only. Participants' dementia diagnosis was determined using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the National Institute of Neurological Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria in most studies (17–22, 25–30, 32–39, 41, 43). Seventeen studies described baseline dementia severity of participants by using MMSE score (17–20, 24, 26–30, 33–37, 43, 46). Except for six studies (23, 31, 32, 38, 40, 41) that did not report participants' age and five studies (18, 19, 28, 34, 36) targeting early elderly; all the remaining studies targeted late elderly participants. Disease duration was

reported in 10 studies (24, 26, 30, 33–36, 43), from 8.92 months to 4.5 years. The most used assessment tool for BPSD evaluation was NPI, which was used in 21 studies (21–26, 28–30, 32–35, 37, 39–44, 46) (**Table 1**).

Risk of Bias Assessment

Ten studies (18–20, 22, 27, 31, 36, 39, 42, 45), including multi-ethnic populations, were evaluated as "Yes" for the question *"Was the sample frame appropriate to address the target population?"* One study (25), including Chinese participants only, was evaluated as "No," and remaining 19 studies (17, 21, 23, 24, 26, 28–30, 32–35, 37, 38, 40, 41, 43, 44, 46) without relevant information were evaluated as "Unclear." In addition, 22 studies (17, 18, 20–22, 26–28, 30–36, 38–40, 42–44, 46) with consecutive sampling, random sampling or all permanent residents were evaluated as "Yes," for the question *"Were study participants sampled appropriately?"* One (41) that excluded high-income earners and one (45) with two RCTs samples were evaluated as "No," and six (19, 23–25, 29, 37) without a description of the sampling method were evaluated as "Unclear." The sample size adequacy question (*Was the sample size adequate?*) showed that all studies did not present the calculation formula; however, we evaluated them as "Yes" because we included only studies with $\geq$ 300 sample size. For study subject description (*Were the study subjects and the setting described in detail?*), 22 studies (17, 19, 21, 23–25, 27–32, 34, 37–42, 44–46) were evaluated as "No" because they did not provide information, such as dementia duration, sex, race, type and severity of dementia, and the remaining eight (18, 20, 22, 26, 33, 35, 36, 43) were evaluated as "Yes" because they presented necessary information properly. All were evaluated as "Yes," for data analysis coverage (*Was the data analysis conducted with sufficient coverage of the identified sample?),* except for one study (44) that presented only "agitation cluster" prevalence without mentioning the symptom in detail. Except for three studies (19, 27, 36) that did not use valid symptom checklists or questionnaires, all other studies were evaluated as "Yes." for the question *"Were valid methods used for the identification of the condition?"* Measurement reliability question (*Was the condition measured in a standard, reliable way for all participants?*) *showed that* except for six studies (23, 25, 28–30, 36) that did not specify the evaluator, all other studies were evaluated as, "Yes." For the question, *"Was there appropriate statistical analysis?"* All studies were evaluated as "Yes." Finally, for the question, *"Was the response rate adequate, and if not, was the low response rate managed appropriately?"* The studies reported responses from all the participants, and they were evaluated as "Not applicable" except for one study (41) that under-reported missing data (**Table 2**).

Prevalence of BPSD in Community-Dwelling Dementia Patients

A study by Lessing et al. (45), which was excluded from the quantitative synthesis, reported the prevalence of agitation, aggression, and rejection as 470/509 (92.34%), 323/509 (63.46%), and 277/509 (54.42%), respectively. Because our quantitative synthesis examined agitation and aggression together, and because the screening tools used in this study were heterogeneous, which is considered a potential cause of very high symptom prevalence, the prevalence in this study was not included in the quantitative synthesis. Also, a study by Costa et al. (44), which presented only prevalence of agitation cluster as 917/1,217 (75.35%) without mentioning the symptom in detail, was excluded from the quantitative synthesis. Finally, a study by Spalletta et al. (34) presented prevalence rates of psychotic, affective, and manic symptoms, respectively as 89/1,015 (8.77%), 297/1,015 (29.26%), and 51/1,015 (5.02%), was excluded from the quantitative synthesis. This is because the classification of BPSD used in this study was very heterogeneous compared to most other studies, making meta-analysis impossible.

Quantitative synthesis was performed for the prevalence of 13 BPSD characteristics. Regardless of the dementia type, the pooled estimated prevalence of the BPSD symptoms were as follows (in descending order): apathy was (32%, 95% CI: 23–41%), depression (29%, 95% CI: 23–35%), anxiety (29%, 95% CI: 23–35%), irritability (27%, 95% CI: 22–33%), agitation and aggression (27%, 95% CI: 21–33%). Sleep disorders (21%, 95% CI: 16–27%), eating disorder (20%, 95% CI: 15–27%), delusions (19%, 95% CI: 14–24%), aberrant motor behavior (15%, 95% CI: 11–21%), wandering (15%, 95% CI: 12–19%), hallucinations (12%, 95% CI: 8–17%), disinhibition (9%, 95% CI: 5–14%), and elation and mania (4%, 95% CI: 2–6%) (**Figure 2**; **Table 3**; **Supplementary Material 4**).

Subgroup Analysis of the Prevalence of BPSD

Subgroup Analysis by Dementia Type

When analyzed according to the type of dementia, the pooled prevalence rates of BPSD characteristics in the mixed sample were as follows (in descending order): apathy (28%, 95% CI: 18–41%), sleep disorders (25%, 95% CI: 19–31%), irritability (24%, 95% CI: 17–32%), depression (22%, 95% CI: 15–30%), anxiety (22%, 95% CI: 14–30%), agitation and aggression (22%, 95% CI: 14–31%). Follwed by, eating disorder (20%, 95% CI: 12–31%), delusions (17%, 95% CI:12–24%), aberrant motor behavior (15%, 95% CI: 8–22%), wandering (15%, 95% CI: 13–17%), hallucinations (11%, 95% CI: 7–16%), disinhibition (10%, 95% CI: 4–17%), and elation and mania (4%, 95% CI: 2–7%). The pooled estimated prevalence of BPSD characteristics in AD patients were as follows (in descending order): apathy (44%, 95% CI: 35–53%), depression (39%, 95% CI: 29–51%), anxiety (38%, 95% CI: 27–50%), irritability (31%, 95% CI: 23–39%), agitation and aggression (31%, 95% CI: 24–39%), delusions (23%, 95% CI: 12–36%), eating disorder (21%, 95% CI: 19–23%). Followed by aberrant motor behavior (20%, 95% CI: 18–22%), wandering (15%, 95% CI: 13–17%), hallucinations (14%, 95% CI: 5–27%), sleep disorder (13%, 95% CI: 11–15%), disinhibition (8%, 95% CI: 5–12%), and elation and mania (4%, 95% CI: 2–7%). The pooled estimated prevalence of BPSD characteristics in VD patients were as follows (in descending order): depression (32%, 95% CI: 22–45%), agitation and aggression (32%, 95% CI: 22–45%), apathy (23%, 95% CI: 14–34%), anxiety (18%, 95% CI: 10–29%), irritability (18%, 95% CI: 10–29%). Followed by wandering (14%, 95% CI: 9–22%), hallucinations (13%, 95% CI:

TABLE 1 | Characteristics of the included studies.

Study	Setting	Country	Ethnicity	Sample size (M:F)	Dementia type	Dementia diagnosis	Dementia severity	Mean age (yr)	Disease duration	Assessment of BPSD	Assessed by
Forsell and Winblad (17)	CS	Sweden	NR	1,101 including 306 dementia patients (46:260)	NR	DSM-III-R	MMSE: -Without depression: 14.6 -With depression: 12.2	Without depression: 86.5 With depression: 87.6	NR	1. DSM-IV (major depression) 2. Comprehensive Psychopathological Rating Scale	Physicians
Klein et al. (18)	CS	US	Multiethnicity (White, etc.)	638 (212:426)	AD: 345 VD: 99 Other: 194	DSM-IV	MMSE: 16.6 ± 7.2	75.2 ± 10.2	4.0 ± 3.0 yr	1. Wandering behavior in the past 2 weeks 2. DSM-IV glossary definitions. (delusions, hallucinations) 3. DSM-IV criteria (sleep disorders) 4. CSDD (depression)	Clinicians by interviewing the patient and caregiver
Teri et al. (19)	CS	US	Multiethnicity (Caucasian, etc.)	523 (raw data was not presented for sex ratio)	AD	NINCDS-ADRDA criteria	MMSE: 20.4 ± 4.9	73.6 ± 6.9	NR	1. 21-item behavior checklist (anxiety, depression, other problematic behaviors: present or absent)	Physician by observation of patient and informant
Bassiony et al. (20)	CS	US	Multiethnicity (Caucasian, African-American, Hispanic)	342 (82:260)	AD	NINCDS/ ADRDA criteria	MMSE: 14.7 ± 7.1	77.2 ± 9.1	4.5 ± 3.0 yr	1. DSM-IV (psychotic symptoms in the past 2 weeks)	Experienced geriatric psychiatrists using input from family members, caregivers and primary care physicians
Lyketsos et al. (21)	CS	US	NR	1,002 including 329 dementia patients (123:206)	AD: 214 VD: 62 Other: 53	DSM-IV	CDR 0.5, 1.0, 2, 3–5	84.2 ± 7.0	NR	1. NPI	Trained psychometrician or nurse
Lyketsos et al. (22)	LS	US	Multiethnicity (White and Black)	842 including 362 dementia patients (132:230)	AD: 258 VD: 86 PD: 6 Other: 12	DSM-IV, NINCDS/ ADRDA criteria	NR	77 ± 5.0	NR	1. NPI	Researchers by fully structured interview of informant

(Continued)

TABLE 1 | Continued

Study	Setting	Country	Ethnicity	Sample size (M:F)	Dementia type	Dementia diagnosis	Dementia severity	Mean age (yr)	Disease duration	Assessment of BPSD	Assessed by
Arbus et al. (23)	CS	France	NR	578	AD	NR	Reisberg classification 2 or 3, 4, 5 or 6	NR	NR	1. NPI	NR
Rolland et al. (24)	CS	France	NR	571	AD	NR	MMSE: 10-29	Without wandering: 77.4 ± 7.1 With wandering: 77.6 ± 6.7	Without wandering: 1.1 ± 1.2 yr With wandering: 1.2 ± 1.2 yr	1. NPI	Based on a structured interview with a caregiver
Xie et al. (25)	CS	China	Chinese	1,540 including 373 dementia patients (223:150)	NR	DSM-IV	CDR 1 or 2	79.9 ± 9.8	NR	1. NPI	NR
Benoit et al. (26)	LS	France	NR	482 (140:342)	AD	DSM-IV, NINCDS/ ADRDA criteria	MMSE -Mild group: 23.5 ± 1.7 -Moderate group: 16.9 ± 2.6	Mild group: 77.2 ± 6.0 Moderate group:77.3 ± 7.8	Mild group: 38.9 ± 26.9 mon Moderate group: 47.4 ± 32.6 mon	1. NPI	Based on a structured interview with a caregiver
Wilson et al. (27)	LS	US	Multiethnicity (African American, etc.)	407 (134:273)	AD	NINCDS/ ADRDA criteria	MMSE -With hallucinations: 17.4 ± 4.1 -Without hallucinations: 19.7 ± 4.3	With hallucinations: 76.7 ± 6.6 Without hallucinations: 74.5 ± 7.7	NR	1. Questionnaire (hallucinations, delusions)	A structured interview administered by a trained research assistant
Peters et al. (28)	CS	Canada	NR	804 including 576 dementia patients (252:324)	NR	DSM-III	MMSE: 20.7 ± 5.6	73.0 ± 8.5	NR	1. NPI	NR
Rolland et al. (29)	LS	France	NR	682	AD	NINCDS/ ADRDA criteria	MMSE: 20.1 ± 4.5	77.4 ± 7	NR	1. NPI	NR
Benoit et al. (30)	CS	France	NR	686	AD	ICD-10, NINCDS/ ADRDA	MMSE: 20.0 ± 4.23 CDR 0.5, 1, 2, 3	77.9 ± 6.8	No apathy, no depression: 13.42 ± 13.09 mon Only depression: 8.92 ± 9.41 mon Only apathy: 13.51 ± 14.06 mon Both apathy and depression: 14.09 ± 14.82 mon	1. NPI	NR

(Continued)

TABLE 1 | Continued

Study	Setting	Country	Ethnicity	Sample size (M:F)	Dementia type	Dementia diagnosis	Dementia severity	Mean age (yr)	Disease duration	Assessment of BPSD	Assessed by
Orengo et al. (31)	RS	US	Multiethnicity (African American, Hispanic, Caucasian, etc.)	385 (383:2)	AD: 82 VD: 70 Other: 226	ICD-9-CM	NR	NR	NR	1. RAS	Administered during a telephone screen (research staff)
Steinberg et al. (32)	LS	US	NR	408	AD: 255 VD: 44 Mixed: 27 Other: 82	Diagnosed in CCSMHA (DSM–III–R, NINCDS/ ADRDA)	CDR 0.5–1, 2, 3–5	NR	NR	1. NPI	Trained examiner, through a structured interview with the caregiver
Rao et al. (33)	LS	US	NR	449 (166:283)	AD: 271 AD + VD: 31 AD + other: 16 VD: 50 Other: 81	DSM-III-R NINCDS-ADRDA, NINDS-AIREN	MMSE -With TBI: 21.8 ± 5.9 -Without TBI: 21.3 ± 5.5	With TBI: 84.54 ± 5.3 Without TBI: 85.1 ± 6.5	MMSE -With TBI: 1.8 ± 1.4 yr -Without TBI: 1.9 ± 1.3 yr	1. NPI	Administered to caregivers or to persons very familiar with the participants
Spalletta et al. (34)	CS	Italy	NR	1,015 (292:723)	AD	NINCDS/ ADRDA	MMSE: 2.7 ± 0.1	74.6 ± 0.2	2.7 ± 0.1 yr	1. NPI (10-item)	An informant rated.
Arbus et al. (35)	LS	France	NR	686 (198:488)	AD	DSM-IV, NINCDS/ ADRDA	MMSE -No depression nor antidepressants at baseline: 20.43 ± 4.09 -Depression and/ or antidepressants at baseline: 19.65 ± 4.33	No depression nor antidepressants at baseline: 77.71 ± 7.03 Depression and/ or antidepressants at baseline: 77.99 ± 6.67	No depression nor antidepressants at baseline: 13.62 ± 13.40 mon Depression and/ or antidepressants at baseline: 12.73 ± 13.38 mon	1. NPI	Are read to the caregiver
Rountree et al. (36)	LS	US	Multiethnicity (White, etc.)	641 (205:436)	AD	NINCDS/ ADRDA	MMSE: 19.5 ± 6.64	73.0 ± 8.50	3.7 ± 2.29 yr	1. Questionnaire (hallucinations, delusions)	NR
Haibo et al. (37)	CS	China	NR	1,271	NR	DSM-IV	MMSE: 16.5 ± 6.3	80.9 ± 6.3	NR	1. NPI	Neuropsychiatrist
Andreasen et al. (38)	CS	Peru, Mexico, Venezuela, Puerto Rico, Cuba, India, China and Dominican Republic	NR	17,031 including 1,612 dementia patients (359:1,251)	AD: 424 VD: 244 DLB: 55 Unspecified: 889	DSM-IV 10/66 algorithm	NR	NR	NR	1. GMS-AGECAT	Employed researcher

(Continued)

TABLE 1 | Continued

Study	Setting	Country	Ethnicity	Sample size (M:F)	Dementia type	Dementia diagnosis	Dementia severity	Mean age (yr)	Disease duration	Assessment of BPSD	Assessed by
Sadak et al. (39)	CS	US	Multiethnicity (White, Black, Hispanic, etc.)	3,768 (1,647:2,121)	AD: 3,338 DLB: 241 Behavioral variant FTD: 189	NINCDS-ADRDA (AD), Third report of the DLB Consortium (DLB), Consensus (behavioral variant FTD), NINDS-AIREN (VD)	CDR 1, 2, 3+	79 ± 6.98	NR	1. NPI-Q	Patient and family caregiver self-reports, review of medical records, and clinical evaluations
Wergeland et al. (40)	CS	Norway	NR	1,000 including 415 dementia patients (273:142)	NR	ICD-10	NR	NR	NR	1. NPI (10-item)	Physicians
Mograbi et al. (41)	CS	Latin America, China, India	NR	829	NR	DSM-IV, 10/66 criteria	CDR 0.5, 1, 2/3	NR	NR	1. NPI 2. ICD (depression)	Interview made with an informant
Vaingankar et al. (42)	CS	Singapore	Multiethnicity (Chinese, Malay, Indian)	399 (124:275)	Dementia	Semi-structured GMS-AGECAT along with CSI-D, CERAD test battery, and HAS-DDS, and also by applying the 10/66 protocol's diagnostic criteria	CDR: 2.2 ± 0.6	80.2 ± 0.3	NR	1. NPI	Trained lay interviewers to the older adults' informant
Connors et al. (43)	LS	Australia	NR	445 (222:223)	AD	DSM-IV	MMSE: 21.1 ± 5.3	78.7 ± 7.3	1.6 ± 1.9 yr	1. NPI (12-item)	A research nurse/psychologist or specialist clinician

(Continued)

TABLE 1 | Continued

Study	Setting	Country	Ethnicity	Sample size (M:F)	Dementia type	Dementia diagnosis	Dementia severity	Mean age (yr)	Disease duration	Assessment of BPSD	Assessed by
Costa et al. (44)	CS	European (England, Estonia, Finland, France, Germany, Netherlands, Spain, Sweden)	NR	1,997 including 1,217 community patients	AD, VD, Other (raw data was not presented)	Diagnosed by expert assessment (i.e, psychiatrist, neurologist, geriatrician, or general practitioner depending on countries' specific diagnostic procedures) and recorded in the medical record, MMSE score of 24 or below, and the presence of an informal caregiver (who visits at least twice a month)	NR	Agitation (+): 82.02 ± 0.22 Agitation (–): 82.88 ± 0.36	NR	1. NPI	As a structured interview with a knowledgeable informant
Lessing et al. (45)	Baseline data from two clinical trials	US	Multiethnicity (White, African-American, etc.)	509	Dementia	Physician diagnosis of dementia or MMSE scores of 23 or less	NR	82.6 ± 8.5	NR	1. ABID (aggression, agitation, rejection)	Caregiver-based rating
Holmstrand et al. (46)	LS	European (Finland, France, Germany, Netherlands, Spain, etc.)	NR	1,163 (431:732)	AD: 629 AD+VD: 71 VD: 186 FTD: 6 DLB: 23 Not specified: 185 Other: 54	NR	MMSE: median 15	With suicidal ideation: median 82 Without suicidal ideation: median 83	NR	1. NPI-Q 2. CSDD	Professionals in health or social care or by medical/ nursing/ social care students with practical experience and at least a Bachelor's degree

ABID, Agitated Behavior in Dementia Scale; AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; CCSMHA, Cache County Study of Memory Health and Aging; CDR, clinical dementia rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CS, cross-sectional study; CSDD, Cornell Scale for Depression in Dementia; CSI-D, Community Screening Interview for Dementia; DLB, dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; FTD, frontotemporal dementia; GMS-AGECAT, Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; HAS-DDS, History and Etiology Schedule–Dementia Diagnosis and Subtype; ICD, International Classification of Diseases; LS, longitudinal study; MMSE, Mini-Mental State Examination; NINCDS/ADRDA, National of Neurological Communicative Disease and Stroke and the Alzheimer's Disease and Related Disorders; NPI, neuropsychiatric inventory; NPI-Q, neuropsychiatric inventory-questionnaire; NR, nor recorded; PD, dementia due to Parkinson's disease; RAS, Ryden Aggression Scale; RS, retrospective study; US, United States; VD, vascular dementia.

CDR 0 = absent; 0.5 = questionable; 1 = present, but mild; 2 = moderate; 3 = severe; 4 = profound; and 5 = terminal.

TABLE 2 | Methodological quality of the included studies.

Study	*Was the sample frame appropriate to address the target population?*	*Were study participants sampled in an appropriate way?*	*Was the sample size adequate?*	*Were the study subjects and the setting described in detail?*	*Was the data analysis conducted with sufficient coverage of the identified sample?*	*Were valid methods used for the identification of the condition?*	*Was the condition measured in a standard, reliable way for all participants?*	*Was there appropriate statistical analysis?*	*Was the response rate adequate, and if not, was the low response rate managed appropriately?*
Forsell and Winblad (17)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Klein et al. (18)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Teri et al. (19)	Yes	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Bassiony et al. (20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Lyketsos et al. (21)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Lyketsos et al. (22)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Arbus et al. (23)	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Rolland et al. (24)	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Xie et al. (25)	No	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Benoit et al. (26)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Wilson et al. (27)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Peters et al. (28)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Rolland et al. (29)	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Benoit et al. (30)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Orengo et al. (31)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Steinberg et al. (32)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Rao et al. (33)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Spalletta et al. (34)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Arbus et al. (35)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Rountree et al. (36)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not applicable
Haibo et al. (37)	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Andreasen et al. (38)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Sadak et al. (39)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Wergeland et al. (40)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Mograbi et al. (41)	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	No
Vaingankar et al. (42)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Connors et al. (43)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable
Costa et al. (44)	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Not applicable
Lessing et al. (45)	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Not applicable
Holmstrand et al. (46)	Unclear	Yes	Yes	No	Yes	Unclear	Yes	Yes	Not applicable

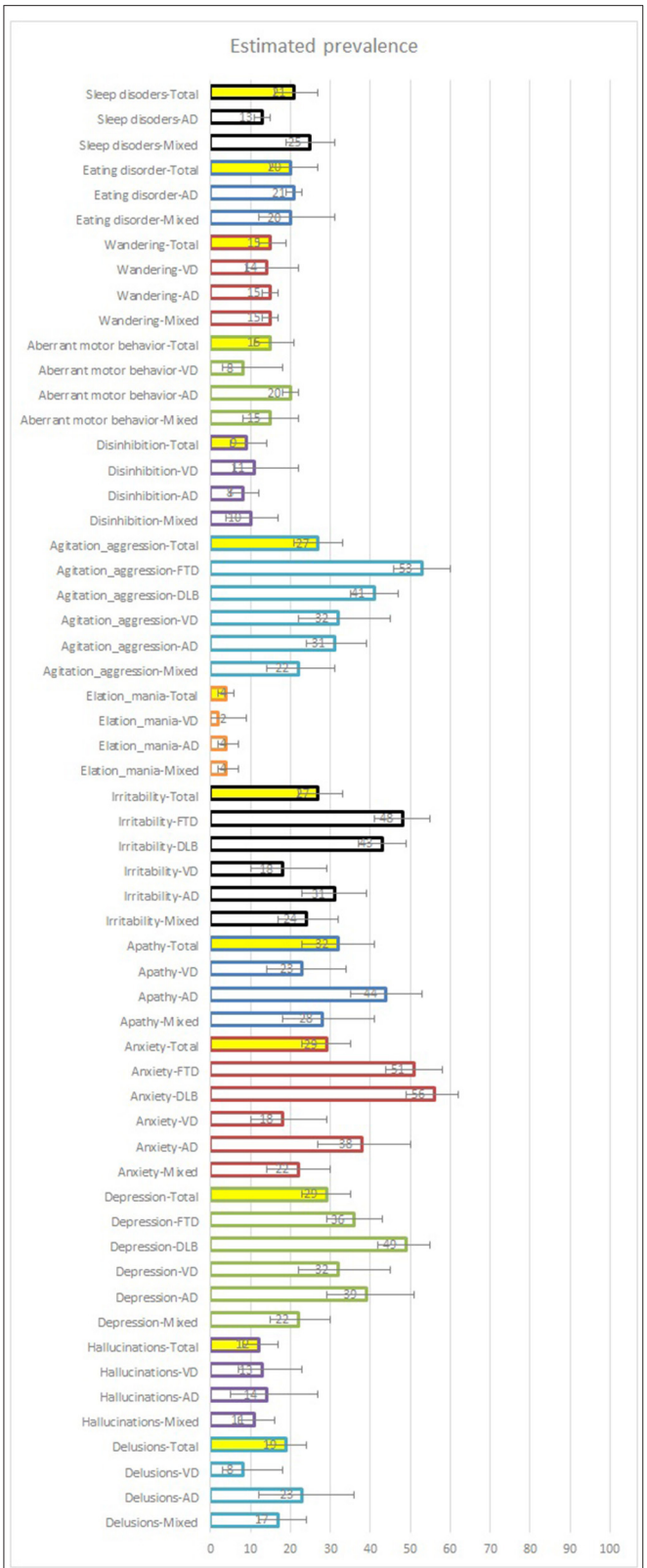

FIGURE 2 | Estimated prevalence of BPSD symptoms. Mixed samples are sample data obtained from studies that did not specify the type of dementia that the participants had. AD, Alzheimer's disease; VD, vascular dementia.

7–23%), disinhibition (11%, 95% CI: 6–22%), delusions (8%, 95% CI: 3–18%), aberrant motor behavior (8%, 95% CI: 3–18%), and elation and mania (2%, 95% CI: 0–9%). The pooled estimated prevalence of BPSD characteristics in DLB patients were as follows (in descending order): anxiety (56%, 95% CI: 49–62%), depression (49%, 95% CI: 42–55%), irritability (43%, 95% CI: 37–49%), and agitation and aggression (41%, 95% CI: 35–47%). Finally, the pooled estimated prevalence of BPSD characteristics in FTD patients were as follows (in descending order): agitation and aggression (53%, 95% CI: 46–60%), anxiety (51%, 95% CI: 44–58%), irritability (48%, 95% CI: 41–55%), and depression (36%, 95% CI: 29–43%) (**Figure 2**; **Table 4**; and **Supplementary Material 4**).

Subgroup Analysis by Dementia Severity

Among the studies that reported the participant's dementia severity at baseline, the dementia severity in the selected studies could classify the severity as mild, moderate, and severe. However, the pooled estimated prevalence of BPSD characteristics in dementia patients with severe symptoms was only available for depression, anxiety, irritability, and agitation and aggression. Among the four symptoms, mild, moderate, and severe estimated prevalence rates of anxiety (30%, 95% CI: 14–50%; 36%, 95% CI: 24–49%; 42%, 95% CI: 37–46%), irritability (30%, 95% CI: 18–44%; 34%, 95% CI: 26–43%; 39%, 95% CI: 34–43%), and agitation and aggression (26%, 95% CI: 13–42%; 32%, 95% CI: 20–46%; 56%, 95% CI: 51–61%), respectively, showed a tendency to increase with increasing dementia severity. However, that of depression (35%, 95% CI: 28–41%; 33%, 95% CI: 22–45%; 34%, 95% CI: 30–39%) maintained a relatively consistently high level in all severity levels. Among the BPSD investigated, the prevalence of depression (33–35%), anxiety (30–42%), apathy (30–42%), and irritability (30–39%) was high, whereas those of hallucinations (7–14%), elation and mania (4–6%), and disinhibition (7–12%) were low, regardless of the severity (**Table 4**; **Supplementary Material 4**).

Subgroup Analysis by Age

Based on age 75 years as the cutoff point, participants' mean age at baseline was classified into early elderly and late elderly; however, only four studies (18, 19, 28, 36) reported data of early elderly participants. The prevalence of all BPSD symptoms was higher in the early elderly than in the late elderly. Of which the respective prevalence in the early elderly was more than double that of the late elderly for delusions (35%, 95% CI: 18–54% vs. 16%, 95% CI: 11–22%), hallucinations (21%, 95% CI: 6–42% vs. 9%, 95% CI: 5–14%), and anxiety (52%, 95% CI: 49–55% vs. 25%, 95% CI: 17–34%). The same trend was observed for elation and mania (9%, 95% CI: 6–11% vs. 4%, 95% CI: 3–7%), disinhibition (27%, 95% CI: 24–31% vs. 8%, 95% CI: 3–14%), and aberrant motor behavior (36%, 95% CI: 32–40% vs. 17%, 95% CI: 11–23%). Among the BPSD investigated, the prevalence of depression (26–42%), anxiety (25–52%), apathy (33–59%), and irritability (26–43%) was high, whereas those of hallucinations (9–21%), elation and mania (4–9%), and disinhibition (8–27%) were low, regardless of the participant's age (**Table 4**; **Supplementary Material 4**).

TABLE 3 | Prevalence of BPSD in community-dwelling dementia patients.

BPSD symptoms	Dementia type	Studies	Estimated prevalence (mean, 95% CI)	I^2 value
Delusions	Mixed	12	17% (12–24%)	97.63%
	AD	7	23% (12–36%)	98.64%
	VD	1	8% (3–18%)	NA
	Total	**18**	**19% (14–24%)**	**97.96%**
Hallucinations	Mixed	12	11% (7–16%)	97.13%
	AD	8	14% (5–27%)	98.95%
	VD	1	13% (7–23%)	NA
	Total	**19**	**12% (8 to 17%)**	**98.10%**
Depression	Mixed	15	22% (15–30%)	60.39%
	AD	7	39% (29–51%)	98.53%
	VD	1	32% (22–45%)	NA
	DLB	1	49% (42–55%)	NA
	FTD	1	36% (29–43%)	NA
	Total	**20**	**29% (23–35%)**	**98.84%**
Anxiety	Mixed	12	22% (14–30%)	98.84%
	AD	6	38% (27–50%)	98.56%
	VD	1	18% (10–29%)	NA
	DLB	1	56% (49–62%)	NA
	FTD	1	51% (44–58%)	NA
	Total	**16**	**29% (23–35%)**	**98.73%**
Apathy	Mixed	11	28% (18–41%)	99.08%
	AD	4	44% (35–53%)	93.97%
	VD	1	23% (14–34%)	NA
	Total	**14**	**32% (23–41%)**	**98.84%**
Irritability	Mixed	11	24% (17–32%)	98.55%
	AD	5	31% (23–39%)	96.91%
	VD	1	18% (10–29%)	NA
	DLB	1	43% (37–49%)	NA
	FTD	1	48% (41–55%)	NA
	Total	**14**	**27% (22–33%)**	**97.97%**
Elation and mania	Mixed	10	4% (2–7%)	95.04%
	AD	4	4% (2–7%)	90.81%
	VD	1	2% (0–9%)	NA
	Total	**13**	**4% (2–6%)**	**93.59%**
Agitation and aggression	Mixed	13	22% (14–31%)	99.05%
	AD	5	31% (24–39%)	96.38%
	VD	1	32% (22–45%)	NA
	DLB	1	41% (35–47%)	NA
	FTD	1	53% (46–60%)	NA
	Total	**16**	**27% (21–33%)**	**98.67%**
Disinhibition	Mixed	11	10% (4–17%)	98.72%
	AD	4	8% (5–12%)	89.26%
	VD	1	11% (6–22%)	NA
	Total	**14**	**9% (5–14%)**	**98.18%**
Aberrant motor behavior	Mixed	10	15% (8–22%)	98.33%
	AD	4	20% (18–22%)	44.00%
	VD	1	8% (3–18%)	NA
	Total	**13**	**15% (11–21%)**	**97.48%**
Wandering	Mixed	2	15% (13–17%)	NA

(Continued)

TABLE 3 | Continued

BPSD symptoms	Dementia type	Studies	Estimated prevalence (mean, 95% CI)	I^2 value
	AD	2	15% (13–17%)	NA
	VD	1	14% (9–22%)	NA
	Total	**3**	**15% (12–19%)**	**79.85%**
Eating disorder	Mixed	6	20% (12–31%)	98.24%
	AD	3	21% (19–23%)	NA
	Total	**9**	**20% (15–27%)**	**97.21%**
Sleep disorders	Mixed	7	25% (19–31%)	96.06%
	VD	3	13% (11–15%)	NA
	Total	**10**	**21% (16–27%)**	**97.12%**

AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; CI, confidence interval; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; NA, not applicable; VD, vascular dementia.

Mixed samples are sample data obtained from studies that did not specify the type of dementia that the participants had or studies that allowed more than one type of dementia.

Sensitivity Analysis

For sensitivity analyses, data outliers were removed in several meta-analyses, including delusions, hallucinations, depression, anxiety, disinhibition, aberrant motor behavior, and sleep disorders. The frequent data outliers were Teri et al. (19), Wilson et al. (27), Peters et al. (28), Rountree et al. (36), and Holmstrand et al. (46). Thus, the sensitivity analyzes had no significant impact on the overall meta-analysis results (**Supplementary Material 4**).

Publication Bias

Funnel plots were generated for all meta-analysis results. Overall, the reported data showed high heterogeneity. Moreover, visual symmetry was confirmed in the funnel plot for only a few cases, including hallucinations with subgroup analyses of dementia severity and age of participants (in sensitivity analysis), elation and mania with subgroup analyses of dementia type, dementia severity, age of participants, and aberrant motor behavior with subgroup analysis dementia type (in sensitivity analysis) (**Supplementary Material 4**).

DISCUSSION

Summary of Findings

In this systematic review, the prevalence of BPSD in community-dwelling populations with dementia was analyzed from previously published 30 large-scale community-based studies (17–46). In particular, subgroup analyses according to the type of dementia, the severity of dementia, age of participants, as well as the individual prevalence of BPSD were conducted. Analyses of the prevalence of 13 BPSD characteristics were conducted. Overall, the prevalence of each BPSD characteristic ranged from 4 (elation and mania) to 32% (apathy) in the pooled samples, from 4 (elation and mania) to 28% (apathy) in the mixed samples, 4 (elation and mania) to 44% (apathy) in AD patients only. The same trend was observed from 2 (elation and mania) to 32% (depression) in VD patients only, 41 (agitation and aggression) to 56% (anxiety) in DLB patients only, and 36 (depression) to 53% (agitation and aggression) in FTD patients only. The prevalence rates of some BPSD characteristics were similar regardless of the type of dementia in the population. The prevalence rates of hallucinations, elation and mania, and disinhibition were low, and the rates were under 15% in the total sample as well as both AD and VD patients only. The prevalence rates of depression and agitation and aggression were high (nearly 30%), mostly in all the sample groups. Interestingly, the prevalence of some BPSD characteristics differed according to the type of dementia. In six of these cases, the prevalence of each symptom in AD patients was 1.72 to 2.88 times greater than that in VD patients: delusions (23% in AD vs. 8% in VD); anxiety (38 vs. 18%); apathy (44 vs. 23%); irritability (31 vs. 18%); elation and mania (4 vs. 2%); and aberrant motor behavior (20 vs. 8%). However, the prevalence of disinhibition in VD patients was 1.38 times greater than that in AD patients (8 vs. 11%). Little differences were found between AD and VD populations for the prevalence of the three symptoms, including hallucinations (14 vs. 13%), agitation and aggression (31 vs. 32%), and wandering (15 vs. 14%). There was not enough data to analyze eating disorders and sleep disorders. Prevalence data of BPSD in DLB and FTD populations were available only for depression, anxiety, irritability, agitation and aggression, and the overall prevalence was higher than 30%. However, since most of the prevalence data on patients with VD, DLB, and FTD are based on three or fewer studies, the reliability cannot be considered high.

Subgroup analysis according to the participant's dementia severity at baseline showed three patterns. (a) The prevalence of symptoms tended to increase as the severity increased: anxiety (30% in mild; 36% in moderate; 42% in severe), irritability (30; 34; 39%), agitation and aggression (26; 32; 56%), delusion (14; 23%; no data), hallucinations (7; 14%; no data), apathy (28; 44%; no data), disinhibition (7; 12%; no data), and aberrant motor behavior (10; 24%; no data). (b) The prevalence of symptom maintained a relatively consistent moderate-to-high level in all severity: depression (35; 33; 34%), eating disorder (22; 22%; no data), and sleep disorders (17; 21%; no data); and (c) the prevalence of symptoms maintained a relatively consistently low

TABLE 4 | Subgroup analysis of estimated prevalence of BPSD symptoms (mean, 95% CI).

	Total	Subgroup 1 (dementia type)				Subgroup 2 (dementia severity)				Subgroup 3 (participant's age)	
BPSD		**AD only**	**VD only**	**DLB only**	**FTD only**	**Mixed sample**	**Mild**	**Moderate**	**Severe**	**Early elderly**	**Late elderly**
Delusions	19% (14 to 24%)	23% (12–36%)	8% (3–18%)*	No data	No data	17% (12–24%)	14% (12–17%)*	23% (14–33%)	No data	35% (18–54%)*	16% (11–22%)
Hallucinations	12% (8–17%)	14% (5–27%)	13% (7–23%)*	No data	No data	11% (7–16%)	7% (5–9%)*	14% (7–23%)	No data	21% (6–42%)*	9% (5–14%)
Depression	29% (23–35%)	39% (29–51%)	32% (22–45%)*	49% (42–55%)*	36% (29–43%)*	22% (15–30%)	35% (28–41%)*	33% (22–45%)	34% (30–39%)*	42% (12–76%)*	26% (18–35%)
Anxiety	29% (23–35%)	38% (27–50%)	18% (10–29%)*	56% (49–62%)*	51% (44–58%)*	22% (14–30%)	30% (14–50%)*	36% (24–49%)	42% (37–46%)*	52% (49–55%)*	25% (17–34%)
Apathy	32% (23–41%)	44% (35–53%)	23% (14–34%)*	No data	No data	28% (18–41%)	28% (25–32%)*	44% (27–62%)	No data	59% (55–63%)*	33% (21–47%)
Irritability	27% (22–33%)	31% (23–39%)	18% (10–29%)*	43% (37–49%)*	48% (41–55%)*	24% (17–32%)	30% (18–44%)*	34% (26–43%)	39% (34–43%)*	43% (39–47%)*	26% (20–33%)
Elation and mania	4% (2–6%)	4% (2–7%)	2% (0–9%)*	No data	No data	4% (2–7%)	4% (2–7%)*	6% (4–9%)	No data	9% (6–11%)*	4% (3–7%)
Agitation and aggression	27% (21–33%)	31% (24–39%)	32% (22–45%)*	41% (35–47%)*	53% (46–60%)*	22% (14–31%)	26% (13–42%)*	32% (20–46%)	56% (51–61%)*	36% (32–40%)*	25% (16–34%)
Disinhibition	9% (5–14%)	8% (5–12%)	11% (6–22%)*	No data	No data	10% (4–17%)	7% (5–9%)*	12% (4–23%)	No data	27% (24–31%)*	8% (3–14%)
Aberrant motor behavior	15% (11–21%)	20% (18–22%)	8% (3–18%)*	No data	No data	15% (8–22%)	10% (7–12%)*	24% (16–32%)	No data	36% (32–40%)*	17% (11–23%)
Wandering	15% (12–19%)	15% (13–17%)*	14% (9–22%)*	No data	No data	15% (13–17%)*	No data	15% (13–17%)*	No data	17% (15–21%)*	12% (11–14%)*
Eating disorder	20% (15–27%)	21% (19–23%)*	No data	No data	No data	20% (12–31%)	22% (17–27%)*	22% (15–31%)	No data	32% (29–36%)*	19% (13–26%)
Sleep disorders	21% (16–27%)	13% (11–15%)*	No data	No data	No data	25% (19–31%)	17% (13–22%)*	21% (14–29%)	No data	26% (24–29%)*	17% (14–21%)

AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; CI, confidence interval; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; NA, not applicable; VD, vascular dementia.

**Results synthesized in three or less studies. Mixed samples are sample data obtained from studies that did not specify the type of dementia that the participants had or studies that allowed more than one type of dementia.*

level in all severity: elation and mania (4; 6%; no data). As for wandering, there were only data on moderate severity (15%); therefore, it was difficult to evaluate the difference according to severity. Subgroup analysis according to the participants' age showed that the prevalence rates of all BPSD characteristics in early elderly were 1.42 (wandering: 17% in early elderly vs. 12% in late elderly) to 3.5 (disinhibition: 27 vs. 8%) times greater than those in late elderly.

In evaluating the methodological quality of the studies using the Joanna Briggs Institute's critical appraisal checklist (14), all studies included an appropriate number of participants, and BPSD was identified with appropriate assessment tools, and statistical analysis was appropriately performed in most studies. However, it was discovered that the sampling method and study subject and setting were not described in detail in several studies.

Differences From Previous Studies

Some systematic reviews on the prevalence of BPSD have been conducted before this current review. However, the current systematic review presents findings that are different from the previous studies. For example, van der Linde et al. (47) included 59 studies and analyzed the longitudinal persistence and incidence of individual symptoms of BPSD. The study found that prevalence of depression (8–57%), anxiety (17–52%), apathy (19–51%), irritability (6–57%), and agitation (18–87%) were high in patients with dementia (47), which is consistent with our findings. Interestingly, this study also found that hyperactivity (i.e., irritability, agitation, and wandering) and apathy showed high persistence and incidence, whereas depression and anxiety showed low or moderate persistence and moderate incidence, and psychotic symptoms showed low persistence with moderate or low incidence (47). This study presents original and valuable findings but does not consider the type of dementia that may affect the occurrence of BPSD, and the authors stated that the heterogeneity of the included studies and environmental factors, which may affect BPSD, need to be considered (47). In this respect, the current findings have a distinctive strength in that, we attempt to consider the heterogeneity of the type of dementia, dementia severity, participant's age, and study settings. In particular, our study highlights that the prevalence rates of anxiety, apathy, and irritability were high in the dementia population but may be higher in patients with AD compared to patients with VD. On the other hand, those of depression and agitation and aggression were both high in AD and VD with no significant difference. As the severity of dementia increased, the prevalence rates of these symptoms also tended to increase, and they were more common in the early elderly than in the late elderly.

Similarly, Zhao et al. included 48 articles and analyzed the prevalence rate of each BPSD symptom in AD patients (48). They emphasized that among BPSD symptoms, the prevalence rates of apathy (49%), depression (42%), aggression (40%), anxiety (39%), and sleep disorder (39%) was the highest in patients with AD (48), which is generally consistent with our findings in AD samples, except for sleep disorder (13%). However, only three studies supported the prevalence of sleep disorders in our review, potentially explaining these differences. Likewise, this study was similar to the current review, except that it was limited to AD patients, was based on studies with sample sizes of 50 or more, and the study settings were not limited (48). However, as shown in the meta-regression results of this study, the study setting may be a factor explaining the difference in the heterogeneity of BPSD prevalence across included studies (48). On the other hand, the current review targets a large sample of more than 300 participants and attempts to reduce potential heterogeneity by confining the study setting to community studies.

Finally, Feast et al. analyzed BPSD, especially in terms of challenges for family carers, including 25 high-quality studies (49). However, this study was not intended to estimate the prevalence of BPSD but to analyze the characteristics of the challenging behavior of patients with dementia for caregivers in family care settings. In addition, this systematic review did not also consider the type of dementia, dementia severity, participant's age, and study settings of the original studies (49). Therefore, the findings in the current review can help expand knowledge about BPSD by combining these findings with those in the existing reviews.

Clinical Implications

Understanding individual BPSD characteristic is important in establishing individualized management strategies for dementia patients in clinical settings. Our analysis found frequent and rare symptoms depending on the type of dementia. According to our findings, apathy, depression, anxiety, irritability, agitation and aggression were common individual BPSD symptoms in AD patients, and depression and agitation and aggression were common in VD patients. In both cases, elation and mania was rare. Data on the prevalence of BPSD in patients with DLB and FTD were very limited due to the lack of relevant studies. Interestingly, as the severity of dementia evaluated by MMSE and/or CDR increased, the prevalence rates of most BPSD characteristics, including anxiety, irritability, agitation and aggression, delusion, hallucinations, apathy, disinhibition, and aberrant motor behavior, increased. However, in the other subgroup analysis, all BPSD prevalence was higher in the early elderly group than in the late elderly group. Considering that the severity of dementia usually increases with age, these results may seem contradictory. We present some hypotheses potentially relevant to this issue. **First**, the most important factor is the lack of data on early elderly among the studies included. The prevalence of BPSD in this population was all based on three or fewer studies. Therefore, in our findings, the prevalence of BPSD in patients with early elderly dementia may have been exaggerated by a small number of studies. **Second**, data on the prevalence of BPSD in severe dementia in this review were mostly absent. However, previously published studies have pointed out that the complaints of some BPSD may be underestimated as the cognitive decline of dementia patients increases (50). That is, the prevalence of BPSD in patients with severe dementia might be underestimated, and our review did not include enough data to investigate it. However, it could potentially be related to the lower prevalence of BPSD in the late elderly population compared to the early elderly population. **Third**, considering that most included studies were on the late elderly, the increase in

the prevalence of BPSD with increased dementia severity may be more relevant data for late elderly dementia patients. In addition, dementia severity and the age of participants might be related to the prevalence of BPSD as independent factors.

Strengths and Limitations

This study systematically reviewed large-scale studies of community-based populations for the first time to understand the characteristics of BPSD incidence in dementia patients. In addition, subgroup analysis according to the type of dementia, dementia severity, and age of participants were used to analyze potential factors related to the prevalence of BPSD. However, the results of this study should be interpreted carefully considering the following limitations:

First, since the data extracted from the studies included in this review were cross-sectional, they did not show the longitudinal trajectory of BPSD. Although our subgroup analysis estimated the trajectory of BPSD symptoms according to MMSE and/or CDR of participants and, it was not for the same population; therefore, it cannot be called a longitudinal trajectory in a strict sense. However, our study may present some findings that are useful for reference in future longitudinal studies. For example, a future longitudinal study could investigate whether some symptoms, such as anxiety, irritability, agitation and aggression, delusion, hallucinations, apathy, disinhibition, and aberrant motor behavior, will increase with increased dementia severity. Will others (e.g., depression, eating disorder, sleep disorders, and elation and mania) remain high or low, and will there be changes according to the progression of dementia and aging of participants? **Second**, one of the major limitations of this review is the heterogeneity in the characteristics of the included patients. Although we limited the studies included in this review about patients with dementia in community-dwelling settings, we cannot rule out the possibility of other various factors, such as the patient's country of residence, race/ethnicity, sex/gender, and underlying diseases, influencing BPSD occurrence. For example, according to a study comparing the prevalence of BPSD in dementia patients in Korea and the UK, the British participants had higher BPSD symptoms except for aggression than the Korean participants (51). However, studies are still required to compare the prevalence or severity of BPSD symptoms according to the population characteristics. This not only enables individualized dementia strategies in the future but can also help to understand the pathogenesis of dementia, including genetic-environmental interactions (52). **Third**, the lack of relevant studies to be included is also a weakness of this review. In particular, there were not enough studies for subgroup analysis, and most of the data on mild and severe VD, DLB, FTD, dementia, and the early elderly were based on three or fewer studies. There were rare reports of dementia type-specific prevalence of BPSD, other than that of AD. This is probably due to the low prevalence of other types of dementia. However, it is still important to identify individual BPSD characteristics in other types of dementia. For example, recently, a study of clinical neuroscience at the University of Cambridge has shown that apathy is an early marker of FTD, and it predicts subsequent cognitive decline (53). Likewise, understanding the occurrence of some BPSD may facilitate early management, as well as personalized management of dementia. In addition to the type of dementia, the prevalence of BPSD according to the severity of dementia, especially in severe dementia, was insufficiently reported. In terms of age, the prevalence of BPSD was mostly focused on the "late elderly." Moreover, there may be other factors to consider to understand the differences in BPSD prevalence. For example, although not a large study, Indian researchers found that patients with late-onset AD had significantly higher severity of delusions, agitation, anxiety, disinhibition, and nighttime behavioral disturbances than those with early-onset AD (54). Also, a study in Japan, though not community-based, examining the relationship between severity of dementia and BPSD, demonstrated that patients with DLB did not show a significant difference in the NPI total score according to CDR staging (55). However, as the CDR increased in the AD group, the NPI total score also increased (55). The difference in the prevalence of BPSD according to patient age or the severity of dementia and potentially the difference between the types of dementia could be further investigated in a community-dwelling sample. **Fourth**, since this study only included large-scale studies involving more than 300 samples, it was not possible to detect the source of potential publication biases such as small-study effects in this field. In addition, heterogeneity of data and potential publication bias were confirmed in most meta-analysis results in the funnel plots. **Fifth**, the scope of our review is the prevalence of BPSD, but not the severity of BPSD. Therefore, the findings cannot be used as reference to confirm the severity of BPSD in community-dwelling patients with dementia. However, the severity of BPSD as well as the prevalence of BPSD has an important influence on the care burden; thus, it is a subject of high research value. **Finally**, the heterogeneity of the assessment tools used to evaluate the prevalence of BPSD in the included studies is also a major limitation of this systematic review. For example, even with the same conditions, heterogeneity in the prevalence of sleep disorders diagnosed by the DSM criteria (18) and the prevalence of sleep disorders screened by NPI (22) is inevitable. Moreover, in the included studies using NPI, there were studies in which the cut-off score for presence of BPSD was 1 point (21, 32, 35, 39, 41, 42), 4 points (22, 23, 25, 34, 37, 40, 44), or not specified (24, 26, 28–30, 33, 43, 46). The low cut-off score on the NPI for frequency of BPSD, are of poor clinical significance and risk to blur evidence increasing prevalence unrealistically. Therefore, our findings should be interpreted with caution.

Suggestions for Future Research

Based on the findings and limitations of this review, we would like to suggest areas to consider in future research in this field. **First**, current large-scale community-based studies on BPSD lack long-term longitudinal follow-up. Long-term longitudinal follow-up studies will deepen our understanding of the characteristics of BPSD, especially in terms of persistence and incidence of individual BPSD according to the type and severity of dementia and the age of participants. **Second**, the patient's country of residence, race/ethnicity, sex/gender, and underlying diseases, as well as the type of dementia and the study setting should be fully considered as potential factors

that can affect the characteristics of BPSD. Ideally, it would be possible to build a multinational cooperative community to compare the characteristics of BPSD across countries based on a homogeneous research setting. **Third**, comparing the BPSD characteristics of non-community-dwelling samples to those of community-dwelling samples may also be a promising research topic, though this may not have been of interest in this study. As described in the introduction section, the current review excluded nursing home or hospital inpatient samples due to referral and selection biases. Criteria for referral of BPSD patients to these long-term care facilities may vary cross-sectionally and/or longitudinally across cultures, regions, countries, and eras. Therefore, considering the possibility that there will be differences in these criteria for referral, it is thought that it will be possible in future studies to comprehensively review and compare the prevalence of BPSD according to each study setting.

CONCLUSIONS

This systematic review tried to analyze the prevalence of BPSD in community-dwelling samples from 13 previously published large-scale studies. Overall, the pooled prevalence of apathy, depression, anxiety, irritability, agitation and aggression, sleep disorders, and eating disorder was higher than 20%, while that of disinhibition and elation and mania was lower than 10%. Interestingly, the prevalence of some BPSD characteristics differed according to the type of dementia. The prevalence of delusions, anxiety, apathy, irritability, elation and mania, and aberrant motor behavior in AD patients was 1.72–2.88 times greater than that in VD samples, while the prevalence of disinhibition in VD patients was 1.38 times greater than that in AD patients. Moreover, the prevalence of some symptoms, including anxiety, irritability, agitation and aggression, delusion, hallucinations, apathy, disinhibition, and aberrant motor behavior, tended to increase as the severity of dementia increased, while that of depression, eating disorder, sleep disorders, and elation and mania tended to be stable. The methodological quality of the included studies is not the best, and high heterogeneity may affect the certainty of the findings. However, the results of this review can deepen our understanding of the prevalence of BPSD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The study was conceptualized by C-YK. The study search, study screening, data extraction, and quality assessment were conducted, and the manuscript was drafted by C-YK and BL. Both authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.741059/full#supplementary-material

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Comorbidity and Treatment in Older Psychiatric In-patients—A Retrospective Study in a Chinese Psychiatric Hospital

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Background: Comorbid somatic diseases increase the death risk and affect the condition, treatment, and prognosis of older psychiatric patients. We investigated the comorbidity and drug treatment in older patients with psychosis.

Methods: This retrospective study used data from 3,115 older psychiatric in-patients hospitalized at the Shanghai Mental Health Center Affiliated to Shanghai Jiaotong University School of Medicine, China discharged from 2005 to 2015. Descriptive analyses of patients' age, sex, treatment drugs, diagnoses (based on ICD-10), and time trend were performed.

Results: Patients' median age was 56 (range, 50-98) years; 1,824 (58.6%) were female. The top five first-level diagnoses were schizophrenia (F20) (n = 1,818, 58.3%), depressive episode (F32) (n = 457, 14.6%), bipolar affective disorder (F31) (n = 151, 4.8%), manic episode (F30), (n = 143, 4.6%), and vascular dementia (F01) (n = 136, 4.4%). Mental (99.9%), central nervous system (85.2%), digestive system (83.5%), cardiovascular system (72.5%), and anti-infective (59.6%) drugs had the highest prescription rates. The combined use of antidepressants, anti-anxiety, anti-arrhythmic, hormones and endocrine system drugs were significantly higher in female than in male patients, while mood stabilizers and genitourinary system drugs significantly more frequent in men. With increasing age, the F20-F29 patients decreased, while F00-F09 patients increased, with the corresponding changes to prescription in those patients. In comparison to that in 2005-2010, the combined prescriptions for genitourinary and cardiovascular drugs increased between 2011 and 2015, and F00-F09 and F40-F48 older patients doubled, accordingly anti-Alzheimer's disease drugs and antidepressants more than doubled. F30-F39 patients increased by 49.1%, and anti-anxiety drugs, mood stabilizers, etc. increased by ≥50%; F20-F29 older patients decreased by 26.7%, while antipsychotics only increased by 4.4%.

Conclusions: This study found the combined drug treatment of somatic diseases, particularly for central nervous, digestive, cardiovascular, respiratory and genitourinary drugs were extremely common among older psychiatric in-patients in China. With increasing age, the F20-F29 patients decreased, while F00-F09 patients increased; the antipsychotics prescriptions decreased, and almost all comorbidity drugs increased. Compared with that in 2005-2010, the older patients with all diagnosis except F20-F29 increased in 2011-2015, and the prescriptions for psychotropic, genitourinary, and cardiovascular drugs increased.

Keywords: older psychiatric patients, somatic comorbidity, combined drug treatment, polypharmacy, mental illness

INTRODUCTION

The worldwide population is aging (1). A direct consequence of an aging population and increasing social pressure is a surge in the number of older mental patients (2). Studies have shown that about 2% of older people suffer from severe mental illness (3). A cross-sectional epidemiological survey from China showed that the weighted 12-month prevalence of mental disorders in patients >65 years old was 4.0% (2.8-5.2%) (4). Another semi-structured interview study from Nepal (5) showed that about 18% of patients >60 years of age may have a diagnosable mental illness, suggesting that older patients are more likely to suffer from diagnosable mental illness.

Older patients with mental disorders, especially severe mental diseases, suffer from more physical and cognitive impairment and social function disability (6), which further damages their physical health. Compared with regular older patients, the risk of somatic comorbidity with mental illness doubles, and the risk of multiple ($\geq$2) somatic diseases increases significantly (odds ratio = 4.1) (7). In fact, about 30-64% of older psychiatric patients suffer from $\geq$1 physical diseases (7–10). As many as 75% of older mental patients re-admitted to hospital suffer from physical comorbidities (11), particularly those affecting the cardiovascular, respiratory, nervous, endocrine, and digestive systems (11, 12), which may be related to an unhealthy lifestyle and diet (e.g., excessive smoking, insufficient dietary intake, and irregular diet) (13–15), side effects of psychotropic drugs (16), metabolic disorders (17), physical activity limitations, and lack of physical exercise (7, 17).

Physical comorbidities increase the risk of death in older patients with psychosis (18); a previous study reported that the mortality rate in older patients with psychosis was almost tripled than that of older persons with mental health (18.0 vs. 9.7%) (19). Simultaneously, physical comorbidities could also affect the severity of mental illness symptoms (20), increase the emergency admission rate, prolong the hospital stay, and increase the number of rehospitalizations (19, 21). Therefore, rapid and effective treatment of the physical comorbidities may greatly benefit the treatment and prognosis of mental illness. However, as attention may focus only on the mental illness, older patients with mental illness may not seek treatment for physical complications (13, 14, 16), or the necessary physical examination could be lacking (22); in such cases, the physical comorbidities may not be found (23–25), have a delayed diagnosis (11), or be improperly treated (23, 26–28). In general hospitals, >52% of older patients took hypnotics or psychotropic drugs (29) or received $\geq$1 psychotropic drug treatment (30) during hospitalization. As many as 84.8% of the in-patients in psychiatric hospitals with severe mental illness have somatic comorbidities, of which 77.7% use drugs for the treatment of somatic comorbidities, and 67.7% multi-drug combination therapy (31).

In many countries, psychiatric and physical diseases are often treated in different hospitals, and doctors often not allowed to access the diagnosis and treatment records of other hospitals due to patient privacy, data protection, and medical system isolation (32). As a result, psychiatric hospitals are often unable to assign a comprehensive and professional diagnosis of physical diseases. In the actual process of diagnosis and treatment, doctors in psychiatric hospitals generally rely on patients or their relatives to provide the diagnosis and treatment records from the general hospital. Therefore, this study aimed to retrospectively analyze relevant data on prescription use of psychotropic drugs and somatic disease treatment drugs in older psychiatric patients to indirectly study the somatic complications and drug treatment of older psychiatric patients, thereby providing new clues for the treatment of somatic complications in older patients with mental illness.

MATERIALS AND METHODS

Study Design and Database

This retrospective, observational, single-center, cross-sectional study was performed at the Shanghai Mental Health Center Affiliated to Shanghai Jiaotong University School of Medicine (China), the second largest psychiatric hospital in China. Data were extracted from the electronic prescription and administration databases. For this study, available drug prescription charts of older in-patients with mental illness, aged $\geq$50 years, discharged from the hospital between January 2005 and October 2015 were analyzed, without any limit in the diagnosis and medication. The database also listed all medications administered to the patient by the medical staff during their stay. All data related to personal identification information, such as name and hospitalized identification number, were anonymized and encoded as data files. If a patient

was hospitalized twice or more during the study period, they were not counted as a new patient provided the International Classification of Diseases (ICD-10) diagnosis remained. The study was approved by the ethics committee of Shanghai Mental Health Center.

The demographic data collected included sex, age at admission, ICD-10 psychiatric diagnosis at discharge, and number and duration of hospitalizations. For the present study, the main psychiatric diagnoses were categorized according to the ICD-10 as follows: (1) organic, including symptomatic, mental disorders (F00-F09); (2) mental and behavioral disorders due to psychoactive substance use (F10-F19); (3) schizophrenia, schizotypal, and delusional disorders (F20-F29) (4) mood [affective] disorders (F30-F39); (5) neurotic, stress-related, and somatoform disorders (F40-F48); and (6) other mental and behavioral disorders (F50-F99). We then analyzed the drug treatment of somatic diseases among the top five diagnoses with the highest number of patients, including schizophrenia (F20), depressive episode (F32), bipolar affective disorder (F31), manic episode (F30), and vascular dementia (F01). Detailed information regarding the primary, secondary, and tertiary diagnoses and subtypes of disease classification based on the ICD-10 is displayed in **Supplemental Table 1**.

All prescribed psychotropic drugs were administered throughout the entire hospital stay. All treatment drugs were analyzed, except those applied topically or Chinese traditional medicine, which may have an ambiguous or unknown mechanism of action. Based on the use and targeted treatment organs/systems, the therapeutic drugs were divided into 11 categories, which are defined in detail in **Table 2**. The first three drug categories (psychotropic drugs, central nervous system drugs, and cardiovascular system drugs) were subdivided based on differences in pharmacological effects (**Table 2**). As during the hospitalization period, patients may receive drugs in different categories or several subcategories within the same category, in this study, we only studied categories or subcategories of drugs without considering the specific drugs; that is, regardless whether the patient used 1 or $\geq$2 drugs in these category, the patient was included in this category of drugs.

Statistical Analysis

We performed a descriptive analysis of the following parameters: age, sex, number of patients receiving a specific kind of drug, and specific category diagnosis. Categorical variables are expressed as numbers (percentages), while continuous variables are presented as medians and ranges, if not normally distributed. Changes in patient numbers were assessed using the Kruskal-Wallis test, and changes in drug frequency tested using the Chi-square test. Differences were considered statistically significant at $P < 0.05$. Analyses were conducted using SPSS version 19.0.

RESULTS

Demographic Data

A total of 6,745 inpatient records were available for extraction, and 3,115 patients included in the analysis by excluding repeated hospitalization records. Of these, 1,291 (41.4%) were men, with a median age of 55 (range, 50-98) years, and 1,824 (58.6%) were women, with a median age of 56 (range, 50-98) years ($z = -3.219$, $P = 0.001$) (**Supplemental Table 2**). **Table 1** shows the distribution of the number of older patients according to age, as well as their main diagnoses based on ICD-10. The most common diagnoses included F20-F29, F30-F39, and F00-F09. Patients with the above three diagnoses accounted for 95.1% ($n = 2{,}962$) of the total number of patients in this study. The remaining 153 patients belonged to the other diagnostic categories. Among them, significantly more ($P < 0.0001$) males than females were diagnosed with mental and behavioral disorders due to psychoactive substance use (F10-F19); however, significantly more female patients were diagnosed with mood [affective] disorders (F30-F39) than male patients ($P = 0.048$). In addition, age differences were significant among patients with different diagnoses ($P < 0.0001$); patients with F00-F09 diagnoses were significantly older than those in the other diagnosis categories (**Supplemental Table 2**).

TABLE 1 | Characteristics of the study population.

Characteristics	Frequencies
Total patients	3,115
- Gender, *n* (%)	
- Male	1,291 (41.4)
- Female	1,824 (58.6)
- Age in years, median (range)	56 (50-98)
- Subgroups divided by age (years, yr)	n (%)
- 50-59 yr	2,117 (67.9)
- 60-69 yr	638 (20.5)
- 70-79 yr	252 (8.1)
- 80-89 yr	96 (3.1)
- 90-99 yr	12 (0.4)
Diagnosis based on ICD-10, *n* (%)	n (%)
- Organic, including symptomatic, mental disorders (F00-F09)	242 (7.8)
- Mental and behavioral disorders due to psychoactive substance use (F10-F19)	34 (1.1)
- Schizophrenia, schizotypal and delusional disorders (F20-F29)	1,969 (63.2)
- Mood [affective] disorders (F30-F39)	751(24.1)
- Neurotic, stress-related and somatoform disorders (F40-F48)	83 (2.7)
- The other mental and behavioral disorders based on ICD-10 (F50-F99)	36 (1.2)

Drug Treatment and In-patient Gender

Table 2 summarizes drug prescription types and rates in older in-patients. The prescription rate of psychotropic drugs in female patients was higher than in male patients, a difference was statistically significant for antidepressant drugs (male 36.9% vs. female 47.3%; $P = 638e\text{-}9$), mood stabilizers (male 44.0% vs. female 40.2%; $P = 0.034$), and anti-anxiety drugs (male 45.4% vs. female 51.9%; $P = 0.0003$). The combined use of antiarrhythmic drugs (male 15.3% vs. female 22.5%; $P = 4.5208e\text{-}7$) and anti-heart failure, anti-shock, and circulatory system drugs (male,

TABLE 2 | Most frequently used drugs of older psychiatric in-patients comorbid somatic diseases in this study.

	Total *n* (%)	Men *n* (%)	Women *n* (%)	$\chi 2$, *P*
1. Psychotropic drugs	3,113 (99.9)	1,290 (41.4)	1,823 (58.6)	0.000, 1.000
1.1 antipsychotics	3,093 (99.3)	1,283 (41.5)	1,810 (58.5)	0.236, 0.627
1.2 antidepressants	1,339 (43.0)	476 (35.5)	863 (64.5)	33.638, **6.638E-9****
1.3 mood stabilizer	1,301(46.8)	568 (43.7)	733 (56.3)	4.513, **0.034***
1.4 anti-anxiety drugs	1,533 (49.2)	586 (38.2)	947 (61.8)	12.888, **0.0003****
1.5 sedative hypnotic drugs	1,430(45.9)	547 (38.3)	883 (61.7)	11.105, 0.001
1.6 anti-Alzheimer's drugs	857 (27.5)	356 (41.5)	501 (58.5)	0.004, 0.947
2. Central nervous system drugs	2,655 (85.2)	1,115 (42.0)	1,540 (58.0)	2.254, 0.133
2.1 antiepileptics and anticonvulsants	2,124 (68.2)	905 (42.6)	1,219 (57.4)	3.725, 0.054
2.2 anti-tremor paralytic drugs	1,318 (42.3)	533 (40.4)	785 (59.6)	0.950, 0.330
2.3 brain metabolism and circulation improvers	462 (14.8)	187 (40.5)	275 (59.5)	0.210, 0.647
2.4 analgesics / antipyretics, analgesics, analgesics	390 (12.5)	179 (45.9)	211 (54.1)	3.642, 0.056
2.5 nerve center agonists, vertigo drugs and other central drugs	776 (24.9)	338 (43.6)	438 (56.4)	1.900, 0.168
3. Cardiovascular drugs	2,257 (72.5)	935 (41.4)	1322 (58.6)	0.001, 0.974
3.1 antihypertensive drugs	1,498 (48.1)	638 (42.6)	860 (57.4)	1.560, 0.212
3.2 lipid regulating drugs	283 (9.1)	107 (37.8)	176 (62.2)	1.695, 0.193
3.3 hypoglycemic drugs	781 (25.1)	327 (41.9)	454 (58.1)	0.077, 0.781
3.4 antiarrhythmic drugs	608 (19.5)	197 (32.4)	411 (67.6)	25.458, **4.521E-7****
3.5 antithrombotic drugs	101 (3.2)	47 (46.5)	54 (53.5)	1.114, 0.291
3.6 anti-angina and coronary heart disease drugs	442 (14.2)	188 (42.5)	254 (57.5)	0.252, 0.616
3.7 anti-heart failure, anti-shock and other drugs for improving circulatory system	1,042 (33.5)	397 (38.1)	645 (61.9)	7.218, **0.007****
4. Digestive tract drugs	2,602 (83.5)	1,068 (41.0)	1,534 (59.0)	1.038, 0.308
5. Genitourinary drugs	506 (16.2)	239 (47.2)	267 (52.8)	8.341, **0.004****
6. Drugs related to bone and joint	459 (14.7)	185 (40.3)	274 (59.7)	0.288, 0.591
7. Respiratory drugs	442 (14.2)	195 (44.1)	247 (55.9)	1.517, 0.218
8. Hormone and endocrine system drugs	391 (12.6)	137 (35.0)	254 (65.0)	7.561, **0.006****
9. Vitamins, minerals and other nutrients	1,546 (49.6)	604 (42.9)	882 (57.1)	2.864, 0.091
10. Anti-tumor drugs	138 (4.4)	38 (27.5)	100 (72.5)	11.510, **0.001****
11. Anti-infective drugs	1,857 (59.6)	783 (42.2)	1,074 (57.8)	0.983, 0.332

The values in bold indicated that the P- value was statistically significant. $^{*}P < 0.05$, $^{**}P < 0.01$.

30.8% vs. female 35.4%; $P = 0.007$) was significantly higher in females than in males; however, male patients (18.5%) received significantly more genitourinary drugs than females (14.6%). In addition, combinations of hormone and endocrine system drugs ($P = 0.006$) and anti-tremor paralytic drugs ($P = 0.001$) also showed significant gender differences. There were no gender differences in the prescription rates of other therapeutic drugs, including those targeting the central nervous system, digestive tract, bone and joint complications, and respiratory system.

Drug Treatment and Psychiatric Diagnosis

We divided the patients into six different first-class diagnostic categories according to the ICD-10 classification criteria and the number of patients and analyzed the relationship between disease diagnoses and the percentage of combination medication (**Supplementary Table 3**). We focused on the top five first-class diagnoses with the largest number of patients (F20, F32, F31, F30, and F01) and the utilization rate of combined treatment drugs for somatic diseases (**Table 3**). The results showed that regardless of the diagnostic classification, psychotropic drugs, especially antipsychotics, had the highest prescription rate (**Supplementary Table 3**).

In patients diagnosed with mood [affective] disorders (F30-F39), the combined use of antidepressants (72.6%) and mood stabilizers (57.3%) was the most common. It is worth noting that even if they were in the same diagnosis in the scope of F30-F39, the combined use of somatic disease treatment drugs would change due to the different primary diagnoses of the patient. To be exact, in addition to the above two drug categories (antidepressants and mood stabilizers), anti-inflammatory drugs (72.2%) were most common in patients with a depressive episode (F32), and antiepileptic and anticonvulsant drugs (74.8%) were most common in patients with bipolar affective disorder (F31). However, compared with several other first-level diagnoses, the combination of cardiovascular drugs (62.9%) and antidepressants (27.3%) were seldom used in patients with manic epochs (F30). Patients with bipolar affective disorder (F31) had the least combined use of digestive tract drugs (73.5%),

TABLE 3 | Major prescribed drugs for somatic complications of older psychiatric in-patients related to the top five psychiatric diagnoses based on ICD-10.

	F20 *n* (%)	F32 *n* (%)	F31 *n* (%)	F30 *n* (%)	F01 *n* (%)
Patients number	1,818 (100.0)	457 (100.0)	151 (100.0)	143 (100.0)	136 (100.0)
Central nervous system drugs	1,600 (88.0)	377 (82.5)	129 (85.4)	119 (83.2)	115 (84.6)
- antiepileptics and anticonvulsants	1,294 (71.2)	337 (73.7)	113 (74.8)	97 (67.8)	35 (25.7)
- anti-tremor paralytic drugs	1,006 (55.3)	73 (16.0)	47 (31.1)	51 (35.7)	22 (16.2)
- brain metabolism and circulation improvers	221 (12.2)	57 (12.5)	17 (11.3)	15 (10.5)	92 (67.6)
- analgesics/antipyretics, analgesics, analgesics	249 (13.7)	43 (9.4)	9 (6.0)	17 (11.9)	25 (18.4)
- nerve center agonists, vertigo drugs and other central drugs	504 (27.7)	46 (10.1)	4.0 (26.5)	45 (31.5)	49 (36.0)
Cardiovascular drugs	1,350 (74.3)	299 (65.4)	101 (66.9)	90 (62.9)	132 (97.1)
- antihypertensive drugs	871 (47.9)	211 (46.2)	71 (47.0)	64 (44.8)	95 (69.9)
- lipid regulating drugs	152 (8.4)	26 (5.7)	11 (7.3)	12 (8.4)	50 (36.8)
- hypoglycemic drugs	471 (25.9)	83 (18.2)	30 (19.9)	30 (21.0)	70 (51.5)
- antiarrhythmic drugs	378 (20.8)	48 (10.5)	19 (12.6)	21 (14.7)	66 (48.5)
- antithrombotic drugs	51 (2.8)	7 (1.5)	8 (5.3)	2 (1.4)	12 (8.8)
- anti-angina and coronary heart disease drugs	219 (12.0)	52 (11.4)	23 (15.2)	20 (14.0)	65 (47.8)
- anti-heart failure drugs, anti-shock drugs, procoagulant drugs, improving circulation activation, etc	581 (32.0)	124 (27.1)	47 (31.1)	40 (28.0)	108 (79.4)
Digestive tract drugs	1,539 (84.7)	368 (80.5)	111 (73.5)	123 (86.0)	133 (97.8)
Genitourinary drugs	225 (12.4)	54 (11.8)	23 (15.2)	24 (16.8)	92 (67.6)
Drugs related to bone and joint	328 (18.0)	48 (10.5)	20 (13.2)	14 (9.8)	12 (8.8)
Respiratory drugs	250 (13.8)	23 (5.0)	15 (9.9)	13 (9.1)	81 (59.6)
Hormone and endocrine system drugs	188 (10.3)	45 (9.8)	17 (11.3)	14 (9.8)	65 (47.8)
Vitamins, minerals and other nutrients	884 (48.6)	188 (41.1)	68 (45.0)	70 (49.0)	121 (89.0)
Anti-tumor drugs	88 (4.8)	15 (3.3)	6 (4.0)	3 (2.1)	13 (9.6)
Anti-infective Drugs	1,133 (62.3)	211 (46.2)	81 (53.6)	80 (55.9)	123 (90.4)

F20, Schizophrenia; F32, Depressive episode; F31, Bipolar affective disorder; F30, Manic episode; F01, Vascular dementia; the data in this table were presented as the number and percentage of patients, patients number (%).

antipyretic and analgesic drugs (6.0%), and anti-Alzheimer's drugs (16.6%). In addition, the combination use rate of almost all subcategories of cardiovascular drugs, hormones, and endocrine system drugs were lowest in patients with depressive episode (F32) (**Table 3** and **Supplementary Table 3**).

Analysis of the combined use of a variety of specific types of physical disease treatment drugs showed that compared with other diagnoses, cardiovascular drugs (97.1%), digestive tract drugs (97.8%), genitourinary drugs (67.6%), and respiratory drugs (59.6%) were the most commonly used in combination with vascular dementia (F01) patients, while central nervous system drugs (88.0%) and drugs related to bones and joints (18.0%) were most commonly used in patients with schizophrenia (F20). Central nervous system drugs (82.5%), genitourinary drugs (11.8%), and respiratory drugs (5.0%) had the lowest combined use rate for patients with depressive episodes (F32). In addition, there were three cases with the least use of drugs for physical diseases, and the drug classification and first-class diagnosis of mental diseases were as follows: cardiovascular drugs and manic episodes (F30) (62.9%), digestive tract drugs and bipolar effective disorder (F31) (73.5%), and drugs related to bone and joint and vascular dementia (F01) (8%).

Time Trend of Drug Prescription

In this study, a total of 442,145 prescription records were originally obtained, and 293,099 records were available for analysis by excluding traditional Chinese medicine and drugs applied topically. In order to analyze the time trend of drug prescription and psychiatric diagnosis, we divided the time covered in this study into two periods: (1) 2005-2010; (2) 2011-2015. Descriptive analysis was performed as a percentage of target drug prescription records among the total number of prescriptions (or the number of target diagnostic patients in the total patients). The results showed that, compared with that in 2005-2010, the percentage of patients diagnosed with F00-F09 (increased from 13.8 to 28.8%) and F40-F48 (from 2.1 to 4.8%) among older psychiatric patients in 2011-2015 more than doubled. The percentage of older patients with F10-F19 (from 0.5 to 0.8%) and F30-F39 (from 16.1 to 24.0%) increased by 60.0 and 49.1%, respectively, while the percentage of older patients with F20-F29 decreased from 66.8 to 40.1% (**Figure 1** and **Supplementary Table 4**).

Regarding psychotropic drug prescriptions in medical records, compared with 2005-2010, the number of psychotropic drug prescriptions in 2011-2015 increased from 44.7 to 57.2%. Among them, antidepressants and anti-Alzheimer's drugs increased the most, both doubling or more, the former increased

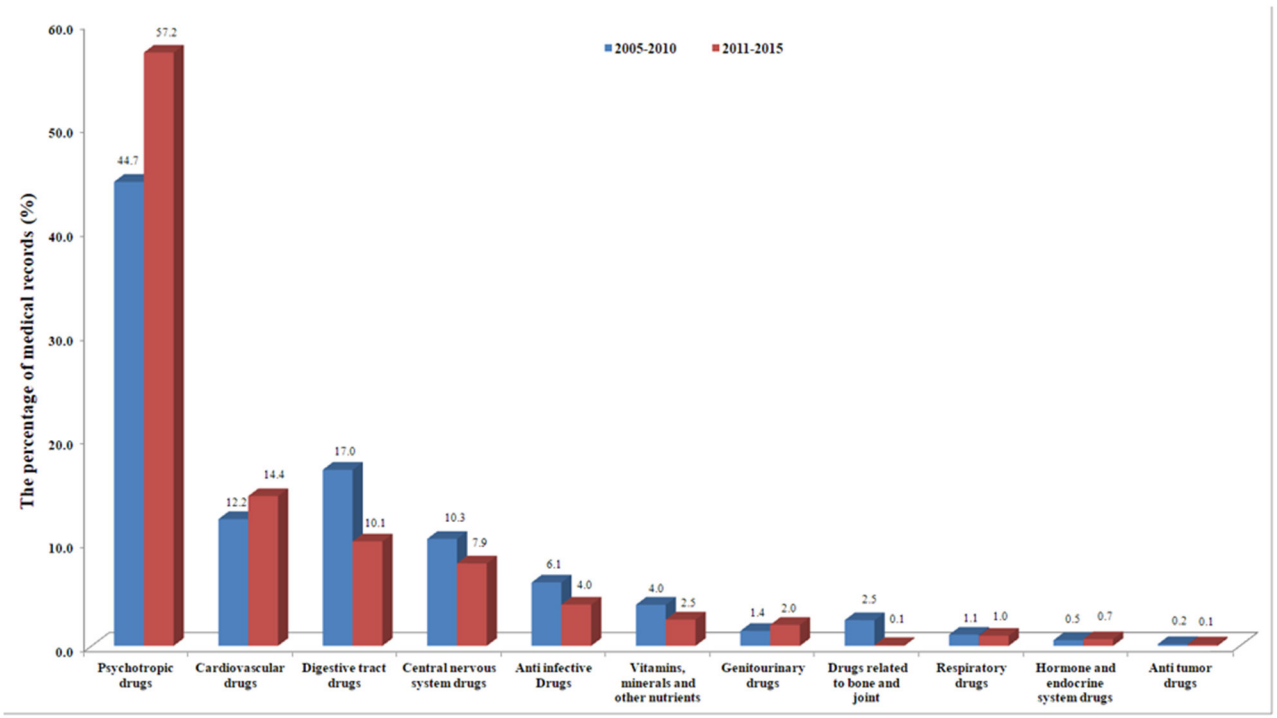

FIGURE 1 | Time trend of drug prescriptions in two time periods of the medical records.

from 4.1 to 8.2%, the latter from 2.1 to 4.5%; followed by anti-anxiety drugs, which increased from 3.1 to 5.6%; mood stabilizers increased from 3.0 to 4.5%, and sedative hypnotics increased from 2.3 to 3.4%. Antipsychotics (from 29.8 to 31.1%) increased the least, only 4.4%. Among the drugs for the treatment of comorbid somatic diseases, genitourinary drugs increased from 1.4 to 2.0%. Cardiovascular drugs increased from 12.2 to 14.4%, among which, antihypertensive drugs increased by 47.4% (from 3.8 to 5.6%), as did other cardiovascular drugs. While digestive tract drugs decreased from 17.0 to 10.1%; central nervous system drugs from 10.3 to 7.9%; anti-infectious drugs from 6.1 to 4.0%; and drugs related to bone and joint from 2.5 to 1.0%. In addition, the number of prescription records of respiratory drugs, hormone and endocrine system drugs and anti-tumoral drugs decreased to varying degrees (**Figure 2** and **Supplementary Table 5**).

Age Trend of Drug Prescription

We then studied the changes in drug prescriptions and psychiatric diagnosis of older psychiatric patients according to age. Accordingly, we created five age groups: 50-59 years old, 60-69 years old, 70-79 years old, 80-89 years old, and 90-99 years old. The results showed that the number of older patients diagnosed by F00-F09 increased significantly with age. However, the number of F20-F29 patients decreased significantly with age. The percentages of other diseases diagnosed in older patients of different ages also varied greatly. For example, the highest percentages of F30-F39 patients were 60-69 years old (23.0%) and 70-79 years old (21.8%), but the percentages in 50-59 years old (13.7%), 80-89 years old (14.2%), and 90-99 years old (5.3%) were significantly reduced (**Figure 3** and **Supplementary Table 6**).

With regard to the age trend of drug prescription, the results showed that with increasing age, the prescription rate of antipsychotics decreased, while cardiovascular drugs, anti-infective drugs, urinary drugs, respiratory drugs and digestive tract drugs were exactly opposite. The percentage of prescriptions for other drugs also varied significantly in different age groups (**Figure 4** and **Supplementary Table 7**).

DISCUSSION

In this retrospective, descriptive study, we examined the drug treatment of mental illness and physical comorbidities and explored the use of psychotropic drugs and physical disease drugs for different sexes and diagnosis. The age of female patients was significantly higher than that of male patients, which may be related to the longer life expectancy of Chinese women (33, 34) associated with the progress of medical technology, the higher possibility of treatment in today's Chinese society, and the higher survival age of older patients with mental illness. These data reflect that the number of older mental patients is gradually increasing in an aging society.

From our findings, mental and behavioral disorders due to psychoactive substance use (F10-F19) were more common in male patients than in female patients ($P < 0.0001$), consistent with their increased exposure to alcohol, drug, and other

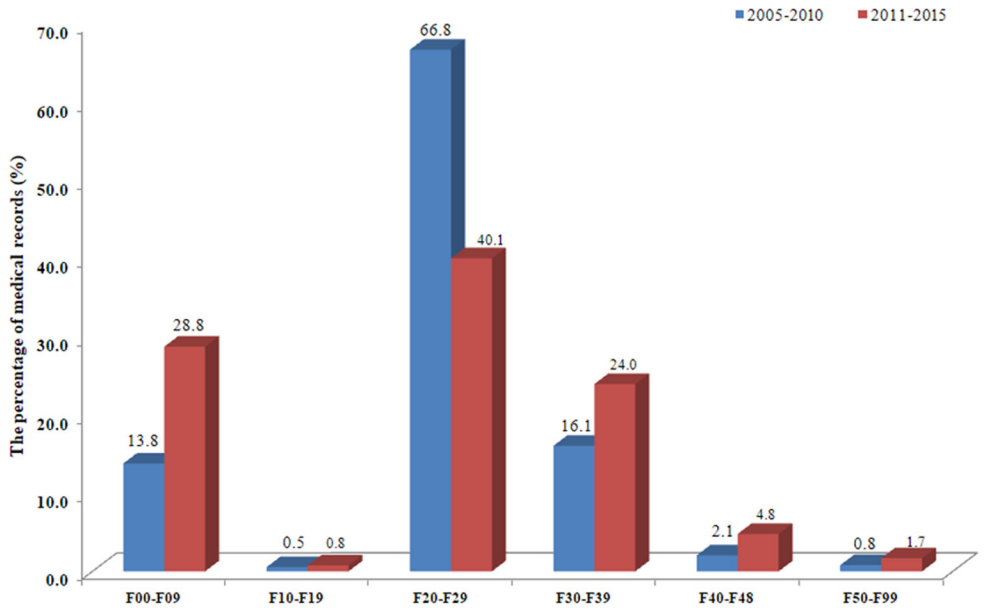

FIGURE 2 | Time trends of major psychiatric diagnoses in two time periods of the medical records.

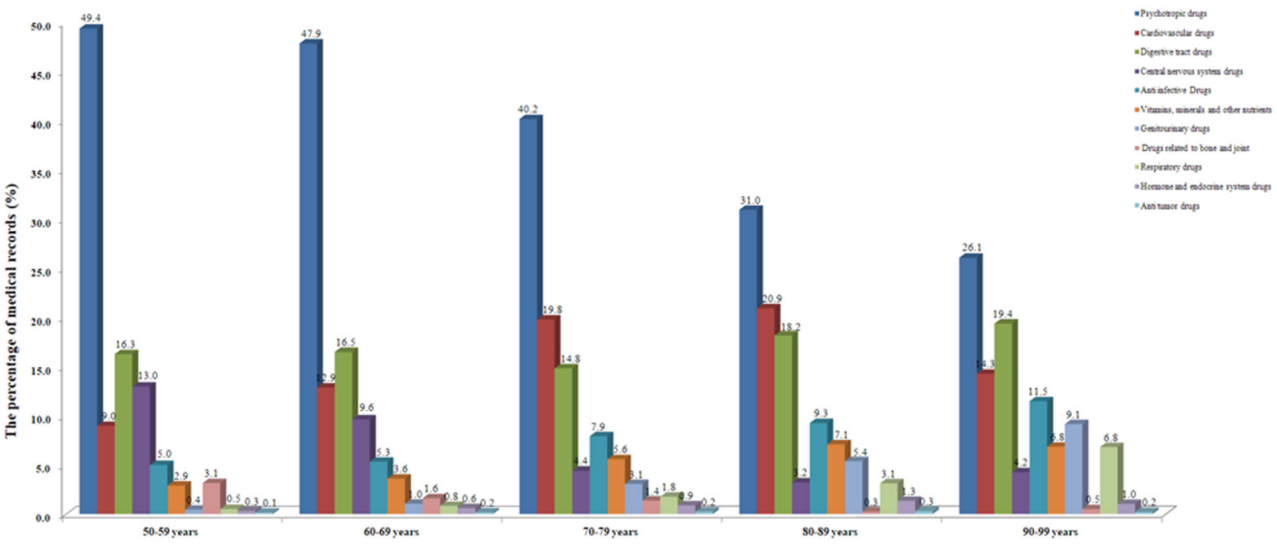

FIGURE 3 | Age trend of drug prescriptions in the medical records in this study.

psychoactive substances (35, 36), whereas mood [affective] disorders were significantly more frequent in female than in male patients ($P = 0.048$), which is related to the higher incidence of depression in women (4). Correspondingly, there were sex differences in the prescriptions of antidepressant drugs (51.9% males vs. 45.4% females) and anti-anxiety drugs (male 36.9% vs. female 47%) (37), and depression accompanied by anxiety disorders or anxiety symptoms was more common in female patients (38, 39). In addition, there were also gender differences in the treatment of other physical comorbidities, such as the combination of antiarrhythmic drugs (male 19.5% vs. female 22.5%; $P = 4.5208E-7$) and anti-heart failure, anti-shock, and circulatory system drugs (male 30.8% vs. female 35.4%; $P = 0.007$), indicating that older female patients with mental illness were more likely to suffer from physical comorbidities, such as arrhythmia and heart failure.

However, compared with female patients, male patients used more mood stabilizers (male 18.5% vs. female 14.6%; $P = 0.004$) and genitourinary drugs (male 18.5% vs. female 14.6%; $P = 0.004$), while female patients used more endocrine system

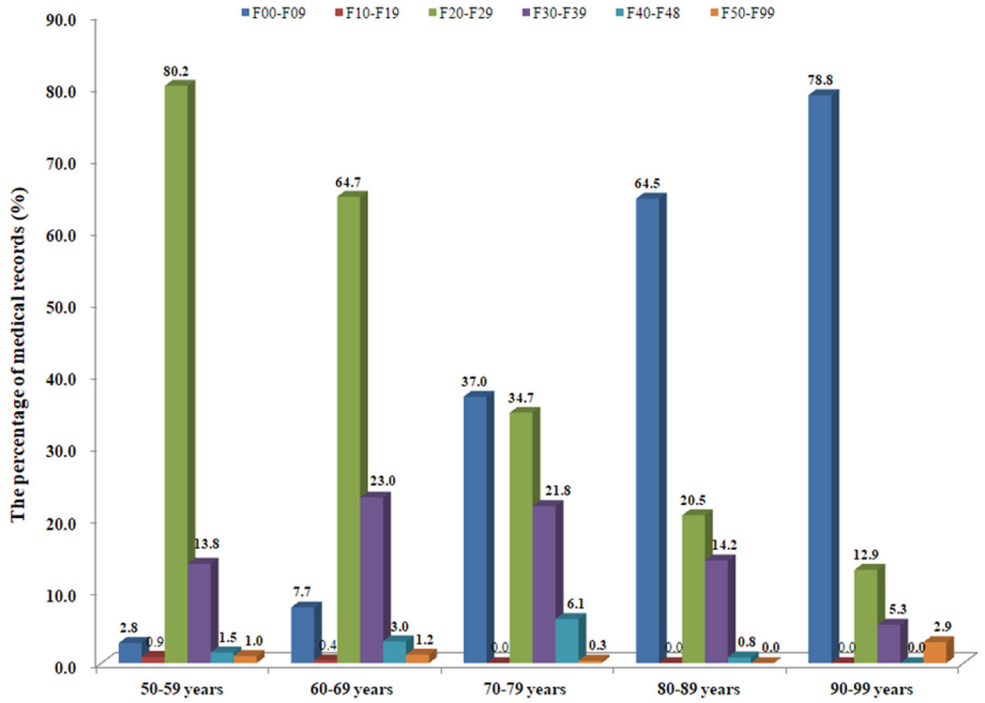

FIGURE 4 | Age trend of major psychiatric diagnoses in the medical records in this study.

drugs ($P = 0.006$) (**Table 2**). These findings were consistent with previous results (26), showing that older male patients with mental illness were more likely to have somatic comorbidities in the genitourinary system, whereas female patients were more likely to have somatic comorbidities in the endocrine system due to hormonal changes. However, this difference may be particularly associated with hormones related to sex differences, which consequently lead to different metabolic disorder patterns (40). Epidemiological studies have showed that, compared with men, women have more sleep problems and depressive symptoms when sex hormones change (41), such as in adolescence, menopause, pregnancy and childbirth. In addition, premenstrual syndrome, premenstrual dysphoria, depression, and mood and anxiety disorders are found in a high proportion of women, which may be related to women's abnormal sensitivity to hormone fluctuations,. The influence of hormones on men may be more directly reflected in the urinary system. With aging, their urinary system is more prone to somatic diseases.

In this study, the number of patients in the first three ICD-10 diagnostic classifications (F20-F29, F30-F39, F00-F09) with the largest number of older mental patients accounted for 95.1% of the total in this study. Meanwhile, compared with that in 2005-2010, we found that the percentage of older patients with several major mental disease diagnoses increased, except F20-F29, from 2011 to 2015, especially diagnoses of F00-F09, F40-F48, and F30-F39 (**Figure 1**). Consistently, we found that the number of prescriptions for antidepressants and anti-Alzheimer's drugs more than doubled, and the number of prescriptions for anti-anxiety drugs and mood stabilizers increased by 80.6 and 50.0%, respectively, while antipsychotic drugs increased only 4.4% (**Figure 2**). This change may be related to China's social and economic development in recent years, increased social pressure, and a sharp increase in the prevalence of various major mental illnesses. It may also be related to changes in diagnostic criteria for mental illness and the level of clinical diagnosis and treatment of mental health in China.

Simultaneously, it is worth noting that the percentages of combined use of somatic disease treatment drugs varied for different diagnostic categories. For example, among the five primary diagnoses (**Table 3**) with the largest number of psychiatric hospitalizations, osteoporosis (7, 42), extravertebral system reaction (8, 43), dizziness and headache (44), and cardiovascular system disease (45) were the most common side effects of first- and second-generation antipsychotic drugs commonly used in clinical practice (46, 47). Therefore, compared with other diagnoses, patients with schizophrenia (F20) often used drugs related to bone and joint drugs (18.0%), cardiovascular drugs (74.3%), and central nervous system drugs (88.0%). The most commonly used central nervous system drugs were anti-tremor paralysis drugs (55.3%), which may be related to the side effects of first-generation antipsychotics (extrapyramidal side effects) (43, 48).

Because F01 patients were significantly older than the other patients in this study (**Table 1**), and because of the disease itself, these patients often experience prominent problems in cognitive function and sleep disorders, and often have physical dysfunctions, such as urinary incontinence and asthma. Therefore, patients with an F01 diagnosis were prescribed combinations of central nervous system drugs, such as sedative and hypnotic drugs (69.9%), and anti-Alzheimer's drugs

(cognitive improvement drugs) (89.7%); cerebral metabolism and cerebral circulation improvement drugs (67.6%); and central nervous system agonists, dizziness drugs, and other central drugs (36.0%). In addition, they were prescribed drugs targeting the digestive system (97.8%), urinary system (67.6%), and respiratory system (59.6%), and almost all subcategories of cardiovascular drugs (97.1%) (**Table 3**, **Supplementary Table 3**). These data indicate that older F01 in-patients may suffer from a variety of physical diseases (≥2 types), suggesting that equal attention should be paid to treating physical diseases and mental conditions.

For F30-F39 patients, the combined use of antidepressants (72.6%) and mood stabilizers (57.3%) was the most common. This result suggested the credibility of the data in this study. In addition, F32 patients used the most anti-anxiety drugs (72.2%) (**Table 3**), as the prescription rate of anti-anxiety drugs in patients with depressive episodes (F32) was very high, suggesting the coexistence of anxiety and depression. This is consistent with reports stating that 37.3% of patients with depression had some type of anxiety disorder, while 74.6% of patients had depression and anxiety pain (49). Approximately 65.4 and 82.5% of older patients with F32 diagnosis used cardiovascular and central nervous system drugs (**Table 3**), suggesting that these patients also had cardiovascular and central nervous system-related diseases (11, 20, 50). For patients with F31 and F30 diagnoses, the combined use of digestive, cardiovascular, and nervous system drugs was very high, consistent with other studies (51).

Regarding drug use, the top three drugs with the highest prescription rate among older mental in-patients were psychotropic drugs (99.9%), central nervous system drugs (85.2%), and digestive system drugs (83.5%). In addition, 72.5% of older patients with mental illness received cardiovascular system drugs (circulatory system drugs) (**Table 2**), suggesting that the central nervous system, digestive system, and cardiovascular system-related diseases may be the most common physical complications in older patients with mental illness. However, unlike some previous reports (7, 8), our results showed that drugs targeting the urogenital system, bones and joints, respiratory system, hormone, and endocrine system were prescribed to 16.2, 14.7, 14.2, and 12.6% of the patients, respectively. This may be related to the study design, in which we only included hospitalized patients, or related to ethnic differences. It is worth noting that the three medical treatment drugs (central nervous system drugs, digestive system drugs, and cardiovascular system drugs) with the highest prescription rates are very widely used in older psychiatric in-patients, and the prescription rate only slightly lower than that of psychotropic drugs, suggesting that we should break through professional barriers between psychiatric specialist hospitals and general hospitals in the future. Chronic somatic comorbidities should be regarded as important in mental illnesses. Moving collaborative prescription and physical examination (22) into the forefront of psychiatric treatment and research (21), and their comprehensive application in clinical practice may be more conducive to the health maintenance and functional recovery of older psychiatric patients and improve their quality of life (42).

Finally, we studied the age trend of psychiatric diagnosis and the number of prescriptions for psychotropic drugs. The results showed that with increasing age, the percentage of older patients diagnosed with F20-F29 decreased, while F00-F09 increased (**Figure 3**). Consistently, the percentage of prescriptions for antipsychotics decreased, while cardiovascular drugs, digestive system drugs, urinary system drugs, respiratory system, anti-infective drugs, etc. increased (**Figure 4**). On the one hand, this finding once again proved that serious mental diseases such as schizophrenia affected life expectancy. On the other, it also showed that aging was a major risk factor for comorbid physical diseases of older patients with mental diseases, and further showed that older mental patients should be more prone to suffering from cardiovascular system, urinary system, digestive system, nervous system, respiratory system, and bone and joint system related diseases, which warned us that special attention should be paid to the treatment and prevention of somatic comorbid diseases in older psychiatric patients.

The strength of this study is that it specifically focused on older patients with mental illness and utilized a complete medical order database, which can more accurately reflect the prescription of all drug treatments for both mental diseases and physical complications. Furthermore, our data also explored the influence of different diagnoses, sex, and other factors on medical treatment of somatic comorbidities. However, there are some limitations in this study. First, we only considered the category of drugs, not the dose, course of treatment, and number of combined drugs; therefore, it was impossible to distinguish one type of somatic disease from multiple somatic diseases. Second, the discharge diagnosis information of some patients was missing, while the admission diagnosis information was complete in our medical record system, we thereby adopted the admission diagnosis for data analysis in this study. However, the discharge diagnosis information sometimes changes, which may limit the causal inference. Third, this study could only indirectly study the physical complications by virtue of treatment drugs, and lacked the accurate diagnosis of physical diseases assigned in general hospitals. Fourth, we are unable to obtain relevant data on patients' economic and social factors, medical insurance information, and living habits, such as smoking and drinking. As we did not analyze these factors, we cannot comment on their effects, which may limit the conclusions of this study. Fifth, this is only a retrospective study, which needs to be further studied and confirmed by prospective follow-up cohort studies in the future. Finally, it is impossible to distinguish the difference in treatment drugs needed by older patients with ≥1 physical diseases.

In summary, this study found that the combined drug treatment of somatic diseases, particularly for central nervous, digestive, cardiovascular, respiratory, genitourinary, and bone and joint problems, was extremely common among older psychiatric in-patients in China, and their percentages varied among the differing diagnoses of mental diseases. With increasing age, older patients with F20-F29 diagnosis decreased, while patients with F00-F09 increased; the prescription of antipsychotics decreased, and almost all drugs for comorbidity treatment increased. Compared with that in 2005-2010, older patients with other diagnosis, except F20-F29, increased between

2011 and 2015, as did the prescriptions for psychotropic drugs, genitourinary drugs, and cardiovascular drugs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Mental Health Center. Written informed consent was not provided because this is a retrospective data analysis, and the data was extracted from the hospital medical record r system, which dated back to 2005.

AUTHOR CONTRIBUTIONS

HL and YZ conceived and designed the study. XWu, XWa, and PS assisted in data collection. KH and YY contributed to the statistical analysis. JR, JZ, and RM wrote the first draft of the paper. TY, LY, PJ, and XS commented significantly to the draft of the paper. CZ and YF finalized the manuscript. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.722329/full#supplementary-material

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CASE REPORT
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Naloxone Alleviate the Severity of Delirium in Hospitalized Patients With Parkinsonism: Three Case Reports

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Purpose: Delirium is common in geriatric with Parkinson's disease (PD). Treatments for delirium have generally been neuroleptics; however, antipsychotics have potential effect to block striatal dopamine D2 receptors and worsen symptom of parkinsonism. We explored whether naloxone can alleviate delirium in PD and other forms of parkinsonism.

Patients and Methods: Patients with parkinsonism who met the delirium criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) received naloxone infusions once or twice daily. Treatment effects were evaluated by the delirium rating scale–revised 98 (DRS-R98), including non-cognitive and cognitive subscales; the Richmond agitation–sedation scale (RASS); and the mini mental status examination (MMSE).

Results: Two patients with primary parkinsonism, one with vascular PD were observed. The daily dose of naloxone was 2.08 ± 0.64 mg (range: 1–4 mg). Medication time last from 1 h to 7 days without side effects observed. Following with naloxone infusions, DRS-R98 scores decreased within 12 h and MMSE scores increased. The psychotic symptoms, disorientation, and attention deficits were alleviated significantly, while RASS scores decreased with naloxone treatment.

Conclusion: Naloxone alleviated psychotic symptoms, improved cognitive dysfunction, and irritability in patients with delirium in the context of PD. The preliminary findings point out that the opioid system may be involved in the pathophysiology of delirium, which may be one of potential treat targets for delirium of PD.

Keywords: naloxone, delirium, Parkinson's disease, parkinsonism, anticholinergic drugs, anti-PD medications

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INTRODUCTION

Nigrostriatal dopamine deficiency is well-recognized as the primary biochemical abnormality in Parkinson's disease (PD). Delirium is common in geriatric with PD, particularly in those receiving anticholinergics and dopamine agonists (1), and increases the risk of dementia, motor impairment, and mortality (2). The pathophysiology of delirium in PD is poorly understood. Neurotransmitter imbalances, such as loss of acetylcholine and/or an excess of dopamine, are thought to be common pathways (3–5). To date, first-line treatments are neuroleptics for delirium, such as haloperidol.

Quetiapine is recommended with the fewest side effects in PD (6). However, antipsychotics except pimavanserin have the potential effect to block striatal dopamine D2 receptors and thus worsen motor features in parkinsonian, and all of them are considered relating to increase mortality in elderly dementia patients (7). The U.S. Food and Drug Administration (FDA) has not approved any agents for delirium treatment.

Researchers found that naloxone enhanced the release of acetylcholine (8, 9) and reduced the content of dopamine (10) in specific cerebral areas in rats. Other studies reported that naloxone could improve spatial working memory impairments by induced scopolamine in animals (11). It also was reported to alleviate or eliminate auditory and visual hallucinations in individuals with schizophrenia (12, 13). Based on known findings, we speculated that naloxone could improve delirium in PD. Delirium is characterized with cognitive defects, including memory impairments, and psychotic symptoms such as hallucinations. We present a case series of three patients with parkinsonism followed up 2 years, they were treated by naloxone infusion for delirium.

MATERIALS AND METHODS

The patient's demographics, concomitant diagnosis, clinical profile, and naloxone use are summarized in **Table 1**. Efficacy of naloxone was evaluated daily during delirium episodes using the delirium rating scale–revised 98 severity scale (DRS-R98) and the Richmond agitation–sedation scale (RASS). Cognitive status was assessed by the mini mental status examination (MMSE) before and after naloxone treatment. All assessments were blinded. Informed consent was obtained from the guardians of all patients, and the ethical issues were approved by the Ethics Committee of the hospital.

RESULTS

Delirium duration (7.75 ± 5.32, range: 1–12 h) (the patient 1 including two treatment intervals) was much shorter than the natural course of delirium (9.03 ± 10.11, range: 0.08–20 days) after naloxone intervention in three patients. Thirteen domain scores of the DRS-R98 severity scale indicated that perceptual disturbances, the hallucinations (2.75 ± 0.50) and sleep-wake cycle disturbances (2.22 ± 1.41) were more prominent problems in view of non-cognitive subscale; long-term memory impairment and visuospatial impairment (both 2.25 ± 0.95) were more severity in view of cognitive subscale before naloxone intervention. Compared to pre-treatment, the occurrence of perceptual disturbances and hallucinations (2.75) significantly descended followed by sleep-wake cycle disturbances (2.22), affective labilities, long-term memory impairment and visuospatial impairment (2.00, respectively), delusions (1.88), thought process abnormalities, motor agitation, orientation problems, and attention deficits (1.75, respectively). The scores are shown in **Table 2**. The daily dosage of naloxone was 2.08 ± 0.64 mg (range: 1–4 mg). The mean duration of naloxone treats was 4.01 ± 3.58 days (range: 1 h−7 days). We observed that naloxone was safe and well-tolerated in all three patients.

Patient #1

This patient was a 66-year-old man, who was diagnosed with PD 8 years previously. For the past 2 years, he had been taking 100 mg/400 mg of benserazide/levodopa and 2 mg of benzhexol four times a day. However, the disease continued to worsen, so entacapone (100 mg) was added twice daily. Twenty days ago, he began to experience hallucinations that thieves were hiding on the second floor of his house, he once hurriedly jumped into a pool in front of his house to chase them. His confusion and behavioral dysfunction were most serious at night, with severe insomnia. According to DSM-5, he was diagnosed with persistent hyperactive delirium; the delirium was due to PD and anti-PD medications.

Benzhexol was discontinued, and benserazide/levodopa was reduced to three times with concomitant of entacapone twice a day. On the night of admission, he was irritable and refused to take medications. The next day morning, the patient reported two thieves were running after him during the night, then naloxone was medicated (**Figure 1A**). The treatment caused the patient somnolence whole day, while psychotic symptoms were not detected on day 1 and next day. aloxone was withheld on day 3 and the patient regained full orientation and showed apparent improvement in delayed recall. However, on the afternoon of the fourth day, he suddenly tore up a box and threw it, and poured water on the bed. He was given a second round of naloxone treatment, and became calm and fell asleep quickly that night. On the morning of the fifth day, he regained clarity of awareness, but still displayed static tremor and bradykinesia. He explained that the previous night he had feared that he was surrounded by about 20 villains who wanted to rob him. Thereafter, naloxone treatment was maintained for 3 days without the recurrence of delirium. There were not antipsychotics or benzodiazepines used in all processes.

During 3 months of follow up, the patient remained functionally and mental stable with combination of 50 mg/200 mg of benserazide/levodopa three times a day and 200 mg of entacapone twice a day.

Patient #2

The patient was a 76-year-old woman diagnosed with secondary vascular PD after a cerebral infarction 6 years previously. She had been taking 50 mg/200 mg of benserazide/levodopa and 100 mg of amantadine three times a day, in combination with 20 mg piribedil twice a day. Her essential hypertension was controlled by nifedipine with normotension. One week before admission, the woman began to manifest disturbances of awareness, composed of vivid, horrible, or absurd auditory and visual hallucinations that were richer at night. Her symptoms were more serious in the 3 days before admission, with insomnia almost whole night. Her diagnosis was persistent hyperactive anti-PD medication-induced delirium. Amantadine and piribedil were stopped, while

TABLE 1 | Patients' demographics, clinical profile, and naloxone usage.

Patient	Age/Sex	Medical diagnosis	Natural course of delirium (days)	Symptoms and signs before naloxone	Lab examination and brain CT or PET	Naloxone protocol	Delirium duration after naloxone (days)
1	66/M	Parkinson's disease, right side PVP, dementia	20	Distractibility, simple, and irrelevant answers to questions, slurred speech, disorientation, persecutory delusion, bradykinesia, postural instability, tremor, and increased muscle tone in RUE.	Serum electrolytes, renal and liver functions within normal limits; CT, cerebral atrophy; following changes in skull and lobe after right side PVP.	NS 250 ml + naloxone 2 mg IV drop in morning on day 1; the drug was withheld in evening owing to somnolence; administered twice on day 2; withheld on day 3 owing to oversedation; reinstated nightly on days 4–8.	<6/24 (the first intervention) <12/24 (the second intervention)
2	76/F	Vascular parkinsonism, vascular cognitive impairment, hypertension	7	Lags in response, disorientation in time and place, anxiety, hallucinations, bradykinesia, unstable gait, right knee tendon reflex (+ + +), bilateral Babinski sign (–).	Serum electrolytes, renal and liver functions within normal limits; CT (16 days before admission): left basal ganglia and thalamus lacunar infarction.	NS 250 ml + naloxone 2 mg IV drop at night on days 1–5.	12/24
3	56/F	Parkinson's disease, depression without psychotic symptoms	2/24	Lags in response, pulling at bedsheets or clothes, time perception errors, disorganized speech, dilated pupils, decreasing limb and body rigidity, improving dyskinesia.	Serum electrolytes, renal and liver functions within normal limits; PD confirmed by PET at 2 week follow-up.	NS 100 ml + naloxone 1 mg IV drop at noon.	1/24

M, male; F, female; PVP, posteroventral pallidotomy; RUE, right upper extremity; NS, normal saline; CT, computerized tomographic scan; PET, positron emission tomography.

TABLE 2 | Baseline DRS-R98 scores and changes after naloxone treatment ($N = 3$).

Item of DRS-R98	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Change difference
(1) Sleep-wake cycle disturbances	2.22 ± 1.41	0	2.22
(2) Perceptual disturbances and hallucinations	2.75 ± 0.50	0	2.75
(3) Delusions	1.88 ± 1.44	0	1.88
(4) Affective labilities	2.00 ± 0.82	0	2.00
(5) Language problems	1.38 ± 0.95	0	1.38
(6) Thought process abnormalities	1.75 ± 0.50	0	1.75
(7) Motor agitation	1.75 ± 0.29	0	1.75
(8) Motor retardation	0	0.75 ± 1.50	0.75
(9) Orientation problems	1.75 ± 0.50	0	1.75
(10) Attention deficits	1.75 ± 0.50	0	1.75
(11) Short-term memory impairment	1.50 ± 1.00	0.25 ± 0.50	1.25
(12) Long-term memory impairment	2.25 ± 0.95	0.25 ± 0.50	2.00
(13) Visuospatial impairment	2.25 ± 0.50	0.25 ± 0.50	2.00

DRS-R98, delirium rating scale–revised 98 severity scale; SD, standard deviation.

benserazide/levodopa was continued. In addition, naloxone was administrated at night (**Figure 1B**). Her delirium vanished completely just after a whole night's good sleep, which notably improved her psychotic symptoms, orientation, and delayed recall. Naloxone was maintained for 5 days and there was no recurrence of delirium. No concurrent interventions were applied.

The patient remained mental stable after 3 months with the same dose of benserazide/levodopa.

Patient #3

A 56-year-old woman began suffering from fatigue and muscle soreness 6 years previously, leading to irritation, anxiety, and occasional suicidal ideation. The diagnosis was presumed to be PD and depression, but her symptoms sometimes worsened with adjusting dose of benserazide/levodopa and occasional fluoxetine. She was restless, and then admitted to our hospital. For the first 3 weeks of hospitalization, the patient received 20 mg of paroxetine with benserazide/levodopa (150 mg/600 mg), carbidopa/levodopa (100 mg/400 mg), and 100 mg of entacapone daily. However, the patient's symptoms remained refractory. Her physician regarded the depressive symptoms as the side effect of levodopa, so anti-PD medications were tapered to stopped. Paroxetine was continued and increased to 40 mg/day. Consequently, the patient developed a lumbering gait with stiffness in the limbs. Then this status was thought to be paroxetine-induced parkinsonism, so the paroxetine dose was halved and supplemented with 150 mg of venlafaxine in prolonged-release capsules, 1.5 mg of lorazepam, and 0.8 mg of

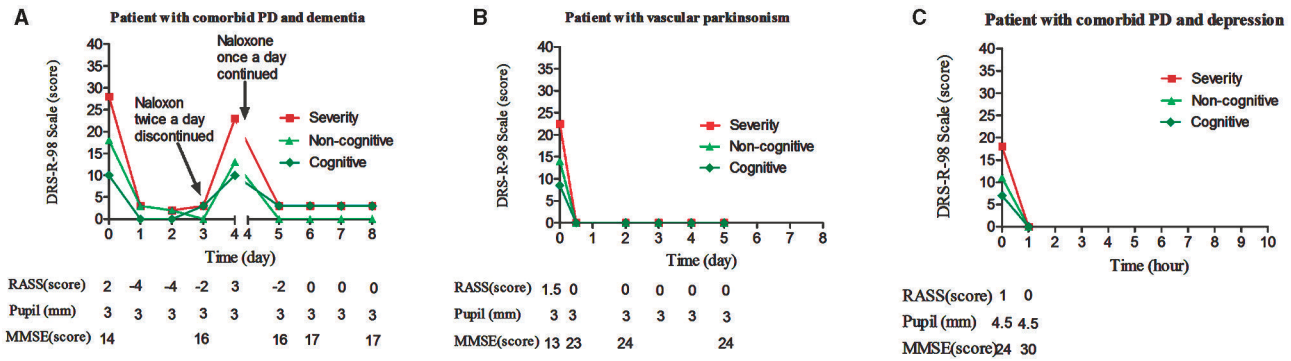

FIGURE 1 | Change in DRS-R98 scores over the study period, and corresponding measurements. **(A)** DRS-R98 severity and RASS scores decreased during each of the two treatment intervals. In the first, under twice-daily naloxone, the RASS was −4, indicating the agitated patient was over sedated on days 1 and 2. The patient was delirium-free and mildly sedated on day 3 without naloxone treatment. On day 4, DRS-R98 severity and RASS scores were 23 and 3, respectively, indicating that delirium had returned. In the second interval, under nightly naloxone only, the patient was delirium-free and mildly sedated on day 5. MMSE scores were 14–16 and stabilized at 17 with remaining cognitive deficits. Corresponding pupil diameter was normal. **(B)** DRS-R98 severity and RASS scores decreased over time. A change in RASS score from 1.5 to 0 indicated that the mildly agitated patient became calm after sleeping 12 h at night. The MMSE score increased from 13 to 23 and stabilized at 24 with remaining cognitive deficits. Corresponding pupil diameter was normal. **(C)** DRS-R98 severity and RASS scores decreased over time. RASS score of 1–0 indicated that the patient recovered from a restless to a normal state. The MMSE score increased from 24 to 30 indicating no cognitive deficits; however, pupil diameter remained 4.5 mm (normally 3 mm). DRS-R98, delirium rating scale-revised 98 (severity scale only; 13 items; maximum score, 39; delirium, >15; resolution, <12); MMSE, mini mental status examination (30 point cognitive test; maximum score 30); RASS, Richmond agitation sedation scale (10 levels; 4, combative; 3, very agitated; 2, agitated; 1, restless; 0, alert and calm; −1, drowsy; −2, light sedation; −3, sedation; −4, deep sedation; −5, cannot be aroused).

alprazolam daily. The patient's parkinsonism worsened. Benzhexol (2 mg) was then used twice daily for 2 days in combination with 0.3 mg scopolamine in order to reduce muscle tone.

Unfortunately, although the patient's muscle tension relieved, she developed a clouding of consciousness characterized by impaired time perception, disorganized speech, and uncontrolled limb movements. She sometimes babbled "porridge on the mosquito net," or ordered her family to open the door or buy vegetables. She was diagnosed with acute hyperactive delirium; delirium due to PD and anticholinergic drugs. Naloxone infusion was carried out (**Figure 1C**). Her delirium was resolved after 1 h of naloxone treatment, which also visibly improved deficits of immediate and delayed recall, although her pupil diameter remained 4.5 mm. During the course of naloxone infusion, she didn't receive any other medications. Over the next 2 days, the patient was able to walk around the ward. After that, her Parkinson's symptoms reappeared with muscle rigidity, bradykinesia, and hyperreflexia, and a diagnosis of PD with depression was confirmed.

Follow-up treatment used a combination of benserazide/levodopa (150 mg/600 mg) and paroxetine (40 mg) with no anticholinergic drugs, and her delirium did not recur.

DISCUSSION

We observed that naloxone improved dramatically delirium in three hospitalized patients with primary PD and secondary vascular PD. The severity of delirium was alleviated rapidly, determined with simultaneous decreases in DRS-R98 scores in both the non-cognitive and cognitive domains. Psychotic symptoms, disorientation, and attention deficits were the first and most symptoms to be improved obviously, and patients became noticeably calmer.

In patient 1 and 2, concomitant use of dopamine preparation and/or dopamine agonists and anticholinergic drugs contributed to the development of delirium (1). Both PD and cognitive decline may be important risk factors for delirium (6, 14). We emphasized that the management of anti-PD-medication-induced delirium is keeping a balance between reducing the causative agent and maintaining motor function. However, we believe that naloxone was associated with the rapid delirium resolution as we observed. First, there was a rapid onset of sedation and the elimination of psychosis in two patients. Second, the dosage of 2 mg twice a day caused over-sedation in patient 1 on initial 2 days, so naloxone dosage had to be halved on the second intervention. These results indicate that naloxone has a dose-dependent effect on delirium, because naloxone itself has not pharmacological sedative effect. Third, premature discontinuation of naloxone caused delirium relapsing in patient 1. It suggested it is necessary to maintain a full course of treatment with naloxone. In this study, various dose of benserazide/levodopa was managed individually for patients involved, since the parkinson's symptom was required to be managed at stable level.

Inouye and colleagues observed that poly-pharmacy is a risk factor for delirium (15). The combination of scopolamine and benzhexol with paroxetine, venlafaxine, and benzodiazepines may have played a role for third patient's delirium. Paroxetine

has potent anticholinergic effect, which can increase the risk of delirium. Anticholinergic drugs are believed to play a fundamental role in delirium (16, 17). However, we consider that resolution methods for delirium unlikely were consequence of attenuation to the effect of anticholinergics. We think naloxone playing a crucial role in delirium resolution, because the patient's symptoms of delirium disappeared after 1 h treatment, but the effects of anticholinergic agents remained, it is verified from her pupils remaining enlarged and locomotion continually improved.

The acetylcholinergic neurotransmitter system is key for the function of alertness, attention, memory, and learning in the central nervous system. Hypocholinergia results in the hallmark "clouding of consciousness" and inattention seen in delirium. Elevation of dopamine can result in frank hallucinations, which is one of causes of agitation in the delirious patient (18, 19). Similar to shown in animals, in patients with delirium, we presumed that naloxone could synergistically complement neurotransmitter imbalances, promoting the release of acetylcholine (8, 9) to improve orientation, attention, and memory impairment, and limiting the increase in dopamine (10) to reduce psychotic symptoms.

Interestingly, naloxone had a rapid-onset effect on sedation or sleep ameliorated in three patients. These findings is consistent with Berger and colleagues' case report, in which Mr. A became "clearly less agitated" after naloxone injection (12), and is also consistent with our previous finding that naloxone could control agitated behavior in delirium after a stroke (20). Accumulating evidences indicate that all three opioid receptors (mu, delta, and kappa) mediate the mechanisms associated with emotional responses and mood control (21). Particularly, naloxone has been proved to active the mu receptor, which in turn interact with dopaminergic and acetylcholine system facilitating neurotransmitter releasing to alleviate cognitive and psychotic symptom (9, 10, 22). This phenomenon suggests a causal relationship with the gamma-aminobutyric acid (GABA)ergic system (23, 24). Agitation in delirium is very complex that needs to be addressed. Some previous studies have reported that antipsychotics such as haloperidol contribute mainly to sedation in the treatment of delirium (25, 26).

Notably, naloxone intervention was free of side effects in our patients, so we could avoid anticholinergic effects and extrapyramidal symptoms that occur frequently on antipsychotics treatment.

There are several limitations in this observational study. The three cases involved in the pilot study limited the statistical power for validity of conclusion. Poly-pharmacy in some cases involved and uncertain neurobiological mechanism make it difficult to explain the efficacy of naloxone on delirium occurred with patients with PD. Few rating scales involved limited the efficacy for evaluating the multiply domains in cognitive functioning for patients in the study. This case series highlighted the clinical significance that naloxone contributed potentially to manage the symptoms in delirium of patients with PD.

The research gives insight into why naloxone may be a promising agent for the treats of delirium in the context of PD. However, we think further pharmacological studies on how effects of naloxone on brain neurotransmitter in patients with delirium are necessary to prove this observation.

CONCLUSION

Naloxone was safe and well-tolerated in our studies. It alleviated psychotic symptoms, improved cognitive dysfunction, and calmed irritability in patients with PD delirium. The results imply that the opioid system is perhaps related to complex interactions between dopamine, acetylcholine, and GABA, which implicate in underlying pathophysiology of delirium. Further observations need provide pilot data to support a double-blind, placebo-controlled clinical trial to demonstrate the efficacy of naloxone in the treatment of delirium in PD and parkinsonism.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Shunde Wuzhongpei hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HJ and JZ: concept and design, data acquisition, analysis and interpretation, statistical analysis, and drafting the manuscript. QH: data acquisition, analysis, and statistical analysis. JP: critical revision of the manuscript. TJ: data analysis. BD: data interpretation and supervision. XD: concept and design and critical revision of the manuscript. All authors read and approved the final manuscript.

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Hardiness in Family Caregivers During Caring From Persons With Alzheimer's Disease: A Deductive Content Analysis Study

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Objective: This study was designed to describe the experiences of family Caregivers' hardiness in caring for Alzheimer's Patients.

Methods: The deductive content analysis method was performed between April 2020 and February 2021 in one of the teaching hospitals in Iran. Fourteen family caregivers of Alzheimer's patients were selected using purposive and snowballing sampling and the data were collected by semi-structured interviews. After that, data were analyzed using Elo and Kingas steps.

Results: The results of this study showed that based on the experiences of family caregivers, the family caregivers' hardiness in caring for Alzheimer's patients is a feature of cognitive ability to deal with stressful care situations and consists of five dimensions of commitment, control, challenge, communication and culture with 22 generic categories that they were nested into this five dimension.

Conclusion: Family caregivers' hardiness is a trait related to the individual and environmental factors, and the prevailing social and cultural conditions affect the individual's perception and experience of hardship and threats, as well as his/her understanding of protective factors and how to use them. Therefore, hardiness should not be interpreted as a simple approach regardless of culture.

Keywords: caregiving burden, family care, dementia, experiences, content analysis

INTRODUCTION

In recent years, the world's older adult population has increased significantly due to increasing life expectancy and decreasing mortality and fertility rates. The World Health Organization (WHO) has reported that in 2019, 703 million people were 65 and older in the world, which is expected to double by 2030 to reach 1.5 billion people. However, this increase in the rate of the older adults population in developing countries such as Iran will occur faster than in developed countries, so that 79% of them will live in developing countries (1).

Aging is an inevitable stage in the life cycle of every individual, which is associated with a wide range of physiological, psychological changes, and especially decreasing in cognitive ability (2). The cause of reduced cognitive ability of the older adults can be due to reduced sensory abilities and mental related to age. Decreased sensory and intellectual abilities lead to the weakening of nervous processes in the older adults and make them prone to cognitive disorders (3). Alzheimer's Disease (AD) is one of the most common types of dementia, characterized by severe disorders of memory, thinking, and behavior (3). The prevalence of age-related Alzheimer's almost doubles every 5 years after age 65 (4).

Since the ability of persons with Alzheimer to perform personal activities decreases, they need to be supported by a caregiver who may or may not be a family member, a formal or informal care provider (5). Due to interdependence between family members, as well as declining household incomes, especially in developing countries such as Iran, and the lack of adequate supportive formal systems, family members assume responsibility for caring for these persons (5). Family caregivers are untrained individuals who do not receive any fee for providing services and at the same time meet the needs of the family and the needs of the care recipient (6). Giving that families provide more than 81% of the care needed by Alzheimer's patients and it is estimated that 7 out of 10 persons with Alzheimer's are cared for at home (2). Since the family caregivers accept another responsibility in addition to previous responsibility, they must be able to adapt to the situation, and this requires the caregiver's ability, competence, and responsibility, and can lead to acute and/or chronic illness in the long term (7).

Considering that the cultural and social conditions prevailing in each country affect care issues (8); In Iran, due to the Iranian culture that is associated with religion and encourages people to take care of their elders, the care of this group of persons are mostly performed by family caregivers (2). It should be noted that due to the lack of appropriate social structures and support systems to facilitate home care in Iran, these caregivers can have different experiences of care that studies have not considered (8).

Background

Caring for Alzheimer's patients is an overwhelming task and a stressful situation for family caregivers; because caregivers play a key role in meeting the physical and emotional needs of these persons, and as the disease progresses, these tasks become heavier and lead to negative complications in the caregiver as a "burden" (5). The most common complications of caring burden in caregivers of Alzheimer's patients are depression, anxiety, stress, and burnout (9, 10). Moreover, negative side effects of the caring burden for the older adults with Alzheimer's include aggravation of symptoms such as irritability, aggression, hallucinations, delusions, and depression, which worsen the quality of life and increase mortality (10). Caring for Alzheimer's patients extremely burdened for family caregivers, some caregivers possess internal resources that modify the effects of caregiving stressors on psychological well-being and cope fairly well and even feel satisfied with the situation (7, 9). Hooker et al. suggested that personal characteristics should be the main factor in making such a difference in people's experience of care. Because it is the psychological characteristics that affect the meaning of care for each person (11).

Hardiness is one of the effective personality traits in stressful situations that have been considered by psychological theorists. This concept makes sense in the face of stressful situations and is considered as a moderator variable in the relationship between stress and the physical and psychological effects of that stressful situation (12). The concept of hardiness has been conceptualized as one of the main structures of personality to understand motivation, excitement, and behavior (12). Hardiness is a combination of attitudes and beliefs that motivate a person to do hard and strategic work in the face of stressful and difficult situations and facilitates turning adversity into an opportunity (13). Individuals with low hardiness are more likely to be affected by stressful situations, but individuals with high hardiness are less likely to experience adverse effects from the situation (14). Kobasa defined the hardiness model as consisting of three dimensions such as commitment (a sense of meaning in life), control (belief to able to influence the events of lives), and challenge (believing that change in life is natural and creates growth opportunities) (12).

Since the stressful situations that arise during the care of Alzheimer's patients are a unique and exhausting situation for family caregivers; hardiness is considered as an important personality trait to enable these caregivers to provide proper and appropriate care to these persons and to prevent problems for both the caregiver and the persons with Alzheimer (15); Because lack of hardiness not only leads to many physical and psychological problems such as fatigue, burnout, depression, sleep disorders, reduced quality of life, and even suicide for the caregiver, it can cause many problems for the Alzheimer's persons, including the possibility of neglect, abuse, poor quality care, ignoring vital needs, aggravation of the disease, and psychological and behavioral symptoms (16, 17). Therefore, knowledge of the status of family caregivers' hardiness in the care of persons with Alzheimer's disease and its effects on quality of life and patient care is essential. This study was designed to understand the experiences of family Caregivers' Hardiness in caring for persons with Alzheimer's disease in Iran based on the Kobasa hardiness model.

METHODS

Design

This study was a deductive content analysis study to achieve to "explain the concept of family caregivers' hardiness in the caring of Alzheimer's patients" that was performed between April 2020 and February 2021.

Participants and Setting

In total 14 family caregivers of Alzheimer's patients were selected by using purposive and snowballing sampling among the caregivers referring to the neurology clinic of hospitals of Tehran. All of the caregivers participating in the study were individuals who were responsible for caring of the patients with Alzheimer's

TABLE 1 | Demographic characteristics of patients and caregivers.

Group	Variables	% (*n*)
Caregiver demograohic characteristics	**Age**	54.57 ± 14.64
	Sex	
	Female	71.4% (10)
	Male	28.6% (4)
	Marital status	
	Single	21.4 % (3)
	Married	71.4 (10)
	Divorced	0% (0)
	Widowed	7.1% (1)
	Relationship	
	daughter	64.3 % (9)
	Son	14.3 % (2)
	Wife/midwife	21.4 % (3)
	Lifestyle	
	Independent	35.7 % (5)
	With patient	64.3 % (9)
	Education	
	Illiterate	14.3% (2)
	Less than diploma	0% (0)
	Diploma	28.6 % (4)
	BS/MS/PhD	57.1 % (8)
	Occupation	
	Unemployed	14.3 % (2)
	Employed	37.5 % (5)
	Retired	21.4 % (3)
	Housewife	21.4 % (3)
	Volunteer	7.1% (1)
	Duration Of Caregiving (hour per day)	9.78 ± 3.04
Patients demograohic characteristics	**Age**	79.07 ± 6.7
	Sex	
	Female	64.3 % (9)
	Male	35.7 % (5)
	Duration Of Illness	6.07 ± 3.66
	Number Of Children	5.07 ± 2.01

disease at home. Nine participants were the daughter of a patient, two participants were the son of a patient and three participants were the spouse of a patient. The mean age of the participants was 54.57 years (see details in **Table 1**). The interview took place with the consent of the caregivers and in one of the clinic rooms or at their home.

Data Collection

In this study, the data collection method was Face-to-face or via Skype or WhatsApp, in-depth and semi-structured interviews conducted by the first author using a combination of targeted (main categories of hardiness model) questions and open-ended questions. Interview duration was 35–90 min (see the list of questions in **Table 2**). As the interview progresses, for more details and deepening interviews, we used to explore questions such as: "can you explain more about this?", "can you give an example?", "when you say… what do you mean?" "are there any other things you want to talk to me about?". Participants were interviewed until data saturation was reached. It has reached a degree of saturation whenever no new categories or suitable theme emerges, or in other words, when the researcher deeply discovers each category and determines its different characteristics and dimensions in different situations (18).

TABLE 2 | List of pre-interview open-ended and targeted questions.

Open-ended questions	Targeted questions
Please describe a day from morning to a night spent caring for your patient?	What makes you committed to caring for your patient? (main category of Commitment.)
What makes you take care of your patient?	How do you control the stressful situation of caring for your patient? (main category of control)
What do you do to deal with care-related problems?	How do you look at patient care? (main category of the challenge)

Data Analysis

Data were analyzed based on the proposed Elo and Kyngäs in three phases (19).

Preparation phase: This phase consists of two parts: selecting the unit of analysis and finding the logical connection of the data with the whole subject. The transcript interviews were considered as a unit of analysis. So, immediately after the end of each interview, the interview was transcribed word by word on paper. Then, transcribed texts were reviewed and re-read several times to immerse in the data to better understand what was going on in the data and understand the participants' feelings and experiences by asking frequently asked questions e.g., what is happening? who speaks? where is this happening? when did this happen? what happened? and why? A general sense of the text was obtained and then the analysis was performed using a deductive approach.

Organization phase: In this phase, the researcher developed an unconstrained matrix derived from the concepts of the Kobasa hardiness model. At this phase, after explicit and implicit concepts were identified in form of sentences or paragraphs from the participants' statements, the researcher assigns preliminary codes to associated meaning units. The next process after coding was to integrate the same preliminary codes into more comprehensive classes. Continuous comparison in the analysis process helped to integrate and summarize similar codes in the form of primary categories and by continuing, continuous comparison of primary categories based on similarities; differences, and proportions, abstraction was done and categorized into generic categories. Generic categories nested into the main categories in the matrix or new categories were created. These processes of coding, categorizing, and extracting themes were performed by the contribution of all three

authors (L.H, M.A.F & H.S.N) independently. The final themes and subthemes were extracted by regular meetings discussions. MAXQDA software was used to manage data and the facility of the process.

Reporting phase: All stages of deductive content analysis and the findings obtained in the present study, including the sampling process, participants' characteristics, data collection, data analysis were reported.

Trustworthiness of Stud

The quality of data and findings were evaluated by credibility, dependability, confirmability, and transferability (20). For ensuring and evaluating the rigor of the study, following approaches were used: an 11-month engagement period in the research setting, member checking, peer debriefing, recording step by step, the interviews, transcribing them immediately after each interview, and evaluating the process of analysis by qualitative research experts.

RESULTS

In this study some generic categories were nested into the main categories of commitment, control, and challenge; but we developed two new main categories such as connection and culture. In the main category of commitment, the "emotional tendencies," "external motivation," "intrinsic motivation," "understanding care," and "responsibility" were developed. In the main category of control, "knowledge of the disease," "promoting knowledge of the caring," "protecting the patient's body and mind," "self-management," "condition management," "caring ability," and "effective communication with the patient" was developed. In the main category of challenge, the "high values of caring," "gaining skills of caring," and "mental well-being" were developed. In the new main category of connection, the "supportive family," "supportive people," and "family supporter" were developed. Finally, in the new main category of culture, "individual values," "adherence to ethics virtues," "religion," and "social values" were developed (see details in **Table 3**).

Commitment

Commitment in family caregivers refers to a person's ability to engage with a situation instead of relinquishing it based on his/her emotional tendencies, being influenced by internal and external motivations, understanding care, and being responsible.

Emotional Tendencies

Based on the experience of family caregivers, what caused them to become involved in the caring situation and not give up caring for their patient was their attachment to family, patient, and sense of belonging, including love to the patient. They showed attachment to their family by loving them, understanding the situation of other family members, and trying to reduce the burden of caring for them and fulfilling their responsibilities to the family. These caregivers showed attachment and a sense of belonging to their patient by living with and accompanying the patient as much as

TABLE 3 | Dimensions of hardiness concepts in family caregivers.

Main categories	Generic categories	Initial categories
Commitment	emotional tendencies External motivation Intrinsic motivation Understanding care responsibility	attachment to family attachment to patient sense of belonging Motivate the family Motivate patient's doctor Motivate the others Motivate the quality of care Motivate the religious beliefs Gain motivation from the pattern of past relationships Perceived care pressure Perceived financial pressure from care Endurance in a caring role Effective caregiver role Accepting the position Acceptance of duty
Control	knowledge of the disease promoting knowledge of the caring Protecting the patient's body and mind self-management Condition managemen t Caring ability Effective communication with the patient	Awareness of the nature of the disease Awareness of the client's cognitive problems Awareness of the client's physical problems Awareness of the client's psychological problems Awareness of the progression of the disease Awareness of care tips Seek awareness of non-human resource care Gain awareness of human resource care Share information with the family Maintaining the patient's mental health Maintain the patient's cognitive power Maintaining the patient's physical health Trying to keep the patient active Calming the mind Keep calm through distance-term care Keep calm through interaction Performance control Rational approach to the situation Provide appropriate care for the patient Problem solving skills Balance life with a caring role Functional capability Cognitive ability Psychological empowerment Involve the patient in the affairs Positive communication with the patient

(Continued)

TABLE 3 | Continued

Main categories	Generic categories	Initial categories
Challenge	High values of caring gaining skills of caring Mental well-being	Gratitude Admonitions to children Reward faith Spiritual excellence Self-care Acquire emotional support skills Acquire functional skills Experience pleasant emotions Satisfaction with the caring role
Connection	supportive family supportive people family supporter	Family financial cooperation Family cooperation in tasks Effective family interaction Consult a specialist Get help from others Family support in care Family psychological support
Culture	Individual values Adherence to ethics virtues Religion social values	Being conscientious Being grateful Understanding the patient's self-sacrifice Preserving the dignity of the client Ethical considerations in interacting with the client Religious beliefs affecting care Religious Behaviors Influence of family norms Learning from life

possible, quitting their job to care for the patient, devoting their time of rest to persons, and loving and depending on the patient.

"What makes me take care of my mother is love, I go to my mother and with love, and that is, I fall in love when I see my mother". (Participant 4)

External Motivation

Motivations gained from family, the patient's physician, and others around them such as relatives and friends made these caregivers more committed to caring for their persons. The family of these caregivers motivates them to continue caring by trusting the caregivers in care and consulting with them in all matters related to the patient, understanding the burden of the caregiver and thanking the caregiver, as well as comforting the caregiver in times of fatigue and distress. Friends and relatives also motivate caregivers by reflecting the quality of caring to caregivers and appreciating from caregivers. It is noteworthy that almost all caregivers emphasized the importance of motivating the patient's physician to care for their ability to continue care. This motivation was created through physician feedback and satisfaction about the quality of care provided by caregivers and provided caregivers with more motivation and ability to care.

"Whatever I say, they accept and trust me and I say this is good for the mother, they accept. If my mother gets worse, they will never complain to me that you made it. Well, that motivates me." (Participant 2)
"When I take him doctor, he gives me a lot of hope, he does not let me be disappointed, he says you worked very well with him, he tells me that considering that he has these conditions, his process is very good, it increases my motivation, it increases my energy, I try harder". (Participant 7)

Intrinsic Motivation

Perceived quality of caring such as improving the patient's condition, the patient's condition is better compared to other persons, persuasive religious beliefs such as have a religious reward, and patterns of past relationships were the intrinsic motivation that causes family caregivers to continue to care.

"When I see that what I have done, has made her condition better, i see that she used to be depressed, now she is better, it makes me more motivated to try harder." (Participant 12)
"I think they might consider me a religious reward, and that motivates me". (Participant 1)

Understanding Care

According to family caregivers, what enables them to properly cope with the difficulties of care and continuing their caring successfully is to understand the care needed and its challenges including the pressures of care and its financial pressures.

"I knew about my mother that this would be a difficult situation, it would be easy at first, but it would get harder and harder over time, so I was prepared". (Participant 10)

Responsibility

The experience of these family caregivers demonstrated that they showed their responsibility to care for their patient by having endurance in the caring role, effectively taking on the caring role, accepting the position, accepting their duty, and these combined factors indicate that they are committed to the position of career.

"I mostly think that what makes me take care of my father now is that I think it is a moral, human and filial duty. In fact, I take care of my father because of its moral, human and filial duties". (Participant 1)
"I fully understood these conditions and accepted that they exist". (Participant 4)

Control

Control refers to the caregiver's ability to influence the situation based on knowledge of the disease, promoting knowledge of the caring, protecting the patient's body and mind, self-management, condition management, caring ability, effective communication with the patient.

Knowledge of the Disease

From the caregivers' point of view, being aware of the nature of the disease, cognitive and psychological problems, the course of the disease, and the points of care required were important in the ability of individuals to control the situation and affect it effectively.

"Well, I'm aware of my mother's illness, I know that Alzheimer's disease is losing its ability, and this disease causes a series of disabilities in its movement". (Participant 2)

Promoting Knowledge of the Caring Role

Searching for information from non-human resources such as (the internet, books, articles), and human resources including (attending caregiver training classes, attending seminars and workshops), and sharing information with family members and other caregivers were some of the ways caregivers improve knowledge to increase their ability to control the situation.

"I tried very hard to get information about the disease from the internet, I bought a book about the disease and read it so that I could control it". (Participant 8)

Protecting the Patient's Body and Mind

During care, family caregivers stated that by trying to improve and maintain the patient's mental and physical health, as well as helping to improve his/her cognitive status by reminding him/her of information and trying to keep him/her active, they tried to improve the situation and illness and prevent from the situation getting worse.

"That is, we constantly tried to maintain his health by encouraging father and asking him to do a series of things". (Participant 1)

Self-Management

During care, family caregivers tried to maintain their composure by doing favorite activities such as yoga, having leisure time, socializing with relatives when they were tired, and controlling the performance of their care and in this way take control of the situation.

"I have a series of courses such as health courses, meditation courses, TM, breathing meditations that I try to relax with. In fact, each of these helped me to be calm". (Participant 6)

Condition Management

Family caregivers stated that they tried to manage the situation through a rational approach to the situation, providing appropriate care to the patient's condition, using different problem-solving techniques, and balancing personal life with the caring role.

"With the management, we tried to solve the problems of forgetting the father. For example, every day that my father wanted to go to work, we checked that is his mobile phone charged? does the workplace key come with it?" (Participant 1)

Caring Ability

Family caregivers stated that by trying to improve their capabilities in functional, cognitive, and psychological dimensions, they acquired the necessary skills and abilities to control the situation and provide appropriate care.

"We have to be very patient, we have to be very resilient, we have to know that this responsibility that we have taken on is hard work and we have to accept it, we have to move forward and not be afraid. We must be strong-willed, not quick to get angry, and quick to get tired. It requires patience and endurance so that one does not get tired soon". (Participant 3)

Effective Communication With the Patient

Family caregivers stated that during the care period, they tried to control the situation and have a positive impact on it by establishing a positive relationship with the patient and involving him/her in doing things.

"I always try to be very supportive, that is, I try to love him very much, so I try to treat him by being kind, by hugging, by using kind words to talk to him". (Participant 3)

Challenge

Challenge refers to the caregiver's ability to turn the stressful situation into an opportunity to grow for them based on an acquisition of the high values of caring, gaining skills of caring, mental well-being.

High Values of Caring

Family caregivers see the caring situation as an opportunity for gratitude and compensation for the patient's past troubles and to teach vital traits such as patience, morals, and understand the importance of respecting adults to their children, as well as an opportunity to improve their spirituality including moving away from worldly issues and making positive changes to their way of life.

"Parents work very hard for us children, maybe my mother, if she was a woman who only cared for herself, would not care about her children, maybe she would not get Alzheimer's, these parents work for me, in hardships and joys and everything, they were with me, so now is the time to compensate them". (Participant 2)
"I see this as a good opportunity for myself; an opportunity that I am very calm when I am with her and I am free from all worldly issues and works". (Participant 7)
"When my father contracted this disease, I have changed my way of life in my work, in my life, and I believe that it was right". (Participant 8)

Gaining Skills of Caring

Family caregivers stated that during their patient care, they acquired many skills including how to take care of themselves to prevent future illness, how to deal with a patient, and how to care for a patient.

"I gained a lot of experience. Maybe now I know things that I did not think, I would want to do or learn in the past. Now, for example,

I have learned the type of caring from a patient, feeding the mother, and all the abilities that a nurse needs, experimentally. I learned a lot of skills". (Participant 9)

Mental Well-Being

Mental well-being is an important structure related to the interpretation of personality and is defined as a positive assessment of life and the balance between positive and negative emotions. Family caregivers achieved this mental well-being during care by gaining satisfaction from their caring role and experiencing pleasant emotions such as the experience of love during caring, not having a guilty conscience, and the best opportunity to see care for themselves.

"Just I feel that I am taking good care of my patient now and I am trying to do the responsibility that I have well, it makes me feel good". (Participant 2)
"I do not regret it at all, I am not upset at all that I agreed to take care of them... I am happy to take care of them, I do not have a guilty conscience that I did not do everything I could for them". (Participant 11)

Connection

The connection refers to the acquisition of power and the ability to influence the stressful position of care in family caregivers through the existence of a supportive family, supportive people, and family supporters.

Supportive Family

Family caregivers tried to gain the strength and power to continue caring by communicating with family members and engaging them in caring and receiving financial assistance.

"Well, my family is with me, when I am tired, my sister comes and does this with her and I rest a little and come back with more strength". (Participant 2)

Supportive People

Family caregivers also tried to increase their strength and ability to cope with the difficulties of the situation by consulting specialists in times of trouble and receiving help from others.

"Well, I hired a nurse, I wanted her to help me and reduce my burden of care, and I have more control over the condition, and not to mess up the house". (Participant 12)

Family Supporter

The caregivers stated that they also provided support to their family members during their care and supported them psychologically and physically. They supported them to maintain the morale of their family members and relieve their feelings of remorse, as well as to reduce their burden of care.

"I pretend to my mother, family, siblings that everything is going well and my father will be fine so that they do not lose hope, but I know this is not the case". (Participant 8)

Culture

Culture also includes a set of individual values, adherence to ethics virtues, religion, social values of the caregiver that affect his/her ability to cope with the stressful situation during care.

Individual Values

Individual values such as conscientiousness, gratitude, and understanding of the patient's self-sacrifice were among the characteristics that enhanced the ability of caregivers to cope with stressful situations.

"I think everyone has a duty and they have to do their duty properly and I have always tried to do my duty properly, I always think that I am a daughter and I must do this. It is my duty to my father and I have to take care of him now". (Participant 1)

Adherence to Ethics Virtues

Caregivers stated that adherence to ethics, including maintaining the patient's dignity and maintaining ethical considerations in interacting with the patient is an important factor that can affect the ability of individuals to cope effectively with stressful situations.

"It is important for me and I try to treat my mother like a mother and child and the respect and those values and those credentials and trusts remain and my mother's respect and dignity is not lost". (Participant 2)

Religion

Religious beliefs and behaviors were other factors that helped caregivers to moderate the severity of the stressful situation for them and increase their ability to cope effectively with the stresses created during care.

"I believe that god has never helpless me, I know that god has always been by my side and helps me and has given me this strength and ability". (Participant 5)

Social Values

Family norms learned by caregivers throughout their lives, abilities learned in life's hardships, and norms governing the community in which they live including respect for the older adults and helping the disabled were social values that helped ability caregivers to get hardier during care.

"We have always learned that we must be behind each other everywhere and always help each other. We vowed to always be together. Maybe that helped us". (Participant 13)

DISCUSSION

This study was the first study to explain the experience of family caregivers' hardiness in caring for patients with Alzheimer's in Iran. The results of the present study confirmed three dimensions of the Kobasa of hardiness model (12), but the notable point is that our finding explained the hardiness concept in family caregivers has two additional dimensions including connection and culture. The dimension of connection (21); could be an

important and influential dimension on individuals' hardiness in dealing with stressful situations. Individuals gain part of their power and ability to deal with stressful situations as a result of connection with other members of society, therefore, the connection is one of the factors that seem to be able to play an important role in creating and maintaining hardiness. In this study, family caregivers stated that during their patient care period, by seeking and receiving help from family members, friends, relatives, and health professionals including nurses tried to cope effectively with the stress of the situation and reduce the burden and its effects on themselves and can become hardier in dealing with the situation. Clark supports this finding; so that they asserted hardy caregivers used more overall transformational coping and help-seeking and receiving more assistance from their family. Also, they found that the family interaction in handling stressful events has a positive effect on the coping strategies of the family caregiver (16). Furthermore informal support networks including family support reduce negative caregiver health outcomes (22). This finding is also in line with the results of another study that confirmed caregivers try to cope with the challenges of the situation in terms of going to support groups and utilizing other community resources (17).

Some researchers have also observed significant differences in stress levels and coping mechanisms used by individuals in different cultures (23, 24). Hardiness is a characteristic related to the individual and his/her environment because the social and cultural conditions governing the individual affect his/her perception and experience of hardship and threat, as well as his/her understanding of protective factors and how to use them and it can mean hardiness to him/her (23). The present study also confirmed this dimension as influential in shaping the hardiness of family caregivers in caring for Alzheimer's patients. Family caregivers in this study emphasized that their values including (conscientiousness, gratitude, and understanding of the patient's self-sacrifice), their religious behaviors and beliefs, and social values including family norms greatly influence their hardiness in dealing effectively with care stress and increase their ability to deal appropriately with the situation and reduce the negative effects of the care burden. Religion provides conditions that are useful for improving the health and well-being of people in stressful situations. Previous studies also have been shown, religion makes a person more hardy in the face of problems and has more control over his/her actions and behavior (25, 26). In general, the unique lifestyle of religious people empowers them to evaluate events as less stressful, or after stress, to see it as an opportunity to grow and strengthen their spirit (26).

Commitment is the first dimension of hardiness in the Kobasa model and refers to a tendency to engage in life activities and have a real interest in curiosity about the world around (27). Family caregivers showed commitment to caring for your patient through emotional attitudes including attachment to the patient and family and a sense of belonging to the patient, motivation from external factors including family, physician, and others, motivation from internal stimuli including quality of care perceived by self, religious beliefs and patterns of past relationships with the patient, understanding of care and responsibility by accepting duty, accepting position, perseverance in the role and effective leadership. Researchers had shown commitment is a unique and powerful predictor of psychological distress; Because caregivers' desire to feel a sense of belonging to caring activities and a sense of belonging to their condition and persons, leads to stability and acceptance of the negative aspects of care by them (15).

Control is the second dimension of hardiness in the Kobasa model. It is as an inner desire to believe and act that one can influence the events of one's life, and this belief in influence occurs in one's effort (13). Family caregivers demonstrate their ability to control the situation by having knowledge of the physical, cognitive, psychological, and care tips needed, improving the knowledge and caring from human resources such as specialists and non-human resources such as books and articles, trying to protect the body and mind the patients, managing mind and performance themselves, managing the situation by using appropriate problem-solving strategies and tailored to the situation, and finally improving their functional, cognitive and psychological abilities and gaining the caring ability. Caregivers' knowledge, self-confidence for managing chronic and acute health conditions of care recipients, alerting clinicians about worrisome changes, self-management, and practicing self-care skills have a significant effect on controlling the situation (28).

Challenge is the third dimension of hardiness in the kobasa model and refers to beliefs that change, rather than being stable, as a natural state of life, creates opportunities for personal growth rather than a threat to one's security (27). Family caregivers confirmed this dimension. They stated that this period of patient care provided them with an opportunity to make up for the patient's past troubles, gain religious rewards through this situation, be able to teach their children good morals and respect for the elders, and let their spirituality grow, as we put them in a category called the high values of care. Family caregivers also stated that this period of care provided them with many skills in how to properly and effectively communicate with an Alzheimer's patient and how to provide care for them, so they stated that a self-taught nurse was now trained. Ultimately, this period of care provided them with an opportunity for mental well-being through the experience of pleasant emotions and the creation of a sense of satisfaction with the role of care and life and the absence of remorse. The previous study confirmed our finding that caregivers who viewed their caregiving activities as an important, meaningful, and rewarding situation for them, were less distressed (15).

One another interesting point in this study was that the participants stated that the existence of community support such as the support of formal community organizations, the support of the health organizations, and social groups can help significantly in improving their hardiness, enhancing their ability to care for patients with Alzheimer's disease, coping well with the care situation, and reducing the negative effects of the care. Based on participants' statements as well as findings from previous studies (29), this social support did not exist in our society. Therefore, we suggest that the impact of this factor on hardiness be further investigated in communities that have organizations that support family caregivers, especially caregivers of Alzheimer's patients. Furthermore, this study includes qualitative information and

cross-cultural analysis of the results is not carried out. Therefore, we suggest it considers in future study.

RELEVANCE TO CLINICAL PRACTICE

Since patients with Alzheimer's disease are mostly cared by family members, nursing care programs should focus on improving the adaptability and hardiness of these caregivers. Recent studies in the nursing profession suggest that the 10 creative factors of Watson's theory in nursing including the formation of the humanistic-altruistic system of values, nurturing faith and hope, cultivation of sensitivity to one's self and others, development of a helping-trusting human relationship, promotion, and acceptance of the expression of positive and negative feeling, use of the creative problem-solving caring process, promotion of transpersonal teaching-learning, provision of supportive, protective, or corrective mental, physical, sociocultural, and spiritual, assistance with the gratification of human needs, and allowance for existential- phenomenological-spiritual forces (30) are related to the categories obtained in this study as a result of examining the experiences of caregivers. So nurses and therapists can plan to improve the family caregiver's hardiness with forming future caregiver hardiness research by considering categories obtained in this study and using Watson's theory as a guide.

CONCLUSION

Concept of hardiness in Iranian family caregivers had three dimensions expressed by Kobasa. But the remarkable point was the impact of the important role of culture in the formation of this feature in family caregivers in Iran. Hardiness by being influenced by religion and personality formed in Iranian culture, allows people to use attitudes and behavioral and emotional values to develop many individual characteristics such as empathy, understanding, responsibility, flexibility, attention, cooperation, tolerance, intelligence efficiency, and optimism and be able to properly deal with stressful situations and be safe from depression and stress. Also to improve the hardiness of family caregivers and reduce the negative effects of the care burden in the caring of Alzheimer's patients, nurses should use their emotional tendencies, helping them by strengthening their social networks, and finally taking into account their values, beliefs, and cultural norms.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1398.1229). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Feasibility and Engagement of Multi-domain Cognitive Training in Community-Dwelling Healthy Elderly in Shanghai

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Background: In recent years, cognitive training has been one of the important non-pharmaceutical treatment methods that could delay cognitive decline and improve quality of life in the elderly. In different types of cognitive training, both the cognitive domains focused on and their training methods widely vary. This study aimed to explore the feasibility and engagement of multidomain cognitive training in Chinese community-dwelling healthy elderly.

Methods: Based on the cluster sampling method, a total of 151 healthy elderly, aged 70 or above, who lived in the neighborhoods in Shanghai met the inclusion criteria and agreed to participate in the study. Among them, 90 participants were assigned to the cognitive training group (intervention group), and 61 were assigned to the no cognitive training group (control group). Participants in the intervention group attended a 1-h multidomain cognitive training course twice a week for 12 weeks (total of 24 times), which targeted memory, reasoning, strategy-based problem-solving skills, etc. The control group did not receive any intervention.

Results: There was a significant increase in test scores of story recall ($t = -8.61$, $p = 0.00$) and Raven's Standard Progressive Matrices (RSPM) ($t = -10.60$, $p = 0.00$) after in-class interventions. The overall completion of homework was 77.78%. Fifty percent of the 90 participants completed self-training. The top three self-training methods were physical exercise, reading books and newspapers, and watching TV. The overall attendance rate of the intervention group was 76.14%, and more than 50% of them had an attendance rate of 77.8%. The attendance rate was positively correlated with years of education and baseline SF-36 (physical functioning, general health, vitality, and mental health) scores, whereas it was negatively correlated with baseline disease index and fatalism of personality indicators ($p < 0.05$).

Conclusion: The elderly with higher educational levels and better physical and psychological conditions had a higher engagement in multidomain cognitive training. The training course proved to be rational, feasible, and effective for community-scale application.

Keywords: healthy elderly, multi-domain cognitive training, feasibility, engagement, community

INTRODUCTION

As one of the non-pharmacological intervention methods, cognitive training results in the efficient improvement of cognitive abilities in the elderly (1, 2). Among various methods of cognitive intervention, two methods are widely practiced, namely, single-domain and multidomain cognitive training. The single-domain cognitive training is applied to non-demented elderly subjects for improving single cognitive function. In this regard, the largest multicenter, randomized, single-blinded intervention study involving 2,832 elderly subjects is the "ACTIVE" (Advanced Cognitive Training for Independent and Vital Elderly Trial), which was launched in 1998 in the United States. The subjects were given single-domain cognitive training on memory, reasoning, and thought processing speed 10 times. Thereafter, four times of booster training were provided 1 year later, and follow-up was conducted at 2, 5, and 10 years after intervention. The results show that the benefits of memory training lasted for 5 years, whereas that of reasoning and thought processing speed lasted for 10 years (3). The other cognitive training method involves the integration of single-domain training to construct multidomain training methods, e.g., integration of social ecological and working memory task, strategy and reasoning training, processing speed training, puzzles, and fitness training (4, 5) to achieve the best training effect in each cognitive domain with widespread impacts (6).

Because most of Chinese elderly care more about their physical condition, cognitive training is not well accepted. Single-domain cognitive training had a higher shedding rate and more limited cognitive improvement. In the past 10 years, we have designed multiple cognitive training contents.

The effects of our cognitive training are reported in previous published papers, including a 5-year follow-up study of multidomain cognitive training for healthy elderly community members, mechanisms in brain imaging, and associations between gene polymorphism and intervention efficacy (7–10). As a continuation of our previous findings, this is the first time that we report the contents as well as feasibility and engagement of multidomain cognitive training methods in elderly from the Chinese community.

Elderly people were given 12 weeks of daily self-training and multidomain in-class cognitive training, including a story recall test, associative vocabulary memory (AVM), irrelevant vocabulary memory (IVM), and Raven's standard progressive matrices (RSPM), etc.

The control group did not receive any class training or intervention. Cognitive assessment was performed on the control group at baseline, at the end of intervention, 6 months after intervention, and 1 year after intervention, including Stroop, NTBE etc. These results are reported in our previous paper, too (7–10).

MATERIALS AND METHODS

Participants

A total of 347 elderly subjects were screened by cluster sampling in a community in Shanghai. The cluster sampling unit was the community under the jurisdiction of the residents' committee.

Inclusion Criteria

In this study, subjects were selected based on the following inclusion criteria: (1) age over 70 years, (2) no history of serious somatic disease, (3) no history of neurological and neuropsychiatric disorders, (4) are sufficiently educated, and (5) no history of severe vision or hearing loss. Enrollment was conducted by two psychiatrists in the community. One psychiatrist was responsible for the enrollment of the intervention group and another for the control group. Every 50 elderly persons were evaluated by one psychiatrist. All participants signed informed consent.

Baseline

The baseline health status of the participants was assessed based on their demographic data, disease index, 36-item Short-Form Health Survey (SF-36) (11, 12), personality indicators (13), and neuropsychological tests, etc.

Multidomain Cognitive Training

Face-to-Face Session

Form of course: Two psychiatrists conducted 1-h face-to-face, multidomain cognitive training to the elderly in the intervention group twice a week for 12 weeks (total of 24 times). In-class tests were performed as part of the course.

Course arrangement: Story recall training (three times), AVM (twice), IVM (twice), RSPM (four times), face and name training (twice), strategy training (twice), learning training to use a map of Shanghai (twice), handicraft making (twice), calligraphy and painting (three times), and fitness exercises (twice). Each training session focused on one method, described below:

(1) Story recall training: The story content was derived from the comprehension and memory section of the revised Chinese version of the Wechsler Memory Scale (WMS), which had two parallel versions. Each version included three stories (A, B, and C) of which B and C were recorded in advance. While the recording of a story was played, participants were presented a slideshow of that story instead of reading or

showing the story cards to them. After that, participants were asked to write down the story in detail. Scores were given according to the WMS operation manual. The final score was the sum of the two test scores divided by two. A higher score indicated better memory. As participants were all over 70 years old and the results were only used for intragroup comparison, we did not convert the scores into standard scores. Then, participants were trained on the spatial-mnemonic method. The training method relied on the fact that visualization of the story plot in the mind could better improve the memory recall capacity instead of just memorizing words.

(2) Face and name training (14, 15): Participants were presented with 12 slides composed of faces and names, each lasting 30 s. After that, participants were randomly presented with slides that contained only faces and were asked to write the correct names to test their memory and association abilities. Faces and names were searched and downloaded from the Internet, and images were formatted into uniform size, pixel, and background. Twelve faces were randomly distributed into three groups, of which two groups were used for testing while the other group was used for practice. The sum of the correct numbers was the score. Higher scores reflected better daily working memory, association ability, and ability to use strategies. Participants were then trained to associate names with facial features in the spatial representation mnemonic method. When memorizing names, the participants were trained to convert them into memorable words based on homophonic sounds.

(3) AVM: The test content was derived from two sets of tests (10 pairs of vocabulary in each set) in association with learning, according to the Chinese revision of WMS. Those vocabularies were made into recordings and slides, which were played at the same time during the test. Five sec after the end of the play, one vocabulary from each pair was played again using the same recording and slide. The order of the presentation was according to the scale. Participants were trained on associative memory skills. In combination with the inner association of each pair of vocabularies, they used helpful methods, such as sensory and categorization association, to memorize. For example, if the words are "east" and "west," their associations are both directions, and if the words are "glasses" and "water," their associations are both colorless and transparent. The more associations the participants made for each vocabulary, the more impressed they were with the words they needed to remember. Recordings and slides were performed three times in different orders of presentation. Associative vocabularies were divided into two categories: easy and difficult. The participant earned one point for each correct word. The scores of easy vocabularies in the three tests were added up and divided by two, and the scores of difficult vocabularies were also added up. The sum of these two scores was then used as the total score of this test. Scores range from 0 to 21 points.

(4) IVM: Test vocabulary was derived from two sets of commonly used vocabularies (each set contained 15 vocabularies) in the Rey Auditory Verbal Learning Test (AVLT), which were prerecorded at a rate of one per second. These recordings were played to the participants, and they were asked to recall as soon as the play stopped. Participants were trained on reduced utilization of their memory units and improved memory effect through strategy training, such as sentence making and classification (15, 16). For example, if the 15 words we used were drum, curtain, doorbell, coffee, school, father, moon, park, hat, farmer, nose, hen, color, house, and river, when using the classification method, participants memorized similar words together, such as park and school, house and curtain, farm and hen. It could reduce the number of memory units. Another method is sentence making. In this way, participants made sentences to transform the irrelevant words into concrete and meaningful sentence. For example, his father is a farmer, wearing a hat and living in a house. There is a school on the left, a park on the right, a river in front, and a hen at home. He was sniffing coffee at home, and when the drum bell rang, he pulled open the curtains to let in the moon. The participant earned one point for each correct word. Scores range from 0 to 15 points.

(5) RSPM: The test content was derived from the SPM. The Chinese version of the RSPM was revised by the National Revision Collaborative Group (Professor Zhang Houcan et al.) in 1985 (17). It is purely a non-verbal and progressively harder intelligence test consisting of 60 pictures with groups A, B, C, D, and E. Group A tests perceptual discrimination, graphic comparison, graphic imagination abilities, etc. Group B tests similar comparison, graphics combination abilities, etc. Group C tests comparative reasoning and graphic combination abilities, etc. Group D tests series relationship, graphic fitting abilities, etc. Group E tests abstract reasoning abilities, such as interchangeability and interleaving. Each test question consists of a large picture with a missing part and six to eight smaller pictures as options. In the test, participants were asked to figure out which of the smaller pictures was the best fit based on the correlation between the images in the larger picture, which was mainly used for the intelligence assessment. The participant earned one point for each correct question. The total score was 30 points. The higher the test score, the better the discriminating, comparative reasoning, serial relation, and abstract reasoning abilities. Researchers explained to the participants how to solve the problem, and then participants discussed problem solving methods with each other in class.

(6) Processing speed (learning to use a map of Shanghai): In a certain period, participants found a specified target according to the road and bus index. The higher the score, the better the ability to understand, use skills, and processing speed. Researchers explained to the participants about the searching method, and then participants discussed the searching method with each other in class. For this part, each test was two points and the total score was 10 points.

(7) Strategy training: In this session, the researchers summarized a series of problem-solving strategies, such as the spatial representation mnemonic, classification, and sentence-making methods (15, 18, 19). They reguided the elderly

TABLE 1 | Baseline demographic data.

	Education years (%)				Gender (%)		Age ($\bar{x} \pm s$)
	<6	6-9	9-12	> 12	Male	Female	
Intervention (N = 90)	30 (33.3)	22 (24.4)	23 (25.6)	15 (16.7)	53 (58.9)	37 (41.1)	74.7 ± 3.7
Control (N = 61)	22 (36.1)	13 (21.3)	17(27.9)	9 (14.8)	30 (49.2)	31 (50.8)	75.0 ± 3.8
Statistical value	0.39[a]				1.38[a]		−0.48[b]
P	0.94				0.32		0.63

a, chi-square value; b, t-value.

to sort out how to apply each strategy pertinently in the set-specific scene.

(8) Puzzle and fitness training: This session consisted of two parts. One kind were handicraft making silk stockings flowers, such as simulated calla lily and crabapple flower, calligraphy writing skills, coloring and drawing training. Another was fitness exercise, including teaching elderly about fitness precautions and aerobics for the aged. Part of this aimed to broaden the hobbies of the elderly and taught them fitness tips.

Homework

The intervention group completed one homework assignment after each two training sessions, including reading passages and answering questions, calligraphy, painting, etc.

Self-Trainings

Combined with personal interests, self-training at home included physical exercise, playing chess and cards, writing, daily life skills, and sensory training, etc. Participants recorded daily training content, duration, and training effects and made a regular self-summary themselves (18).

Statistical Analysis

The original data were scientifically coded according to the principles of statistics. Epidata3.1 was used to establish the database, and SPSS24.0 was used to perform statistical analysis. Descriptive statistical analysis, Chi-square test, *t*-test, analysis of covariance (ANCOVA), repeated measure analysis of variance, and correlation analysis were used for the statistical analyses of the data.

RESULTS

Demographic Data

At baseline, 90 elderly people in the intervention group and 61 in the control group were enrolled. There were no statistically significant differences in gender, age, and educational level between the two groups (**Table 1**). At the end of the intervention, 83 elderly people in the intervention group and 51 in the control group were followed up.

In-class Test Outcomes

A total of 12 in-class tests were conducted during the cognitive training period, including story recall, AVM, IVM, RSPM, face and name training, and map of Shanghai test with an average completion rate of 96.44% (**Table 2**). By using the paired *t*-test, we found statistically significant differences in story recall and RSPM before and after training ($p < 0.05$). Scores of these two tests were improved after training, and the mean scores of the other four tests were also improved to varying extents (**Table 3**).

Homework

After the face-to-face multidomain cognitive training session every 2 weeks, homework was assigned 12 times, including reading training (five times), calligraphy training (four times), and painting training (three times). The number of people who completed homework is shown in **Table 4**. The overall completion of homework was 77.78%.

Self-Training

At the beginning of multidomain cognitive training, self-training tasks were assigned mainly based on the participant's own interests. Self-training instruction manuals and recorded forms were provided to each of the participants. A total of 45 valid records were received at the end of the 12-week training program, accounting for 50% of the 90 participants. According to daily records, the descending order of training content in accordance with the complete number of participants was physical exercise, reading books and newspapers, watching TV, playing chess and cards, calligraphy, listening to music, hand-knitting, singing, and dancing, listening to the radio, using the computer, etc. (**Table 5**).

Attendance and Its Influencing Factors

The cognitive training attendance rate was calculated as (attendance times/24) ×100%. Among the 90 participants in the intervention group, 23 elderly had a 100% attendance rate. The specific attendance for each cognitive training is shown in **Figure 1**. The average attendance rate of the intervention group was 76.14%, and those with attendance rates over 50% accounted for 77.8% of the total number of participants (**Table 6**). Attendance was positively correlated with the education level, baseline SF-36 physical functioning factor score, baseline SF-36 general health factor score, baseline SF-36 vitality factor score, baseline SF-36 mental health factor score, and negatively correlated with baseline disease index, personality index fatalism factor score ($p < 0.05$) (**Table 7**).

DISCUSSION

Feasibility

This training course was an improvement and supplement to our previous training methods in which most of the elderly had difficulty in reading due to vision impairment when using the Shanghai map (20). The completion rate was improved by equipping the elderly with magnifying glasses during the training time. In the previous study, most participants reported a higher difficulty level of face and name training methods, leading to a reduced completion rate. Therefore, we adjusted

TABLE 2 | Multidomain cognitive training in-class test results.

	SR1	SR2	AV1	AV2	IV1	IV2	FN1	FN2	RSPM1	RSPM2	PS1	PS2
Attendance	87	78	76	72	72	74	75	69	67	63	59	65
Completion	81	72	75	71	66	68	74	67	67	63	58	63
Completion rate	93.1	92.3	98.7	98.6	91.7	91.9	98.7	97.1	100.0	100.0	98.3	96.9

SR, Story recall; AV, Associative vocabulary; IV, Irrelevant vocabulary; FN, Face and name; RSPM, Raven's Standard Progressive Matrices. PS, Processing speed.

TABLE 3 | Scores of in-class tests.

	Baseline		Post-intervention		*t*	*P*
	$\overline{X}$	s	$\overline{X}$	s		
SR	10.09	3.29	13.60	5.12	−8.61	**0.00****
AV	12.24	4.77	12.28	4.08	−0.09	0.93
FN	1.70	1.82	1.84	1.77	−0.60	0.55
IV	3.52	1.86	3.93	2.05	−1.61	0.11
RSPM	10.35	5.10	15.54	5.70	−10.60	**0.00****
PS	5.96	3.33	6.28	3.06	−0.90	0.37

*SR, Story recall; AV, Associative vocabulary; IV, Irrelevant vocabulary; FN, Face and name; RSPM, Raven's Standard Progressive Matrices; PS, Processing speed. Raw **$p < 0.01$.*

TABLE 4 | Homework completion.

Week	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8	No.9	No.10	No.11	No.12
Homework	Read	Paint	Read	Calligraphy	Read	Calligraphy	Paint	Read	Calligraphy	Paint	Read	Calligraphy
Completion Number	80	82	80	75	74	74	67	58	64	63	60	63

TABLE 5 | Self-training engagement.

	PE	R	WT	CC	C	M	SD	HW	LR	CU
Number	36	34	25	11	9	8	8	6	4	2

PE, Physical exercise; R, Reading books or newspaper; WT, Watching TV; CC, Playing chess and cards; C, Calligraphy; M, Listening to music; SD, Singing and dancing; HW, Hand-woven; LR, Listening to the radio; CU, Computer using.

the training difficulty in this study. The average scores before and after the intervention were 1.70 and 1.82 points (total score of 12 points), which were higher than those of 1.37 and 0.81 points in our previous study, but still lower than the scores of 2.3 and 4.2 points as reported in Cavallini's study (14). It might be related to the higher educational level of the elderly in their study. The average completion rate of 12 tests of in-class multidomain cognitive training was 96.44%, indicating that this cognitive training module had good operability and compliance. Because there was no requirement for writing words in Raven's reasoning test, the completion rate reached 100%, and the operability was the best. Likewise, due to more written content and higher vocabulary requirements, the completion rate of the story recall test remained low. Among the elderly, who insisted on completing this training, the effectiveness of the training was clearly reflected. In addition, some elderly reported that there were too many pictures to remember, suggesting that future studies can be performed with a lesser number of pictures.

The previous study shows that playing cards or mahjong has a significant positive effect on protecting cognitive functions in elderly individuals (21). Handicraft, calligraphy, and painting are also included in this intervention. The elderly subjects usually express strong interests with a high compliance rate, and such training items need to be added in future studies. Regarding the homework, all the elderly who completed the training rated it as moderately difficult. In future studies, homework could be set to match the training content in class so as to achieve better intervention effects.

Out of the self-training methods, most elderly subjects still opt for physical exercise, reading, and watching TV as their main training items although electronic devices are increasingly becoming popular. In this study, based on the completion rates, physical exercise ranked first. Previous studies show that physical

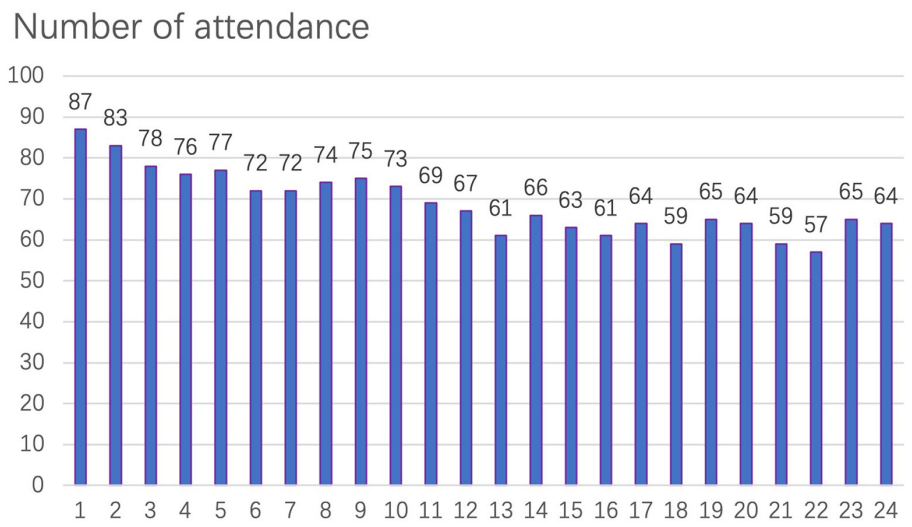

FIGURE 1 | Cognitive training attendance.

TABLE 6 | Attendance of the intervention group.

Attendance (%)	$p < 25\%$	$25\% \leq p < 50\%$	$50\% \leq p < 75\%$	$75\% \leq p < 100\%$	$p = 100\%$
Number (proportion)	9 (10.0%)	11 (12.2%)	9 (10.0%)	38 (42.2%)	23 (25.6%)

exercise is positively correlated with cognitive abilities in healthy elderly (22–24). Both elderly subjects who follow routine exercise all their life (25) or participate only at the later stage (26) can improve their cognitive function. A study involving the Chinese elderly community shows that long-term adherence to square dancing is also beneficial to improve mild cognitive impairment (27). In the future, physical exercise–associated cognitive training should be promoted to improve cognitive function in aged individuals.

Engagement

Previous studies suggest that a sensitive age of cognitive decline may be between 71 and 75 years of age (28–30). Thus, we selected elderly subjects over 70 years of age for the intervention group. In other studies, the attendance rate of single-domain training has been reported as 67% (18), whereas that in our previous study was 72.05% (19). After summing up the previous research experiences, we adopted the method of multidomain cognitive training and adjusted the training content to improve the learning interest of the elderly. Through health education, recreational activities, gifts, and other methods, the overall attendance rate of the intervention group was improved to 76.14%. The decrease in attendance rate in the later stage might be attributed to the cold weather condition and upcoming Spring Festival engagements. Therefore, it can be suggested to arrange the training sessions avoiding the seasons of inclement weather conditions and traditional festivities to obtain maximum attendance rate in future large-scale studies.

TABLE 7 | Correlation between attendance and baseline assessment.

	PCC	*p*
Education level	0.235*	0.026
MMSE	−0.038	0.724
Disease index	−0.224*	0.034
PF	0.313**	0.003
RP	−0.018	0.870
BP	0.185	0.081
GH	0.214*	0.042
VT	0.391**	0.000
SF	0.146	0.170
RE	0.198	0.062
MH	0.220*	0.037
pi Extraversion	−0.158	0.136
pi Vulnerability	0.018	0.869
pi Self-efficacy	−0.077	0.471
pi Neuroticism	0.064	0.546
pi Fatalism	−0.268*	0.011

Raw $p < 0.05$; **$p < 0.01$. PCC, Pearson correlation coefficient.*

The correlation analysis of attendance rates showed positive correlations between higher attendance rates and higher education level, the more positive fatalism, and better physical and mental health conditions. Jessica et al. (31) found in a large sample study that education level is one of the major predictors of cognitive intervention effects. Consistently, the

attendance rate was positively correlated with education level in this study, suggesting that education level might be a potential factor affecting the cognitive training outcomes. The elderly subjects having low education levels were comparatively slow in understanding the intervention method and consequently had poor test scores, which affected their confidence level and interests in learning. Therefore, their attendance was significantly decreased, and some of them even dropped out at a later stage. The elderly subjects with poor physical or mental health conditions also had lower attendance rates due to illness or mobility problems. Hence, those with more positive fatalism were more likely to receive cognitive training at the individual level.

Our previous study shows that the cognitive function of the intervention group was superior to that of the control group after multidomain cognitive training, indicating that participants could benefit from cognitive training. Therefore, it is more important to encourage the elderly with less education and poorer physical and mental health to participate in cognitive training (8). For example, we can promote the benefits of cognitive training through more popular science. The effectiveness of cognitive training combined with aerobic exercise training is also reported for elderly in poor body health. For the elderly with poor mental health, we can combine cognitive training with psychological intervention to increase their participation in class to achieve better training effects.

In future studies, we should consider the inhibitory effects in elderly subjects with low education levels. We should also modify the training strategies to improve participation rates by decreasing the difficulty level of intervention methods and grouping the subjects by comparable education levels. The use of intelligent intervention devices for online assessment, such as immersive 3-D virtual reality games, is shown to improve cognition by affecting discrimination, attention, and processing speed (32). In the recent study, we develop an APP named "Adaptive Cognitive Evaluation- Chinese Version" (33), which could implement cognitive training while reducing travel time for elderly subjects with mobility disabilities. Training compliances also need to be improved by including cognitive-behavioral therapy (CBT) for those with negative fatalism of personality indicators in future studies.

In this study, considering the feasibility and engagement of participants, we selected multiple cognitive domains to design multidimensional cognitive interventions, including memory, reasoning, and strategy training. The engagement of the elderly was significantly better than that of the single-domain cognitive training (9). In future studies, we hope to focus on the cognitive domain of each subject's cognitive impairment, so that personalized comprehensive training may lead to better engagement and more targeted and effective results.

Strengths and Limitations

As in several other studies, there are also certain pros and cons in this study, which should be considered when interpreting the results.

This study comprehensively explored a set of cognitive intervention methods suitable for community-dwelling healthy elderly in China. Multidomain cognitive training has the capacity to cover different cognitive domains with higher dimensions and more comprehensive intervention effects. Moreover, the face-to-face cognitive training mode had good interaction, thus suitable to enhance interpersonal skills and increase social network.

The study limitations include the high average age of the participants (over 70 years old), whose attendance rates could be affected by various underlying factors, such as bad weather and sudden physical deterioration. In addition, the face-to-face training method requires a higher education level and better physical condition, both of which were compromised to a certain extent in this study.

CONCLUSIONS

Multidomain cognitive training courses proved to be rational, acceptable, and effective in improving cognitive functions in the elderly population. The elderly with higher educational levels, better physical and psychological conditions had higher engagement during the training course.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital of Tongji University (Approval # LL (H)-09-04). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WF and ZY: study conception and design. WF: administrative support. ZY and XW: data analysis and interpretation. All authors have read, approved the final manuscript, collection and assembly of data, and provision of study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Cross-Sectional Study on the Cross-Talk of the COVID-19-Related Degree of Loneliness and the Etiological Factors Among the Elderly in Central China

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Background: The outbreak of COVID-19 has undoubtedly influenced the normal lifestyle of people worldwide, including the Chinese population. This study attempted to do supplementary research to the current situation of loneliness as well as the related risk factors among the elderly in the province in central Chinese during the COVID-19.

Methods: We conducted a cross-sectional study in one of the central Chinese provinces (Henan Province) from December 2020 to March 2021 using a multistage sampling method, and 568 elderly people without cognitive impairment were interviewed. The UCLA Loneliness Scale, Pittsburgh Sleep Quality Index (PSQI), Physical Activity Rating Scale (PARS-3), and Quality of Life Questionnaire SF-36 were adopted to collect information. We used univariate and multivariate logistic regressions to analyze the factors resulting in severe loneliness among the elderly with seldom or regular participation in physical exercises.

Results: During the epidemic in central China, the elderly suffering from loneliness syndrome accounted for 34.2%, of which 15.5% were severely lonely. Risk factors for severe loneliness were quality of life (OR: 7.129), sleep quality (OR: 3.778), seldom exercise (OR: 4.170), poor economic status (OR: 1.769), and negative attitude toward the prospects for the epidemic control (OR: 4.033). By grouping the participants in terms of physical activity, we found that the quality of life (OR:5.778) was a significant risk factor than sleep quality (OR:2.939) in the seldom exercise group, while the only risk factor in the regular exercise group was the quality of life (OR: 5.021).

Conclusion: There was an increase in the degree of loneliness among the elderly during the epidemic, and physical activity played an active role in relieving the severe loneliness of the elderly. Therefore, for the sake of the elderly, regular participation in physical exercises should be encouraged during the duration of the epidemic.

Keywords: COVID-19, elderly, loneliness, sleep quality, quality of life, physical activities

BACKGROUND

Loneliness can be defined as one's emotional and psychological stress due to isolation from social activities or living in an unfrequented place (1). Loneliness is one of the important indicators for evaluating social health, and it is also a major public health problem (2). There are European countries that appoint ministers of loneliness specialized in dealing with the issue of social loneliness (3). The sense of loneliness mainly affects physical health and psychological behavioral mechanisms. This in turn exerts influence on physiological functions, neuroendocrine effects, perception of stressful events, immune function, sleep quality and healthy behaviors etc (1, 4). Heavier loneliness predict exaggerated responses to acute stress, leading to elevated interleukin-6 (IL-6), interleukin-1 beta (IL-1B), monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor alpha (TNFa), proinflammatory cytokines and glycoprotein etc. These biomarkers are associated with the incidence of cardiovascular disease (5–9). The sense of loneliness simultaneously reduces the quality of life (10), and increases the risk of illness and all-cause mortality (11–13). The psychological impact of loneliness is more obvious (14–16). Greater loneliness stimulates neuroendocrine dysregulation (17). By reducing the dendritic branches of the hippocampus and prefrontal cortex, it triggers the long-term activation of the hypothalamic–pituitary–adrenal axis (the HPA axis), thereby reducing nerve reserves, resulting in a decrease in memory and learning ability, and a decrease in cognitive function, leading to dementia and Alzheimer's disease (18). Other psychological problems caused by loneliness include depression, anxiety, schizophrenia, suicide, etc (4, 15, 19). Persistent loneliness is, however, associated with worse health outcomes, depression, psychiatric disorders, and behavioral abnormality among older adults (20). Studies have shown that longer periods of loneliness may worsen depression, anxiety, aggressive behavior, and cognitive complications (21). Other studies have also supported the fact that loneliness can increase the rate of morbidity and mortality by affecting both physical and mental health in critically ill patients, including individuals suffering from cardiovascular disorders (4, 22). Thus, the efforts to minimize the loneliness-related psychological stresses are not only important for research purposes but also crucial for improving the quality of life in the elderly, especially those who are terminally ill or suffer from irreversible degenerative diseases. Therefore, monitoring and investigating the exact reasons for loneliness is notable and meaningful in the context of geriatric healthcare support (20, 23).

With the outbreak of the COVID-19 pandemic, all the countries have been confronted with great challenges globally. World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) believe that social distancing is one of the most efficient prevention strategies (24), despite of the result of social isolation. Different from loneliness, social isolation is an objective separation, while loneliness is a subjective separation (25). Both social isolation and loneliness have been shown to be harmful to health, such as reducing a healthy lifestyle, causing physiological reactions such as increased blood pressure and increased inflammatory response to stress (26). Studies have shown that social isolation has a greater impact on mortality than loneliness (29% vs. 26%) (27, 28). Conducted research from the perspective of brain neural mechanism, study reported individual subjectived perception of social isolation is one of the important risk factors of mortality in humans (17). Several studies have shown that social isolation will activate the hypothalamic-pituitary-adrenocortical axis, and it negatively affect a wide range of physiological, behavioral, and health outcomes (29, 30). During a 20-year follow-up investigation, the researchers found that the effects of loneliness and social isolation are synergistic: the impact of loneliness increases with the increase in the degree of social isolation, and the impact of social isolation on health also increases with the increase in the degree of loneliness (31, 32). This synergy has been confirmed in previous epidemiological retrospective studies. According to a study of 6, 231 South Korean residents who were quarantined for 2 weeks during the 2015 Middle East respiratory syndrome (MERS) pandemic (33) as well as another study of 1, 656 Koreans who were quarantined for 2 weeks (34), and an online survey of the quarantined people during the SARS pandemic, problems in varying degrees emerged about the physical and mental health of the quarantined (35) and increased with the lengthening of the quarantine time. It's worth noting that all interviewees described a sense of isolation. These observations are consistent with the results of studies in many countries during past disease (e.g., SARS, Ebola, H1N1 influenza, and Middle East respiratory syndrome) outbreaks. Social isolation causes the loss of normal contact with others, resulting in a sense of loneliness, as well as increased levels of stress, fear, and depression (36). Similarly, another retrospective study of the above-mentioned major epidemics shows that social isolation and loneliness have caused the occurrence of higher mortality rates to the elderly (25). Amongst all the age groups, the elderly population has been the most vulnerable and predisposed to high risk for COVID-19 infection and has accounted for the highest mortality rate, with or without any comorbid complications (37). In the United States, for example, 78% of the COVID-19-related deaths occurred in the age group of 65 years and over. In addition, the highest death toll among the elderly can be attributed to the age-associated declined immunity and/or suppressed immunity due to chronic comorbid complications, leading to the quick infection during the COVID-19 pandemic. Moreover, a significant portion of the elderly suffer from neurological and neuropsychiatric disorders and are most likely to remain in the persistently inflamed condition, resulting in the worst treatment outcomes once contracted COVID-19 (38). According to the global population census, China has the largest aged population in the world, where individuals aged 60 years and over occupy 18. Seventy percentage of the total population (39). In view of the present pandemic situation worldwide, controlling and preventing the pandemic outbreak will take a comparatively longer time in China. The prolonged pandemic may lead to most costly psychological cost (25). when the aged individuals are considered, social isolation and induced loneliness are more likely to cause negative impacts on their physical, social and psychological health, resulting in poor quality of life (38, 40, 41). Therefore, unlike the younger population, a slight rise in the

duration of the lonely period during the pandemic may have dire consequences for the elderly (42).

Loneliness is one of the key challenges that must be addressed during the Covid-19 pandemic. As the epidemic continues, the degree of loneliness may increase (2). The elderly experienced social isolation and loneliness during the epidemic prevention and control period. The dual pressure of physical and psychological may cause more severe loneliness, and the health status of the elderly who have previously suffered from mental illness may be over-magnified (43). Even if when young people are under the dual effects of loneliness and social isolation, their antibody response to influenza immunity will turn worse, and the antibody response will become the lowest (44). In previous studies on factors related to loneliness in the elderly, sleep disorders, self-health evaluation, education level, socioeconomic status, physical activity, etc. are all associated with loneliness, while sleep disorders, self-health evaluation, physical activity have a two-way correlation with loneliness (15, 23, 45–48). Among the studies on interventions for loneliness, most studies include more social support, maintain social network, one-to-one interventions, supported living group interventions, community-based group interventions, new technologies (such as mobile communication, TV, Internet, etc.) (36, 49–51), shared activity plan (such as exercise, adult learning, etc.), traveling (52), playing games (43), doing sports, psychological therapies, social service, animal therapy, befriending and skill development etc (53). However, during the epidemic prevention and control period, limited social resources and social isolation requirements have restricted most interventions. A review study demonstrated that most of the physical activities of the elderly were accumulated through tourism, but this was unrealistic during the epidemic. In addition, although the use of mobile phones and the Internet can alleviate loneliness, it is reported that the elderly are less inclined to use technical communication to make social connections (54). Physical activity has a moderating effect on the elderly's sense of loneliness, but most of the researches mainly focus on the elderly's daily physical activities, not on purposeful physical exercise. A regression analysis study conducted by the University of London showed that loneliness was negatively correlated with daily physical activity. However, when covariates such as gender, age, education level, health status, and economy were added, loneliness had nothing to do with physical activity (52). It is necessary to conduct research on subjective physical exercise rather than daily physical activity of the elderly during the epidemic, because continuous physical activity can reduce cardiovascular risk, reduce disability and weakness, and enhance the independence and quality of life of the elderly (55). Thus, the present study aimed to investigate the current situation of loneliness among the elderly undergoing COVID-19 prevention and cure and assess the influence of the etiological factors like age, gender, education status, quality of life, sleep quality, income, exercise participation, and attitude toward the prospects for epidemic control, etc. Furthermore, we conducted the analysis to evaluate the impact of physical exercise on the management of loneliness in the elderly by grouping the study participants according to the etiological factors. In the light of this analysis, certain physical exercise therapies were suggested in order to effectively intervene in the loneliness syndrome in the elderly during the COVID-19.

MATERIALS AND METHODS

Study Area and Participants

This study was conducted from December 2020 to March 2021. Henan Province was selected as the research area in this study for its geographic location in China. As a populous area located in central China, Henan Province had always been China's transportation hub and the most migrated area in central China. It definitely became one of the most populated provinces undergoing tremendous pressure for epidemic prevention and control since the outbreak of the COVID-19 pandemic. The surveyed areas are distributed in three sections of Henan: Pingdingshan, Xinyang, and Nanyang. Pingdingshan is located in the central part of Henan Province. Xinyang is 150 kilometers from Wuhan, Hubei Province, and Nanyang is 140 kilometers from Xiangyang, Hubei Province. Strict prevention and control measures were implemented in all of the three areas. Therefore, we believe that the selected research area is representative.

The inclusion criteria of the targeted population were: (1) age $\geq$ 60 years; (2) permanent resident; (3) not diagnosed with Alzheimer's disease (AD); (4) having clear awareness and can communicate with investigators without barriers, and (5) understood the contents of this survey and agreed to participate with voluntary cooperation. While the exclusion criteria included: (1) non-resident population; (2) elderly subjects suffering from any acute disease during the investigation; (3) elderly subjects with spinal or lower limb fractures in the past 6 months; (4) elderly subjects who couldn't walk independently; and (5) elderly persons suffering from malignant tumors, chronic renal insufficiency, etc. We further confirmed with the family members of the elderly participants to rule out the diagnosis of AD. All participants signed the written informed consent prior to their participation, voluntarily accepted the interview, and completed the questionnaire designed to investigate the participants' cognitive function, demographic characteristics, (include age, gender, education status, family income, and whether living alone or with family members/friends, etc). The calculation based on the sample size was supposed to be 5–10 times the influencing factors that were estimated 38 totally. We set the total number of valid questionnaires to no <380, and planned to collect no <200 questionnaires in each region. In the end, a total of 608 questionnaires were collected, and 568 of them were valid.

Survey Scales

UCLA Loneliness Scale

The UCLA Loneliness Scale has retest reliability of 0.89. It consists of 20 items, each of which is evaluated with a 4-level score system. Nine of the 20 items are evaluated in the opposite way. The total score of this scale ranges from 20 to 80, with the score ranges 20–34 indicating low-level loneliness, 35–48 for medium-level loneliness, and 49–80 indicating high-level loneliness, respectively. The higher score corresponded to the

higher degree of loneliness, and a score of ≥ 49 was considered severe loneliness in this study (56, 57).

Quality of Life Questionnaire SF-36

The SF-36 is internationally recognized as a universal assessment system for measuring the quality of life with high reliability and reproducibility (58). The SF-36 general scale was divided into 8 dimensions, involving Physiological Functioning (PF), Role-Physical (RP), Bodily Pain (BP), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH), and General Health (GH). For example, item 3 in the dimension of Physiological Functioning is to evaluate the ability to "bend over, bend knees and squat", a score of 3 indicating no obstacles, a score of 2 indicating few obstacles, a score of 1 meaning many obstacles. The sum of the scores of the 8 dimensions is the total quality of life score. The higher the score was, the better the quality of life was. A total score of >117 indicated the good quality of life in this study (58, 59). In this study, the Cronbach α coefficient of the scale is 0.874

Pittsburgh Sleep Quality Index (PSQI)

PSQI is a self-reporting questionnaire assessing the quality of sleep over a one-month interval. Seven components were included in the scale concerning subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping medication, and daytime dysfunction. The total score of PSQI ranged from 0 to 21, with >7 indicating poor sleep quality or sleep disturbances (60). The scale is widely used in the assessment of sleep quality of all kinds of people, and has good reliability and validity. The Cronbach α coefficient is 0.84, and the retest reliability is 0.86 (61).

Physical Activity Rating Scale (PARS-3)

PARS-3 categorizes the level of participation in physical activity from the three dimensions, such as physical exercise frequency, exercise time, and the intensity of exercise, including 1 item in each dimension, and each of these dimensions is evaluated with a 5-level scoring system. The score of physical activity participation is presented as physical exercise intensity multiplied by exercise time and exercise frequency. The highest score for physical activity participation is 100 points, and the lowest is 0. Between the two extremes, the score of ≤4 points refers to the infrequent exercise participation, and the score of ≥43 points corresponds to the considerable amount of exercise. In this study, the Cronbach alpha coefficient of this scale was 0.85 (62).

Sociodemographic Variables

Demographics of the participants were collected by a self-designed questionnaire survey documenting the participants' age, gender, economic status, education status, and attitude toward the prospects for COVID-19 control and so on. The survey was conducted on a voluntary basis.

Quality Control

Four investigators were recruited to conduct the survey, who received standardized training involving the principles and the strategies of conducting the survey prior to the study. The training involved making identical conversations, use of suggestive language, choice of time and location to distribute the questionnaire, and strategies of distributing the questionnaire. Moreover, considering the realistic fact that some of the elderly might not be able to read, we specified common descriptive language. During the entire process of the survey, we strictly abode by the local policies and regulations for COVID-19 prevention and control. The purpose of all the efforts was to ensure that the survey was performed and completed under the same experimental conditions.

Statistical Analysis

In this study statistical analysis on the data was performed by using SPSS statistical data 25.0. Data entry into the computer was performed by two researchers repeatedly so as to ensure the accuracy of it. Sample data on demographic characteristics and related factors affecting loneliness of the elderly were described by frequency and percentage. The degree of loneliness in the elderly who participated in the survey was regarded as the dependent variable, and the content in the general data was regarded as the independent variable. In addition, the elderly were investigated by being grouped into regular exercise group and seldom/infrequent exercise group. Binary unconditional logistic regression was firstly conducted to make univariate analysis, and then multivariate regression analysis was performed on the factors with significant results by adjusting age as a fixed factor. The OR value of the factors affecting the loneliness of the elderly and their respective 95% confidence intervals (95% CI) and P values were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Subject Characteristics

A total of 608 questionnaires were distributed during the study period, while 568 questionnaires were finally completed. There are 336 women, accounting for 59.1% of the total number. The age of the survey subjects ranged from 60 years old to 90 years old, and the proportion of elderly people between 60 and 75 years old occupies the highest 85%.102 among them had an education background of university or above, accounting for 18% of the total number. The number of people with poor economic status was 118, accounting for 20.8% of the total number. There were 342 people with a better quality of life, accounting for 60.2% of the total number 394 people had better sleep quality, accounting for 69.4% of the total. According to the result of the physical activity survey, the rates of regular exercise and seldom exercises were 80.1% and 19.9%, respectively. During the COVID-19 period, the proportion of loneliness among the elderly in the central province of China accounted for 34.2%, of which 15.5% were found severely lonely. According to the survey of attitude toward the prospects for the prevention and control of COVID-19, 12% of the participants showed a negative attitude (**Table 1**).

Univariate Analysis of Related Influencing Factors of Severe Loneliness Among the Elderly

By the univariate logistic analysis of the influencing factors related to the degree of severity of loneliness in the elderly, we found that economic status, the quality of life, sleep quality, physical activity, and attitude toward the prospects for epidemic control were statistically significant contributors to the severity of loneliness in the elderly ($P < 0.05$), while age, gender, and education status were not significantly correlated with the degree of loneliness in the elderly. Risk factors for severe loneliness were the quality of life [odds ratio (OR): 7.129, 95% confidence interval (CI)], poor sleep quality (OR: 3.778, 95% CI), seldom/infrequent exercise (OR: 4.170, 95% CI), poor economic status (OR: 1.769, 95% CI), and negative attitude toward the epidemic control (OR: 4.033, 95% CI).

By comparing the univariate logistic regression of the loneliness severity-related etiological factors between the regular and seldom/infrequent exercise groups, we showed that the quality of life and sleep quality both had significant impacts on the severity of loneliness in the elderly. The most interesting aspect in the regular exercise group was that negative attitude toward the epidemic control exerted a greater influence upon the elderly suffering due to severe loneliness, compared with that of the seldom/infrequent exercise group (**Table 2**).

TABLE 1 | Demographic details of the study participants.

Factors		*N* = 568	%
Age group	>75	85	15
	60 to 75	483	85
Gender	Female	336	59.1
	Male	232	40.9
College or above	Yes	102	18
	No	466	82
Poor economic status*	Yes	118	20.8
	No	450	79.2
Good quality of life*	Yes	342	60.2
	No	226	39.8
Good sleep quality*	Yes	394	69.4
	No	174	30.6
Regular Exercise*	Yes	455	80.1
	No	113	19.9
Severe loneliness*	Yes	88	15.5
	No	480	84.5
Negative attitude toward epidemic control	Yes	68	12
	No	500	88

**Poor economic status indicates household income ≤50% of local GDP per capita, with "no" indicating household income>50% GDP per capita in the local area instead; SF-36 score ≥117 indicates good quality of life, while the score <117 indicates poor quality of life; PSQI≤7 indicates good sleep quality, while PSQI > 7 indicates poor sleep quality; PARS-3 score >4 indicates regular participation in exercise, PARS-3 score ≤4 indicates seldom participation in exercise; UCLA score ≥49 indicates severe loneliness, UCLA score <49 indicates less loneliness.*

Multivariate Analysis of Related Influencing Factors of Severe Loneliness Among the Elderly

The multivariate logistic regression analysis of the factors for severe loneliness in the elderly by setting age as a fixed factor indicated that the significant influencing factors toward the severe loneliness in the elderly with seldom exercise were quality of life (OR: 5.778, 95% CI: 1.731–19.281) and sleep quality (OR: 2.939, 95% CI: 1.134–7.615) ($P < 0.05$), while as for the elderly with regular exercise, the only influencing factor of severe loneliness was the quality of life (OR: 5.021, 95% CI: 2.521–10.036) ($P < 0.05$; **Table 3**).

TABLE 2 | Univariate logistic regression analysis of related influencing factors of severe loneliness among the elderly.

Factors		Total			Regular exercise			Seldom exercise		
		n	Severe loneliness%	OR (95%CI)	*n*	Severe loneliness%	OR (95%CI)	*n*	Severe loneliness%	OR (95%CI)
Age	>75	85	20	1.758 (0.993 3.112)	58	13.8	1.356 (0.602 3.055)	26	38.5	1.602 (O.651 3.947)
	60-75	483	14.5		398	10.6		86	31.4	
Gender	Male	232	14.7	1.115 (0.700 1.777)	196	10.2	1.148 (0.631 2.089)	36	39	
	female	336	16.1		260	11.5		76	31.5	
Education status	NO	466	14.8	1.317 (0.752 2.306)	369	10	1.576 (0.798 3.112)	97	33	1.354 (0.443 4.135
College or above	YES	102	18.6		87	14.9		15	40	
Good quality of	NO	226	8.4	7.129*** (4.146 12.256)	158	22.8	5.986*** (3.116 11.49)	73	45	5.610** (1.971 15.964
life	YES	342	20.2		298	4.7		39	12.8	
Poor sleep	YES	174	28.7	3.778*** (2.364 6.036)	114	19.3	2.682** (1.465 4.910)	60	46.6	3.675** (1.561 8.651
quality	NO	394	9.6		342	8.2		52	19	
Regular	NO	112	33.6	4.170*** (2.557 6.801)						
Exercise	YES	456	11							
Poor ecoNomic	YES	118	22	1.769* (1.061 2.949)	90	16.7	1.891 (0.983 3.640)	28	39	1.366 (0.563 3.313
Status	NO	450	13.8	4.033*** (2.305 7.055)	366	9.6	3.325* (1.393 7.933)	84	32	2.043 (0.904 4.616
Negative	YES	68	35, 3		30	26.7		38	44	
attitude	NO	500	12.6		426	10		74	28	

**P<0.01; **P<0.005; ***P<0.001; CI, confidence interval; OR, Odds ratio.*

TABLE 3 | Multivariate analysis of related influencing factors of severe loneliness among the elderly in terms of physical activity.

Factor	OR	95%CI	*P*
Seldom exercise (*n* = 112)			
Age*	1.03	0.965 1.100	0.373
Good quality of life (NO vs. YES)	5.778	1.731 19.281	0.004
Poor sleep quality (YES vs. NO)	2.939	1.134 7.615	0.026
Regular exercise (*n* = 456)			
Age*	1.001	0.955 1.049	0.968
Good quality of life (NO vs. YES)	5.021	2.521 10.036	0.000

*Fixed in the model. *Age was set as a continuous variable in the multivariate analysis.*

DISCUSSION

This study was mainly designed to study the level of loneliness among the elderly in the central Chinese province during the COVID-19 prevention and control period, concluding that the severe loneliness of the elderly was mostly related to the quality of life, sleep quality, economic status, and the physical status activity. The results of this study were consistent with previous research reports (45, 63, 64). Based on our findings, age, gender, and education status didn't have a significant correlation with the severity of loneliness among the elderly, despite the results of few studies showing that loneliness was highly correlated with age. This inconsistency might be attributed to the wider age ranges of the participants (20 vs. 50 vs. 80 years old) in those studies (21). To better understand the impact of age-associated etiological factors on the degree of loneliness, we selected the participants aged 60 years and above. In the light of our study, better economic status had a protective effect on the occurrence of loneliness, which was in line with the conclusion of the European research studies. However, earlier studies have revealed that compared with the elderly, loneliness exerted a higher impact on middle-aged people (50–59 years old) in poverty (65). This study also investigated the attitude of the elderly toward the prospects for COVID-19 control and found that only 12% of the elderly showed a negative attitude. Based upon the multivariate analysis, it was found that the attitude toward the prospects for the epidemic control did not increase the risk of severe loneliness, regardless of the group with regular exercise or seldom exercise.

It has been observed that the health and psychological complications due to loneliness are more serious than those before the epidemic (34.2 vs. 28%) in the background of COVID-19 among the elderly in the central China province (66). Studies from the United States and Europe have also indicated that loneliness-associated elderly suffering has been drastically growing during the period of acute outbreaks of COVID-19 (20, 42). According to the research performed by Groarke's team from the United Kingdom, poor sleep quality and difficulty in performing regular exercise were believed to be the major factors for loneliness during the initial lockdown period of the COVID-19 outbreak (67). The results of our research eventually backed up the hypothesis that sleep quality could have an impact on the occurrence of severe loneliness, which was similar to the results of the study conducted in Shandong Province in China (68). The impact of sleep on loneliness is mainly in terms of quality of sleep and sleep satisfaction and is irrelevant to the length of sleep (69).

According to other studies, critical reasons for the growing proportion of loneliness among the elderly during the COVID-19 pandemic have been the restricted social isolation and activities during the period of disease prevention and control measures. Social isolation was discovered to be primarily related to the degree of loneliness (42, 43), since separation from the outside world reduced the time the elderly spent on physical activities and thus brought about an increase in the sedentary time, eventually resulting in the decreased physical health and sense of happiness, and consequently a sharp decline in the quality of life (52). Physical activity has been found to play an active role in carrying out effective interventions in the loneliness of the elderly (64). It's also a practical means of improving old people's quality of life, physical health, and sleep quality (52, 70). Similarly, our research showed better sleep quality in the regular exercise group than in the seldom exercise group (53.6 vs. 25%). Furthermore, the quality of life for the elderly in the regular exercise group was also better than that in the seldom exercise group (65.2 vs. 34.6%). The multivariate regression analysis indicated that the main risk factors for the onset of severe loneliness in the elderly in the seldom exercise group were the quality of life and sleep quality, while the major risk factor for severe loneliness of the elderly in the regular exercise group was simply the quality of life. In other words, our results suggest that regular physical exercises function effectively to alleviate the severe loneliness in the elderly during and post-COVID-19 when the epidemic prevention and control measures are still in effect.

Although the advisable exercise time is considered to be 150 mins per week (64) and group exercises are assumed to have a better impact on the intervention in the loneliness of the elderly (71), regular participation in physical activities and the implementation of group exercises during COVID-19 prevention and control were difficult tasks than during non-epidemic period. In view of this situation and based upon the results of our study, it is suggested that the elderly should maintain a minimum amount of exercise as 1–2 times a week for 21–30 mins of walking or calisthenics with radio music, or 1–2 times a week for 11–20 mins of jogging and so on, for the purpose of relieving or reducing the stress of loneliness. In addition, social interactions through the internet and group fitness exercises with the aid of communication tools have also been proved helpful in reducing loneliness among the elderly (72).

There inevitably existed some limitations in this study. Firstly, it was restricted to the cross-sectional design. Secondly, since Henan province was the only selected study area, the survey data from other provinces were lacking. Therefore, follow-up studies involving more provinces in the future are supposed to be conducted to further validate our findings.

This was a pilot study to evaluate and assess the current situation of loneliness among the elderly in central China and the related influencing factors during COVID-19. The COVID-19 pandemic definitely increased the severity of loneliness among the elderly. It takes a long, long time and more effort to improve the quality of life of the elderly. The intervention of physical

activities is often easier and may be effective in a short time. On the premise of adhering to the epidemic prevention and control measures, physical activity intervention was a more practical and effective short-term means compared with improving the quality of life and sleep quality of the elderly. In summary, encouraging the elderly to participate in physical activities may have positive effects on their quality of life and also play an active role in reducing the risk of severe loneliness.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PL, C-LT, and JJ designed the research protocol and performed the study. PL analyzed the data. W-bQ, JZ, and Z-JC performed the investigation. JJ drafted the manuscript. PL, JJ, C-LT, W-bQ, JZ, and Z-JC read and revised the manuscript. All authors read and approved the final version of the manuscript.

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Research Hotspots and Trends in Music Therapy Intervention for Patients With Dementia: A Bibliometrics and Visual Analysis of Papers Published From 2010 to 2021

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Background: As a serious public health problem, dementia has placed a heavy burden on society and families. Evidence suggests that the use of music therapy as a non-pharmacological intervention has certain advantages with respect to reducing the behavioral and psychological symptoms of dementia (BPSD) and improving the cognition and mental status of dementia patients. However, research trends and hotspots regarding music therapy intervention for dementia analysis have not been systematically studied *via* bibliometric analysis.

Methods: We searched the Web of Science Core Collection (WoSCC) for texts published between January 1, 2010, and October 31, 2021, and visualized country, institution, journal, keyword co-occurrence, keyword emergence and keyword clustering.

Results: A total of 217 articles from the WoSCC database were analyzed. In this research field, the annual number of publications has generally shown a slowly increasing trend, and the United States has the most publications and the most frequent cooperation among countries. University College London (UCL) has the most extensive influence among research institutions. Among articles, those published in the JOURNAL OF ALZHEIMER'S DISEASE were the most numerous, with 20 such articles being published, accounting for 9.22% (20/217) of the total. Comprehensive analysis of five clusters *via* biclustering shows that the research hotspots in this field during the past 11 years have mainly focused on the autobiographical memory, cognitive function, mental state and BPSD of dementia patients.

Conclusion: This study conducted a bibliometric and visual analysis of relevant studies concerning music therapy intervention for dementia patients. Psychological problems faced by dementia patients and the topics of quality of life, individualized music therapy, the mental state of caregivers and other related topics may be important research directions in the future. Therefore, the question of how to develop standardized research protocols and identify unified efficacy evaluation indicators should be a focus of and difficulty for future research.

Keywords: dementia, music therapy, research hotspots, bibliometric analysis, biclustering analysis, CiteSpace, Web of Science

INTRODUCTION

According to a survey by the World Health Organization in 2021, more than 55 million people worldwide suffer from dementia, a number which is rising at a rate of 10 million new cases per year (1). The number of dementia patients worldwide is expected to exceed 150 million by 2050, and the cost of treatment is expected to double by 2030 (2). As the country with the largest number of dementia patients, China accounts for approximately one quarter of global prevalence of dementia (3). Clearly, dementia has become a serious public health problem, placing a heavy burden on society and families. Alzheimer's disease (AD), as the main type of dementia, leads to a loss of function and cognitive and behavioral issues in patients (4), and 90% of dementia patients exhibit behavioral and psychological symptoms of dementia (BPSD), which become manifest as excitement, sleep disorder, anxiety and aggressive behavior (5). These symptoms reduce the quality of life of patients and caregivers (6), increase the cost of care, and entail severe challenges for family caregivers (7), even leading to a deterioration of the relationship between family members (8).

Management of BPSD, cognition and mental status in dementia patients is mainly divided into drug intervention and non-pharmacological intervention categories (9). However, drug interventions are often accompanied by adverse reactions, increasing the risk of death among patients (10), and may lead to cognitive decline and an increase in the number of falls among patients (11). The safety and effectiveness of drug interventions remain controversial (12). Compared with drug interventions, non-pharmacological interventions are more effective in improving cognition and reducing BPSD in dementia patients (13, 14). A number of studies have shown that non-pharmacological intervention has a low level of risk, can effectively manage BPSD symptoms in dementia patients (15), and can accomplish personalized nursing interventions according to the situation of patients and their families (16), which can improve patient quality of life and enhance caregiver satisfaction (17), so this approach is a scientific and effective nursing intervention.

As an important intervention in the non-pharmacological treatment of dementia, music therapy is mainly divided into the categories of active music therapy and passive music therapy (18), that is, active participation in singing, instrument playing and music creation, and passive listening to music. As a nonverbal therapy (19), music therapy is not affected by the course of the disease and can be used at all stages of dementia (20). Participating in singing activities can effectively reduce patients' excited-aggressive moods (21), improve their quality of life, reduce pressure on caregivers, and promote the happiness of family members (22). Personalized music therapy based on patients' musical memory can reduce BPSD (23, 24). A study of 60 patients with moderate to severe dementia who received music therapy intervention reported improvement in psychiatric symptoms and reduced frequency and severity of BPSD (25). Evidence shows that music therapy seems to be effective, but there is no systematic and comprehensive report concerning visual analysis of research hotspots and development trends in music therapy regarding the non-pharmacological management of dementia.

Publications have shown that music therapy appears to be effective in the intervention of dementia. However, as far as we know, no one has systematically analyzed the subject of this field by means of bibliometric analysis. Therefore, this study aims to research hotspots and trends in music therapy intervention for patients with dementia from 2010 to 2021 through bibliometrics. As an effective statistical method, bibliometrics and visual analysis can not only evaluate the published literature but also predict development trends in this field, thus providing a relevant basis for subsequent studies (26). Therefore, based on the WoSCC database, this study used the CiteSpace and gCLUTO software to examine trends and co-occurrence matrices, aiming to analyze the research status, hotspots and development trends in this field, help relevant researchers strengthen their understanding of this field and promote the benign development of relevant research in this field.

MATERIALS AND METHODS

Data Collection and Search Strategy

A search of the Web of Science Core Collection (WoSCC) database for studies published between January 1, 2010, and October 31, 2021, regardless of language, was performed by using the following search parameters: [TS = (music Therapy) OR TS = (music)] AND TS = (dementia).

Inclusion criteria: 1. Journal articles concerning music therapy intervention in dementia; 2. Publication period between January 1, 2010 and October 31, 2021; 3. Article type is 'Article'.

Exclusion criteria: 1. Review, conference paper, letter, comment, etc.; 2. Duplicate literature.

Two independent reviewers (SY and ZL) conducted a search according to the retrieval strategy, filtered the articles according to the inclusion and exclusion criteria, imported the qualified literature into Endnote (X9.1) in an appropriate format for subsequent operations, performed a cross-check between the two reviewers, and consulted a third reviewer (FYZ) concerning any discrepancies. To reduce deviation, the search and data extraction were completed on November 6, 2021, and the flow chart is shown in **Figure 1**.

Data Analysis

Data Extraction and Network Analysis

Employing the basic characteristics of the WoSCC database, number of papers, publication year and publication country were extracted and summarized, and then a line chart, national literature volume map and international cooperation map were drawn. Then, we imported the data into Citespase 5.8. R1 in refworks format, set the time parameters to between January 1, 2010 and October 31, 2021, year per slice = 1, and set other parameters to the default values, adjusting as needed to draw the network hotspot map.

Keywords Biclustering Analysis

The gCLUTO software (version 1.0, Graphical CLUstering Toolkit, a graphical front-end for the CLUTO data clustering

library developed by Rasmussen, Newman, and Karypis from the University of Minnesota) (27) was used to conduct a biclustering analysis of high-frequency keywords. First, qualified literature from the WoSCC database was imported into Bibliographic Item Co-Occurrence Matrix Builder (BICOMB, version 2.0, designed by Professor Lei Cui from China Medical University) to construct a co-occurrence matrix of high-frequency keywords, and then a cluster analysis was conducted using gCLUTO, clustering method will use the repeated bisection, I^2 as the optimization function, and cosine function as the similarity coefficient, and set other parameters to the default values, to generate a matrix visualization and a mountain visualization to show the relationship between high-frequency keywords and the source literature as a means of identifying research hotspots related to music therapy interventions for patients with dementia.

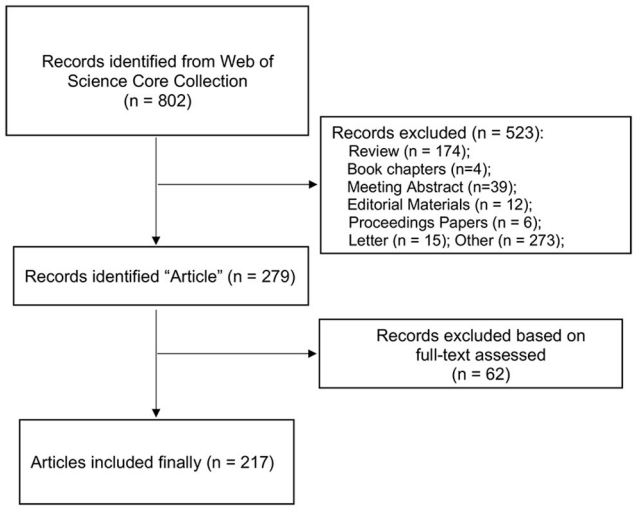

FIGURE 1 | Flowchart of included and excluded studies.

RESULTS

Publication Years and Country Distribution

As an important index, changes in the number of articles can directly reflect research trends in the use of music therapy as an intervention for dementia. After screening, a total of 217 qualified articles were included, as shown in **Figure 1**. The results in **Figure 2** show that the overall number of articles in this research field was low between 2010 and 2021 and that research began to appear and increase slowly in 2011, with the largest number of articles being published in 2018 (34 articles). Although there was a slight decline in 2016 (12 articles) and 2019 (24 articles), the overall annual number of articles showed a slow upward trend. The summary results of annual publications from the top 10 countries in terms of the number of published articles between 2010 and 2021 (**Figure 3A**) showed a similar trend to that of overall publications in this field. However, in 2020, **Figure 2** shows an increase in the number of published articles, while **Figure 3A** shows the opposite result, indicating that the emerging countries contributed to the number of publications in this field gradually increased and that this trend had a certain degree of influence.

A total of 30 countries have contributed to scientific research concerning the use of music therapy for dementia (**Figure 3B**),

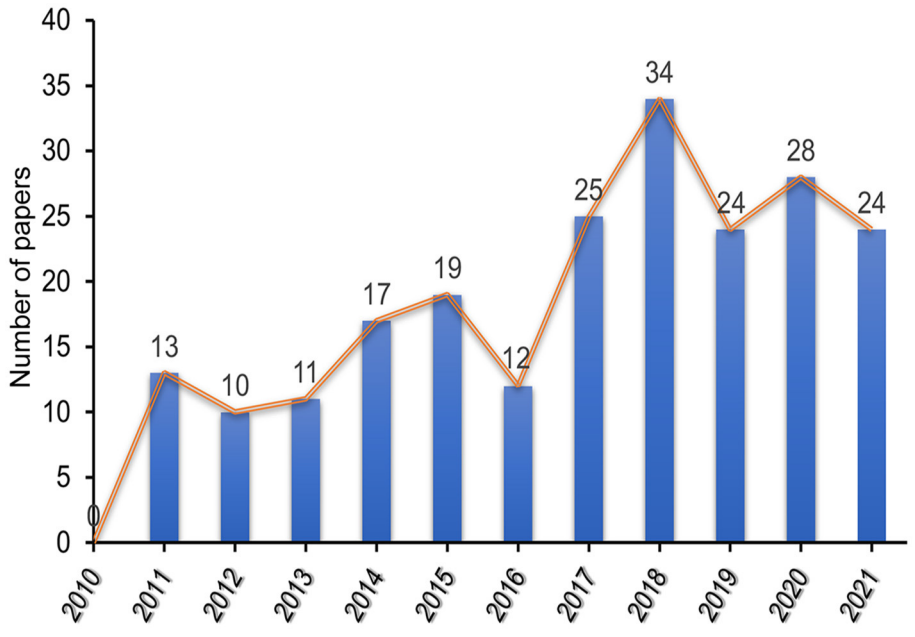

FIGURE 2 | Annual trend chart of publications included in WoS database from 2010 to 2021.

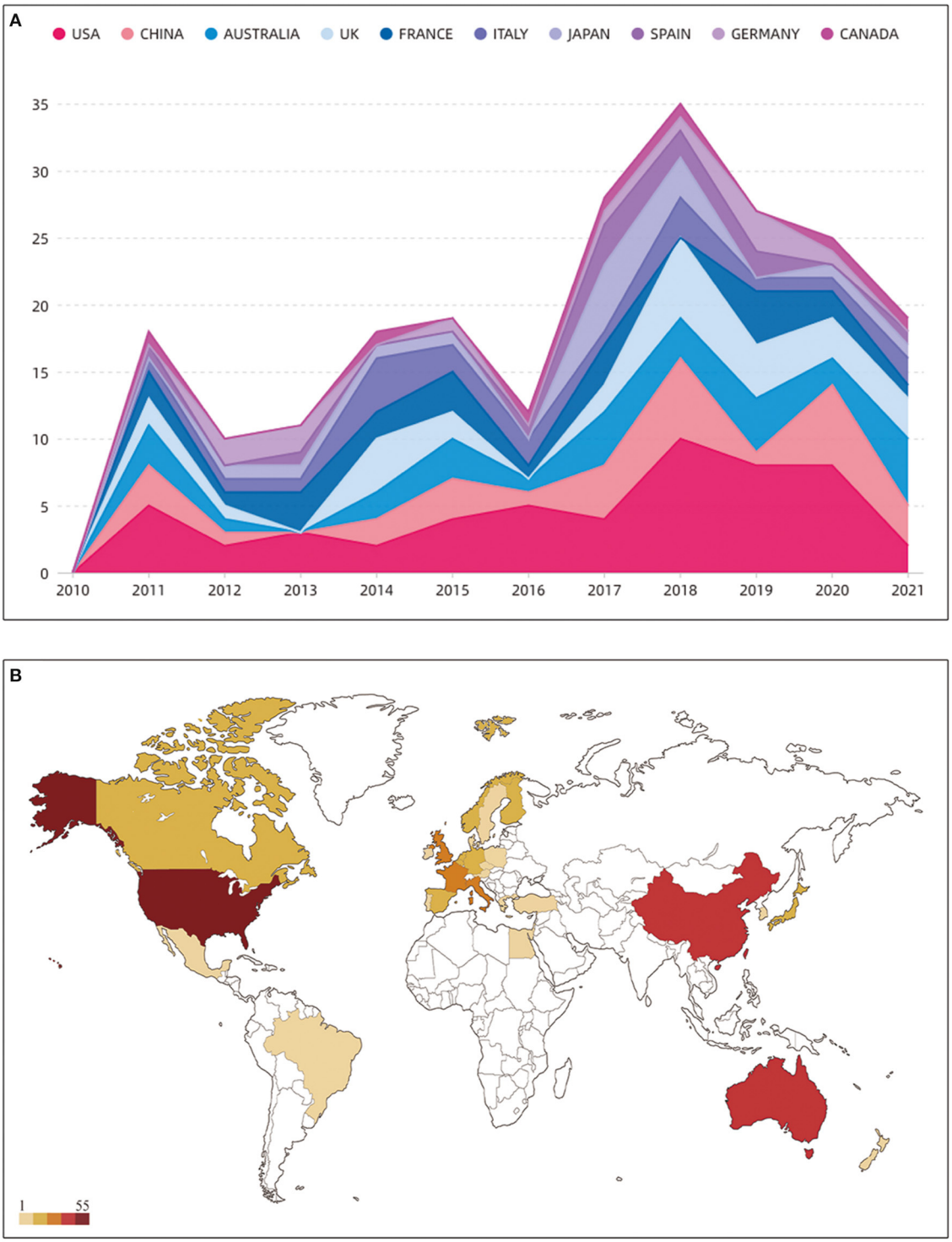

FIGURE 3 | (A) The growth trends of the top 10 countries in terms of the number of published articles from 2010 to 2021. **(B)** Geographical distribution of music therapy for dementia publications.

and cooperation among countries in this field is shown in **Figure 4**. After using CiteSpace to analyze country nodes, the top 10 countries in terms of number of publications and center value between 2010 and 2021 are presented in **Table 1**, in which center value is positively correlated with number of cooperative relationships. The top 3 countries in terms of the number of

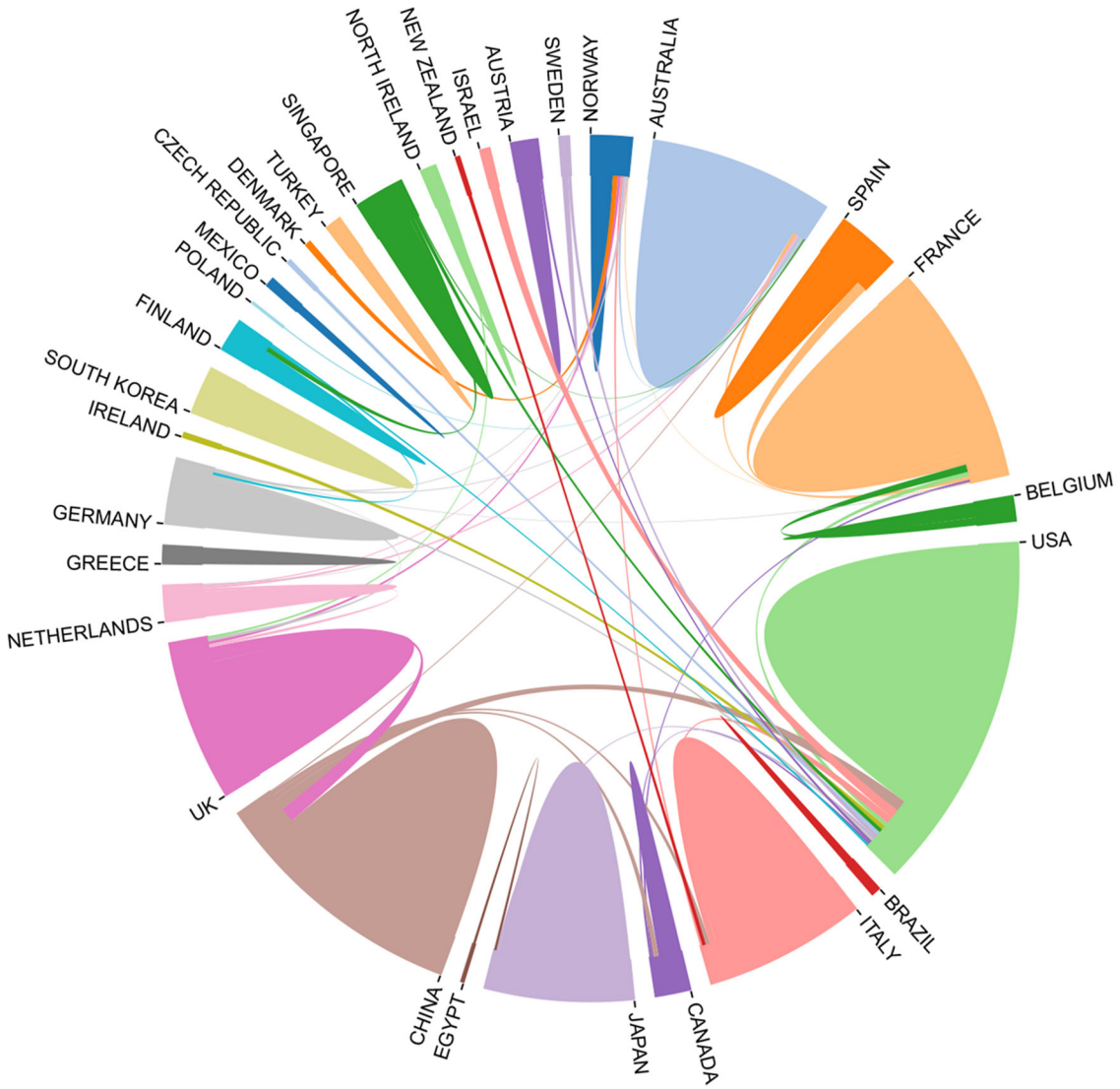

FIGURE 4 | The cooperation of countries in the field of music therapy for dementia from 2010 to 2021.

publications are the USA, China and Australia. Concerning countries that had a central value > 0.5 after selection, the analysis results show that the USA (publications: 53, centrality: 0.93), UK (publications: 27, centrality: 0.89), Italy (publications: 19, centrality: 0.65), New Zealand (publications: 2, centrality: 0.59) and the Netherlands (publications: 5, centrality: 0.59) have a high degree of influence in the field. Among these countries, the United States has outstanding advantages in this field, having produced the largest number of publications, and has cooperated with most countries in this field. It is worth noting that New Zealand ranks 21st in publication volume (publication: 2) but 4th in centrality (centrality: 0.89), which indicates that although New Zealand published few articles, the country has close relations and cooperation with other countries in this field.

Distribution of Issuing Institutions

Institution nodes were analyzed by using CiteSpace, and a cooperative network diagram was constructed. Nodes represent institutions, and wires represent cooperation relationships between institutions. The generated cooperation network diagram contains 471 nodes and 880 wires, indicating that a certain degree of exchange and cooperation took place among institutions. The cooperation network can thus be seen, as shown in **Figure 5**. **Table 1** lists the top 10 institutions according to number of publications and center values. The top 4 institutions with the largest number of publications are University College London (publications: 9), Western Sydney University (publications: 5), Mie University (publications: 5) and the University of Lille (publications: 5). Institutions that had a central value > 0.05 included University College

TABLE 1 | Top 10 countries and institutions in terms of number of publications and center value between 2010 and 2021.

Items	Publication			Centrality		
	Ranking	Name	Number	Ranking	Name	Number
Country	1	USA	53	1	USA	0.93
	2	China	30	2	UK	0.89
	3	Australia	28	3	Italy	0.65
	4	UK	27	4	New Zealand	0.59
	5	France	22	5	Netherlands	0.59
	6	Italy	19	6	China	0.49
	7	Japan	14	7	Denmark	0.30
	8	Spain	11	8	Canada	0.30
	9	Germany	11	9	Australia	0.21
	10	Canada	7	10	Norway	0.21
Institution	1	University College London	9	1	University College London	0.07
	2	Western Sydney University	5	2	Aalborg University	0.06
	3	Mie University	5	3	University of California, San Francisco	0.06
	4	University of Lille	5	4	University of Lille	0.04
	5	University of Paris Descartes (Paris 5)	4	5	The University of Texas at Austin	0.02
	6	University of California, San Francisco	4	6	University of California, Davis	0.02
	7	Macquarie University	4	7	University of Toronto	0.02
	8	University of Pavia	4	8	University of Pavia	0.01
	9	The University of Texas at Austin	4	9	Anglia Ruskin University	0.01
	10	Aalborg University	4	10	Western Sydney University	0.01

London (publications: 9, centrality: 0.07), Aalborg University (publications: 4, centrality: 0.06) and the University of California, San Francisco (publications: 4, centrality: 0.06). According to comprehensive analysis of publication volume and central value, University College London is the main institution in this field and has the most extensive network of cooperative relationships.

Most Active Journals

A total of 104 academic journals published articles concerning the use of music therapy for dementia. The top 10 journals published a total of 71 articles, accounting for 32.71% (71/217) of total records. Among these journals, the *JOURNAL OF ALZHEIMER'S DISEASE* has the highest number of publications, with a total of 20 articles, accounting for 9.22% of the total (20/217). We also summarize the citations, IF (2020), and WoS categories of these journals in **Table 2**, and these categories are basically divided into Geriatrics and Gerontology, Psychiatry, Neurosciences, and Nursing. It is worth noting that the most cited journal was also the *JOURNAL OF ALZHEIMER'S DISEASE* (IF = 4.472), which demonstrates its significant influence in the research field.

Analysis of Co-occurring Keywords

Co-occurrence analysis of keywords can allow for a better understanding of research hotspots in this field. The keywords co-occurrence diagram is shown in **Figure 6**. Keywords with a high frequency in the 760 nodes include "dementia" (164 times), "Alzheimer's disease" (92 times), "music" (68 times), "music therapy" (67 times) and "older adult" (65 times). Keywords with higher central values include "behavior" (0.16), "agitation" (0.14), "elderly people" (0.10), "emotion" (0.09), "cognition" (0.07) and "caregiver" (0.05). High-frequency keywords are mainly based on different intervention measures and intervention groups, while high-central value keywords are closely related to the symptoms and nursing aspects of dementia patients.

Research Frontiers Detection

The keyword outburst and keyword time zone map can more clearly display research hotspots and their changing trends and provide direction for follow-up research in this field. In **Figure 7**, 'social interaction' and 'decline' have been common keywords since 2020, and **Figure 8** shows that the research field has begun to focus on the behavior of dementia patients at an early stage. Over time, research has begun to focus on the psychosocial aspects of dementia. It is worth noting that the common keyword and emergent word categories in the 2021 time zone map both include 'social interaction', indicating that current research pays more attention to social interaction and communication among dementia patients and reflects the latest research trends in this field.

Keywords Biclustering

A total of 28 high-frequency keywords were obtained from the included studies, accounting for 5.98% of all keywords (**Supplementary Table 1**). The 28 high-frequency keywords were divided into 6 clusters. The visualization matrix of high-frequency keywords and source articles is shown in **Figure 9A**. The row labels denote high-frequency keywords, and the

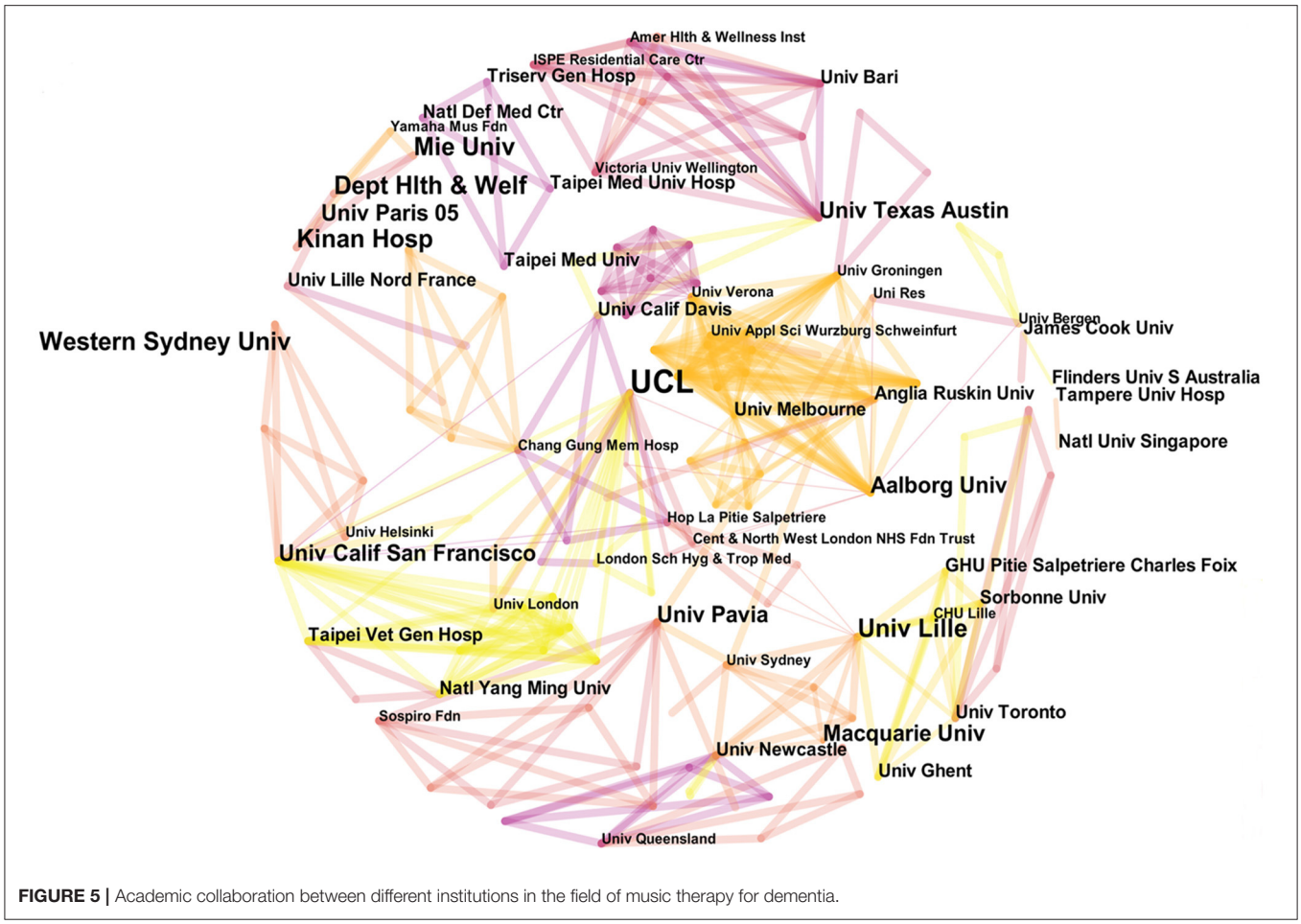

FIGURE 5 | Academic collaboration between different institutions in the field of music therapy for dementia.

column labels indicate the source articles. The darker the color is, the higher the frequency of the keywords. Mountain visualization is used to verify the effect of the visualization matrix (**Figure 9B**), and each mountain represents a cluster. The height of the mountain is proportional to the similarity within the cluster, the volume of the mountain represents the number of high-frequency keywords in the cluster, and red indicates a low standard deviation within the cluster; otherwise, this factor is shown in blue. After analyzing high-frequency keywords in each cluster, the topic of each cluster is summarized to identify research hot spots in this field and assist subsequent research.

Cluster 0: The effect of long-term care on agitation in Alzheimer's patients.
Cluster 1: Effects of individualized music therapy on older patients with dementia.
Cluster 2: Effects of music on autobiographical memory, emotion and cognitive function in patients with Alzheimer's disease.
Cluster 3:Music therapy in the context of improving memory and cognitive impairment.
Cluster 4: Effects of music therapy on anxiety, depression and cognitive function in patients with dementia.
Cluster 5: Mental stress and BPSD symptoms in patients with Alzheimer's disease in nursing homes.

DISCUSSION

The analysis of annual publications, international cooperation and institutions shows that in this research area, annual publications generally show a slowly increasing trend and that the United States has the most publications and the most frequent cooperation among countries. Most research institutions in this field are universities, among which UCL has the strongest comprehensive influence. Although analysis of China's international cooperation and institutions shows that its number of publications ranks second, the central value of China is low, and the country has a lack of influential research institutions in this field. Combined with high-frequency keywords, keyword emergence and the keyword time zone map, we found that the current hotspot in this field is the psychosocial care of patients with dementia. In the time interval chosen, this research field paid more attention to the management and care of the cognitive behavior and function of patients with dementia in the early stage of the disease and explored the mechanisms potentially underlying this aspect. As time

TABLE 2 | Summary of the top 10 journals.

Journal	Published numbers (%)	Total citations	IF 2020	WoS Categories
Journal of Alzheimer's disease	20 (9.22%)	56	4.472	Neurosciences
Aging and mental health	11 (5.07%)	49	3.658	Geriatrics and gerontology; Psychiatry
International psychogeriatrics	6 (2.76%)	40	3.878	Psychology; Clinical geriatrics and gerontology; Gerontology psychiatry
Geriatric nursing	6 (2.76%)	4	2.361	Geriatrics and gerontology; Nursing
American journal of Alzheimer's disease and other dementias	5 (2.30%)	15	2.035	Geriatrics and gerontology; Clinical Neurology
Journal of clinical and experimental neuropsychology	5 (2.30%)	13	2.475	Psychology; Clinical; Neurology; Psychology
Geriatrics and gerontology international	5 (2.30%)	7	2.73	Geriatrics and gerontology
Frontiers in medicine	5 (2.30%)	2	5.093	Medicine; General and internal
International journal of geriatric psychiatry	4 (1.84%)	41	3.485	Geriatrics and gerontology; Psychiatry
Geriatrie et psychologie neuropsychiatrie de vieillissement	4 (1.84%)	5	0.838	Psychiatry; Psychology

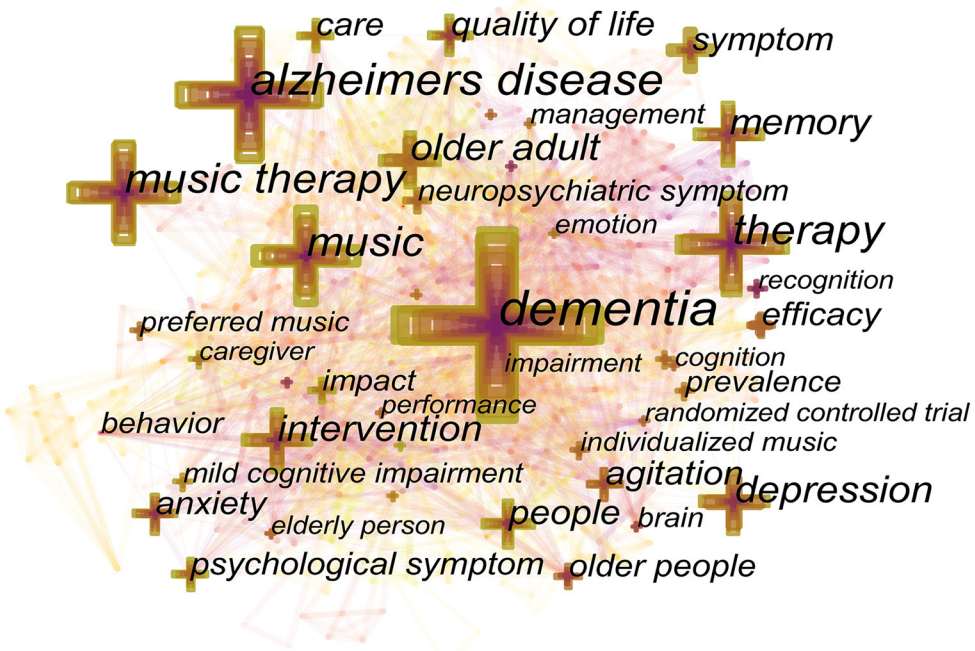

FIGURE 6 | Keyword co-occurrence diagram.

progressed, the literature also began to pay more attention to the mental health of patients. Comprehensive analysis of the six clusters found in the biclustering shows that the research hotspots in this field over the past 11 years have mainly focused on autobiographical memory, cognitive function, mental state and BPSD among dementia patients.

In China, dementia has become the fourth leading cause of death among elderly individuals after cancer, heart disease and cerebrovascular diseases (28), which places great pressure on and causes pain to dementia patients, their families, caregivers, and even society as a whole and seriously affects the quality of life of these individuals. The 2018 Guidelines for the Diagnosis and Treatment of Dementia in China indicate that non-pharmacological treatment should be the first choice for psychiatric and behavioral symptoms of dementia and that personalized treatment should be conducted to achieve the best efficacy (29). However, relevant research concerning non-pharmacological intervention remains incomplete. Some dementia patients and their families have insufficient understanding of the disease, resulting in a

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2011 - 2021
semantic dementia	2011	3.11	2011	2012	
temporal variant	2011	2.36	2011	2012	
recognition	2011	4.99	2012	2013	
alzheimer disease	2011	3.03	2012	2013	
autobiographical memory	2011	3.65	2013	2013	
inventory	2011	2.51	2013	2013	
agitated behavior	2011	2.6	2014	2015	
plasticity	2011	2.59	2014	2014	
brain	2011	2.67	2016	2016	
perception	2011	2.61	2017	2017	
leukocyte telomere length	2011	2.4	2018	2018	
cognitive functioning	2011	2.4	2018	2018	
session	2011	2.4	2018	2018	
social interaction	2011	3.2	2020	2021	
decline	2011	3.2	2020	2021	

FIGURE 7 | Top 15 keywords with the strongest citation bursts.

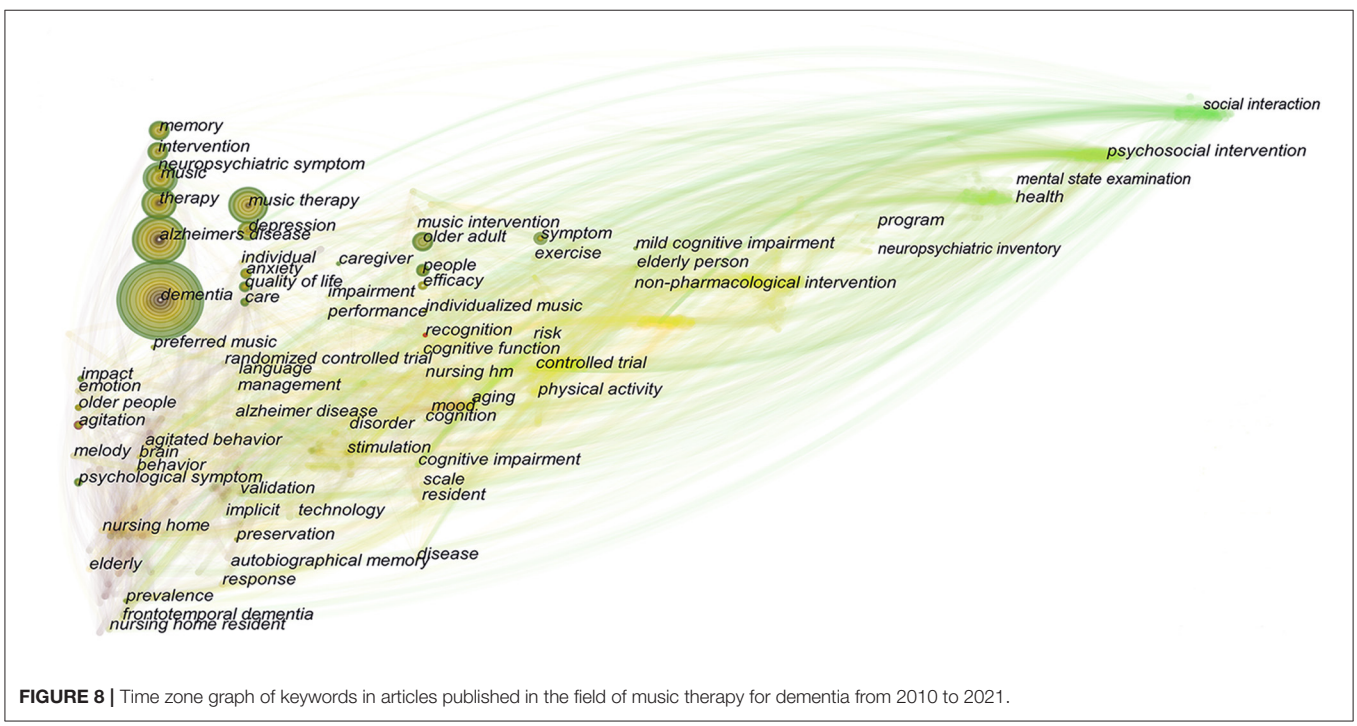

FIGURE 8 | Time zone graph of keywords in articles published in the field of music therapy for dementia from 2010 to 2021.

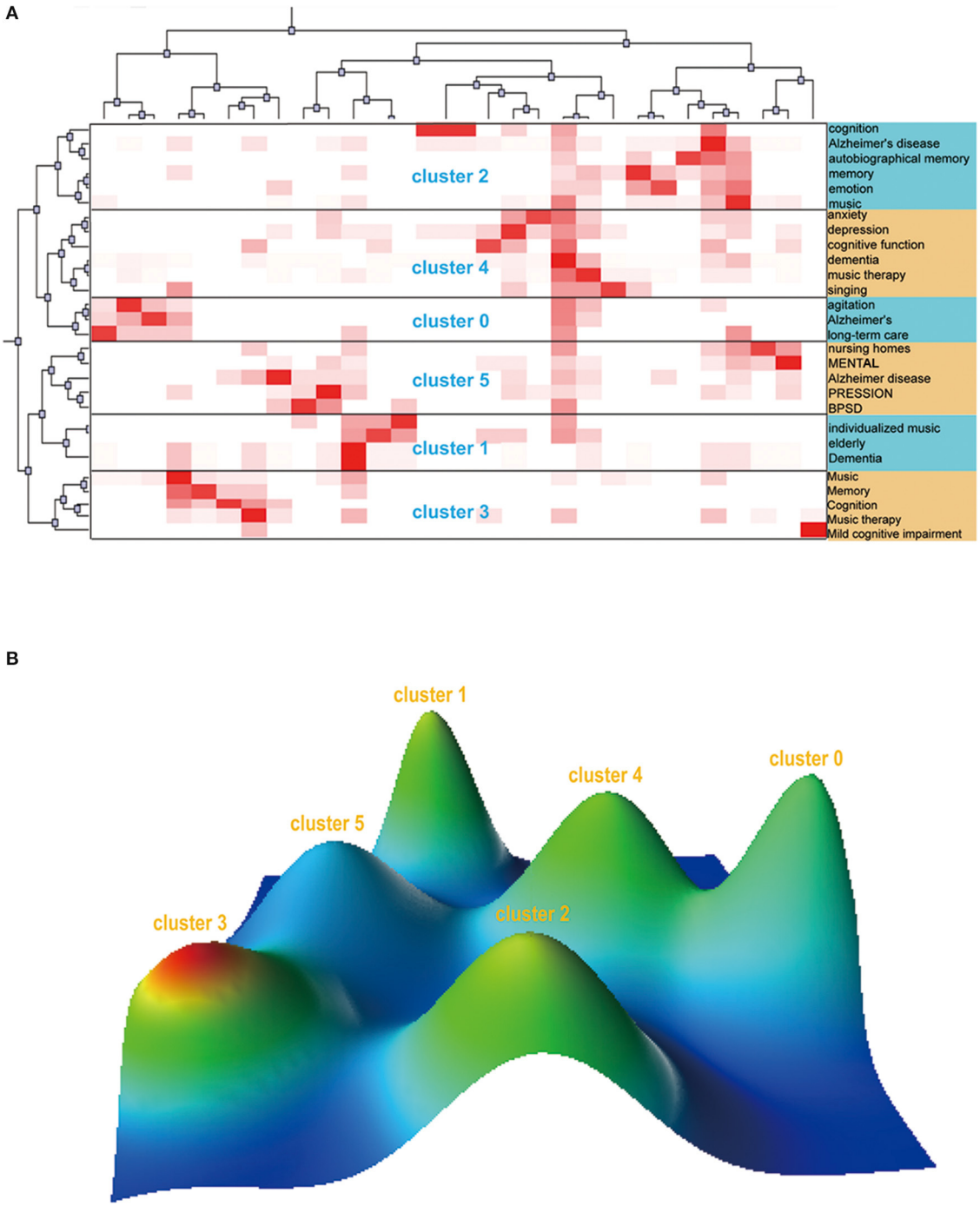

FIGURE 9 | The biclustering result of highly frequent keywords and source articles in the field of music therapy for dementia from 2010 to 2021. **(A)** Matrix visualization of biclustering of 28 high-frequency keywords and source articles. **(B)** Mountain visualization of biclustering of 28 high-frequency keywords and source articles.

low attendance rate, difficult care and many problems (30) as well as a lack of exchange and cooperation with other countries and institutions in this research field in China. Therefore, in order to strengthen diagnosis and nursing and improve the health and nursing systems, China should further strengthen exchanges and cooperation with international institutions to carry out in-depth research concerning music therapy intervention for dementia patients, improve the influence of this aspect of this field, and provide more help to dementia patients.

Behavioral and psychological symptoms are the most common symptoms of dementia, with patients often experiencing anxiety, depression, sleep disturbances, apathy and irritability. The physical and mental health of the sufferer is also impaired by life disorders associated with eating difficulties and a strong sense of loneliness (31). Different types of eating difficulties caused by cognitive impairment have been reported to contribute to malnutrition in dementia patients and to increase their risk of respiratory infections (32). Several studies have shown that a lack of social communication in patients with dementia is associated not only with higher mortality but also with increased BPSD and psychological symptoms such as depression and loneliness (33, 34), among which loneliness and isolation are closely associated with dementia. One study of 12,030 participants showed that loneliness increases the risk of dementia by 40% in older adults (35), and another study of 1,547 dementia patients showed that nearly one-third of patients experience moderate social isolation and loneliness (36). Although the causal relationship between loneliness and dementia has not been clearly established (37), enhanced social communication has shown certain benefits in preventing loneliness and improving of cognitive function in dementia patients (38, 39).

Through a comprehensive analysis of the five clusters in the keywords biclustering, it can be concluded that the research hotspots in this field in the past decade have mainly focused on the autobiographical memory, cognitive function, mental state and BPSD of dementia patients. Research in this field were more focused on Alzheimer's patients, aiming to improve the mental symptoms and cognitive behavior of AD patients through music therapy, thereby improving their quality of life. As a common neurodegenerative disease, AD is the most important type of dementia. Symptoms of AD include progressive memory degeneration, language impairment, depressive symptoms and hallucinations, and the disease is accompanied by pathological changes such as cerebrovascular amyloidosis and inflammation (40). Although genetic factors are considered to be the greatest risk factor for AD, the underlying pathogenesis of AD remains unclear, and there is no effective treatment for AD (41). As a non-pharmacological therapy for the treatment of AD, the potential mechanisms of music therapy mainly include the following aspects: (1) improving patients' cognitive neural efficacy and thus affecting neuroplasticity; (2) promoting the regeneration and repair of neurons; (3) affecting hormone levels to prevent deterioration due to the disease; and (4) enhancing autobiographical memory and reducing mental symptoms (42).

At present, the daily life of dementia patients consists mainly of routine nursing care, and the caregiver plays an important role in the treatment process. Nursing homes have become a choice for many families because of the difficulty of caring for individuals with the disease. However, while this approach does relieve pressure on family members, it also entails psychological problems such as guilt and depression (43, 44). In China, more than 90% of dementia patients are cared for by family caregivers. Due to a lack of corresponding social support, family caregivers face great stress and suffer from mental and physical health problems (45). In a UK study involving 1,283 dementia patients, close to 50% of family caregivers reported feeling lonely, and close to 20% of family caregivers reported experiencing severe loneliness (46). Therefore, the psychological status of patients' family members should also be considered, since doing so can also have a positive effect on the nursing care of dementia patients.

As one of the main forms of music therapy, listening to the individual's favorite music or actively participating in musical instrument playing and singing can arouse patients' positive emotions and strongly stimulate changes in neuroplasticity. This method can play a benign role in the treatment of neurological diseases to varying degrees (47). Targeted memory music recall therapy has produced positive effects in improving the cognitive ability and happiness of elderly people (48). Although the underlying therapeutic mechanism of music therapy is unclear, such therapy has been shown to be effective and cost-effective as a nonpharmacological intervention in the treatment of mild to moderate depression in elderly individuals (49), and studies have shown that music therapy can also relieve anxiety by regulating mood (50). Some dementia patients suffer from depression, anxiety and other symptoms, so the use of music therapy has broad clinical value and can also improve the mental state of caregivers (51). In general, music therapy has certain advantages in the treatment of dementia, but there is a lack of a standardized treatment protocol for music stimulation of dementia patients, resulting in differences in treatment results. Most outcomes related to mood and spirit have been measured by self-assessment questionnaires, which may also affect the reliability of the results (52).

Strengths and Limitations

This study is the first visualization analysis in this field based on 217 related research articles concerning music therapy intervention for dementia patients in the WoSCC database in the past 11 years. Excel, CiteSpace and gCluto were used to categorize the articles, and systematic statistics are collected concerning countries, institutions, keywords and journals, and categories were assigned according to high-frequency keywords. The co-occurrence matrix clearly and intuitively shows the research status of and trends in this field, and this study can serve as a reference for future research directions in this field.

However, this study also faces certain limitations. We only analyzed the WoSCC database, and there were only a small number of studies that met the criteria, so we could not include all relevant studies concerning the use of music therapy for dementia patients, which might entail that the literature included is incomplete and thus cannot fully reflect research hotspots and trends. Although we set the literature type to "Article" and read the full text for screening purposes, there are differences in literature quality, which may also entail certain deviations in research results.

CONCLUSION

This study conducted a bibliometric and visual analysis of relevant studies concerning music therapy intervention for

dementia patients in the WoSCC database, and the results indicated that the United States has the most publications and the most frequent cooperation among countries in this field and that and emerging countries are also gradually increasing. Psychological problems faced by dementia patients and the topics of quality of life, individualized music therapy, the mental state of caregivers and other related topics may be important research directions in the future. Therefore, the question of how to develop standardized research protocols and identify unified efficacy evaluation indicators should be a focus of and difficulty for future research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SY and FZ: study conception and design. LL and DC: administrative support. ZL, YZ, and LZ: collection and assembly of data. LZ, BL, XW, and ZL: data analysis and interpretation. SY and FZ: manuscript writing. All authors final approval of manuscript and contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.860758/full#supplementary-material

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SYSTEMATIC REVIEW
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Effect of Physical Exercise on Cognitive Function of Alzheimer's Disease Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trial

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This review aims to systematically review the effects of physical exercise on the cognitive performance of patients with Alzheimer's disease (AD) and its mechanisms of action. Databases such as Web of Science, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched until December 2021. A randomized controlled trial (RCT) to assess the effect of an exercise intervention (compared with no exercise) on patients with AD. The measures included cognitive function [Mini-Mental State Examination (MMSE), Alzheimer's Disease assessment scale-cognitive (ADAS-Cog), Montreal cognitive assessment scale (MoCA) and Executive Function (EF)]. The methodological quality of the included literature was assessed using the Physiotherapy Evidence Database (PEDro) scale. Twenty-two studies (n = 1647, mean age: 77.1 ± 6.3 years) were included in the systematic review, sixteen of which were included in the meta-analysis. A systematic review and meta-analysis revealed that physical exercise positively affects cognitive performance in older patients with AD. However, the positive effects of the intervention should be interpreted with caution considering the differences in methodological quality, type, frequency, and duration of exercise in the included studies. Future studies should consider the design rigor and specification of RCT protocols.

Keywords: Alzheimer's disease, cognition, physical exercise, systematic review, meta-analysis

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease that has no known treatable cure (1). As the disease gradually destroys brain structures (e.g., hippocampus and internal olfactory cortex) (2), it leads to loss of cognitive mental functions, including memory, language, attention, and perception, reduced activities of daily living, and diminished quality of life (3).

The global increase in the prevalence of AD is closely linked to the aging of the population (4). According to the World Alzheimer's Disease Report 2021, more than 55 million people worldwide are living with cognitive impairment, which is expected to

reach 78 million by 2030 (5). The direct cost to American society of caring for patients with AD was estimated at $305 billion in 2020 and was expected to exceed $1 trillion by 2050 (6). The high cost of treatment prevents 75% of people with dementia worldwide from being effectively diagnosed and treated (5).

Although not all studies support it, there is growing evidence that physical exercise can prevent cognitive decline and dementia (7–10). Physical exercise, such as aerobic (11–13), stretching (14), resistance (15), or combined exercises (16–20), may delay and prevent cognitive decline in older adults with AD. Therefore, physical exercise emerges as one of the most promising, effective, and least expensive strategies to prevent and delay cognitive decline in patients with AD (21, 22).

Numerous studies have shown that physical exercise is associated with positive effects on brain health (23–25). High levels of aerobic exercise have been associated with improved brain volume and factors of cognitive decline (26, 27). Some studies have shown that aerobic exercise can boost brain plasticity (28), reduce hippocampal atrophy (29), and even increase the hippocampus (30). Physical exercise appears to affect brain atrophy positively in older adults with AD (31). Cognitive impairment is one of the forms of brain atrophy presentation, which results in difficulty in controlling physical mobility in patients with AD (32). Regular exercise at an appropriate intensity and physically demanding level may stimulate some cognitive functions in older adults with AD (33). Therefore, physical exercise appears to be one of the active strategies to resist brain atrophy in older adults with AD.

Several reviews have been published on the effects of physical exercise on the cognitive performance of older adults with AD (19, 34–37). Some reviews concluded that the intervention was beneficial for global cognitive impairment (19, 35). Others concluded that the intervention effect was not beneficial (36); some meta-analyses concluded that physical exercise improved cognition in the AD group with an effect comparable to donepezil (38). By way of example, physical exercise can improve cognition. Previous studies have confirmed that physical activity can improve cognition in AD patients, but the dose-effect relationship between physical activity and AD is not clear. Moreover, systematic reviews are lacking for analyzing the type, intensity, frequency, and duration of physical exercise interventions in patients with AD.

Therefore, the purposes of this review were (1) to systematically review the effects of physical exercise on the cognitive performance of patients with AD; (2) to determine the dose-effect of physical exercise on patients with AD, and (3) to explore the mechanisms underlying the effects of physical exercise on the cognitive performance of patients with AD. To this end, we developed a conceptual model of physical exercise interventions for the cognitive performance of AD patients (**Figure 1**).

METHODS

Data Sources and Search Strategies

The study of this systematic review and meta-analysis followed the PRISMA guidelines (39). Three databases, including Web of Science, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched for literature written in English only. The search terms used include "Alzheimer's" or "Alzheimer's disease" or "AD" or "dementia" and "exercise" or "physical exercise" or "aerobic exercise" or "resistance training" and "cognitive function" or "executive function." The search strategy was determined by three investigators, with two investigators working independently on the search task and the third involved in resolving any search disputes. The search covered the period from creating the database to December 31, 2021.

Study Selection

The criteria for inclusion in the study were (1) design: randomized controlled trial (RCT); (2) sample: at least one group of participants with a diagnosis of Alzheimer's disease type dementia in older adults (mean age 65 years or older), excluding other diagnoses of dementia or MCI; (3) intervention: aerobic, resistance, or stretching type of physical exercise was performed; (4) outcome: at least one executive function or cognitive function was measured. The following studies were excluded from systematic evaluation: (1) non-interventional studies; (2) non-exercise type studies of intervention modalities; (3) theoretical studies, descriptions of treatments, or methodological protocols; (4) review articles; and (5) non-English language articles.

Data Extraction

Two investigators (WL and JL) retrieved and collected data, and potential disagreements were resolved by joint discussion with two other investigators (JC and QL). Data collected from each study included subject characteristics (mean age, number of genders), intervention protocol (exercise type, frequency, duration, intensity), indicators of cognitive outcomes, intervention effects, and pre- and post-intervention outcomes (expressed as mean ± standard deviation). The conversion was performed using the formula $SD = SEM \bullet \sqrt{n}$ for studies that provided standard error of the mean (SEM) for outcomes. When the outcomes data were expressed as mean and confidence interval (CI), the formula for conversion of CI to SD was $SD = \frac{upper\ \text{limit} - lower\ \text{limit}}{3.92} \bullet \sqrt{n}$ (40). If some studies only displayed graphs containing means and standard deviations, the GetData Graph Digitizer was used for digitizing and extracting the data (41). All studies included in the meta-analysis were used for data synthesis, regardless of their methodological quality.

Qualitative Analysis

The methodological quality assessment of each study was conducted independently by two reviewers (JZ and YW) using the Physiotherapy Evidence Database (PEDro) Scale (42). The PEDro scale was developed to assess the quality of a treatment or intervention study design, including assessment of randomization, blinding, attrition, design, and statistics. According to the PEDro scale scoring rules, each item was scored independently, with "yes" being scored as "1" and "no" or "unclear" as "0," and the maximum score for the ten criteria was 10. The possible risk of bias was determined from the extracted information, with <5/10 being rated as "high" risk

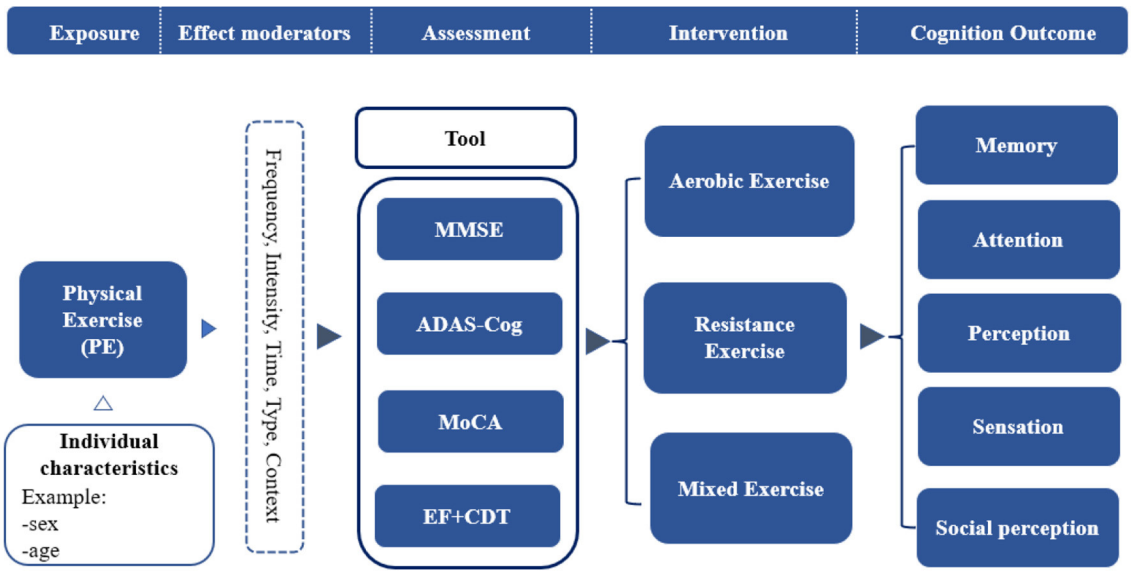

FIGURE 1 | A conceptual model of physical exercise intervention for cognitive performance.

and more than 5/10 as "low" risk (43). If the details in the article were unclear, we judged the risk of bias as "unclear" and contacted the corresponding author for more information. If the corresponding author did not provide clarification within ten working days, the item was scored as "0."

Statistical Analysis

Review Manager Software V.5.3 was used for statistical analysis of the combined data. Statistical significance was defined for bilateral $p < 0.05$. The combined data effects were presented using the mean difference (MD) and the corresponding 95%CI of the continuous effects. If data were available and no significant heterogeneity was detected, a fixed-effects model was used to calculate the combined effect. Otherwise, a random-effects model was applied. Statistical heterogeneity was assessed using the I^2 statistic. However, when heterogeneity between studies was high ($I^2 > 75\%$), overall pooled analysis was considered inappropriate; clinical or methodological heterogeneity was considered a potential cause. Heterogeneity between studies was explored using the $\chi 2$ test and Higgins I^2 values (44). Studies with different intervention types were divided into subgroups for analysis based on different factors, given the potential heterogeneity between studies.

RESULTS

Study Selection

A total of 2,862 literature records were initially identified according to the proposed search strategy. Two investigators (WL, JL) screened by abstract and title, and apparently irrelevant records were excluded. A total of forty-eight potential studies were included for further evaluation. Of these, sixteen studies that did not provide physical exercise and ten studies that did not involve cognitive outcomes were excluded. Finally, twenty-two studies were eligible for inclusion in the systematic review, and the data from sixteen studies were extracted for meta-analysis. The detailed literature selection and screening process are described in **Figure 2**.

Study Characteristics

The characteristics of selected studies are detailed in **Table 1**. A total of twenty-two RCTs involving 1,647 AD participants (age 77.1 ± 6.3 years) were included in the study for review. The included studies were from sixteen countries, namely Brazil (16, 45, 47), France (18, 46, 48), USA (50, 54, 56), Italy (13, 53), Nigeria (17), Netherlands (49), Denmark (11), Germany (15), Egypt (12), Finland (19), Iran (51), Albania & Spain (14), Sweden (52), Australia (20), and China (55). Participants were from the community, social centers, social clubs or individuals, memory clinics, or hospitals. All studies reported identified inclusion and exclusion criteria for the diagnosis of AD participants. The study interventions contained aerobic, resistance, stretching, or mixed exercise (aerobic, resistance, balance, and stretching exercises). Nine studies performed a single aerobic training session, including supervised aerobic, walking, or cycling training (11–13, 48, 50, 53–56). Eleven studies used mixed exercise modalities, combining aerobic, resistance, balance, stretching, or cognitive training (16–20, 45–47, 49, 51, 52). Besides, two studies were conducted on resistance exercise (15) and stretching exercise (14), respectively.

The frequency of interventions ranged from 2 to 5 times per week for 30–70 min each. The duration of the interventions ranged from 9 to 52 weeks. Participants had heart rate reserve (HRR) from 40 to 80%, maximum oxygen uptake (VO2max) from 60 to 70%, and maximum heart rate (MHR) from 60 to 80% in the inclusion studies. Furthermore, six studies did not

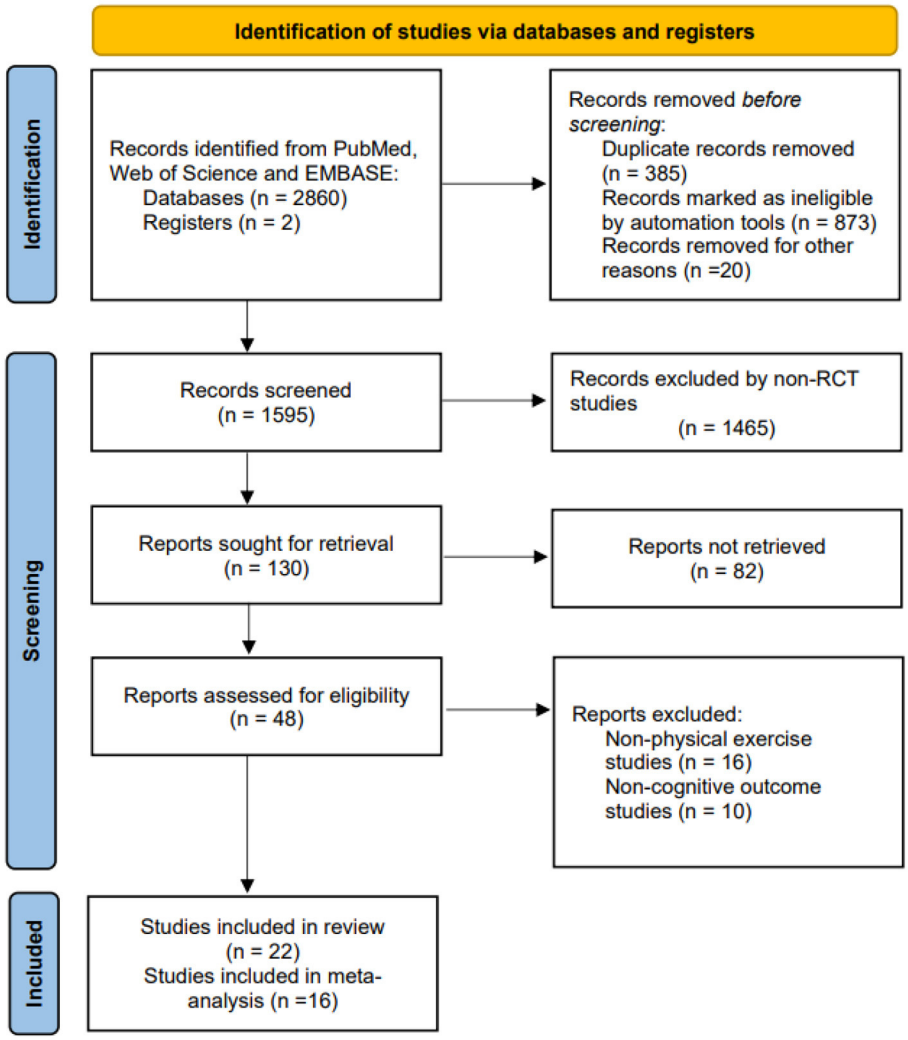

FIGURE 2 | PRISMA flowchart of included and excluded studies.

describe the intensity of intervention exercise (13–15, 20, 45, 47). The control group interventions generally utilized low-intensity activities/exercises such as social activities, stretching exercises, or health education.

Meta-analysis was used to analyze cognitive outcomes, including cognitive functions, mental health, and executive functions. Various measurement tools were used to assess studies in the same or similar cognitive domains, including the MMSE, ADAS-Cog, MoCA, CAMCOG, CDT, and others. Of the studies included in the meta-analysis, thirteen studies measured the MMSE (11, 13–20, 45–47, 49, 52, 53, 55), four measured the ADAS-Cog (20, 52, 55, 56), six measured the executive function (EF+CDT) (16, 19, 49, 50, 54, 56), and two measured the MoCA (12, 51).

Quality Assessment

Twenty-two studies included in the systematic review were identified with the PEDro score to assess methodological quality. Only one study had a PEDro score of 5, and the other twenty-one studies had a PEDro score of ≥6, indicating good quality. Nevertheless, we also found fewer studies on participant and therapist blinding in the PEDro quality assessment. Only three studies blinded participants, and only one study blinded therapists. Details of the raw records are shown in **Table 2**.

Effects of Interventions

A total of thirteen of the included studies showed significant cognitive and executive functions changes (11–17, 19, 20, 51, 53, 55, 56), and nine studies showed no significant differences in cognitive and executive functions (45–50, 52–54).

Thirteen studies involving 820 participants measured the effect of physical exercise on cognitive function in patients with AD using the MMSE (11–20, 45–47, 49, 52, 53, 55). The meta-analyses showed a significant improvement in cognitive function

TABLE 1 | Characteristics of the inclusion studies.

ID	Author, year (Country)	Age (years)	Subjects male/all	Duration (min*tim*wk)	Intensity	Intervention exercise	Exercise categories	Cognitive outcome	Effect
1	Aguiar (45) (Brazil)	EG: 78.6 ± 8.4 CG: 74.7 ± 7.4	9/34	40*2*20	NA	Interchangeably between sessions A (aerobic activity) and B (resistance exercise and balance training)	ME (AE, RE, BE)	MMSE	Cognition remained unchanged in both groups
2	Arcoverde (16) (Brazil)	EG: 78.5 CG: 79	NA/20	30*2*16	60% VO_2max	Treadmill, stretching, big muscles groups	ME (AE, RE, FE)	MMSE CDT (EF)	EG showed improvement in cognition
3	Barreto (46) (France)	EG: 88.3 ± 5.1 CG: 86.92 ± 5.8	14/91	60*2*24	Moderate intensity	Multicomponent training: coordination and balance exercises, muscle strengthening, aerobic exercise (mostly walking)	ME (AE, RE, BE, CE)	MMSE	Cognitive function did not display differences
4	De Oliveira Silva (47) (Brazil)	EG: 81.22 ± 8.88 CG: 77.54 ± 8.05	11/27	60*2*12	70% VO_2max or 80% MHR	Multimodal training: balance, aerobic, and strength training and stretching	ME (AE, RE, BE, FE)	MMSE CDT (EF)	Cognition improvements were not observed in patients with AD
5	Enette (48) (France)	77.9 ± 7.6	19/52	30*2*9	EG1: 70% MHR, moderate EG2: 80% MHR, vigorous	EG1: continue aerobic training EG2: interval aerobic training	AE	MMSE	No significant change in cognitive performance after interventions
6	Gbiri (17) (Nigeria)	EG: 68.7 ± 3.4 CG: 70.6 ± 3.3	14/31	70*2*12	Each station 80% start, 10% progression (interval)	Motor functions, gait, posture, cognition, balance and productivity	ME (FE, BE)	MMSE ADAS-Cog	A significant improvement in cognition
7	Henskens (49) (The Netherlands)	EG1: 87.0 ± 7.2 EG2: 86.1 ± 5.9 EG3: 85.1 ± 4.6 CG: 84.7 ± 4.6	20/87	30-45*3*26	Progressive increase	Alternating strength and aerobic sessions	ME (AE, RE)	MMSE EF	No significant effects in cognitive functions
8	Hoffmann (11) (Denmark)	EG: 69.8 ± 7.4 CG: 71.3 ± 7.3	113/200	60*3*16	Moderate-to-high intensity, 70–80% MHR	Aerobic exercise in the ergometer bicycle, cross trainer, and treadmill	AE	MMSE ADAS-Cog	Neuropsychiatric symptoms were significantly less severe
9	Holthoff (15) (Germany)	EG: 72.4 ± 4.3 CG: 70.7 ± 5.4	15/30	30*3*12	NA	Trained lower body on a movement trainer	RE	MMSE EF	Executive function improvement in the EG
10	Kemoun (18) (France)	81.8 ± 5.3	NA/31	60*3*15	Light to moderate, 60–70% FCR	Walking, equilibrium and stamina exercises	ME (AE, BE)	ERFC	Intervention group improved, while the control group decreased
11	Morris 2017(50) (USA)	EG: 74.4 ± 6.7 CG: 71.4 ± 8.4	37/78	30-50*3-5*26	From 40–55% to 60–75% of HRR	Aerobic exercise course	AE	EF	No clear effect of intervention on Memory and Executive Function
12	Nagy (12) (Egypt)	65-73	30/60	45-60*3*12	Moderate-intensity 40–50% HRR ∼ 50–70% HRR	Aerobic exercise	AE	MoCA	A statistically significant differences were observed in MoCA–B scores
13	Ohman (19) (Finland)	EG1: 77.7 ± 5.4 EG2: 78.3 ± 5.1 CG: 78.1 ± 5.3	129/210	60*2*52	Low intensity	Aerobic, strength & endurance, balance, and executive functioning training	ME (AE, RE, BE)	MMSE CDT (EF)	Executive function was improved in the HE group

(Continued)

TABLE 1 | Continued

ID	Author, year (Country)	Age (years)	Subjects male/all	Duration (min*tim*wk)	Intensity	Intervention exercise	Exercise categories	Cognitive outcome	Effect
14	Parvin (51) (Iran)	67.4 ± 8.8	NA/26	40-60*2* 12	NA	Progressive combined exercises with visual stimulation, including muscle endurance, balance, flexibility, and aerobic exercises with eyes closed and opened	ME (AE, BE, FE)	MoCA	A significant improvement in cognitive function, particularly in short-term and working memory, attention, and executive function
15	Todri (14) (Albania & Spain)	81.7 ± 5.24	40/90	40*3*24	NA	Stretching and respiratory exercise	FE	MMSE	A significant effect on the difference between groups
16	Toots (52) (Sweden)	85.1 ± 7.1	45/186	45*2.5*16	SE: 40%MI & 45% HI BE: 27%MI & 63% HI	High Intensity Functional Exercise (HIFE) program,	ME (AE, RE, FE)	MMSE ADAS-Cog	No superior effects on global cognition or executive function
17	Venturelli (13) (Italy)	EG: 83 ± 6 CG: 85 ± 5	NA/21	30*4*24	NA	Supervised walking aerobic exercise	AE	MMSE	EG did not show a significant improvement in cognition, CG showed a significant decreased
18	Venturelli (53) (Italy)	EG1: 84 ± 7 CG: 84 ± 10	22/80	60*5*12	Moderate intensity	Walking	AE	MMSE	No significant changes in cognitive function (MMSE scores)
19	Vidoni (54) (USA)	EG: 71.2 ± 4.8 CG: 72.2 ± 5.3	38/117	30-50*3-5* 52	Moderate-intensity 40–50% HRR ∼ 50–70% HRR	Supervised aerobic exercise	AE	EF	No effect of aerobic exercise on cognitive measures
20	Vreugdenhil (20) (Australia)	74.1(51-89)	16/40	30-60*7*16	NA	Walking, upper and lower body strength and balance training	ME (AE, RE, BE)	MMSE	Cognitive function improved in EG
21	Yang (55) (China)	EG: 72.0 ± 6.7 CG: 71.9 ± 7.3	33/50	40*3*12	70% MHR	Cycling training	AE	MMSE ADAS-Cog	Cognitive function improved in aerobic group
22	Yu (56) (USA)	77.4 ± 6.8	53/86	40-60*3*24	EG: 50–75% HRR CG: <20% HRR	EG: cycling exercise; CG: stretching	AE	ADAD-Cog EF	A significantly less than the natural increase in cognitive function

min, minute; tim, time; wk, week; NA, Not Applicable; VO_2max, maximal oxygen consumption; MTP, Maximal Tolerated Power; MHR, maximum heart rate; HRR, heart rate reserve; MI, moderate intensity; HI, high intensity; FCR, reserve cardiac frequency; ME, mixed exercise; AE, aerobic exercise; RE, resistance exercise; BE, balance exercise; CE, coordination exercise; FE, flexibility exercise; ADAS-Cog, Alzheimer's Disease assessment scale-cognitive; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment scale; CDT, Clock draw test; EF, Executive Function; ERFC, Rapid Evaluation of Cognitive Functions test (French version).

TABLE 2 | Assessment of quality of study design using PEDro.

ID	Study	Eligibility and source	Random allocation	Concealed allocation	Groups similar at baseline	Participants blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intension -to- treat analysis	Between -group difference reported	Point estimate and variability reported reported	Total
1	Aguiar 2014	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
2	Arcoverde 2014	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
3	Barreto 2017	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10
4	De Oliveira Silva 2019	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10
5	Enette 2020	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	7/10
6	Gbiri 2020	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	8/10
7	Henskens 2018	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
8	Hoffmann 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
9	Holthoff 2015	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6/10
10	Kemoun 2010	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6/10
11	Morris 2017	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
12	Nagy 2021	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
13	Ohman 2016	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
14	Parvin 2020	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
15	Todri 2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	7/10
16	Toots 2017	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
17	Venturelli 2011	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
18	Venturelli 2016	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
19	Vidoni 2021	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
20	Vreugdenhil 2012	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
21	Yang 2015	Y	Y	N	Y	N	N	N	Y	Y	N	Y	5/10
22	Yu 2021	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10

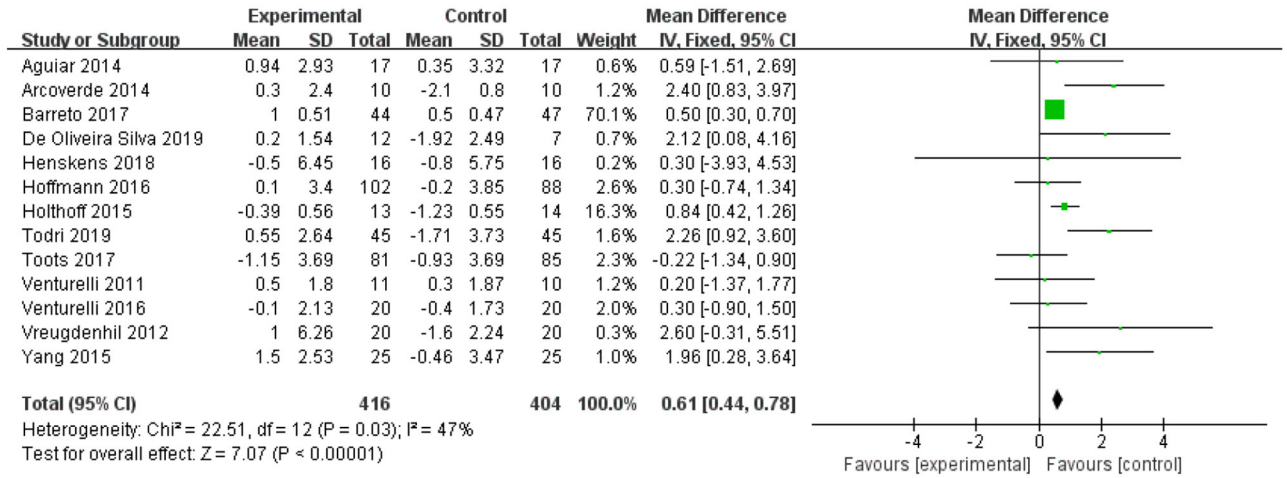

FIGURE 3 | Forest plot for physical exercise interventions on cognition function (MMSE).

with physical exercise ($n = 820$, MD = 0.83, 95% CI = 0.43 to 1.23, $p < 0.00001$; $I^2 = 47\%$, fixed-effect model; **Figure 3**).

Four studies assessed the effect of physical exercise on cognitive function using the ADAS-Cog (20, 52, 55, 56). The meta-analysis showed a significant improvement in MD scores of cognitive functions with physical exercise ($n = 335$, MD = −3.533, 95% CI = −6.9 to −0.16, $p = 0.04$; $I^2 = 57\%$, random-effect model; **Figure 4**).

Two studies were performed to assess the effect of physical activity on cognitive function using MoCA (12, 51). Both studies showed a positive effect of physical exercise on cognitive function. Nevertheless, the meta-analysis showed no significant improvement in MD scores of cognitive functions ($n = 86$, MD = 3.53, 95% CI = −2.00 to 9.05, $p = 0.21$; $I^2 = 95\%$, random-effects model; **Figure 5**).

Six studies analyzed the effects of physical exercise on executive function (16, 19, 49, 50, 54, 56). The meta-analysis showed no significant improvement in MD scores of cognitive functions with physical exercise ($n = 439$, MD = 0, 95% CI = −0.04 to 0.04, $p = 0.91$; $I^2 = 0\%$, fixed-effects model; **Figure 6**).

DISCUSSION

This review examined the effects of physical activity on the cognitive function of older patients with AD. Although 41% of the studies in the systematic review did not show a positive intervention effect, there was a significant improvement in the cognitive performance of patients in 59% of the studies. In the meta-analysis, the studies using the MMSE ($p < 0.0001$) and ADAS-Cog ($p = 0.04$) measures of cognitive performance both showed significant improvements, while the studies using the MoCA ($p = 0.21$) and EF ($p = 0.91$) tests did not show significant improvements. Thus, we identified that physical exercise interventions are beneficial for improving cognitive function in AD patients.

Several previous meta-analyses reported a significant positive effect of physical exercise interventions on attenuating a cognitive decline in patients with AD (57–59). The present study was consistent with using the MMSE test for significant positive effects of exercise on cognitive performance interventions. In this study, the percentage of significant studies was higher when analyzing aerobic exercise separately than mixed exercise. For example, aerobic exercise interventions were significant in 67% of the included studies; mixed exercise was 55%. Notably, the benefits of aerobic exercise on cognitive performance in patients with AD appear to be at least similar to the minimal clinically significant differences (MCID) reported in previous studies (60).

Although the findings of this study meta-analysis support the effect of physical exercise on cognitive improvement in patients with AD, it is difficult to determine whether the cognitive improvement is due to the type of exercise (aerobic, resistance, stretching, or mixed), the amount of exercise, or the intensity of exercise. This review includes three exercise types: aerobic exercise, resistance exercise, stretching exercise, and mixed exercise. Both resistance and stretching exercises separately showed a positive effect of the intervention. However, 45% of the studies in mixed exercise did not show a positive effect of the intervention. Moreover, the least amount of exercise in all studies was 540 min (48), and the most were 7,800 min (54), and neither study found a significant cognitive improvement effect. Therefore, this means that the relationship between the amount of exercise and the effect of exercise is not clear. As for exercise intensity, of the fifteen studies in the included literature that involved moderate exercise intensity, 47% had positive intervention effects, while 53% had insignificant effects (**Table 1**). It remains to be verified that moderate exercise intensity is the recommended criterion, as mentioned in previous studies (61, 62).

The strength of this systematic review is the methodological design, in which the construction of a conceptual model is methodologically focused on the study of the mechanisms of

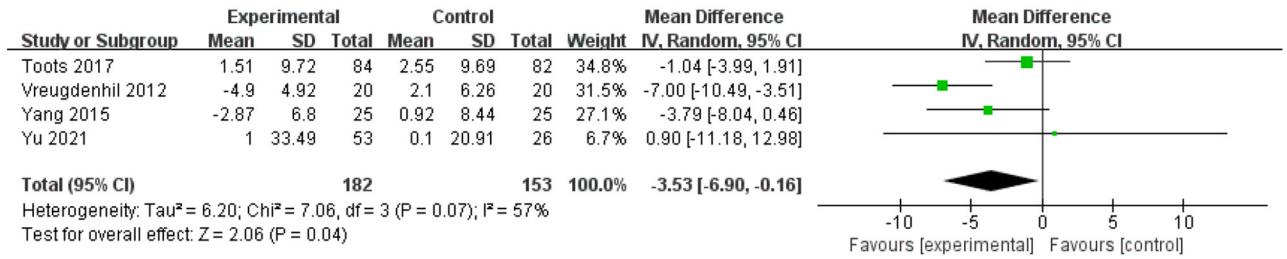

FIGURE 4 | Forest plot for physical exercise interventions on cognition function (ADAS-Cog).

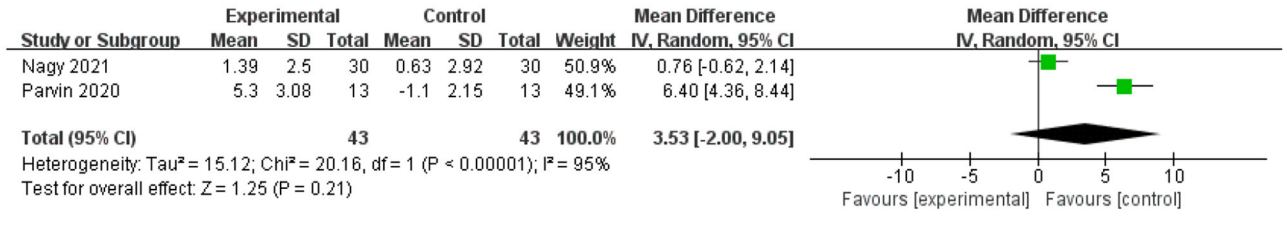

FIGURE 5 | Forest plot for physical exercise interventions on cognition function (MoCA).

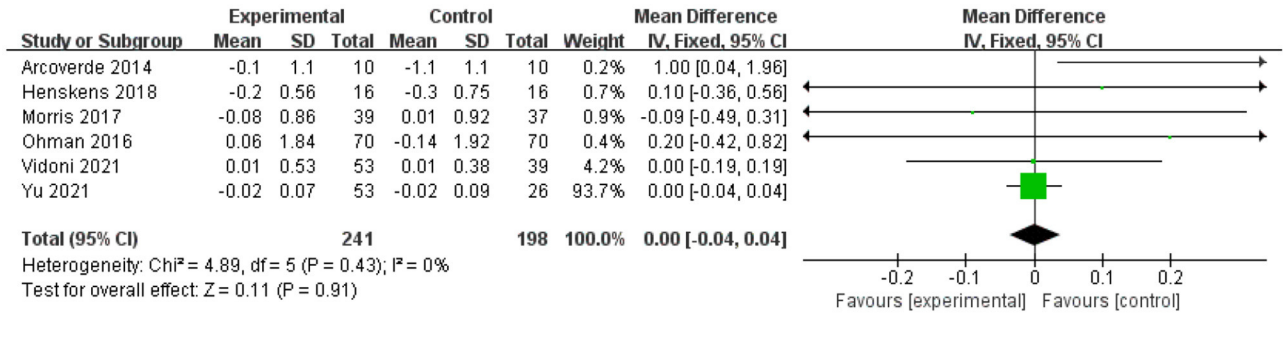

FIGURE 6 | Forest plot for physical exercise interventions on execution function.

physical exercise (63). First, we propose a "conceptual model of physical exercise interventions for the cognitive performance of patients with AD." Second, the present study focused on different types of physical exercise, including the intensity, duration, and categories of exercise. In addition, the meta-analysis included randomized controlled trials to ensure the quality of the study literature. The current study also has some limitations. First, the included studies used different measurement instruments and had methodological compatibility issues, which may affect our interpretation of data integration and findings. Second, heterogeneity exists across intervention characteristics, including type, intensity, frequency, and duration of exercise. The type of included studies varied, such as aerobic exercise, resistance exercise, stretching exercise, or mixed exercise; the duration of each exercise session ranged from 30 to 70 min, and the duration ranged from 9 to 52 weeks. Therefore, the optimal design of intervention studies remains unclear, and further research is necessary. Third, the different levels of quality of the included studies and the methodological heterogeneity may lead to our interpretation of the results. Fourth, based on the current systematic review and meta-analysis of studies, we found few studies reporting analysis of the effects of combined interventions (only two), such as physical exercise with cognitive training interventions and physical exercise with pharmacological interventions. We will focus on the above issues in future studies. Additionally, since it is not possible to blind participants in physical exercise intervention experiments; therefore, such bias in the study design may exist.

CONCLUSION

Physical exercise interventions effectively improve cognitive performance in older patients with AD, which may indicate the potential value of physical exercise in improving cognitive performance and preventing conversion to severe dementia in patients with AD. However, considering the differences in methodological quality, type, frequency, and duration of exercise in the included studies, the positive effects of the intervention

should be interpreted with caution. More rigorous designs and standardized RCT protocols will be considered for future studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

WL and JL: data collection. JZ and YW: data analysis, conception, and design. WL, JL, JC, and QJ: research design, writing the manuscript, and revision. All authors contributed to the article and approved the submitted version.

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Seeking bridge symptoms of anxiety, depression, and sleep disturbance among the elderly during the lockdown of the COVID-19 pandemic—A network approach

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Background: Besides physical changes, elderly adults are prone to have mental disorders such as anxiety, depression, and sleep disturbance, and the pandemic of COVID-19 worsened the situation. However, internal relationships and co-occurrence of psychopathologies were scarcely examined. Therefore, in the current study, through network analysis, we inspected relationships among symptoms of depression, anxiety, and sleep disturbance and identified key symptoms that espoused the disease.

Methods: We asked 1,302 elderly adults to fill in Patient Health Questionnaire-2 (depressive symptoms), the Generalized Anxiety Disorder-2 (anxiety symptoms), and the Youth Self-rating Insomnia Scale (sleep disturbance) and then constructed three networks for elderly adults, male elderly, and female elderly. *Via* network analysis, we accomplished four goals. First, we identified symptom with the highest centrality (i.e., strength) index for each network; then, we found the strongest correlation (i.e., edges) in each network; thirdly, we confirmed specific nodes that could bridge anxiety, depression, and sleep disturbance; the last was to compare networks based on genders. Network stability and accuracy tests were performed.

Results: Networks of elderly adults, male elderly, and female elderly were stable, accurate, and intelligible. Among all networks, "Nervousness"- "Excessive worry" (GAD-1- GAD-2) had the strongest correlation, and "Nervousness" (GAD-1) had the highest strength and bridge strength value. When we made a comparison between female elderly's and male elderly's networks, except for the significant difference in the mean value of "Difficulty initiating sleep" (YSIS-3), the findings showed that the two networks were similar. Network stability and accuracy proved to be reliable.

Conclusions: In networks of anxiety, depression, and sleep disturbance, anxiety played a conspicuous role in comorbidity, which could be a target for practical intervention and prevention.

KEYWORDS

depression, anxiety, sleep disturbance, elderly, network

Introduction

In China, the aging population occupies 17.88% of the total demographic composition (the cut-off age is 60) (1). Getting aged can bring both cognitive and emotional changes. Previous studies proved that aging-induced gut microbiota compositions were the main causes of cognitive decline (2), and elderly adults were impressionable to mental disorders, such as depression (3). Physical and mental illness perturbed elderly adults' routine life and impaired their behaviors and cognitive capabilities. However, compared to other populations, studies into the elderly' mental health were rare. Thus, attention to the aging population is necessary for alleviating the national economic burden and helping aged population improve a sound life.

However, the COVID-19 is a challenge for elderly adults, with an infection rate of 25.3% (4). As well as the general population which increased smoking, video playing and drinking frequency (5) and health care workers who were beset by suicidal ideation (6), elderly adults were victims of the COVID-19 suffering from anxiety, depression and poor sleep quality (7, 8). Moreover, due to city lockdown, diagnosis of mental disorders or cognitive function decline was delayed (9). Hence, probing into elderly adults' mental health is necessary for early diagnosis and intervention.

Among negative mental and physical problems, sleep disturbance such as nocturnal and earlier waking are widespread and striking (10). Generally, female elderly report more sleep disturbance (11). Malnutrition, lack of exercise, long-time TV watching, and illness can be stressors of sleep disturbance (12). Superficially, sleep disturbance hinders elderly adults from performing daily roles such as taking care of children or driving. However, sleep disturbance can damage physical health by causing slips/falls (13) or dizziness and impair cognitive function (14). Moreover, sleep disturbance is positively related to mental disorders such as depression and anxiety (15), though few studies were done to correlations between sleep disturbance and mental health for the aged population. On the background of city lockdown, delving into the relationship between sleep disturbance, anxiety, and depression is meaningful for elderly adults in both diagnosis and intervention.

Major depression, consisting of symptoms including anhedonia, hopelessness, losing appetite, and abnormal weight changes, has a growing trend in the aged population and is more prevalent in female elderly (3). Moreover, as a common comorbidity of depression, though exclusive studies on the anxiety of elderly adults are scarce, anxiety alone is another deleterious psychological burden for elderly adults and is more common in female elderly (16). There is a body of studies stressing external risk factors such as a pandemic that can elicit depression or anxiety, whilst few have done into the concurrence of sleep disturbance, depression, and anxiety, especially in the aged population, even sleep disturbance is strongly correlated to psychopathologies (17). Moreover, previous studies mainly emphasized the unidimensional causal relationship that treatment of depression or anxiety demonstrated an alleviation in sleep quality (18) while ignored that sleep quality improvement can espouse the rehabilitation of depression and anxiety. In the current study, we aimed to reveal the bidirectional relationship between sleep disturbance, anxiety, and depression, in which poor sleep quality can cause anxiety or depression while anxiety or depression plays a reactive role in enfeebling sleep quality.

However, traditional statistical methods cannot reveal bidirectional relationships since traditional theories such as the latent approach hold the view that all visible variables are independent and loosely allied to present latent variables (19). However, symptoms such as waking up earlier, nervousness, or feeling depressed are dynamically interwoven with each other in both mental disease diagnosis and treatment. In other words, improvement or degeneration of either waking up earlier, excessive worry, feeling depressed, or other visible symptoms could inevitably cause changes in the whole symptom structure. In order to manifest latent variables as well as interactions among symptoms, in the current study, we applied a newly proposed method, network analysis, to reveal the complex interactions among symptoms composing sleep disturbance, depression, and anxiety (20). According to network analysis, complicated psychopathology emerges from the interactions among visible variables (21). Therefore, different from a simple combination of symptoms, it can be that elderly adults trap in a depressive mood for spasmodic waking up earlier and during the night, being unable to fall asleep deepens their depressive mood. Moreover, network analysis provides us with a new perspective to evaluate how symptoms (nodes) function and how symptoms interweave with each other (edges) (22). Hence, we can identify consequential symptoms and relationships to guide more effective treatment and interventions.

As a short summary, in the current study, we asked 1,302 elderly adults to obtain a straightforward view of both symptoms of depression, anxiety, and sleep and symptoms' interactions, targeting to clarify critical issues in intervention and prevention.

Methods

Participants

We recruited 1,302 (male = 409, female = 893) participants from Harbin, Heilongjiang Province, to fill in questionnaires posted on Wenjuanxing (https://www.wjx.cn), an online questionnaire platform. All participants signed electronic informed consent before the assessment. Ethical committee of the *** university approved this study (Reference number: 202112220084).

In participants selection, we obeyed the following criteria: (1): over 60 years old, without gender restriction; (2): attended the test with informed consent; (3): stayed in Harbin during 12th November 2021 to 15th November,2021, the period of city lockdown. Participants were excluded from the current study: (1): participants' health conditions might diminish for a lethal disease including heart, lung, brain, and other critical diseases; (2): usage of anti-anxiety or anti-depression medications; (3): refused or could not complete the questionnaires; (4): failed to provide completely informed consent owing to cognitive or behavioral disability; (5) in clinical trials of other psychopathological drugs; (6): did not stay in Harbin from 12th November, 2021 to 15th November,2021.

Measurements

Generalized Anxiety Disorder- 2 (GAD-2)

The Generalized Anxiety Disorder Scale (GAD-2) is a valid and reliable assessment to screen generalized anxiety symptoms (23). The Chinese version also has good psychometric properties for identifying anxiety (24). Participants answered two questions about the frequency of core anxiety symptoms over the last 2 weeks. Each item scores from 0 (not at all) to 3 (nearly every day) (25). Higher scores indicate more severe anxiety propensity. In the current study, GAD-2 had high Cronbach α values of 0.89, 0.93, and 0.91 for the elderly, male elderly, and female elderly groups, respectively.

Patient Health Questionnaire (PHQ-2)

The two-item Patient Health Questionnaire (PHQ-2) is widely used in screening for depressive symptoms (26). All participants were asked about the frequency 0 (not at all) to 3 (nearly every day) of experiencing given depressive symptoms in the last 2 weeks and higher scores indicate more severe depressive symptoms. The Chinese version of PHQ-2 has been proved to be valid and reliable (27), and in the current study, PHQ-2 has high Cronbach α values of 0.84, 0.84, and 0.89 in the elderly adults, male elderly and female elderly groups respectively.

Youth Self-rating Insomnia Scale (YSIS-3)

In the current study, we selected 3 questions from YSIS-8 (28), a 5-point Likert questionnaire assessing sleep disturbance in the last month. Participants answered 3 questions about "Difficulty initiating sleep," "Difficulty maintaining sleep" and "Early morning awakening" scoring from 1 (Very Satisfied) to 5 (Very Unsatisfied). Total scores in this questionnaire ranged from 3 to 15. Higher scores indicated poorer sleep quality. The previous study proved YSIS-3 in Chinese to be valid and reliable (29). Cronbach α values of 0.93, 0.94, and 0.93 indicated a high internal consistency of YSIS in the current study.

Statistical analysis

Item check

All analyses were done by R (Version 4.1.2). *DescrTable* in R-package *compareGroups* was used to check item informativeness. Mean value, standard deviation (*SD*), kurtosis, skewness of items, and polychoric correlations were assessed first. Item informativeness was assessed by the mean value of standard deviation [i.e., $\pm$ 2.5 standard deviations (*SD*) around mean standard deviation (*SD*)] (30). In other words, an informative item should have a value in the range of $\pm$ 2.5 standard deviations (*SD*) around the mean item's standard deviation (*SD*), otherwise, the item was non-informative.

In network estimation, an Extended Bayesian Information Criterion (EBIC) model with the least absolute shrinkage and selection operator (LASSO) was used to establish networks (31). Partial correlation analysis, keeping all other variables constant, was computed to indicate the association of each pairwise variables and form networks. Moreover, to get a sparse and intelligible network, LASSO and EBIC were chosen to remove spurious correlations (32). In network analysis, nodes represent symptoms or variables, and edges represent partial correlation coefficients between two nodes (33). Higher correlations are shown in thicker and more saturated edges. Positive and negative correlations are shown in blue and red, respectively (34). In the part of estimation and visualization, we applied the R-packages *qgraph 1.9* and *bootnet 1.5* (31, 34).

In psychological network analysis, strength (i.e., the sum value of all absolute edge weights between one specific node and other nodes connected to it.) is the reliable and necessary centrality index that must be computed (35). Closeness (i.e., the inverse of the sum value of distances between one node and all other nodes in the network) or betweenness (i.e., fractions of

short paths pass one specific node) are not suitable to measure nodes' importance in psychological networks (35).

Network stability and accuracy

We used an R package *bootnet* (version 1.5) (31) to test networks' stability and accuracy. First, we applied non-parametric bootstrapping to test the edge weights accuracy with 95% bootstrap *CI*s (36). In the previous study, large edge weights *CI*s indicated poor accuracy of edges (37). Then we investigated centrality stability with case-dropping subset bootstrap by measuring the correlation stability coefficient (*CS-coefficient*), which represents the maximum proportion of dataset that can be removed when two data sets maintain the association above the 0.7 level with a 95% confidence interval (33). A previous study recommended a *CS-coefficient* value should be preferably above 0.5 and should not be lower than 0.25 (38). Besides testing edge weights accuracy and centrality stability, we also tested whether there were significant differences between edges and nodes using the *bootstrap difference test*. In this step, the null-hypothesis test was checked to see if zero existed in the bootstrapped *CI*s (38).

In addition, to test network stability and predictability, a metric quantifies how well one node can be estimated by all its neighboring nodes (39), was estimated by *mgm* (Version 1.2-12) in R (39). High predictability indicates strong mutual interactions in the network and vice versa (40). Bridge symptoms are represented by one or more nodes that can strengthen interactions among mental disorders (41) by *bridge* function in the R package *networktools* (Version 1.4.2) (42). In the current study, the bridge symptoms centrality was represented by bridge strength.

Comparison of the network structure between genders

To compare two networks (i.e., elderly male and elderly female), we applied a permutation test, the Network Comparison Test (NCT), which was conducted with 1,000 permutations through "*NetworkComparisonTest*" (43). First, we tested the null hypothesis that there was no statistically significant difference between the two networks' global strengths (i.e., the absolute sum of all node strength) (44). Besides, we tested the null hypothesis that all edge weights in two networks did not differ significantly. Moreover, we tested the variance of individual edge weights in two networks using the Holm-Bonferroni value of 0.05.

TABLE 1 Statistical description.

Group	Variables	Label	*N*	*Mean*	*SD*	*Skew*	*Kurtosis*	*Predictability* (R^2)
Elderly	GAD-1	Nervousness	1,301	0.50	0.84	1.67	1.88	0.65
	GAD-2	Uncontrollable worry	1,301	0.41	0.74	1.96	3.33	0.69
	PHQ-1	Anhedonia	1,301	1.40	0.73	1.93	3.26	0.77
	PHQ-2	Sad mood	1,301	1.37	0.74	2.09	3.71	0.75
	YSIS-3	DIS	1,301	1.76	1.13	1.46	1.18	0.72
	YSIS-4	DMS	1,301	1.88	1.21	1.25	0.47	0.77
	YSIS-5	EMA	1,301	1.83	1.19	1.37	0.80	0.77
Male	GAD-1	Nervousness	409	0.53	0.86	1.60	1.60	0.61
	GAD-2	Uncontrollable worry	409	0.41	0.75	1.95	3.29	0.68
	PHQ-1	Anhedonia	409	1.42	0.73	1.86	2.97	0.79
	PHQ-2	Sad mood	409	1.39	0.73	1.95	3.17	0.78
	YSIS-3	DIS	409	1.67	1.09	1.75	2.26	0.76
	YSIS-4	DMS	409	1.83	1.20	1.37	0.81	0.79
	YSIS-5	EMA	409	1.75	1.13	1.52	1.42	0.80
Female	GAD-1	Nervousness	892	0.49	0.83	1.70	2.01	0.68
	GAD-2	Uncontrollable worry	892	0.41	0.74	1.95	3.33	0.70
	PHQ-1	Anhedonia	892	1.39	0.73	1.97	3.40	0.76
	PHQ-2	Sad mood	892	1.37	0.74	2.14	3.93	0.74
	YSIS-3	DIS	892	1.80	1.14	1.34	0.78	0.71
	YSIS-4	DMS	892	1.90	1.21	1.19	0.32	0.76
	YSIS-5	EMA	892	1.87	1.22	1.30	0.56	0.76

Results

Descriptive statistics and item check

First, items' informativeness (i.e., standard deviation (SD), mean value, kurtosis, skewness) was computed and shown in Table 1. We found no items were poorly informative (i.e., 2.5 *SD* below or above the mean level of items' *SD*).

Network structure and centrality measures analysis

Three raw networks of the elderly, male elderly, and female elderly were shown in Supplementary Figure S1, respectively, and the partial correlation matrices were enclosed in Supplementary Tables 1–3.

Elderly network

In the network with predictability (i.e., R^2) of all elderly adults (Figure 1A), the edge of "Nervousness"- "Uncontrollable worry" (GAD-1-GAD-2) had the strongest correlation, followed by the edge of "Difficulty maintaining sleep"— "Early morning awakening" (YSIS-4-YSIS-5) and the edge of "Anhedonia"— "Sad mood" (PHQ-1-PHQ-2).

For centrality indices presented in Figure 1D, we reported strength and bridge strength for 3 networks, respectively. In the network of elderly adults, "Nervousness" (GAD-1) had the highest strength value, followed by "Early morning awakening" (YSIS-5) and "Uncontrollable worry" (GAD-2). In the part of bridge strength, "Nervousness" (GAD-1), "Sad mood" (PHQ-2), and "Uncontrollable worry" (GAD-2) had the highest bridge strength values.

Male elderly network

In the network of male elderly (Figure 1B), most weighted edges were the same as those in the elderly adults' network. From centrality indices, "Nervousness" (GAD-1), "Uncontrollable worry" (GAD-2), and "Difficulty maintaining sleep" (YSIS-4) had the highest strength values. As for bridge strength shown in Figure 1D, "Nervousness" (GAD-1), "Uncontrollable worry" (GAD-2), and "Sad mood" (PHQ-2) had the highest centrality values.

Female elderly network

In the network of female elderly (Figure 1C), "Nervousness"— "Uncontrollable worry" (GAD-1-GAD-2), "Difficulty maintaining sleep"- "Early morning awakening"

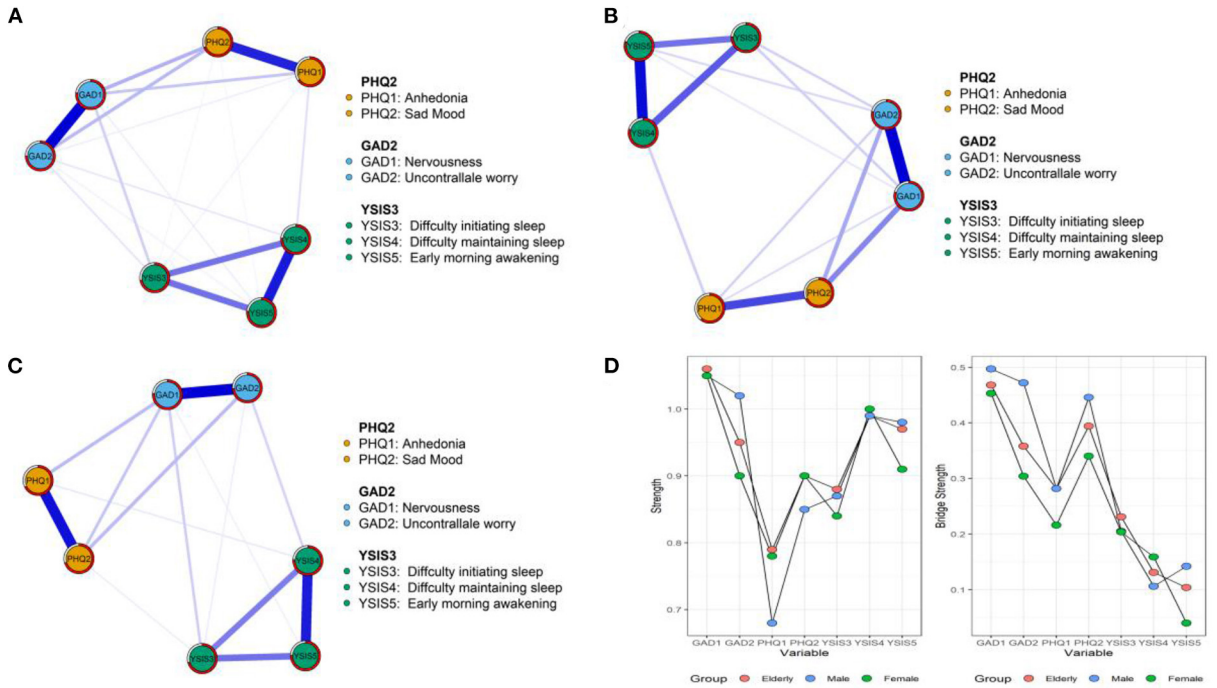

FIGURE 1
The network structures of anxiety, depressive symptoms, and sleep quality. **(A)** All elderly. **(B)** Male elderly. **(C)** Female elderly. **(D)** Strength and bridge strength values.

(YSIS-4-YSIS-5) and "Anhedonia"- "Sad mood" (PHQ-1-PHQ-2) had the strongest correlations. As for node strength, "Nervousness" (GAD-1) had the most strength, followed by "Difficulty maintaining sleep" (YSIS-4) and "Early morning awakening" (YSIS-5). As bridge strength presented in Figure 1D, nodes of "Nervousness" (GAD-1), "Sad mood" (PHQ-2), and "Uncontrollable worry" (GAD-2) had the highest centrality values, which were the same as the elderly adults' network.

Network accuracy and stability

Predictability values of the three networks were 0.76 ($M_{predictability} = 0.73 \pm 0.06$), 0.80 ($M_{predictability} = 0.75 \pm 0.07$), and 0.74 ($M_{predictability} = 0.73 \pm 0.03$), indicating that one specific node can be predicted or explained by its neighboring nodes at the rate over 73% (Table 1).

In the edge weights accuracy test (Supplementary Figure S2), bootstrapped *CI*s were narrow, indicating that edges in three networks were reliable. In addition to edge weights accuracy and case-dropping bootstrap, in the non-parametric bootstrap procedure, edge weights and node centrality indices differed statistically significant, as shown in Supplementary Figures 3, 4.

Moreover, in the network of elderly adults, male elderly and female elderly, strength and predictability [$r_s = 0.91^{**}$ (0.51; 0.99); $r_s = 0.93^{**}$ (0.61; 0.99); $r_s = 0.87^{*}$ (0.34; 0.98)] were significantly related with each other, indicating that predictability was reliable. Besides, in the network of the elderly adults, there were significant correlations between *SD* and predictability [$r_s = 0.83^{**}$ (0.21; 0.97)] and between strength and predictability [$r_s = -0.94^{**}$ (-0.99;−0.63)]. In the network of male elderly, mean value and predictability correlated at a significant level [$r_s = 0.89^{**}$ (0.40; 0.98)] so as *SD* and bridge strength [$r_s = -0.97^{***}$ (-1.00;−0.82)]. In the network of female elderly, *SD* and bridge strength [$r_s = -0.85^{**}$ (-0.98;−0.29)] correlated at a significant level (Figure 2).

Networks comparison between two sexes

As mentioned above, we investigated differences between the male elderly network and female elderly network through Network Comparison Test (NCT). First, as shown in Figure 3A, we tested the strength difference of the two sexes through NCT (male = 3.36, female = 3.29, $S = 0.02$, $p = 0.62$). Then in Figure 3B, from the perspective of the edge weights (1,000 permutations) test, the results showed no significant difference among edge weights in two networks ($M = 0.17$, $p = 0.32$). In Figure 3C, from *t*-test between mean item scores, we found that there were no significant differences in items' mean value ($p > 0.05$) except for item "Difficulty initiating sleep" (YSIS-3) ($p < 0.05$).

Discussion

In the current study, we asked 1,302 elderly adults to fill in three reliable questionnaires and analyzed the symptom structures of sleep disturbance, anxiety, and depression. Several results are worth discussing.

Our findings indicated that in networks of elderly adults, male elderly and female elderly, "Nervousness" - "Uncontrollable worry" (GAD-1- GAD-2) had the strongest association which meant that on symptom level, Nervousness (GAD-1) and Uncontrollable worry (GAD-2) interplayed in engendering anxiety. The current results proved that compared to traditional statistical approaches, network analysis could better reveal intrinsic interactions between observable variables. Uncontrollable worry is a cognitive phenomenon related to repetitive concerns or thinking about potential negative events, hazards, or risks (45), and nervousness is an uneasy feeling to cope with imminent disasters. Due to the impact of filial piety in Confucius's concept (46), in a typical Chinese family,

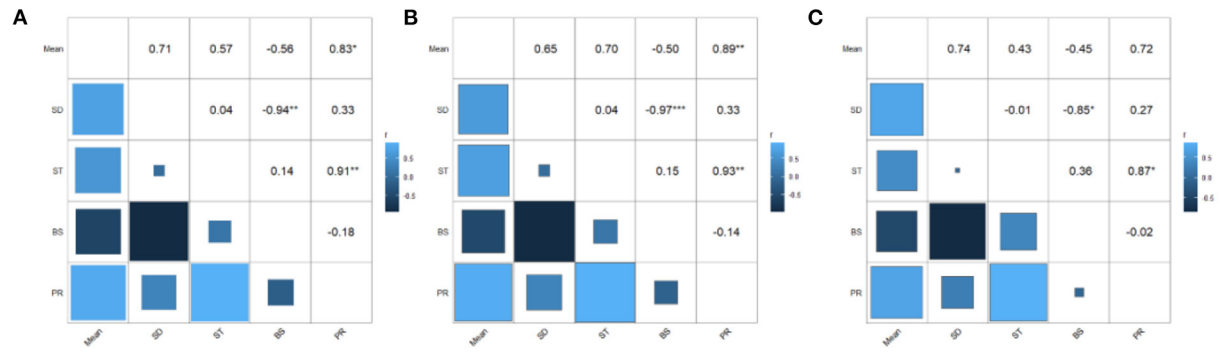

FIGURE 2
The matrix of correlations between mean value, standard deviation, strength, bridge strength, and predictability. **(A)** Elderly adults. **(B)** Male elderly. **(C)** Female elderly.

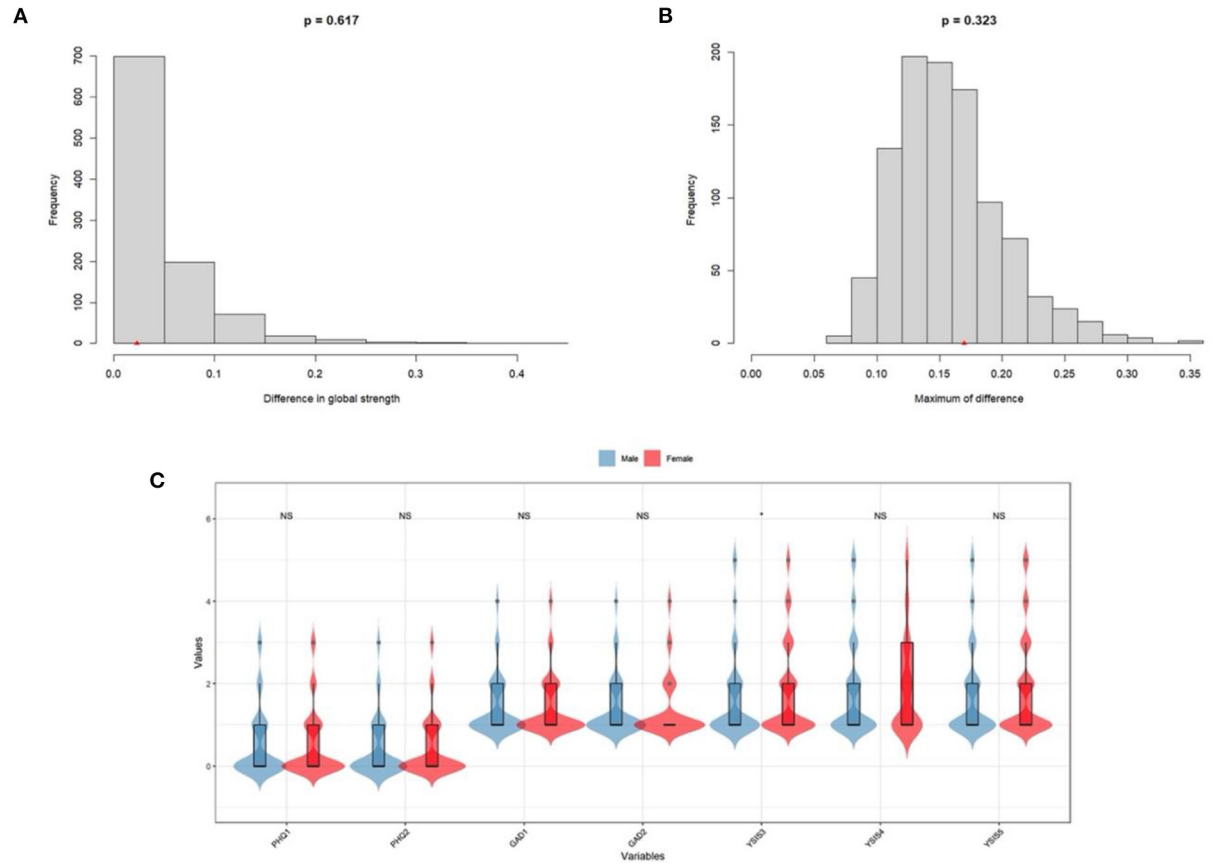

FIGURE 3
Network comparison between male elderly and female elderly. **(A)** Global strength. **(B)** Edge weights. **(C)** Mean scores on items between male elderly and female elderly.

elderly adults are regarded as the leaders in making decisions and cultivating younger members. Meanwhile, younger members should venerate and care for elderly members. Thus, Chinese elderly adults are particularly worried about illness or poverty from which they may fail to support and lead the family or become a heavy burden to their children for physical illness and low social-economic status (47). In this reactive chain, elderly adults' great concerns for the family can strengthen their nervousness about imminent issues. Besides medication treatment, mindfulness therapy (MT), acceptance and commitment therapy (ACT), moving to emptiness (MET) and cognitive-behavioral therapy (CBT) are effective in anxiety mitigation (48, 49).

The strong correlation of "Difficulty maintaining sleep"—"Early morning awakening" (YSIS-4-YSIS-5) across three networks clarified that observable sleep complaint factors mutually interact. "Difficulty maintaining sleep" is measured by increased wake time, frequency of arousals, and periodic limb movements during sleep (50). Due to age-related changes in circadian rhythm timing and behavioral changes, elderly adults cannot maintain deep sleep for a long time (10). Stress, alcohol consumption, lack of exercise (51), and lack of social support (52) can further impair sleep quality. We evinced the association between YSIS-4 and YSIS-5 was that elderly adults could not keep asleep for their stress or illness. Thus, they left their beds earlier, seeking for relief or treatment. The experience of waking up earlier perturbed elderly adults' sleep quality through long-time day naps, and elderly adults failed to sleep well during the night. Pharmacological interventions display meaningful outcomes with better sleep patterns (53).

We have found that "Anhedonia"- "Sad mood" (PHQ-1-PHQ-2) had a strong connection which implied that elderly adults lost interest in the time of feeling depressed, and in the depressive mood, elderly adults felt like doing nothing. Lack of social support, chronic diseases, and substance abuse are risk factors for depression (3). Compared to youths, elderly adults are more prone to be anhedonia virtually of less curiosity. In the status of anhedonia, elderly adults attribute internally that they are bootless, the root of depression or sad mood. It is a reactive chain that elderly adults' depression can deepen anhedonia. In treatment, psychotherapy (54) or even physical activities (55) can effectively ameliorate symptoms.

Though in the network comparison, networks between male elderly and female elderly did not differ significantly in global strength or edge weights, variances in node strength and bridge strength are worthy of discussion. In both networks of the male and female elderly, "Nervousness" (GAD-1) had the most centrality strength and bridge strength value, indicating that anxiety was the prominent symptom in anxiety, depression, and sleep disturbance manifestation and linkage. Furthermore, "Uncontrollable worry" (GAD-2) had the second strongest node strength and bridge strength in the network of male elderly, suggesting that anxiety symptoms were outstanding and critical in releasing male elderly's anxiety, depression, and sleep disturbance. We boldly infer that in Chinese families, male elderly manage family expenditure and income. As a result, male elderly tend to exhibit high levels of anxiety in the confrontation of less income (e.g., city lockdown) and physical illness, and without intervention, anxiety symptoms can drag male elderly into depression or sleep disturbance.

However, compared to male elderly, females demonstrated more sleep disturbance in later life since in the network, "Difficulty maintaining sleep" and "Early morning awakening" (YSIS-4 &YSIS-5) had the second and third highest node strength. Our finding was consistent with a previous study, which found that females suffered more from sleep problems than males (11). In China, females are required to undertake housework. The COVID-19 has profound physical and psychological impacts on female elderly. Higher standard in sanity, more familial member to be cared and less space for leisure activities can be regarded as stressor of sleep disturbance.

Limitation

As if using GAD-2, PHQ-2 and YSIS-3 were convenient for elderly adults to fill in forms in a short time, seven questions could not comprehensively reveal symptoms structures. In further studies, more items should be contained. Moreover, to delineate the developmental process of anxiety, depression, and sleep disturbance, longitude studies should be done. Demographical information on occupation, marital status, educational level, and socioeconomic status should also be counted in further investigation.

Conclusion

In the current study, we included anxiety, depression, and sleep disturbance to construct three networks of elderly adults, male elderly and female elderly, respectively. The results showed that "Nervousness" and "Uncontrollable worry" (GAD-1- GAD-2) had the strongest correlation implying that network analysis, this newly proposed methodology, could present ingenuous relationships in variables. Moreover, clinically, key symptoms and symptoms links were pointed out for intervention and diagnosis so that clinicians can alleviate symptoms within less time and with greater treatment outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Faculty of Psychology, Beijing Normal University (Reference Number: 202112220084). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study design: XL. Data collection: LZ and QL. Analysis and interpretation: LZ, YT, and WH. Drafting of the manuscript: LZ. Critical revision of the manuscript: ZM, WH, HN, SW, YL, ZZ, and SZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.919251/full#supplementary-material

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