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Insights in aging psychiatry: 2021

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Insights in aging psychiatry: 2021

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EDITORIAL
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Editorial: Insights in Aging Psychiatry: 2021

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Editorial on the Research Topic

Insights in Aging Psychiatry: 2021

INTRODUCTION

Over the coming decades, the worldwide population aged 65 and older is projected to triple to 1.5 billion by mid-century (1). The continuously growing share of older person in the population rose concerns regarding seniors' mental healthcare as one out of five individuals aged 60 years and above reported having mental or neurological disorders, and these accounted for 6.6% of all disability adjusted life years (DALYs) (1, 2). Given the burden that mental illnesses pose on healthcare, social security systems and economy, also severely affecting individuals' wellbeing, the present Research Topic was launched to shed light on novel developments, and to inspire further interest and new research efforts in the field of Aging Psychiatry. Major challenges in this sector are represented by the need to identify the multiple risk and vulnerability factors contributing to the onset of mental disorders in seniors (potentially taking advantage of new data mining techniques that will overcome the limitations of traditional explanatory statistical analysis models), and the urgency to guarantee a successful and dignified aging for persons with mental health conditions (especially when they belong to minority groups). An additional demanding task is to establish definite guidelines for assessment and treatment, also considering the opportunity offered by the global diffusion of technology.

Findings and perspectives from contributors of this Research Topic highlight the need to promote a person-centered mental healthcare in the elderlies, considering their multiple and interdependent vulnerabilities, which often derive from long-lasting stressful conditions due to the intersection of ageism and other contextual factors (poverty, sexual discrimination, social isolation for the present pandemic, etc.).

STRESSORS AND RISK FACTORS INCREASING SENIORS' VULNERABILITY TO MENTAL DISORDERS

Given the need for screening high-risk groups to prevent the onset of the most frequent mental illness in the elderlies (i.e., depression) several studies tried to identify vulnerability factors using different techniques and algorithms. By developing a predictive model for depressive disorders using stacking ensemble and naive Bayesian nomogram, Byeon et al. evidenced the necessity to continuously evaluate multiple risk factors (i.e., stress perception, subjective health, consumption of polyunsaturated fatty acids, mean daily sitting hours, and mean daily sleeping hours) together with various measurable factors such as social support. The resulting graphical calculating device (the nomogram) can be used in primary care to

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visually and easily identify groups of seniors at higher risk for depressive disorders and to monitor multiple (and probably not independent) risk factors. Since symptoms of senile depression in the early stage are mild (and seniors usually visit the doctor's office only in case of severe symptomatology) the presented innovative method will ease the process of detecting and managing depressive disorders in older people living alone since the first manifestation of symptoms, thus reducing the risk of developing cognitive impairment that is usually observed in late life depression.

Indeed, Zhang M. et al. by exploring the effect of neuropsychiatric symptoms on cognitive impairments in patients with late-life depression (LLD) demonstrated that emotional, behavioral, and psychotic manifestations impacted cognition. This confirms that behavioral and psychiatric symptoms should be comprehensively evaluated in clinical practice, not only as a potential predictive marker for cognitive decline but also for their significant effect on prognosis (3). The results suggest that early evaluation and interventions for psychiatric symptoms, especially behavioral manifestations during periods of recovery, are of great significance for improving the long-term prognosis of LLD patients.

The loss of physiologic reserve, which manifests in seniors as exhaustion, weakness, low physical activity, slowness, and weight loss (with one/two symptoms characterizing the pre-frailty geriatric syndrome and three or more the frailty state) is another risk factor for the onset of a mental disorder, particularly depression. Zhang L. et al. actually demonstrated, in a big longitudinal cohort of retired seniors in China, that the slowness, weakness and exhaustion components of both syndromes were associated, in the short and long term, with an increased risk of depressive symptoms when other additional risk factors (socio-demographic characteristics, health conditions, and status) were removed. Since slowness, weakness and exhaustion are early markers of depression, and share some risk and pathogenic factors with mood disorders (e.g., the presence of low grade inflammation) interventions designed to prevent the onset of depressive symptoms are very useful. They may, in the long-term, reduce the frail syndrome occurrence in middle-aged and older adults and block the cycle of frailty leading to disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes (e.g., falls, delirium, and urinary incontinence) (4).

Long-lasting stressful conditions may cause exhaustion of resilience factors and increased depression also in formal and informal caregivers of patients with dementia as demonstrated by Bussè et al. In their paper, they showed that self-perceived psychological stress-related symptoms were significantly increased after 1 year of COVID-19 pandemic compared to baseline measurements. Notably, depression was the most frequently reported symptom 1 year after the pandemic onset, followed by irritability, anxiety, and sleep disturbances. Increased levels of depressive symptoms were predicted by female gender, lower education, perceived isolation, and overwhelm at the onset of the pandemic. Since restrictions imposed by the SARS-CoV-2 coronavirus pandemic led to a significant disruption of health and formal care services (5, 6), an additional burden was posed on informal caregivers, particularly those of patients with dementia and other neurocognitive disorders. Support interventions targeting multiple levels of the stress/health model could produce a significant improvement in caregivers' wellbeing, while psychoeducational interventions may relieve anxiety, enhance awareness and healthy behaviors and reduce family conflicts.

Genetic heritage (particularly the presence of mutations associated with a progressive neurodegenerative disease such as Huntington's disease) and defined personality profiles may be additional risk factors for the onset of psychiatric disorders in the long-term. Moschini et al. showed that the number (within the non-pathological range) of trinucleotide repeats in the Huntingtin gene (the DNA mutation responsible for Huntington's disease) is associated with definite personality traits in people experiencing a subjective decline in cognitive function who progressed to a Mild Cognitive Impairment, but not in those who remained stable. In particular, lower levels of conscientiousness and energy, and higher levels of emotional stability were correlated with higher number of repeats, and both associated with progression of cognitive decline and neuropathological findings consistent with Alzheimer's disease. These associations were independent from possible confounding variables and were not influenced by the presence of depressive symptoms, suggesting that the repeat length below the pathological threshold does not affect mood, although it may mediate the effect of personality traits on neurodegeneration and progression of cognitive decline.

Finally, belonging to gender and or sexual minority groups could be a further stressor negatively impacting on the health, wellbeing, and successful aging outcomes of older people. For example, the growing population of individuals who identify as lesbian, gay bisexual, transgender, queer, intersex, asexual and other (LGBTQIA+), are more exposed to stress factors due to the intersections of ageism, homophobia, biphobia, transphobia, racism, or poverty (7). In their opinion article, Pereira and Banerjee argument that older LGBTQIA+ people are subject to unique stressors associated with their minority status, and may face double discrimination due to their age and their LGBTQIA+ identity, making them more likely to experience health disparities. Older LGBTQIA+ individuals represent a diverse group of people who are still exposed to adversity, stigma, marginalization, and discrimination, with a greater probability of isolation, less social support, and therefore more at risk for having worse physical, mental, and social health indicators. Heteronormative aging models do not adapt to the specific needs of older LGBTQIA+ people and are marked by a double stigmatization lens (LGBTQIA+-phobia and ageism).

TAILORED APPROACHES TO PSYCHIATRIC DISORDERS IN OLD AGE

In a comprehensive perspective paper, Banerjee et al. discuss the importance of the multi-dimensional framework of dignity as the anchor to a person-centered mental healthcare for the elderlies. They highlight the various components of dignity in older people, the impact of ageism and mental health interventions based on rights, respect, and equality (including dignity therapy) for older adults and encourage an urgent call for action for a legally binding United Nations convention on the human rights in this population.

One of the aspects considered in the previous perspective paper, i.e., the need to protect people with impaired decision-making ability, in the respect of the person's dignity, was the focus of the study by Wied et al. in which the systematic development and implementation of support tools to enhance informed consent processes (the so-called enhanced consent procedures/ECP) for lumbar puncture treatment in persons with dementia is described. Eight possible tools were developed by involving an interdisciplinary transnational expert group (including a standardized interview, lists of keywords, priority cards, etc.) which should be proposed to patients by facilitators with a person-centered attitude. Authors conclude that the proposed tools should be selected (and not administered as a whole in their standard form) according to patients' individual needs and resources and to abilities (e.g., qualifications) of the practitioner. Their findings can serve as a selection of possibilities to support patients with dementia in decision-making and might help practitioners achieving an appropriate balance between the autonomy and protection of patients in complex decision-making.

Indeed, treatment strategies (as well as the perception of neuropsychiatric symptoms) in dementia care centers are not standardized (at least in Italy) as highlighted by a multicenter national survey performed through a semi-structured interview by D'Antonio et al. Results showed that the perceived frequency of neuropsychiatric symptoms was 74% and they were detected by means of a clinical assessment for 96.3% or a caregiver interview for 97%. The survey also revealed differences in symptoms perception, treatment options (where most of the centers apply non-pharmacological treatments) and observed side effect according to the clinical setting. The authors explained such variability by the absence of clear guidelines, by differences in patients' characteristics and by clinical practice based on subjective experience, highlighting the need of guidelines for the pharmacological treatment of neuropsychiatric symptoms in dementia.

New treatment strategies may include individualized interventions as reported by Ishimaru et al. who developed a new assessment tool (the Photo Assessment of Living Environment -PA-LE-) to understand the environmental context of delusion of theft in dementia, the most prevalent form of delusion in the elderlies suffering from cognitive decline. Familial interviews were conducted to assess the phenomenological features of the disorder and non-pharmacological approaches were tailored to the patients' environmental and psychological states, referring to the interview and the proposed innovative tool PA-LE. This included environmental adjustment or increasing self-esteem. Antipsychotics were also prescribed. Environmental and psychological triggers of delusion were improved by the interventions, and the patients had uneventful courses without active delusions. Authors concluded that evaluating patients' homes using photos could detect the environmental context of delusion of theft among patients with Alzheimer's dementia and assist in case management.

Additionally, some relief from psychiatric symptoms (particularly depression) may come from the opportunity offered by the global diffusion of technology, as demonstrated by Yang et al. who investigated the effect of internet use on depressive symptoms on 7,801 adults over 60 from the 2018 China Family Panel Studies. Results showed that older adults who used the internet reported lower depression scores particularly in those with higher frequency of use and especially in the younger group and in females. Moreover, using the Internet for social contact and entertainment decreased depression scores, but when the Internet was used for learning, working, and for commercial activities, the relief of depressive symptoms disappeared. This would suggest that Internet usage determined some relief from depression by increasing the frequency of contact with children and life enjoyment. Thus, policies should be designed to ensure that all ages have easy access to the Internet.

CONCLUSION

Overall, contributions of the present Research Topic covered a wide variety of issues related to the psychiatry of aging, ranging from identifying neuropsychiatric symptoms, their impact not only on patients but also on caregivers, and to physicians' perceptions and treatment strategies. Furthermore, particular attention was paid to individual needs and the right to make conscious decisions for healthcare, highlighting the fact that the elderlies, and particularly those from minority groups, should be considered in their complexity and the scientific world should promote new actions in this direction.

AUTHOR CONTRIBUTIONS

GS, NB, and FP contributed to conception and design of the paper. NB and FP wrote the first draft of the manuscript. GS supervised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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OPINION
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Successful Aging Among Older LGBTQIA+ People: Future Research and Implications

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INTRODUCTION

As the world population continues to increase, so does the number of older people. According to the United Nations' World Population Aging report (1), one in five people will be over 65 by the year 2050, providing greater visibility of the diversity among older people, particularly with respect to sexual orientation and gender identity. For instance, more than 39 million people in the U.S. are age 65 years or older including 2.4 million people who identify as lesbian, gay bisexual, transgender, queer, intersex, asexual and other (LGBTQIA+) (2). Since older people represent a growing demographic group, new and important challenges around successful and dignified aging arise for those who belong to gender and or sexual minority groups.

As more inclusive policies are enacted in countries around the world to address the social and legal needs of older LGBTQIA+ people (3), the reality of this diverse group of people will also become better known, including stress factors due to the intersections of ageism, homophobia, biphobia, transphobia, racism, or poverty (4). Therefore, older LGBTQIA+ people are subject to unique stressors associated with their minority status, and may face double discrimination due to their age and their LGBTQIA+ identity, making them more likely to experience health disparities (5).

LGBTQIA+ OLDER PEOPLE: WHO ARE THEY?

In many countries around the world, older LGBTQIA+ people grew up in a time when their sexual orientation and gender identity were considered mental illnesses and their sexual activities criminal or sinful acts. Being heterosexual and cisgender were the only valid identity labels accepted and, consequently, LGBTQIA+ people were invisible, marginalized, socially excluded, and discriminated against (6).

Before the human rights movements of the 1970's, and the Stonewall riots, laws did not acknowledge spouses and/or partners, healthcare services and healthcare access was hindered by the fear of discrimination, and most people were less likely to self-identify or disclose their identities. This invisibility created many obstacles when receiving formal care and kept LGBTQIA+ identities hidden from scientific research, making it difficult to obtain accurate data for this population. Past rejection by family members and friends may have enhanced the impacts of sexual stigma and adversity, forcing them to face social isolation, emotional distress, and health related problems. Notwithstanding the challenging and threatening start to their lives, many older LGBTQIA+ people now live comfortable with their sexual identities and display a manifest resilience to the stresses they felt earlier in their lives (7).

Factors such social isolation, difficulties in accessing health care, lack of social and family support, greater probability of not having children, and greater probability of having had lifetime exposure to experiences of discrimination and social stigma related to sexual and gender identity status (8) are all associated with the presence of negative health outcomes (9, 10). This reality is congruent with the Minority Stress Theory (10), which states that living with stressors throughout one's life negatively impacts on the health, well-being, and successful aging outcomes of older LGBTQIA+ people.

When compared to older heterosexual and cisgender people, older LGBTQIA+ people systematically show worse mental health outcomes (11); namely, more depression and anxiety (12–14), more emotional distress (15), less sexual and relationship satisfaction (16), more loneliness (17, 18), and higher risk of suicide (19). Associated with these disparities may be factors that accentuate vulnerability, such as living with Human Immunodeficiency Virus (HIV) infection (20, 21) and stigma internalization (22, 23). All these factors make the mental health needs of older LGBTQIA+ people an important concern, while creating the need to look for specific strategies to minimize these risks and, simultaneously, promote their successful aging.

WHAT IS SUCCESSFUL AGING FOR LGBTQIA+ OLDER PEOPLE?

There is not a consensus regarding the definition of successful aging. However, we could define it as the ability of older people to manage the specific challenges of this stage of life in a prosperous and satisfactory way, with good functional, physical, and cognitive capacity, and an active involvement in psychosocial life (24). This definition contrasts with the notion of aging as pathology (25), which is centered on deficits and losses.

To adjust this definition further for older LGBTQIA+ people, we should include criteria that transcend the merely biomedical; namely, subjective criteria based on the experiences of older LGBTQIA+ people (26). Here, the following factors are usually included: mental health variables, coping strategies, social relationships, attitudes, emotional well-being, community involvement and continuous learning (27), resilience around negative social constructions of LGBTQIA+ identities (28), and the constant challenges associated with the aging process and successive coming-outs (29).

Many older LGBTQIA+ people may have developed strategies to deal with adversity at younger ages that prove useful in the latter parts of their lives (30, 31), helping them develop coping strategies that are potentially generalizable to other developmental tasks involved in the aging process. Thus, in turn, can provide psychological benefits for individuals (32). Many of these tasks involve a proactive response to various adverse situations and hostile environments (33, 34), usually involving LGBTQIA+-phobia and ageism.

In this sense, several protective factors have been identified in developing resilience against marginalization and heteronormativity (35) among older LGBTQIA+ people, including high levels of self-esteem and self-efficacy (36) [associated with a higher quality of life experience (37)], mastery (30), and hope (38) (associated with better mental health). On the other hand, maintaining the ability to bounce back from adverse situations and respond to hostile environments—and, consequently, reduce the risk of vulnerability in more advanced stages of the life cycle—for many older LGBTQIA+ people involves the development of families of choice, as well as community or underground groups (39, 40). The goal of these associations is obtaining social support and the reinterpretation of the processes of normalization of life sequences not in compliance with heteronormativity, as well as the possibility of redefining success in their life projects as a valid LGBTQIA+ person (41).

FUTURE RESEARCH: POTENTIAL AREAS AND STRATEGIES

It is clear that older LGBTQIA+ people face specific challenges that their heterosexual and cisgender peers do not. Hence, it is important to develop community-based studies that provide more information on the particular challenges they face in navigating the aging process. Thus, we present a list of topics that could be explored in order to deepen knowledge about successful aging among older LGBTQIA+ people, from a global perspective:

Health Care and Health Care Access

Assessing the quality of health care, the impact of experiences of discrimination on access to physical and mental health care, as well as the protective and positive factors that can facilitate health experiences of older LGBTQIA+ people, will be vital to promoting their successful aging. Although there is already an important body of research investigating accessing physical and mental healthcare, there are gaps in the pre-existing research, such as service, policy and research innovations that should further expand the knowledge in this field.

Caregiving

Given that older LGBTQIA+ people often depend on families of choice to access social support and sometimes there are no structured support networks at all, it is important to assess what particular obstacles they face when receiving/seeking care, because the invisibility present in scientific research perpetuates this gap. At the same time, support structures and health professionals working with older LGBTQIA+ people often ignore their gender and sexual identities, forcing them to go back into the closet and endure again the isolation and erasure of an identity that took them so long to form and maintain.

Cultural/Affirmative Competence

Older LGBTQIA+ people are more reluctant to seek out elder care centers, home and meal support programs, or other community support services because of the anticipation of rejection. After decades of exposure to experiences of discrimination and stigmatization based on their sexual and gender identities, many older LGBTQIA+ people assume that they will not be welcome in these structures. To understand the dynamics of these processes is fundamental to optimizing competent interventions.

Social Isolation and Loneliness

Maintaining social networks and sources of social support is essential for successful aging, as it positively influences quality of life, physical and mental health, and happiness for older LGBTQIA+ people. Loneliness and isolation, by contrast, increase the risk of vulnerability, especially in older people. This vulnerable group may be at an enhanced risk due to prolonged minority stress and social ostracization.

Wellness, Health Behaviors, and Quality of Life

Behaviors that promote well-being, such as not smoking, not drinking alcohol, practicing physical activity, or seeing the doctor regularly, are important factors in successful aging. Just as the minority stress experience significantly influences health disparities, creating an environment of well-being will reduce the risk of vulnerability.

Impact of Discrimination

Many older LGBTQIA+ people have had very different generational experiences from those of contemporary LGBTQIA+ youth in most Western societies, where there is more openness and relatively safer spaces in which to express their sexual and gender identities. However, there are still many regions, countries and societies where these identities continue to be criminalized, either by laws or by social norms that force older LGBTQIA+ people to remain in the closet, with all the health costs associated with this isolation.

HIV/AIDS

HIV impacts the LGBTQIA+ community, and older LGBTQIA+ people are no exception. The fact that HIV has become a chronic condition that allows people to live many more healthy years than in the 1980s and 1990s means there are many older LGBTQIA+ people who are HIV-positive, but who may experience the triple stigma of HIV, sexual minority status, and ageism.

Independence/Loss of Decision Making

Given the likelihood of older LGBTQIA+ people having less social support, the maintenance of emotional and physical autonomy, as well as the ability to make life decisions about aging problems, such as economic issues, legal planning, end-of-life decisions, retirement decisions, among others, may represent important challenges in the search for answers free from judgment and prejudice.

Spirituality, Religion, and Religiosity

For many older LGBTQIA+ people, spirituality and religion can serve as an important resource for maintaining peace and dignity at this stage of the life cycle. However, many religions are themselves centers of stigma and prejudice, leading many people to avoid religious institutions. Understanding how these dynamics may affect successful aging is fundamental.

Life Course Trajectories

Many LGBTQIA+ people experience the need to carry out different developmental tasks throughout their lives, such as identity formation, stigma management, coming-out experiences, and adjusting to changes arising from family and social transformations, thus creating the need to assess the potential risk of the course of these trajectories.

Lifetime Trauma

Examining the impact of traumatic and adverse experiences throughout the life cycle is an important task for studying the conditions of successful aging in LGBTQIA+ populations. Unfortunately, many people have gone through experiences of discrimination and victimization that could have severe consequences when it comes to maintaining their well-being, health and quality of life in general.

Cultural Differences and Global Initiatives

Globalization and the widespread use of the internet have made it possible to understand the phenomena that affect the lives of older LGBTQIA+ people on a global scale. The different social structures in which they live represent a cultural challenge for research, but at the same time an opportunity for cross-cultural comparisons, which will inform how best to work with older populations in ways that are inclusive and affirmative, based on respect for diversity and human rights.

COVID-19 Pandemic

The COVID-19 pandemic has meant many challenges for older people in general, due to their increased vulnerability to the disease, and for older LGBTQIA+ people in particular, due to the fact that lockdown measures imposed by most governments have accentuated pre-existing disparities; namely, social isolation, less advantageous health outcomes, discrimination in access to health care, or difficulties in managing complications associated with COVID-19. Research into their "dual vulnerability" during the pandemic is increasing. A recent exploration of the lived experiences of older transgender adults in India revealed the burden of ageism and gender/sexual identity, marginalization, lesser priority for healthcare, and multi-faceted existential threats during the lockdown (42). Spirituality and community rituals emerged as important resilience factors.

Intersectional Approaches

The identity experience of older LGBTQIA+ people is diverse and multifactorial, often marked by experiences of marginalization. An intersectional approach to the study of their successful aging constitutes an opportunity to validate their sexual and gender identities while accommodating the rapid demographic, social and generational changes to which they are subject.

Qualitative Studies

More qualitative studies that document the needs and vulnerabilities, but also the protective factors associated with the successful aging of older LGBTQIA+ people are needed, as this will allow us to dig deeper into the reality of their life experiences.

Longitudinal and Population Studies

Carrying out longitudinal and population-based studies will allow for the assessment of vulnerability trajectories over time, as well as the identification of the groups most exposed to risk. Doing so will help to anticipate appropriate preventive interventions.

Examining Different Contexts and Different Generations

The experience of LGBTQ+ people vary by context and time. LGBTQIA+ people living in a more progressive/friendly context will have very different experiences than their counterparts living in more restrictive contexts. The same principle is relevant for LGBTQIA+ people born in the 1950s and those born in the 1980s. For instance, the New Gay Teenager hypothesis claims that LGBTQIA+ youth today are different from previous cohorts and are more like other youth, regardless of sexual orientation (43). In contrast, the aging thesis claims that LGBTQIA+ youth today face experiences similar to their counterparts in the past, and thus they are still considered to be high-risk youth with special needs in terms of social services (44). Therefore, examining differences between age-groups within the framework of aging is necessary to better understand the successful aging process.

Innovative Studies

Future studies that may be developed regarding successful aging with older sexual minorities need to offer methodological responses based on the incorporation of measures sensitive to the diverse nature of older LGBTQIA+ people, focused on the ability to achieve hidden-within-hidden populations.

Despite enormous social and scientific advances in LGBTQIA+ aging, most people remain invisible when it comes to areas of intervention, services, policy, and formal research. The articulation of the topics that we propose here with the creation of visibility and validation of older LGBTQIA+ people will allow us to create structural changes that will positively affect their lives, involving community partners who will inform us about their strengths and vulnerabilities. Working on this strategy will allow the creation of affirmative and culturally responsible programs and policies, directly contributing to the elimination of invisibility and, as such, with direct implication in psychogeriatrics, promoting equality and a sense of belonging, which are fundamental for successful aging.

RESEARCH IMPLICATIONS IN PSYCHOGERIATRICS

Until a few decades ago, the aging of LGBTQIA+ people was completely invisible to researchers. Despite much being done, and despite the population's rapid growth, they remain invisible in many segments of society, including in aging services, policies, and research (45). Therefore, we present a set of important implications for directly promoting the successful aging of older sexual minorities:

Intervention

Models of successful aging among older LGBTQIA+ people should incorporate the identification of modifiable factors to promote people's well-being, integrating different possible configurations in the responses to the specific needs assessed. In this sense, it is useful that interventions can be based on an aging perspective that emphasizes critical reflexivity, allowing micro and macro views of structural issues that may be interfering with interventions; namely, heteronormativity, heterosexism, homophobia, biphobia or transphobia (46). With this, professionals working with older LGBTQIA+ people will be better informed about the social dynamics that will allow them to intervene more effectively in key areas such as: the effects of stigma and prejudice on physical and mental health; working with families of origin and of choice; the management of difficulties associated with legal inequalities that may exist; overcoming existing barriers to health care and eliminating or reducing inequalities; management of formal psychosocial support structures; and offering responses focused on alleviating specific problems for older LGBTQIA+ people, among others.

Theoretical Work

Theoretical construction in the field of LGBTQIA+ aging must be aware of the current socio-historical contexts, ready to offer conceptual contributions and provide explanatory models that accommodate a broad and intersectional view of what it means to age successfully for older LGBTQIA+ people (47). It is likely that minority stress models or resilience models will not be enough to support investigations and should be complemented by critical gerontology models or health equity promotion models. This means that existing social structures must be challenged to recognize the psychosocial processes of aging, reject heteronormativity, and offer validity and attention to the discourses of the most fragile LGBTQIA+ identities, such as bisexual, transgender, or queer identities.

Social Policy and Legislation

Older LGBTQIA+ people need legal protection from discrimination based on their sexual gender identity status, including access to physical, mental, and occupational health care, living arrangements, and eliminating disparities (48). In this sense, it is necessary for governments and policymakers to incorporate the needs of older LGBTQIA+ people in their political agenda. These decisions must be informed by competent investigations about their real needs, as well as by partnerships with community organizations working to advance the rights of LGBTQIA+ people, based on the principles of active participation and social change.

Promoting Visibility

From a life cycle perspective, the aging of LGBTQIA+ people is often accompanied by the existence of hurdles associated with their sexual and gender identity status, creating invisibility and often causing older LGBTQIA+ people to return to the closet at this stage of life (49). This movement represents a setback in life trajectories and is usually accompanied by feelings of anticipation of rejection (especially in a residential context); it is also associated with the impossibility of freely expressing one's sexual and/or gender identities, thus losing opportunities to offer care and support adjusted to their needs. It is therefore critical to challenge invisibility and allow older LGBTQIA+ people to voice their needs as well as have more positive appraisal of their identities in daily life.

Expanding Knowledge

It is necessary to use the strategy of fighting for the rights of older LGBTQIA+ people through the research that is produced. It is crucial to obtain reliable data that will help arrive at a greater and deeper understanding of their needs, as this will allow us to offer tailored and more effective responses. On the other hand, it will be convenient to create local, regional, and national forums to discuss these needs, as this will allow for broader visions of what is really needed and, in this way, create opportunities to expand this knowledge to mass media and educational spaces throughout society.

Creating Effective LGBTQIA+ Aging Infrastructures

Improving the aging process of older LGBTQIA+ people is a complex challenge with many important tasks. To offer opportunities for improvement, the existence of effective infrastructures is essential, from organizations that promote the rights of older LGBTQIA+ people to the possibility of offering specific structures for people that accommodate their needs. Many older LGBTQIA+ people may not want a specific home just for themselves, but most likely prefer to be in a home where their needs as an LGBTQIA+ person are respected and valued (50). This will also promote social cohesion and social connectedness in this community.

Access to Education/Training Opportunities

Professionals who work with older people and are involved in the task of offering competent and adequate care services to their clients should actively seek training programs at the university level, specifically targeted at aging and LGBTQIA+ topics, in each of their areas of intervention, whether in the field of physical, mental, or social health (51). With this, they will be able to improve their skills, adjust services and directly contribute to the successful aging of older LGBTQIA+ people (52).

Human Dignity

A human rights framework based on human dignity is critical to bringing about change in promoting the well-being of older LGBTQIA+ people. The dignity of older people is a multidimensional construct that involves self-respect, social acknowledgment, independence, and privacy (53), but which can be negatively affected by ageism, homophobia, biphobia, or transphobia. For this reason, an approach based on human dignity will be fundamental.

The knowledge generated by researching the aging experiences of LGBTQIA+ people should be disseminated by all agencies working with older people, guiding the implementation of future investigations without omitting sexual and gender identities. This approach is essential for creating visibility, but also for recommending best intervention practices. Older LGBTQIA+ people represent a heterogeneous group of people, and this expansion of knowledge will allow an understanding of the mechanisms inherent to the trajectories of subgroups within the LGBTQIA+ community, offering safer clues for the promotion of successful aging.

THE WAY FORWARD

Older LGBTQIA+ people represent a diverse group of people who are still exposed to adversity, stigma, marginalization, and discrimination, with a greater probability of isolation, less social support, and therefore more risk of having worse physical, mental, and social health indicators. Heteronormative aging models do not adapt to the specific needs of older LGBTQIA+ people and are marked by a double stigmatization lens (LGBTQIA+-phobia and agism). The result is a thick invisibility, which is incompatible with the creation of formal and informal environments that promote successful aging and the fight against loneliness and social isolation. By conducting studies based on the investigation of the needs and lived experiences of older LGBTQIA+ people that integrate critical and adjusted perspectives, it will be possible to more effectively address the risk and protective factors that older LGBTQIA+ populations face around the world.

The application of multi-level resilience models should also be very helpful in future research on successful aging, since LGBTQIA+ older adults experience multiple stigmatizations and consistently show health disparities (54). Consequently, informal caregiving may play an important role in successful aging within the LGBTQIA+ community, and affirmative key competencies should be developed for working with this population.

Despite the risks and vulnerabilities that older LGBTQIA+ people experience, positive health outcomes in later life are also possible, especially resilient pathways where psychological resources (e.g., positive identity appraisal) and social resources (e.g., social connectedness) are associated with health-promoting behaviors, which in turn facilitate good overall health into older age (55). These findings suggest that the interaction of social and psychological factors can help LGBTQIA+ older adults to maintain good health and foster successful aging, even within an environmental context of marginalization (56). Therefore, successful aging is possible in older LGBTQIA+ individuals, as psychological and social resilience resources may compensate for the impact of disadvantage.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Dignity of Older Persons With Mental Health Conditions: Why Should Clinicians Care?

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With a steady increase in population aging, the proportion of older people living with mental illness is on rise. This has a significant impact on their autonomy, rights, quality of life and functionality. The biomedical approach to mental healthcare has undergone a paradigm shift over the recent years to become more inclusive and rights-based. Dignity comprises of independence, social inclusion, justice, equality, respect and recognition of one's identity. It has both subjective and objective components and influences life-satisfaction, treatment response as well as compliance. The multi-dimensional framework of dignity forms the central anchor to person-centered mental healthcare for older adults. Mental health professionals are uniquely positioned to incorporate the strategies to promote dignity in their clinical care and research as well as advocate for related social/health policies based on a human rights approach. However, notwithstanding the growing body of research on the neurobiology of aging and old age mental health disorders, dignity-based mental healthcare is considered to be an abstract and hypothetical identity, often neglected in clinical practice. In this paper, we highlight the various components of dignity in older people, the impact of ageism and mental health interventions based on dignity, rights, respect, and equality (including dignity therapy). It hopes to serve as a framework for clinicians to incorporate dignity as a principle in mental health service delivery and research related to older people.

Keywords: dignity, human rights, older people, ageism, elder abuse, mental health

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PREMISE: DIGNITY IN MENTAL HEALTH CARE FOR OLDER PEOPLE

The world's population is aging rapidly with persons aged 65 or older projected to reach 1.5 billion by 2050 (1). Approximately 20% of them will have mental health conditions such as dementia, depression, anxiety and substance use, often complicated by physical and psychosocial comorbidities (2). Implicit and explicit biases that negatively influence their care include the triple jeopardy of ageism, mentalism, and ableism (3). The concept of dignity is complex and forms the ethical basis for enhancing a person's sense of wellbeing and quality of life, especially for persons with mental health conditions. Our neurobiological understanding of late-life mental health conditions has improved significantly over the last few decades, but there is an urgent and significant unmet need to incorporate the principles of dignity within mental health service delivery

(4). This is particularly important to address for clinicians caring for older persons who must respect the human rights and the autonomy of every person. Incorporating dignity in the care of older persons takes on greater importance, due to their multiple and interdependent vulnerabilities such as physical, psychological, cognitive, and social frailty, interacts with dependence on others, loneliness, social isolation, polypharmacy, medical comorbidities subjecting them to human rights abuses, loss of autonomy and poorer access to healthcare. Promoting their dignity and protecting older persons against stigma, discrimination, violence, abuse and neglect enhances clinical outcomes and quality of life.

Practical models for promoting the principles of dignity, and a rights-based approach to mental health care, serve as a moral, ethical, and legal anchor to support the independence and autonomy of older persons with mental health conditions (5–7). Most older persons have higher ratings of successful aging despite declining physical and cognitive function and satisfied with their quality of life (8), however with speedy population aging, there are several others with increased needs of support. These include people with chronic medical illnesses, geriatric depression and anxiety, as well as neurocognitive disorders. Besides functional recovery, optimum management of their conditions also needs to preserve their independence, respect, autonomy and rights. Even though most of these concepts are of a Western origin, transcultural connotations are common. This assumes a special significance in light of the United Nations Convention for Rights of People with Disabilities (UNCRPD), which views human rights as an *"instrument with an explicit, social development dimension"* (9). There are currently 82 signatories to the Convention who agree that fundamental freedoms should be at the core of healthcare in conditions of disability, which include psychiatric disorders. The UNCRPD changes the approach from viewing the *"mentally disabled"* as "subjects of charity needing medical and social protection" to "individuals with human rights who can participate in society and informed decision-making with appropriate care" (10). This furthers the concept the autonomy and free will beyond the geographical and cultural boundaries. Besides, autonomy in a mental health setting, but also in other contexts of vulnerability, is often an ideal that can become a fallacy if structural factors are ignored; in some settings, the ideal of autonomy should be framed as interdependency (11–13). Controversies about the cultural acceptability of the concept of "autonomy" aside, it is only one of the dimensions of dignity, which is a much more holistic concept in healthcare. The social context of care, process of caregiving, challenges associated with aging and psychiatric symptoms: all can be potentially grounded in recognition of the individual's abilities, respecting the free will, preventing health inequalities and recognition of diversities, all of which constitute dignified mental healthcare in daily practice (14). As global health inequalities are widening, more so in light of the ongoing Coronavirus Disease 2019 (COVID-19) pandemic, incorporating dignity in mental health services and planning become more important. Non-inclusion of such practices in mental health policies and programmes have led to poor healthcare access, stigma, inadequate social welfare benefits and discrimination in older people (15, 16).

WHAT CONSTITUTES DIGNITY: DIFFERENT DIMENSIONS

Dignity is a complex multi-dimensional construct with a high likelihood for various subjective interpretations. It is difficult to have an universally agreed definition for such an abstract concept. Nevertheless, people are usually able to recognize when an individual's dignity is violated, and also when dignity in care is enhanced. Hence, when we talk about the need for dignity in mental health, there needs to be a shared understanding among clinicians, patients, caregivers and policy-makers alike (14, 17).

Dignity has often been conceptualized in sync of human rights in being of *"value or worthy"* and enjoying the *"deserved respect."* The United Nations Universal Declaration of Human Rights states that *"All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act toward one another in a spirit of brotherhood"* (18). This is translated in the Constitution of the World Health Organization (WHO) when it is stated that *"The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of age, race, religion, political belief, economic or social condition"* (19).

In the practice of medicine, dignity gradually became a focus for physicians and medical researchers. In more recent debates, it has been invoked in questions of bioethics of human genetic engineering, human cloning, and end-of-life care (20). In June 1964, the World Medical Association issued the Declaration of Helsinki that says at article 11: *"It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects"* (21). The Council of Europe, on 4th April 1997, at Oviedo, approved the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. The Convention states that *"Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine"* (22).

A phenomenological analysis of how care providers perceived dignity as a core value in healthcare promotion in older people revealed that it was constituted by three primary components: worthiness, autonomy, and identity (23). The authors state that these themes reflected the principles of nursing practice to improve the older patient's health potential. Ivbijaro et al. (24) highlighted that dignity is not simply a medical strategy but rather a holistic outlook to healthcare which involves both service users and providers. They mention cultural sensitivity, kindness, respect, empathy, independence, autonomy and self-esteem as the various dimensions of dignified mental healthcare for older people. Targeting these attributes in various settings through collaborative care can enhance the quality of life of seniors who are mentally ill. Further, principles of dignity can also help counteract ageist attitudes, negative beliefs and social stereotypes about "being old" both among the general public and mental healthcare professionals (25). It's also vital how service consumers understand dignity themselves. A recent meta-synthesis explored the "understandings of dignity" from the perspective of older adults in the Nordic countries (26). The need for recognition and visibility formed the overarching theme and also an important unmet need in healthcare. There was a critical need to balance between *"toning down their illness to gain more independence"* vs. *"losing a voice by being less visible to the society."* Hence, besides autonomy and independence, the need for social visibility also formed a vital component of dignity. In lines with the same, mental health first aid delivery based on dignity has shown to be an effective public health intervention tool for improving knowledge, attitude and practices (27). Informed decision-making, participation in healthcare, providing audience to the voices of persons with mental illness and a non-judgemental approach formed the main components.

Based on this evidence, personal dignity can be understood in two interconnected ways: *internal* (how I see myself) and *external* (how others see me) (28). Each is dependent on the other. Hence, as a mental health professional it is essential to have an inclusive, empathetic and non-discriminative approach to consider the individual as *"an independent human being"* rather than just a *"subject of care."* This brings in the sense of "subjectiveness" and "individualism" which are important constructs of self-dignity (26). The temptation to stereotype older adults into a single homogenous group takes away their individuality, contributes to the increased stigma associated with older age and increases the risk of denying them their dignity. Based on ethical principles, dignity has also been conceptualized as autonomy/self-determination, non-maleficence, ensuring justice, and veracity (right to know and participate in their treatment process) (20).

It is clear from the discussion above that dignity involves various attributes which reinforce each other. Also the perceptions vary based on needs and care-providing. Unfortunately, most of the interventions and guidelines speak about *"needs and should"* in dignified mental healthcare rather than highlighting the processes of change (28, 29). Dignity in true sense is both structural and interpersonal. These dynamics need to be considered while imbibing it into mental health interventions. A common fallacy is attributing lack of dignity solely to psychological causes while it is divorced from "symptoms" which essentially have a medical model. This dichotomy is potentially harmful (30). It is high time that the premise of dignity and rights in mental healthcare of older adults are considered through a biopsychosocial model. Maintaining respect, optimum medication to ensure functional independence and granting social recognition as an individual go hand-in-hand and hence no single dimension of personal dignity can exist in a vacuum. As Clancy et al. (26) state that the effect of mental illness is to make older people invisible to the society and their voices unheard, it is the onus of healthcare providers to protect them from this *"cloak of invisibility."*

DIGNITY: HOW DOES IT INTERSECT WITH PSYCHOSOCIAL HEALTH

Collaborative care is the cornerstone of mental health services in older people. This requires both empathy and community support. There is growing evidence that clinical empathy–the medical professional's cognitive understanding of the emotions of people with mental illness combined with emotional attachment–directly enhances therapeutic efficacy (31). Increasingly, training in empathetic behavior must be a priority among healthcare professionals caring for the elderly (32). While delivering mental health services for older people, it is important to consider the social determinants of health, which are dynamic throughout the life-course, especially in later life. Social determinants of health are the conditions in which people are born, grow, live, work and age and which are shaped by the distribution of money, power and resources at global, national and local levels (33). These undergo complex interaction with genetic factors, personal experiences as well as the social environment to influence psychological wellbeing. The various dimensions involved in mental illness that also influences personal dignity and human rights in older people are depicted in **Figure 1**.

Social determinants may play a role as risk factors for mental health problems (unemployment, poverty, inequalities, stigma and discrimination, poor housing, adverse childhood experiences, violence, abuse, drug and alcohol abuse, poor general health, caring duties), while others may be protective factors (social protection, resilience, social networks, positive community engagement, positive spiritual life, hope, optimism, good general health, good quality family interactions, positive intergenerational relationships) (34, 35).

By acting on social determinants of health, it is possible to contribute to promote the older adults' dignity and a better subjective mental health and well-being of older people, to build the capacity of communities to manage adversity, and to reduce the burden and consequences of mental health problems. Disadvantages because of mental health problems in old age damage the social cohesion of communities and societies by decreasing interpersonal trust, social participation and civic engagement (36). The present-day nosology-focused symptom-triggered psychiatric care often aim at relieving the signs of illness and reduce hospitalization. This can at times deprive the voices of the service-users with their exclusion from the management plan. According to Minoletti (37),

> *"dignity for persons with mental disorders is exercising citizenship, with a sense of empowerment and control over their lives, and demanding the same rights (e.g., the right to decide where to live, whom to meet, whom to love, where to work, etc.) and take the same responsibilities (e.g., respecting the laws, voting, volunteering, paying taxes, etc.) as other citizens."*

Hence, besides symptom resolution, enjoying citizenship, feeling respected (as well as self-respected), honored, and inclusive are vital components of care in a mentally ill older adult. This makes the resultant mental healthcare for older adults comprehensive and patient-centered rather than bureaucratic and directive.

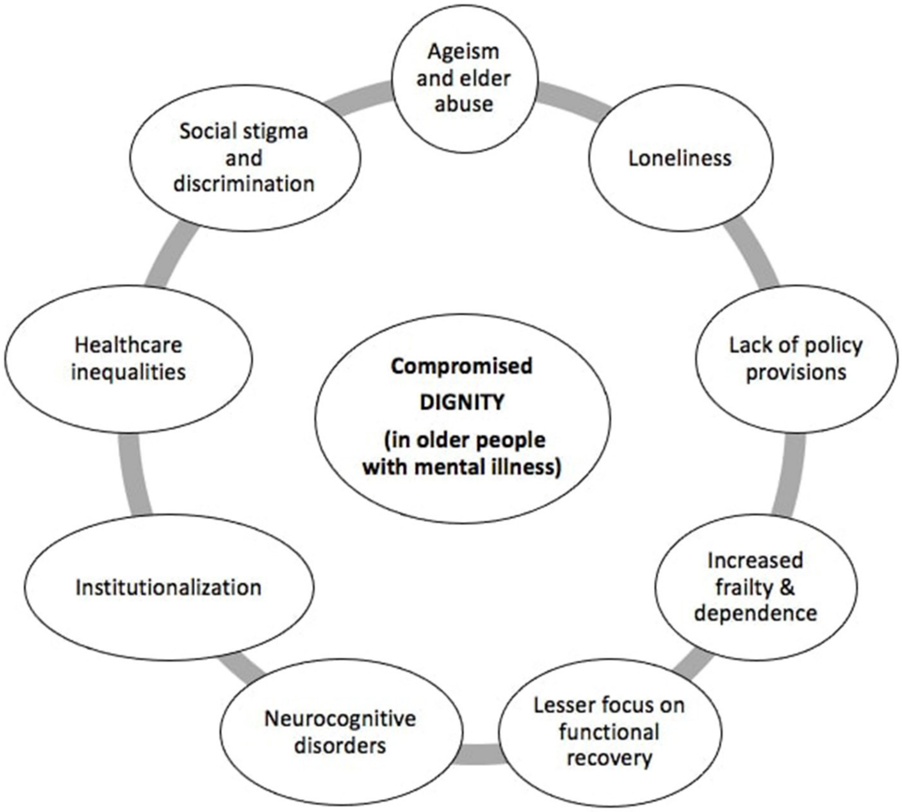

FIGURE 1 | Various factors that impose threat to dignity in older people living with mental illness.

AGEISM AND ELDER ABUSE: FUNDAMENTAL THREATS TO HUMAN RIGHTS AND DIGNITY

Ageism manifests in various forms throughout the life course and is most impactful in old age. It is the stereotyping, prejudice and discrimination against an individual based on his/her age or the aging process (38). Coined in 1969 by Robert Butler, it primarily denotes ageist attitudes against senior citizens, although it is also rooted in sexism and racism (38). The World Health Organization (WHO) Global Report on Ageism was developed by the High Commissioner for Human Rights, the United Nations (UN) Department of Economic and Social Affairs as well as the United Nations Population Fund (UNPF) (39). The report calls upon healthcare policies, intergenerational and multi-disciplinary interventions to combat ageist behavior against older people, considering ageism as a major barrier to personal dignity and social visibility (39). Ageism is widespread across places providing health and social care, in workplace, the media, etc. to an extent nearly 50% of the global population have some or the other variation of ageist thoughts, which is much more prevalent in the low-and-middle-income countries (40). Ageism has shown to compound the stigma against mental illness, especially in neurodegenerative disorders as old age is often equated with the process of *"disease and decay."* This can lead to a *"double jeopardy"* in the psychiatrically ill older population (41). Human-rights based approach targeting inequalities and discrimination in healthcare can restore inclusion, dignity and autonomy in psychogeriatric care and thus address the long-term issue of ageism.

Ageism also leads the concerning social evil of elder abuse, which is high in institutional settings. Based on WHO data, one in six individuals above 60 years age have experienced some form of abuse in the community settings within the last year (42). Ageism affects not only the older adults mentally ill but also who care them. Often it is perceived that care older adults with mental health conditions less prestigious than other positions in the health care systems, with prejudice for the professionals' career, self-esteem and their own mental health (42). Family members of older adults with mental health condition may also be victim of stigma and discrimination, with loss of personal projects and resources (including financial ones). Both ageist attitudes and consequent elder abuse have peaked during the COVID-19 pandemic and their intersections with human rights crisis, marginalization and loss of dignity in older people are quite prominent (43–45). Banerjee et al. (46) propose the complex interplay of ageism (and other forms of discrimination in older people), self-stigma, health inequality, and elder abuse that leads to compromised dignity which in association with factors such as frailty, dependence, social isolation and medical morbidities lead to "human rights crisis" in older people. The processes of *"rudeness, dismissal, indifference, disregard, objectification, condescension, intrusion, restriction, labeling, discrimination, contempt, deprivation, abjection, revulsion, and assault"* lead to violation of dignity in healthcare and reinforce ageist behaviors in the service providers (47). Incorporation of principles such as care, empathy, respect for individual identities, focus on safety, non-judgmental approach and social justice into geriatric mental healthcare can help combat ageism and elder abuse in lines with the Global Strategy and action plan on aging and health and the Decade of Healthy Aging 2021–2030 (48, 49).

WHAT IS WARRANTED IN MENTAL HEALTHCARE AND AREAS OF INTERVENTION?

Most older people want the same as everybody else in the general population. They want services that are reliable and dependable, easy to access and with competent staff that are sensitive and recognize diversity. When they have health needs, older adult people like to have these needs managed in a collaborative way (50). This requires a supportive community. Older people want to be close to their families if they need to receive treatment in hospital (8, 24, 35). We need innovation for this to be achieved, taking the patient's view into account and may have to adapt and use new technology in an ethical and responsible way. A review of empirical and theoretical literature on dignity in the care of older people revealed that staff attitudes and behavior, environment, culture of care, specific care activities and staff training form the major factors in deciding personal dignity. Sense of purpose and need for recognition in daily life were important considerations for dignity while in mental healthcare there was a constant tussle between degree of dignity and autonomy especially in severe mental illness and dementia (37, 43, 46). The practical wisdom of mental health professionals, social workers, case managers and policy makers and their perceptions about what constitutes dignity are vital in determining the operational interventions at place in mental healthcare settings for older people (37, 46).

Health and social professionals need to receive special education and training to care older adults with mental disorders with dignity. To educate professionals, caregivers and the lay public in mental health issues in old age is necessary to reduce the burden of mental disorders. All health and social professionals should receive information according to a knowledge based curriculum on mental health issues in old age at undergraduate and postgraduate levels. Such curriculum should include the special significance in old age of the interdependence of mental, physical and social factors and the prevention and health promotion including recreational and spiritual issues (51, 52). Recovery-oriented and person-centered practices need to be at the core of healthcare. The various areas through which principles of dignity can be incorporated in psychosocial care for older people are mentioned in **Table 1**.

TABLE 1 | General areas of dignity-based mental health interventions.

- Addressing stigma and discrimination in individuals with mental illness
- Combat ageism
- Prevention and management of elder abuse
- Day care facilities and housing security
- Vulnerable populations (low socio-economic status, homeless, sexual minorities, migrants and displaced populations, nursing home residents [**Table 2**], etc.)
- Management of physical/social frailty and falls
- Ensure privacy and sexual health
- Optimizing psychiatric medication and focus on functional recovery/independence
- End-of-life considerations and informed decision making
- Dignified care in neurocognitive disorders
- Use of technology (digital literacy)
- Research in dignity-based mental healthcare/lived experiences of consumers and their caregivers
- Focus on respectful communication and social recognition as "individuals" (rather than patients)
- Inclusion of older people with mental illness/their families in interventions and policies
- Work with other sectors of society (justice, welfare, security forces, economy, etc.) to promote protection against ageism and to prevent ageist attitudes.

TABLE 2 | Ensuring dignity-based care for older people in nursing homes/residential facilities (50, 55–59).

- Optimal pain management
- Improving communication within and outside the facility (in-person and digital)
- Respect in daily conversation
- Foster independence in functioning (self-care: choice of living, eating, dressing, etc.)
- Good nutrition and hydration
- Ensure decent physical appearance, personal and oral hygiene
- Healthy interactions with the staff
- Age-friendly environment for mobility and safety
- Supervision for security and prevention of abuse
- Adequate ward design for ensuring privacy and sexual rights
- Group activities, exercise and engagement within the facility
- Prevent loneliness and isolation
- Restrict empirical use of psychotropic medications
- Residential care plan to include principles of dignity
- Involvement in decision-making to the extent possible
- Special care for those with severe mental disorders and dementia
- End-of-life care (avoid unnecessary and painful prolongation of life)
- Dignity therapy for older persons and their families in case of comorbid terminal illness

Sheltered Housing, Residential, and Nursing Care Homes and Hospitals

Many older people will be requiring nursing, residential and sheltered homes. Research shows that well-trained staff sensitive to their dignity and independence provide them emotional security, better quality of life and reduce risk of falls (50). Religious, spiritual and cultural values also need to be considered and incorporated into care planning (7, 53, 54). Evidence-based facets of dignity-promoting interventions in nursing home/residential settings are summarized in **Table 2**.

Independence is to be encouraged. More sensibility is needed in order to understand needs and desires of people for whom it is difficult to verbalize their preferences, such as in advanced dementia, confusional states and others. Such approaches generally need well-trained staff who knows well the older individual and his or her life history (50).

Hospital managers need to play a role in ensuring that the institution promotes dignity and that staff have the capabilities to provide dignity in care, for instance by avoiding treating older people like children. Ward design can either support privacy, autonomy and dignity or make patients more vulnerable by making it harder to promote individuality (54, 60, 61). Research has suggested that bringing in pieces of their own furniture and household belongings including photographs supports the recognition of individuality (50, 53, 62).

One of the greatest challenges to care delivery in sheltered, residential and nursing care settings is that of balancing risk management with privacy whilst supporting maximum independence. There need to be environmental, relational, and procedural structures in place to ensure that the older adult have as much independence and privacy as possible whilst reducing risk because many people's greatest fear when they enter such accommodation is loss of independence (54, 60).

While good staff communication skills are fundamental to the promotion of dignity in older adults, this is a skill that can be trained. Older people living with mental illness should routinely be asked about how they would like to be addressed, and there should be meaningful interactions between those who care for the older adult and the older adult being cared for in order to avoid social isolation (59).

Dementia

In addition to the treatment interventions offered, an important goal in the care of dementia is supporting quality of life, dignity and comfort: this should remain central to treatment and care delivery. Meaningful attention should be paid to the activities of daily living, the choice of treatments offered and the involvement and engagement of the individual and their family to enhance and maintain the individual's dignity (63).

Intervention programme that include the individual's family network is helpful. Family care giver's health needs should always be considered: positive health in family care givers may improve the well-being of the person with dementia and prevent care givers burn out affecting their own mental health balance. This promotes dignity by offering opportunities to care persons at the place of their choice (64).

Decision-Making and Dignity

It is necessary to develop national frameworks to protect people with impaired decision-making ability, in the respect of the person's dignity, and in accordance with the article 12 of the UN Convention on the rights of persons with disabilities (10). Substitute decision making (SDM) arrangements including informal surrogate through proxies appointed by the care recipient when still competent to those who are Court-appointed. SDM measures and actions must be in the interests of the incapacitated person and their continuing necessity should be reviewed regularly. They can be tailored based on national policies and socio-cultural norms. Mechanisms should be in place for appeal and for review as well as for reporting of alleged mistreatment by SDMs (20).

Recommendations: Role of Dignity Therapy

The population is aging and multimorbidity and co-morbidity is no longer the exception. People who care for older adults must be willing to understand the effects of multimorbidity and co-morbidity to promote dignity and the rights of older adults.

The quality of care people with dementia receive in hospital has raised concerns in many quarters and the need for clinicians to focus on dignity for people in hospital or receiving end of life care is very important (65). In addition to having a legal framework to support dignity and the rights of older adults we also need to provide practical tools for those who care for older adults to use. Applying these tools will help the older adult to maintain their autonomy and improve their self-identity and sense of purpose.

Dying with dignity in older people is very important to relatives and to the individual concerned and the end of life presents a further challenge to older adults (66). Factors that are associated with dignity in death for an older person are complex and include the type of multi and co-morbidity, quality of relationships with family including siblings and with caregivers, enjoyment of good days prior to death, feeling contented, not feeling lonely or a burden and maintaining a feeling of being in control. We need to ensure that end of life care promotes a sense of dignity and purpose and Dignity Therapy (DT) as a psychotherapeutic intervention for people near the end of life has been explored and has the potential to enhance the dignity of the older person.

A 2005 Canadian study showed that 91% of participants were satisfied with DT with 75% of participants reporting an enhanced sense of dignity (67). DT is one of the few non-pharmacological interventions that can be useful in older adults at the end of life however this is not routinely taught in clinical practice and we should recommend this approach as an additional tool in the armory of clinicians working with older adults in end of life care.

DT is not new and is well-accepted by family members (68). Sixty family members of people who had participated in DT and later died were surveyed to understand their perspectives on DT and 95% of respondents said that it helped their loved ones and 78% reported that it had heightened their loved one's sense of dignity and reduced their suffering (68). 65% of the family members felt that this form of therapy constitutes the most important part of healthcare and nearly all of them wanted to recommend it to other families confronting a terminal illness.

A randomized controlled trial in patients with a terminal prognosis receiving palliative care in hospital or community setting compared DT with client-centered care and standard palliative care (69). Though reduction of patient distress was same in all the three interventions, DT was significantly more likely to improve family's stress, quality of life and sense of purpose in those affected. A 2015 systematic review of DT concluded that there is robust evidence to support its acceptability and suggested the need for further research into how and in what settings it should be provided (70). Another systematic review of DT in palliative care by Martínez et al. (71) showed that DT was effective in reducing psychological distress, enhancing resilience and improving depression and anxiety scores. Non-randomized studies have reported significant gains in existential distress, death anxiety and psychosocial measures, which warrant further study. Even though, DT has been used mostly in palliative care, the principals involved be translated to routine clinical care of older people so that inclusion, compassion, sense of purpose, quality of life and person-centered approach can be used rather than a purely symptom-triggered diagnosis-based management.

WAY FORWARD: CALL FOR A UN CONVENTION ON RIGHTS FOR OLDER PEOPLE

As professionals from different backgrounds and regions of the world we collectively pledge to employ a human rights-based lens aimed to reduce the burden of ageism, mentalism, and ableism permeating virtually every aspect of older persons' lives (3). "Leave no one behind (LNOB)" is at the heart of the United Nations' (UN's) 2030 Sustainable Development Goals (SDGs) (72). The UN's Decade of Healthy Aging (2021–2030) strives for all persons to enjoy peace, prosperity, and a healthy planet (48). These commendable aspirations are clearly not the reality of countless older persons who have suffered needlessly for decades. *"What you permit, you promote."* Let us not permit this status quo. Let the lives sacrificed by older persons not be in vain by ensuring a positive change for the human rights of every generation of older persons. A global paradigm shift is required to transform the deeply-rooted stigma against older persons to one where every older person can fully enjoy their life with dignity and with respect. An urgent call for action is needed for a legally binding United Nations convention on the human rights of older persons.

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

DB drafted the first version of the manuscript with contributions from KR, CM, and GI who also edited the manuscript. The final version was read and approved by all the authors. All authors were involved in conceptualization.

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Supported Decision-Making in Persons With Dementia: Development of an Enhanced Consent Procedure for Lumbar Puncture

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The right to make autonomous decisions is enshrined in law. However, the question how persons with cognitive deficits can be enabled to make autonomous decisions has not been satisfactorily addressed. In particular, the concept of supported decision-making and its implementation into practice has been poorly explored for persons with dementia (PwD).This article describes the empirical development and implementation of support tools to enhance informed consent processes (so called enhanced consent procedures/ECP) for PwD on whether to undergo lumbar puncture. In the end of the process of pilot testing and further development of the tools, the following tools were defined: (1) Standardized Interview Structure, (2) Elaborated Plain Language, (3) Ambience and Room Design, (4) Keyword Lists, (5) Priority Cards, (6) Visualization, and (7) Simplified Written Informed Consent (Patient Information), as well as the general attitude (8) Person-Centered Attitude of the facilitator. As the development, implementation and evaluation of ECP tools is one objective of the transnational ENSURE project, we also include an overview of future empirical procedures. So far, our findings can serve as a selection of possibilities to support PwD in decision-making and help practitioners achieve an appropriate balance between the autonomy and protection of PwD in complex decision-making situation. Future studies should address the question if the proposed set of tools is effective to enhance informed consent processes in PwD.

Keywords: dementia, supported decision-making, informed consent, autonomy, lumbar puncture

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INTRODUCTION

Individual autonomy encompasses self-determined decision-making in medical and research contexts. The UN Convention on the Rights of Persons with Disabilities (UN-CRPD) is a human rights treaty that recognizes persons with disabilities, such as persons with dementia (PwD), as persons before the law with legal capacity and obliges state parties to support their ability to make decisions with legal effect (1). Similarly, the International Guidelines for Heath-related Research Involving Humans of the Council for International Organizations of Medical Sciences state that "adequate time and resources must be provided for informed-consent procedures" and that "researchers should use evidence-based methods for imparting information to ensure comprehension" (2).

The British *National Institute for Health and Care Excellence* (3) provides general recommendations on how to involve PwD in decision-making and how to provide information adequately (https://www.nice.org.uk/guidance/ng97). However, supported decision-making (SDM) in PwD requires further research. Its implementation in practice is rudimentary and the conceptual and theoretical framework vague. A systematic review of SDM in PwD (4) shows that it is–if at all–mostly applied in care and everyday-life contexts, but plays little role in treatment and research decisions.

In order to make treatment and research decisions, PwD need to participate in an informed consent (IC) process, which requires that: (1) a competent person (2) makes a free choice (3) following adequate information disclosure (5). Information disclosure is part of the IC process into which it would be possible to integrate SDM. Such approaches are called enhanced consent procedures (ECP) (6).

The "combined SDM model" (7), we adopt here combines decision-support with competence assessment. Decision-support has three possible outcomes: (1) Decision-making capacity (DMC) of PwD improves sufficiently to make an informed decision, and substitute decision-making becomes unnecessary; (2) DMC improves but decision-support was insufficient or inadequate and must be modified and provided again or; (3) DMC does not improve despite decision-support, and the PwD remains unable to make an informed decision.

The assessment of whether a person is competent is based on a concept of mental capacity that implies cognitive functioning. Grisso and Applebaum (5) defined four functional abilities: the ability to understand information, to appreciate its relevance, to reason it, and the ability to express a choice. Based on this concept they developed and validated a widely used instrument to assess mental capacity, the MacArthur Competence Tool (MacCAT) (5). Nowadays the MacCAT serves as a "gold standard" for the assessment of patients decisional capacity.

Beyond ethico-legal requirements, the highly internalized IC process is characterized by different attributes, such as the transfer of a huge amount of information (8), the use of technical medical terms, the separation of roles into experts and laypersons, and a potentially resulting imbalance of power (9, 10).

Further research is needed on how to implement SDM in PwD, how to enhance IC processes for PwD in treatment and research decisions, and how to provide adequate decision-support.

This study is part of the broad transnational ENSURE project (Enhancing the Informed Consent Process: Supported decision-making and capacity assessment in clinical dementia research). The development, implementation, and evaluation of tools to enhance the IC process for PwD is one of the transnational project partner's four objectives.

First steps toward achieving this objective are to identify appropriate support measures and to examine their potential for transfer to different decision-making situations. We choose the decision for lumbar puncture because (1) lumbar puncture constitutes a medical procedure whose IC process is precisely defined, (2) it is an important part of diagnostic work-up in certain cases (3), and (3) many clinical trials conducted with PwD include lumbar puncture. Against this background, the aim of this article is to outline the empirical development of decision-support, so called tools, to enhance this process.

METHOD

Development of Tools

Based on five defined criteria, those more general support measures were selected from the systematic literature review (4) that should be considered in the tools. The following five criteria were defined: (1) multiple answers, (2) compliance with published recommendations by experts on the capacity to give consent, (3) compliance with the (clinical) experience of the ENSURE team's experts, (4) effectiveness and (5) practicability. The support measures selected with the help of the named criteria, were ordered and bundled afterwards on the starting point of complexity reduction. The process of the development of tools as well as the five criteria for selecting support measures identified in the systematic literature review (4) are described in detail elsewhere (11).

Pilot Testing and Further Development of Tools

The defined tools and their application instructions were piloted and further developed in two processes. On the one hand, the first drafts of tools were implemented in real clinical IC procedures for a lumbar puncture from January 2018 and optimized together with the applying physician. Therefore, ethical approval was obtained from the local ethics committee of the University Hospital Frankfurt. On the other hand, the further development included an iterative process involving discussions among the members of the Ensure Consortium (ethicists, legal experts, nursing scientists, physicians, psychologists). This process was used to revise content and structure of the tools and to reflect upon ethical and practical challenges until consensus regarding appropriateness was reached. Issues like overburdening, overcompensation, sidestepping memory, interpersonal leverage, oversimplification, issue framing, and criteria for allocation of the support were discussed within the consortium.

Recruitment, Participants, and Setting

Together with our practice partners we recruited persons with suspected dementia that had been admitted to a psychogeriatric ward because of subjectively experienced cognitive impairment. Lumbar punctures had been recommended to the patients by their physicians for diagnostic work-up. Thus, we introduced the newly developed tools in an IC process that would have occurred anyway. In few cases the LP war performed immediately after the ECT, usually within 1 to 2 days after it.

Fourteen persons with suspected dementia participated in the ECPs, 11 of whom had been diagnosed with dementia or mild cognitive impairment (MCI) at the time of discharge from hospital. One ECP had to be terminated due to strong emotional stress of the participant. Of the 14 ECP conducted, 10 people with dementia or MCI (7 women, 3 men) could be finally included in the study. The participants were on average 67.5 years old (range 54–78). Two of them were diagnosed with Alzheimer's at the time of hospital discharge, four with unspecified dementia, and four with MCI. The participant's mean Mini Mental State Examination (MMSE) score was 24.3 (range 21–27).

Training of the Physician

The physician who was in charge of the lumbar puncture was trained to use the tools, and the entire ECP was carried out on a hypothetical case. One researcher (TW) attended all ECPs and assisted the physician with the implementation of the tools. A thirteen-page moderation-plan was written for conducting the ECPs.

Optimization of the Tools

Following the first implementation, we successively adjusted and optimized the applied tools regarding their feasibility. The attending researcher (TW) discussed each conducted ECP with the physician. They reviewed observations made during the ECP and jointly identified optimization potential. Subsequently the research team refined the tools again. The adjustments made are displayed in **Table 1**. For example, we initially used one keyword list containing bulleted keywords to describe the three information sequences, understanding the disease, understanding the treatment, and understanding the risks and benefits (Mac-CAT). The first interviews revealed that our participants were overwhelmed by the variety of keywords and were constantly searching for the related keywords on the list. We therefore decided to employ one list for each of the three information sequences.

TABLE 1 | Adjustments to applied support tools.

Tool / Attitude	Adjustments
Person-centered attitude	• The person-centered attitude of the facilitator was initially handled as an independent tool before it was decided to define it as a basic attitude that must be practiced as a basis for the application of other tools • After telling the patient about a suspected diagnosis of dementia, we took a break. We emphasized that dementia was suspected (especially at the initial diagnosis)
Standardized interview structure	• We included standardized breaks after each information sequence • If a participant wanted something repeated, we instructed the physician to repeat the whole information sequence (Mac-CAT) • We instructed the physician to assist in reproducing information if necessary, e.g., by naming keywords from the required responses (Mac-CAT) • We added missing information
Elaborated Plain language	• Sentences and wording were continually simplified, e.g., "We can use the needle to withdraw a few milliliters of spinal fluid." "We can take a little spinal fluid *via* the needle."
Ambience and room design	• We chose another room in preference to the doctor's room (room for occupational therapy) • Before participants were brought in, we prepared the room (tidiness, fresh air, heating)
Keyword lists	• We divided up the keywords and employed one list for each of the three information sequences • The keyword lists were taken back after each check of understanding so that participants had a maximum of one list in front of them
Priority cards	• We instructed the physician to ask our participants to explain the significance of only the "important" cards, rather than all of them
Visualization	• We changed the pictogram The spine was drawn more realistically and transparently Person on the picture was depicted as more ageless
Enhanced written Consent form (patient) information	• Modified according to the new pictogram

Note: Mac-CAT, Mac Arthur Competence Assessment Tool; e.g., for example.

RESULTS

In the end of the process of pilot testing and further development of the tool, the following tools were defined: (1) Standardized Interview Structure, (2) Elaborated Plain Language, (3) Ambience and Room Design, (4) Keyword Lists, (5) Priority Cards, (6) Visualization, and (7) Simplified Written Informed Consent (Patient Information), as well as the general attitude (8) Person-Centered Attitude of the facilitator. Instructions for use have been formulated for each tool.

General Attitude: Person-Centered Attitude of the Facilitator

Current research into decision-making needs and demands of PwD shows that the facilitator's attitude should be person-centered (4). This means providing subtle support and considering PwD as equal partners in the decision-making process, rather than taking over decision-making (12). Even if it seems self-evident, person-centeredness must be borne in mind and practiced, and we instructed physicians to have such an attitude during the IC process. In this respect, relationship aspects of communication need to be considered (13). In our written schedule, we gave such advice as:

- Invite participants, welcome them using their names.
- Introduce yourself with first, last name and function, if not yet known.
- Offer participants a chair and something to drink.
- Take a seat yourself.
- Establish and maintain eye contact.
- Provide time for questions, allow breaks if necessary.
- Clarify that you are available to take further questions after the ECP; say goodbye.

Prior to implementation, advice and recommendations were discussed with the physician.

Tool 1: Standardized Interview Structure

When obtaining IC, a structured approach and an open interview-style appeared crucial. To structure the IC process and reduce its complexity, information could therefore be presented in shorter segments (14), and the understanding of the PwD verified (14–16). In dementia care networks, PwD recognized the need for a decision more easily when others raised and introduced topics slowly, and clearly initiated the decision-making process (17). Besides a clear structure, the interview-style should encourage dialog and enable PwD to express themselves (16). Furthermore, decision-making should consider the pace of PwD, i.e., allow extra time or slow down the discussion where necessary (12, 14, 16–18).

To provide a supportive structure, we decided to use the MacArthur Competence Tool (MacCAT-T) to obtain IC and assess competency to consent to treatment. The Mac-CAT interview is performed in a standardized way by providing fixed sequences of information and then asking questions, inter alia, to verify understanding (5). Furthermore, the physician raises the decision-making topic and introduces it slowly, and it is clear when decision-making begins. We instructed the physician to ask the PwD for questions after each information sequence, and breaks were offered frequently.

To explain the IC procedure and clarify the structure of the ECP for the physician, we designed a detailed plan of the IC procedure (written schedule) in accordance with the MacCAT-T. It included an exemplary script and the timely application of further tools.

Tool 2: Elaborated Plain Language

The consideration of language aspects (15, 16, 18) may help PwD understand and minimize verbal demands. Schatz et al. (19) describe ways to improve the presentation of information in IC processes. By applying the first rule of so-called plain language to "use language the audience knows and feels comfortable with" (20) and referring only to the two positively evaluated characteristics of the otherwise criticized Elderspeak [e.g., (21)], we introduced elaborated plain language (EPL) (19). It is a clear and simple language with four main attributes. The EPL was applied throughout the ECP.

(1) We focused on the reduction of syntactical complexity, which means shortening sentences and using fewer subordinate clauses. We used only one subordinate clause per main clause and avoided convoluted sentences.
(2) We introduced semantic elaborations, which refer to the provision of further information (expansions) and an iteration of keywords by allowing them to "move" from sentence to sentence: "*There are also **side effects** in the investigation. The most common **side effect** is **headache**, which can occur up to five days after the withdrawal of spinal fluid. The **headaches** improve when you lie down and drink a lot.*"
(3) We limited the vocabulary, which means we avoided technical terms, e.g., "image of the brain" rather than "CT scan."
(4) We focused on neutral prosody that includes the avoidance of a slow speaking rate, high pitch, and short sentences (21).

Tool 3: Ambience and Room Design

In order to facilitate decision-making and clarify choices (15), describe how caregivers simplify the decision-making environment by removing unimportant objects and keeping things tidy. Under "keeping it simple" (18) write that care staff recommend avoiding distracting and noisy environments, e.g., with too many attendees. Moye et al. (14) also recommend minimizing background noise.

To avoid sidetracking stimuli, we chose a separate room for the IC process in preference to the doctor's office. The room, which is usually used for occupational therapy, has no telephone connection or computer access, and is located at the end of the corridor of the ward. We asked the physician to leave her phones outside during the IC process and told other health care practitioners on the ward not to disturb us for the next 30 min. In addition we placed a "please do not disturb" sign on the door and closed it. Apart from the patient (and sometimes a relative), only two persons attended the process (researcher, physician). The selected room has a large window providing natural light. The table the attending persons were sitting at was kept tidy.

Tool 4: Keyword Lists

While Smebye et al.(15) describe compensating for the failing memory of PwD by using aids and props, Haberstroh et al. (22) recommend memory-based strategies that reduce verbal memory loads and facilitate verbal retrieval. PwD understanding improved in a study by Rubright et al. (23), who enhanced the IC process with a memory and organizational aid that introduced, for example, summarized key elements. Moye et al.(14) recommend summarizing "[...] key aspects of information, such as reviewing key risks and benefits of each treatment, prior to asking the patient for treatment preference."

To achieve this, we applied additional lists with bulleted key information. We summarized the most important information by using easy-to-read language, and wrote the key points on a number of lists, each containing a manageable amount

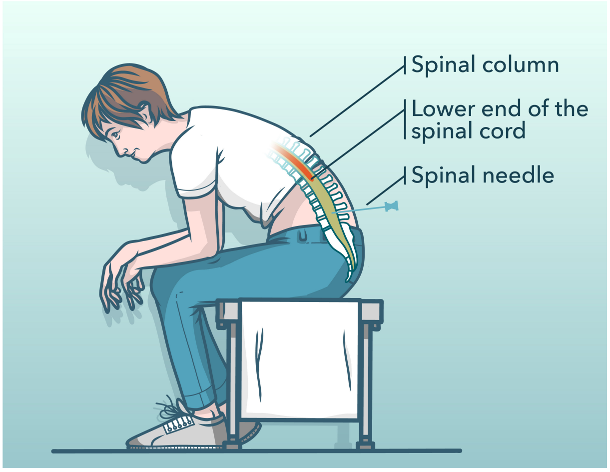

FIGURE 1 | Illustrating pictogram of the diagnostic procedure used for the enhanced consent procedure.

of information. The keyword lists were provided in addition to verbal information, thus utilizing iteration by presenting information repeatedly (spoken and written).

We instructed the physician to hand over each list after the information had been provided verbally, ask the PwD to summarize what he or she had been told, and then to take the list away before starting the next information sequence.

Tool 5: Priority Cards

To help PwD draw conclusions, compare the influence of lumbar puncture with its alternatives, and gauge its risks and benefits with respect to their situation and everyday life, we developed so-called priority cards. The communication framework Talking Mats, which aims to facilitate communication in the decision-making process (24), inspired this process.

Priority Cards enable PwD to visualize the risks and benefits of treatment on a single card containing a visual scale (important, not important). We asked PwD to use the scale to organize each card in accordance with their priorities. Furthermore, they had the option to express their own views on the treatment. During the ECP, the attending researcher wrote such reasons down on a blank card. After organizing the cards, we asked our participants to explain why the "important" cards were significant to them, and what effects the risks and benefits would have, regardless of whether they provide their consent.

Tool 6: Visualization

Featherstonehaugh et al. (18) describe how care staff tried to facilitate PwD's decision-making by "showing" alternatives, or using visual representations, such as pictures of a menu. Such non-verbal content aspects could be considered, to support the understanding of PwD in more complex situations by minimizing verbal memory load (13). A clinical strategy to maximize decisional capacity involves the use of such cues as pictures and diagrams (14).

We developed a pictogram to help PwD understand the treatment, and more specifically, the puncture site of the needle and the posture during treatment (see **Figure 1**). The aim of the pictogram is to simplify and iterate verbal information through visualization: *"In a spinal tap, fluid is taken from the spinal canal. For this purpose, you will be stung below the spinal cord with a needle (pointing gesture toward back). [...] For the withdrawal of the spinal fluid, you need to sit (or lie) still for some time. [...] (pointing gesture toward pictogram)."*

Directing the attention of PwD to important aspects (6, 23) could reduce the complexity of the process and indicates to PwD what is particularly significant. Hence, we introduced pointing gestures within the ECP, e.g., "*We also record the conversation (pointing gesture toward recording device).*"

Tool 7: Enhanced Written Consent Form (Patient Information)

We prepared our own enhanced written consent form (patient information) in preference to the hospital's to allow more time to decide (18), to avoid coercing the PwD (17), and to enable decisions to be revoked or modified (16).

We wanted to give PwD the opportunity to read received verbal information again (iteration) and to permit them to review their preliminary decisions, thus facilitating ongoing consent. Re-reading the information in a more relaxed atmosphere, possibly with a trusted person, may trigger further questions, which could then be clarified in another discussion with the physician. Signing the consent form was mostly postponed until later.

Written patient information was kept short (two pages) and delivered information in the same sequence as the verbal presentation. It includes visualization, hence the developed pictogram (see Tool 6). We simplified the enhanced written consent form information by using elaborated plain language[1].

DISCUSSION

This article describes the systematic development of support-tools for an ECP for lumbar puncture treatment for PwD. By involving an interdisciplinary transnational expert group, ethical, legal, and practical concerns were all considered equally. Our practical experience increased during each ECP, e.g., how to elicit the opinions of PwD, how often to offer breaks, how manageable the number of keywords on a single keyword list is, and how to apply elaborated plain language.

First observations of the researcher who assisted the implementation process (TW) support the assumption that many tools could simplify the IC or at least did not cause negative effects on the participants. For example, the visualization *via* pictogram "explained everything" to one participant, it appeared "a bit scary" to another. While the standardized interview structure enabled dialog in some cases, in other cases, the questions were perceived as "intensive" and participants seemed to feel tested by the physician. A deeper analysis of the interview and observation data will provide important insights. The applying physician evaluated the ECP as useful and intend to maintain some tools in future ICs.

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[1] We are ready to share the latest version of the written patient information and other relevant material with interested researchers and clinicians upon request.

The next steps of our project included an empirical evaluation of the tools within a small sample of PwD which is described elsewhere (11). The study provides initial indications that some participants felt supported by individual tools and that the targeted reduction in complexity in the informational dimension was successful in some cases. This enabled us to include their views as users of the support-tools and the ECP. A follow up study with the inclusion of patient's perspectives and assessment of patient's satisfaction should be performed in a larger cohort.

In this step the tools were not yet been evaluated in terms of their effectiveness (e.g., improved understanding, appreciation, reasoning, or overall score of mental capacity) but rather in terms of their feasibility, acceptability and appropriateness for the affected PwD. This evaluation was based on problem-centered interviews with every ECP participant. An additional small study was conducted, to investigate dementia researchers view on the developed tools (25). In brief, we performed an online survey with 19 dementia researchers from Germany and Portugal and evaluated the tools in terms of 4 implementation criteria. Overall, all researchers had a very positive attitude toward the support tools, whereby the tools person-centered attitude of the researcher and elaborated plain language were the most highly rated of the eight tools. Our findings also indicated that familiar support tools were assessed more favorably than those that were previously unknown. This demonstrated that the participating dementia researchers were open to the use of decision support measures in PwD and were willing to apply the support tools in practice.

We recognize that every PwD must be considered and treated as an individual with his or her own views, needs, abilities, and impairments. Therefore, we do not recommend applying all eight tools in standard form, but rather suggest selecting tools according to the individual needs of the single PwD and the resources (e.g., time and room availability) and abilities (e.g., qualifications) of the practitioner. Our findings can serve as a selection of possibilities to support PwD in decision-making and help practitioners achieve an appropriate balance between the autonomy and protection of PwD in complex decision-making.

Future studies should address the question if the proposed set of tools is not only feasible but also effective to enhance informed consent processes in PwD.

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 Ethikkommission des Fachbereichs Medizin der Goethe Universität Frankfurt, Deutschland. The patients/participants provided their written informed consent to participate in this study.

ENSURE PROJECT: ENHANCING THE INFORMED CONSENT PROCESS

The ENSURE Consortium was a transnational project team of interdisciplinary researchers: Goethe-Universität Frankfurt (Julia Haberstroh, Frank Oswald, Johannes Pantel, Theresa Wied), Ruhr-Universität Bochum (Jakov Gather, Matthé Scholten, Jochen Vollmann), Universidade da Coruña (Nathalia Álvarez Lata, José-Antonio Seoane), Universidade Católica Portuguesa (Ana Sofia Carvalho, Pablo Hernández Marrero).

AUTHOR CONTRIBUTIONS

TW and JH: substantial contributions to the conception and design of the work. TW, JH, JP, JG, MS, JV, and FO: substantial contribution to the analysis or interpretation of data for the work. TW and TK: substantial contribution to the acquisition of data. TW, JP, and JH: drafting the work or revising it critically for important intellectual content. TW, JH, JG, JQ, TK, FO, MQ, MS, JV, and JP: provide approval for publication of the content and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Neuropsychiatric Symptoms Exacerbate the Cognitive Impairments in Patients With Late-Life Depression

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Background: Neuropsychiatric symptoms (NPS) and cognitive impairments are both common in patients with late-life depression (LLD). However, the relationship between NPS and cognitive functions in LLD patients remains unclear. The current study aims to explore the effects of NPS on cognitive impairments in LLD patients.

Methods: Two hundred and sixty-two LLD patients and 141 normal controls (NC) were recruited. Exploratory factor analysis was used to extract factors from the Neuropsychiatric Inventory (NPI). Correlation, mediation, and moderation analyses were used to explore whether NPS exacerbated the cognitive impairments in LLD and whether NPS exhibited different effects on cognitive impairments in acute-state LLD (aLLD) and recovery-state LLD (rLLD).

Results: Three main factors were extracted from the NPI, including emotional, behavioral, and psychotic factors. The patients with LLD exhibited worse cognition and higher NPI scores, and the scores of NPI-total and three extracted factors were negatively associated with cognitive scores. The mediation analyses exhibited that NPI-total and behavioral factor scores increase the difference in cognition scores between LLD and NC groups. The mediation analyses exhibited that behavioral factor score played a greater effect on impairing MMSE in the rLLD group than in the aLLD group. Additionally, behavioral factor score was in a trend to be negatively associated with Mini-Mental State Examination (MMSE) score changes at a one-year follow-up ($p = 0.051$).

Conclusions: NPS, especially behavioral symptoms, exacerbate cognitive impairments in LLD and may contribute to residual cognitive impairment in rLLD patients. Early intervention for behavioral symptoms in LLD patients may be beneficial to their long-term clinical prognosis.

Keywords: late life depression, cognitive function, neuropsychiatric symptoms, mediating effect, moderating effect

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INTRODUCTION

Late-life depression (LLD), defined as major depression occurring in an older adult (60 years or older), is a global public health problem that severely limits psychosocial function and increases mortality (1, 2). In addition to persistent low mood and decreased activation, cognitive impairments (such as impairments in information processing speed, episodic memory, and executive function) are also common in LLD patients (3–5). Additionally, sustained cognitive deficits in individuals suffering from LLD have been associated with higher depression relapse rates, poorer responses to antidepressant treatment, accelerated rates of functional decline, and progression to dementia (5–9). A previous study suggested that cognitive impairments persisted in 94% of LLD patients with cognitive deficits at baseline, despite have reached depression remission (10), suggesting that there may be other factors influencing cognition other than depression. Therefore, it is important to explore which other factors may influence cognitive function in patients with LLD because they may inform early intervention and lead to better prognosis.

Neuropsychiatric symptoms (NPS) are non-cognitive, behavioral, or psychiatric symptoms such as aberrant motor behavior, irritability, anxiety, and hallucinations (11). NPS are associated with a higher burden of neuropathologic markers of dementia (12), more brain lesions (13), worse cognitive functions (14), greater functional impairment (15), and poorer quality of life (16). Large-sample longitudinal studies also supported the idea that NPS such as anxiety, apathy, and nighttime behaviors were associated with a more rapid rate of cognitive decline (17–20). Specifically, Palmer et al. found that apathy, but not depression, was associated with progression from amnestic-MCI to dementia, indicating that there may be a differential impact of different NPS on the dementia course (21). Patients with LLD often undergo aging of the brain with deterioration of the cerebral white matter, measured by white matter hyperintensities (WMH). WMH were found to be associated with significant preclinical NPS as well as hippocampal atrophy (22), which is considered a risk factor for developing cognitive impairment. Moreover, in a recent systematic review, Piras et al. identified several potential factors with confounding effects on the risk association between depression and dementia, including hypothalamic-pituitary-adrenal axis dysfunction, activation of inflammatory pathways, neuroanatomic changes, vascular risk, and metabolic and genetic factors (23). Thus, although the relationship between cognition and NPS is not entirely clear, numerous investigations have shed some light on the potential neurobiological links between NPS and cognitive impairments, as discussed above. In short, previous studies have pointed out that NPS were strongly correlated with cognitive decline across the spectrum from normal cognition to dementia (24), implying that NPS might be one of the risk factors for dementia.

Unlike the form of depression that occurs in young adults, LLD patients show more somatic symptoms and NPS (25, 26). Moreover, LLD patients with NPS always exhibit poorer clinical prognoses. For instance, apathy and reduced appetite in LLD were found to be associated with an increased risk of all-cause mortality (27). Comorbid anxiety in LLD has been found to increase the burden of depression, as reflected by quality of life, physical disability, and increased health care use (28). Ji et al. suggested that all insomnia symptoms were positively associated with depressive symptoms and that nighttime insomnia symptoms were indicative of poor cognitive performance (29). Bingham et al. found an association between cerebrovascular risk and treatment outcomes of LLD patients with psychotic features (30).

However, a limited number of studies to date have comprehensively evaluated the various kinds of NPS in patients with LLD, and the relationships between NPS and cognitive function in LLD patients has not been fully elucidated. Thus, the present study aimed to explore the relationships between NPS and cognitive impairment in LLD patients by using mediation and moderation analyses. Based on what has been mentioned above, it was hypothesized that NPS exacerbate cognitive impairments in LLD patients and contribute to persistent cognitive impairment during recovery periods. This study provides a deeper understanding of how NPS and cognitive impairment interact with each other and provides new insights into the treatment strategies of cognitive impairment in LLD patients.

MATERIALS AND METHODS

Participants

Two hundred sixty-two LLD patients were continuously recruited from The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), and 141 normal controls (NCs) were recruited from the communities in Guangzhou, China. All participants or their legal guardians provided written informed consent to take part in the study. This study was approved by the ethics committees of The Affiliated Brain Hospital of Guangzhou Medical University.

The inclusion criteria for patients with LLD were as follows: the patients were $\geq$60 years of age, had at least one episode of depression after the age of 60, and met the criteria for major depression in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. The NC subjects were aged 60 years or older without psychiatric disorders and exhibited normal cognitive function. The cut-off scores to classify cognition as normal for the NC subjects were based on MMSE thresholds adjusted by their years of education. For subjects who were illiterate, the cut-off was 17 points; those who received education through primary school had a cut-off of 20 points; and those who received education equal to and over middle school had a cut-off of 24 points. In addition to the MMSE, NC subjects were also evaluated by other scales, such as ADL, to exclude those with possible cognitive impairment.

All participants were evaluated by at least two psychiatrists to assess their clinical characteristics. The exclusion criteria of all participants were as follows: (1) history of other major psychiatric disorders, such as bipolar disorder and schizophrenia; (2) family history of schizophrenia and bipolar disorders; (3) physical illness that may induce emotional abnormalities, such as anemia and hypothyroidism; (4) neurological disease, such as brain tumor and stroke; and (5) drug or alcohol use disorders.

The severity of depressive symptoms was measured using the 17-item Hamilton Depression Rating Scale (HAMD-17). The patients with LLD were further divided into two groups based on HAMD scores: recovery-state LLD (rLLD) with HAMD <17 and acute-state LLD (aLLD) with HAMD ≥ 17 (31).

Neuropsychological Assessments

The participants underwent a full-scale battery of neuropsychological tests to evaluate cognitive functions. The battery included the following: (1) global cognition: Mini-Mental State Examination (MMSE); (2) memory: auditory verbal learning test (AVLT) and Rey-Osterrieth Complex Figure (ROCF)-delayed recall test; (3) language ability: Boston naming test (BNT) and verbal fluency test (VFT); (4) information processing speed: symbol digit modalities test (SDMT) and Trail Making Test (TMT)-A; (5) executive function: Stroop color and word test (SCWT)-C and TMT-B; and (6) visuospatial skill: ROCF-copy test and clock drawing test (CDT). The scores in each cognitive domain were calculated by transforming each of the test scores to standardized z scores and summing the scores from the two tests. Notably, for the tests measured by timing, including the SCWT-C, TMT-A, and TMT-B, lower scores indicated better performance. Thus, the scores were converted to the reciprocal before they were converted to the standard score (32).

Neuropsychiatric Assessment

Neuropsychiatric symptoms were assessed by using the Neuropsychiatric Inventory (NPI), which includes delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior (Ab. Mot Beh), sleep disturbances, and eating disturbances (33). The presence of symptoms for each item during the past 30 days was asked with a screening question. Once this was endorsed, specific questions were asked to clarify their frequency, severity, and burden for caregivers. Each item's score could range from 0 to 12 and reflected both severity and frequency ratings, with 0 corresponding to the absence of symptoms and 12 corresponding to its maximum frequency and severity.

Statistical Analyses

Statistical Package for Social Sciences version 23.0 (IBM SPSS 23.0, Chicago, IL, USA) was used to perform the statistical analyses. Demographic and clinical variables were analyzed using *t*-tests and one-way analysis of variance (ANOVA) for continuous variables, and chi-square (χ^2) tests were used for categorical variables. Cognitive functions were compared with analysis of covariance (ANCOVA). Control variables included age, sex, and education years. Statistical significance was defined as $p < 0.05$.

Preliminarily, 12 *t*-tests were used to assess between-group differences in NPI. Exploratory factor analysis was subsequently used to extract the main factors from the NPI for all of the participants. Factor analysis describes variability among observed correlated variables in terms of a potentially lower number of unobserved variables called factors. In the present study, we hypothesized that the factors represented the common variance in the 12 items of the NPI. Each item score was entered as a variable of interest in the factor analysis. Factor analysis was performed using the principal component estimation method (with eigenvalues >1) and VARIMAX method for factor rotation. Factors extracted from the NPI were then used in partial correlation, regression, mediation, and moderation analyses. Partial correlation analyses were used to explore the correlations between NPS and cognitive functions after adjusting for age, sex, and education years, and the regression analyses were used to further explore the significance of the correlations. As for the follow-up data, partial correlation analyses were used to explore the correlations between NPS and MMSE scores change after adjusting for age, sex, and education years.

Mediation analyses were performed for NPI-total scores and main factors screened in exploratory factor analysis. The mediation model was established when the following conditions were met: (1) the independent variable (IV) had a significant effect on the dependent variable (DV); (2) the IV significantly predicted the mediator; (3) the mediator significantly affected the DV; and (4) exclusion of the mediator from the model decreased the effect of the IV on the DV. For the present mediation analyses, dichotomous variables of NC and LLD groups were regarded as the IV, neuropsychological indicators were regarded as DVs, and NPI-total scores and scores of extracted main factors were regarded as mediators. In addition, for the moderation analyses, dichotomous variables of aLLD and rLLD groups were regarded as the IV, neuropsychological indicators were regarded as DVs, and NPI-total scores and extracted main factors were regarded as moderators. PROCESS 3.2 was used to investigate the mediating and moderating relationships among the variables (34). Indirect effects were estimated with 5,000 bootstrapped samples. Moreover, the Sobel test was performed to verify whether the mediating effect was significant.

RESULTS

Demographic and Clinical Characteristics, Neuropsychological Assessment, and Neuropsychiatric Symptoms

Information on the demographics, clinical symptoms, and cognitive functions of all participants is listed in **Table 1**. Significant differences were found in years of education, HAMD scores, NPI-total scores, MMSE scores, and scores in all domains of cognitive function between the NC group and LLD group ($p < 0.001$). There were significant differences in all of the NPI items (except for disinhibition) between the NC group and LLD group ($p < 0.05$) (**Figure 1**). Euphoria item has zero variance, and thus is not included in the analysis.

Factor Analysis

The KMO measure in this study was 0.726, indicating appropriate correlations among NPI items. In addition, Bartlett's test of sphericity showed that statistical significance was less than 0.001, thereby confirming the goodness-of-fit of the model.

Based on the NPS item scores, three factors were extracted by using exploratory factor analysis. The NPI items with

TABLE 1 | Demographic, clinical symptoms, and neuropsychological information.

Variables	NC ($n = 141$)	LLD ($n = 262$)	$F/\chi^2/t$	p value
Age (years)	67.72 ± 5.42	68.43 ± 7.04	−1.128	0.260
Sex (male/%)	41 (29.1%)	61 (23.3%)	1.629	0.202
Education years	10.76 ± 3.03	8.11 ± 4.07	7.369	$p < 0.001$
Age of onset (years)	NA	59.94 ± 11.21	/	/
Disease duration (years)	NA	5.41 ± 7.95	/	/
Numbers of episode	NA	2.18 ± 2.45	/	/
HAMD	1.81 ± 2.37	12.17 ± 8.25	−18.902	$p < 0.001$
NPI-total	2.62 ± 5.00	23.60 ± 17.70	−17.792	$p < 0.001$
MMSE#	27.28 ± 1.89	21.38 ± 5.49	99.402	$p < 0.001$
Memory#	1.04 ± 1.19	−0.88 ± 1.62	115.938	$p < 0.001$
Language ability#	1.12 ± 1.00	−0.99 ± 1.57	154.537	$p < 0.001$
Informationprocessing speed#	1.01 ± 1.29	−0.82 ± 1.68	97.356	$p < 0.001$
Executive function#	0.83 ± 1.38	−0.63 ± 1.56	68.075	$p < 0.001$
Visuospatial skill#	0.97 ± 0.62	−0.81 ± 1.91	83.407	$p < 0.001$

NC, normal control; LLD, late life depression; NA, Not applicable; HAMD, Hamilton Depression Rating Scale; NPI-total, total scores of Neuropsychiatric Inventory; MMSE, Mini-mental state examination; # adjusted for age, sex, education years.

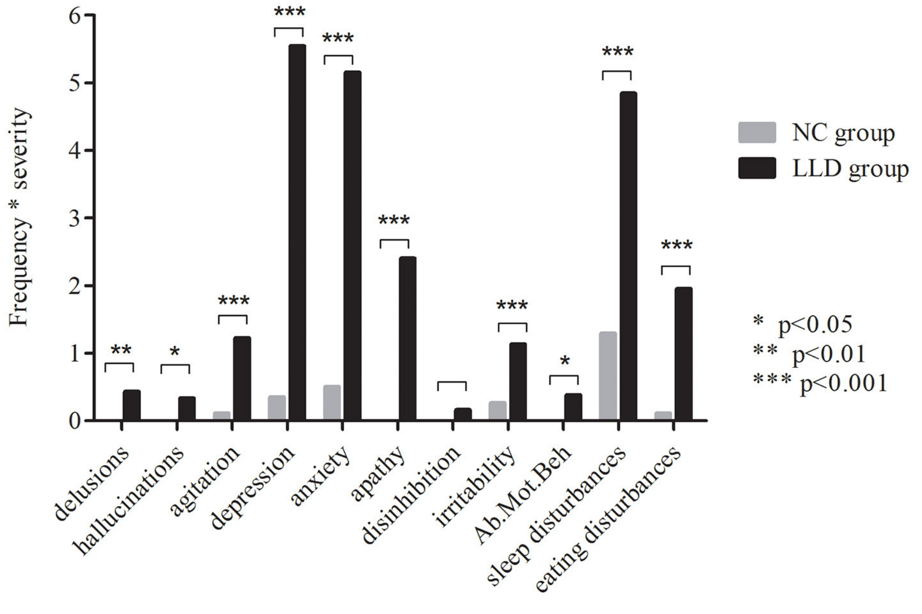

FIGURE 1 | Neuropsychiatric symptoms in NCs and LLD patients. The figure shows the scores of Frequency * Severity in NCs (in gray) and LLD patients (in black), as assessed by NPI; euphoria item has zero variance, thus is not included in the analysis; NC, normal control; LLD, late life depression; Ab. Mot Beh, aberrant motor behavior.

a saturation threshold >0.40 were included in 3 factors. Factor 1 described emotional symptoms, which included depression, anxiety, apathy, sleep disturbances, and eating disturbances. Factor 2 described behavioral symptoms, which included agitation, disinhibition, irritability, and Ab. Mot Beh. Factor 3 described psychotic symptoms, which included hallucinations and delusions (**Table 2**). The variance in Factor 1, Factor 2, and Factor 3 was 2.87, 1.66, and 1.61, respectively. The explanatory power of Factor 1, Factor 2, and Factor 3 was 26.1, 15.1, and 14.6%, respectively. The total explanatory power of the three factors was 55.7% of the total variance.

The three factor scores for the NPI presented for the NC and LLD groups are shown in **Supplementary Table 1**. Among the three factors, only the emotional factor and behavioral factor scores were significantly higher in the LLD group than in the NC group ($t = -16.688$, $p < 0.001$; $t = -4.239$, $p = 0.001$, respectively).

Correlations Between NPS and Cognitive Functions

NPI-total scores and emotional factor scores were negatively correlated with MMSE scores and scores in all cognitive function domains. Behavioral factor scores were correlated with MMSE, memory, language ability, and visuospatial skill scores, while psychotic factors were correlated with MMSE and language ability scores ($p < 0.05$) (**Table 3**). Linear regression showed that the correlations between MMSE, memory, language skill, and NPS scores were maintained, while some of the correlations between other cognitive domains and NPS scores disappeared. The detailed results are shown in **Supplementary Table 2.**

Mediation Analysis

Considering the close relationship between NPS and cognitive functions, the present study subsequently conducted a mediation analysis to explore their relationships. Overall, we discovered three mediation models (**Figure 1**). First, the total effect of the NC/LLD groups on MMSE scores was $\beta = -4.501$ ($t = -10.012$, $p < 0.001$). The indirect effect of groups on MMSE through NPI-total was -1.418 ($z = -4.761$, $p < 0.001$) (**Figure 2A**). Second, the total effect of the NC/LLD groups on the information processing speed subscale score was $\beta = -1.595$ ($t = -9.654$, $p < 0.001$). The indirect effect of groups on information processing speed through NPI-total was -0.317 ($z = -2.703$, $p < 0.01$) (**Figure 2B**). The above results showed that NPI-total score as a partial mediator exacerbated the cognitive impairments in the LLD group evidenced by reduced MMSE and information processing speed scores.

Since three factors were extracted in the current study, we further explored which factors contributed most to the mediating effect. We found a mediation model involving the behavioral factors. The total effect of the NC/LLD groups on MMSE scores was $\beta = -4.501$ ($t = -10.012$, $p < 0.001$). The indirect effect of groups on MMSE through behavioral factor was -0.187 ($z = -2.027$, $p < 0.05$), indicating that the behavioral factor score as a partial mediator exacerbated the cognitive impairments in the LLD group evidenced by reduced MMSE scores (**Figure 2C**).

No significant mediating effect for the other NPI factors on the association between groups and cognitive functions was found.

TABLE 2 | Communalities and rotated factor matrix across all subjects.

	Communalities #		**Rotated factor matrix**		
	Initial	**Extraction**	**Factor 1**	**Factor 2**	**Factor 3**
Delusions	1.00	0.78	0.16	0.20	**0.84**
Hallucination	1.00	0.74	0.11	0.02	**0.86**
Agitation	1.00	0.52	0.23	**0.68**	−0.03
Depression	1.00	0.77	**0.86**	0.14	0.04
Anxiety	1.00	0.65	**0.79**	0.18	−0.01
Apathy	1.00	0.23	**0.45**	0.16	0.06
Disinhibition	1.00	0.58	−0.06	0.72	0.23
Irritability	1.00	0.47	0.36	**0.57**	−0.16
Ab.Mot Beh.	1.00	0.25	0.07	**0.48**	0.11
Sleep disturbances	1.00	0.58	**0.75**	0.03	0.08
Eating disturbances	1.00	0.58	**0.72**	0.03	0.25

Euphoria item has zero variance, thus not included in the factor analysis; factor 1, emotional factor; factor 2, behavioral factor; factor 3, psychotic factor; Ab. Mot Beh, aberrant motor behavior; # Extraction method: Principle component analysis; Rotation method: Varimax with Kaiser Normalization; in bold the variables included in each factor according the saturation threshold >0.40.

Moderation Analysis

Because of the existence of a mediating effect of NPS on cognition in the LLD patients, the present study subsequently explored the differential effects of NPS on cognition between aLLD and rLLD patients. There were 192 rLLD patients and 70 aLLD patients. The demographics, clinical symptoms, cognitive functions, and NPS for each group are listed in **Supplementary Table 3**. We discovered only one moderation model. The effects of aLLD/rLLD groups and behavioral factors on MMSE scores were $\beta = -2.258$ ($t = -3.384$, $p < 0.001$) and $\beta = -2.524$ ($t = -2.870$, $p = 0.005$), respectively, which manifested significant negative effects of both LLD and behavioral factors on MMSE scores. A moderating effect of behavioral factors on MMSE scores between the aLLD and rLLD groups was found, with $\beta = 1.249$ ($t = 2.367$, $p = 0.019$), suggesting that the behavioral factor had a greater effect on impairing MMSE scores in the rLLD patients than in aLLD patients (**Figure 2D**).

Since it is possible that the illness duration has a moderation effect on general cognition, we also performed the moderation analysis of illness duration on MMSE scores between rLLD and aLLD patients. However, we didn't find the moderation effect with $\beta = 0.138$ ($t = 0.775$, $p = 0.439$).

TABLE 3 | Correlations between NPS and cognitive function in all subjects.

	MMSE	**Memory**	**Language ability**	**Information processing speed**	**Executive function**	**Visuospatial skill**
NPI-total	−0.397***	−0.388***	−0.420***	−0.382***	−0.306***	−0.354***
Emotional factor	−0.379***	−0.355***	−0.387***	−0.380***	−0.308***	−0.316***
Behavioral factor	−0.184**	−0.189**	−0.194**	−0.087	−0.082	−0.190**
Psychotic factor	−0.172**	0.112	0.126*	0.062	0.087	0.090

*Data are represented with r, *p < 0.05; **p < 0.01; ***p < 0.001, adjusted for age, sex, and education year; NPI-total, total scores of Neuropsychiatric Inventory; MMSE, Mini-mental state examination.*

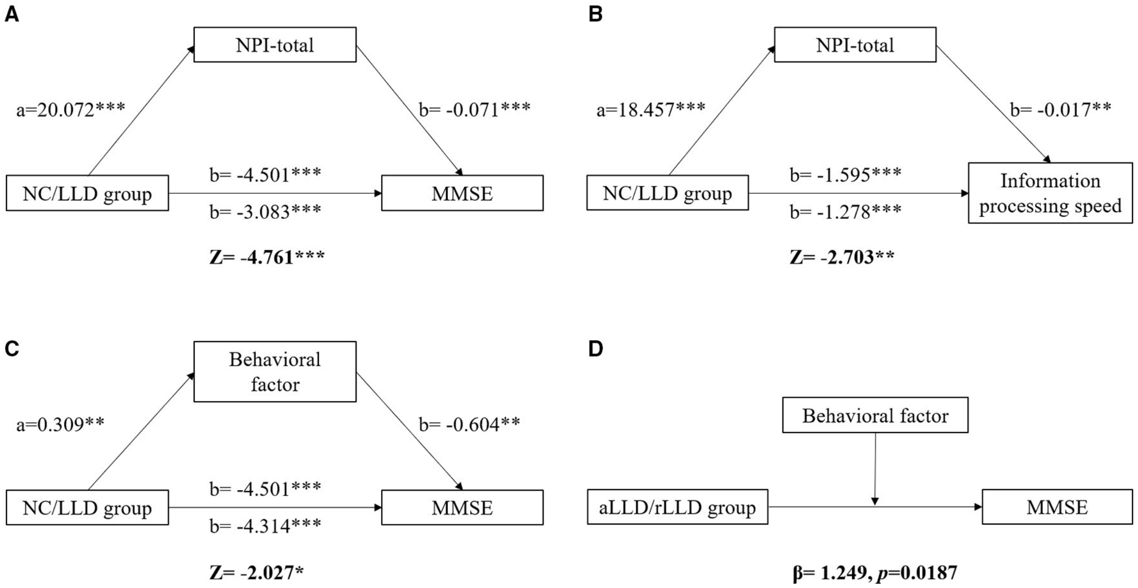

FIGURE 2 | The mediating and moderating effect of NPS on cognition. Differences of MMSE and information processing speed between NC and LLD groups were mediated by NPI-total **(A, B)**. Difference of MMSE between NC and LLD groups was also mediated by behavioral factor **(C)**. The NPI-total and behavioral factor are both the partial mediator for the relationship between NC/LLD groups and the cognitive functions. The MMSE difference between aLLD and rLLD groups was moderated by behavioral factor **(D)**. Behavioral factor played a greater effect on impairing MMSE in rLLD group than in aLLD group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Follow-Up Study of the MMSE

Sixty-one NCs and 85 LLD patients received a follow-up assessment after one year. As the sample size of follow-up is relatively small, we take all of them as a group to perform the next analysis. Partial correlation analysis found that the behavioral factor scores at baseline shown a trend to be correlated with changes in MMSE scores ($r = 0.164$, $p = 0.051$) (**Figure 3**).

DISCUSSION

In the present study, we first used the NPI to evaluate NPS in patients with LLD in a large sample size and demonstrated the mediating and moderating effects of NPS on cognitive functions in LLD patients. The main findings were as follows: (1) The LLD group exhibited significantly worse cognitive functions and higher NPS scores than the NC group. (2) NPI-total scores mediated differences in MMSE and information processing speed scores between the NC and LLD group. Moreover, behavioral factor also mediated the difference in MMSE scores. (3) Behavioral factor moderated the difference in MMSE scores between the aLLD and rLLD groups, and was in a trend to be positively associated with changes in MMSE scores at the one-year follow-up.

Previous studies have demonstrated that both LLD and NPS are risk factors for cognitive decline and dementia (17, 35), but the relationship between NPS and cognitive impairment in LLD patients has remained unclear. The present study found that NPS exhibited a negative mediating effect on cognitive function in patients with LLD, suggesting that NPS exacerbated cognitive impairments in LLD patients. It has been repeatedly reported that NPS were associated with the risk of incident MCI or more rapid progression to severe dementia (17, 19, 36). The reasons may be the following: (1) NPS may be a consequence of dementia pathology, such as Alzheimer's disease (AD) (13). The key brain regions underlying the behavioral, emotional, and psychotic factors are affected in patients with AD and LLD, and therefore, NPS might be a very early non-cognitive manifestation of dementia in LLD. (2) NPS may be generated by brain vascular disease and subsequent changes in white matter (e.g., WMH). There is a vascular depression hypothesis of LLD, and vascular lesions in the brain may lead to the occurrence of NPS. (3) Dementia-related biomarkers may be involved. A recent study found that tau protein was deposited in specific brain regions of LLD patients and that the deposition was severe in LLD patients with NPS (34). Tau deposition might etiologically link LLD and NPS. As tau pathogenesis is widely recognized in dementia, it is not surprising that LLD patients with NPS exhibit worse cognition. The present study also found a trend in correlation between behavioral factor scores and changes in MMSE scores at one year, indicating that behavioral symptoms at baseline might contribute to the prediction of future cognitive decline, no matter in LLD patients or NCs. However, these results should be carefully interpreted due to the small sample size and the heterogeneity in the LLD group. Large sample sizes in follow-up studies are needed to explore the predictive power of NPS on global cognitive decline in those with LLD.

The present study extracted three factors from the NPI, which was consistent with some previous studies in patients with AD (37, 38). However, only 55.7% of the variance

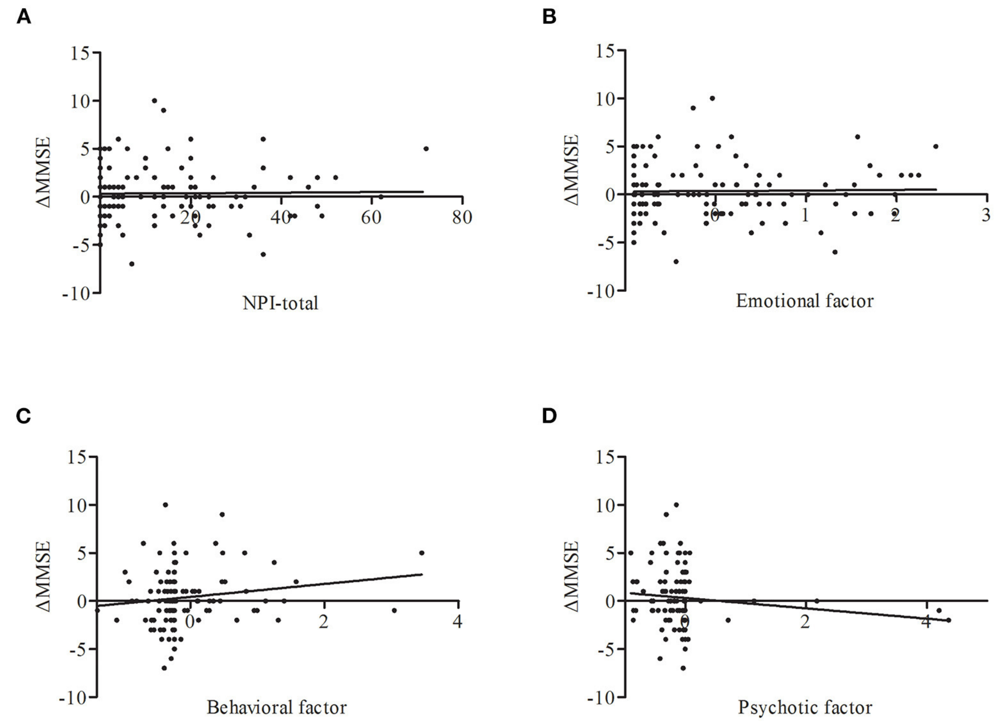

FIGURE 3 | Correlations between ΔMMSE and NPS including NPI-total **(A)**, emotional factor **(B)**, behavioral factor **(C)**, psychotic factor **(D)** across all subjects. Only behavioral factor on baseline has a trend to be correlated with the change of MMSE score ($r = 0.164$, $p = 0.051$). ΔMMSE, MMSE score (baseline)-MMSE score (one year), adjust for age, sex, and education years.

could be explained. Spalletta and his colleagues studied 1015 AD patients, supporting 5 main syndromes based on the NPI (apathetic, affective, psychomotor, psychotic, and manic syndrome) that explained >76% of the variance (39). Reasons that the total explanation of the variance reached 76% may be as follows: first, the relatively large sample size, and the 1015 AD patients were newly diagnosed resulting in high homogeneity; second, the incidence of NPS in AD patients (especially for those with serious dementia) is higher than that in LLD patients, and the common symptoms were more concentrated in AD. In another study, Serra et al. recruited 101 AD patients and 56 MCI patients and extracted 5 main factors based on the NPI, accounting for 55.18% of the variance, which is similar to the present study (40). Therefore, not every study was able to explain a high percentage of the variance.

NPS factors may have different neurobiological underpinnings (37), and their effect on cognitive decline may be different. The most associated NPS factor with a mediating effect in patients with LLD has been underresearched, which limits early intervention possibilities. Our study supported the idea that behavioral factor, including disinhibition, agitation, irritability, and aberrant motor behavior symptoms, made the most critical contributions to the mediating effect on global cognition. Given that behavioral symptoms made great contributions to the mediation of global cognition, the mediation by information processing speed might be the combined effect of the three factors, indicating that emotional symptoms and psychotic symptoms were less associated with cognitive functions in this population with LLD. A recent publication using latent class analysis supported that irritability appeared to be the determining factor in the conversion to dementia in MCI samples (41). The neurobiological substrates underlying these relationships may be the association between irritability and lower fractional anisotropy in the anterior cingulate, which supports the idea that irritability was correlated with greater alterations in white matter hyperintensities. In a five-year follow-up study, more severe baseline agitation and aberrant motor behavior were associated with subsequent AD progression (42). The role of agitation in AD progression was clear in those with mild and moderate dementia (43), and aberrant motor behavior has been shown to predict mortality (44). We speculated that agitation, aberrant motor behavior, and progression of cognitive decline and functional deterioration in AD are related to dysfunction in the same brain regions, with some neurobiological changes connected with them (45). Disinhibition has rarely been evaluated, so little is known about its mediating effect on cognition, indicating the need for further investigations of disinhibition in the future. It is noteworthy that, to date, most of the related evidence on the neurobiology of the above behavioral symptoms, such as irritability and agitation, comes from the dementia literature with little data from those with LLD despite its prevalence. Assessments of biomarkers in CSF or other neuroimaging studies in LLD patients are needed to explore the mechanism by which behavioral symptoms exacerbate cognitive impairments in patients with LLD.

The present study also found a moderating effect of behavioral factor on the difference in MMSE scores between the aLLD and rLLD groups, suggesting that behavioral symptoms played a greater role in exacerbating cognitive impairments in rLLD. Therefore, cognitive impairment did not recover simultaneously with depressive symptoms during the recovery periods, which may be due to the continuous existence of NPS, especially the behavioral symptoms. Most of the studies addressing the presence of NPS have focused on emotional symptoms. For instance, O'Connor suggested that depression in older people is typically accompanied by lowered mood and great anxiety and agitation (46). The present findings showed that other NPS symptoms, especially behavioral symptoms, exerted a role, although anxiety and depression have been the most widely explored NPS in other studies. A possible explanation for our moderating effect is as follows: anxious and depressive symptoms included in emotional factor are likely to be reactive, temporary, and linked to the self-awareness of being cognitively and/or functionally affected. Thus, emotional symptoms may be more influential during acute episodes of LLD. When emotional symptoms tend to be stable during recovery periods, persistent behavioral symptoms start playing a more prominent role. What's more, we found that illness duration was not a moderating factor on the general cognition, as reported in previous studies (47, 48). We speculated that the reasons may be as follows: (1) the heterogeneity in the LLD group; (2) differential medication histories in rLLD and aLLD groups; and (3) subjective recall bias.

NPS are common in those with LLD, but few effective and safe treatments exist. The lack of reliable NPS measurement and lack of enough attention to the role of NPS in LLD may have mainly contributed to the situation. Our results suggested that the NPI might be an effective scale to assess NPS in those with LLD. Furthermore, our study is meaningful in optimizing the treatment strategies for LLD, emphasizing treating behavioral symptoms during the recovery periods. In addition to cognition enhancers, clinicians may indirectly improve cognitive functions in the long term by treating NPS as early as possible. Since there are currently no antidepressant drugs that can improve both emotional symptoms and cognitive symptoms (49), psychotherapy such as cognitive behavioral therapy (CBT) and some physical therapies such as transcranial magnetic stimulation (TMS) may be helpful. Antipsychotic drugs can also be applied if needed. We suggest that the whole-course management of depressive symptoms and other related core symptoms should be incorporated in the routine treatment for depression instead of focusing only on remission from depression.

There were some limitations in the present study. First, the study used scales to assess NPS and cognitive functions without incorporating biomarkers in CSF/blood samples or neuroimaging, such as positron emission tomography (PET), into the analysis. A few patients may have complicated the analysis with early neurodegeneration, resulting in mixed effects. Moreover, the mechanisms underlying the influence of NPS on cognition could not be clarified. Future studies incorporating these biomarkers will provide a deeper understanding of the underlying mechanisms. Second, the present study did not exclude the possible effect of drugs because many patients with LLD were taking variable doses of antidepressant medication. Third, due to the lack of dynamic assessment of patients' symptoms, the trajectory of symptom change was unclear. Thus, the dynamic relationship between depression episodes and cognitive functions still needs to be further explored. Fourth, as NPS in NC is not as common as in LLD patients, the unbalanced sample sizes between the groups might have influenced the statistical power. Last, the one-year follow-up may have been too short; thus, the predictive efficacy of NPS on cognitive decline needs to be further elucidated.

In summary, the present study showed that NPS (especially behavioral symptoms) exacerbated cognitive impairment in LLD patients and might contribute to residual cognitive impairments during recovery periods. Moreover, behavioral symptoms may serve as a potential predictive marker for LLD patients at higher risk for cognitive decline. Our findings provide a deeper understanding of the relationship between NPS and cognitive impairment in LLD patients and highlight that NPS should be comprehensively evaluated in clinical practice because of their significant effect on prognosis. Early evaluations and interventions for NPS, especially behavioral symptoms during recovery periods, are of great significance for improving the long-term prognosis of LLD 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 Committees of the Affiliated Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MZ designed the study, analyzed and interpreted the data, and wrote the manuscript. BC and XZ designed the study, analyzed and interpreted the data, and revised the manuscript. YN designed the study and revised the manuscript. HZ, QW, NM, ZW, XC, QP, SZ, MY, and GL assessed the subjects. All authors contributed to the article and approved the submitted version.

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Internet Use and Depressive Symptoms Among Older Adults in China

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This study investigated the effect of using the Internet on depression symptoms of older Chinese, based on 7,801 adults aged over 60 years from the 2018 China Family Panel Studies. Results showed that the elderly who used the Internet reported lower depression scores, and the more frequent they use Internet, the lower their depression scores. Moreover, using the Internet for social contact and entertainment decreased the depression scores of the older adults, but when using Internet for learn, work, and commercial activity, the relief of depressive symptoms disappeared. Therelief of depression symptoms through Internet use were heterogeneous among different groups: the elderly aged 60–70, women, rural residents, and those with lower education attainment. Moreover, Internet use decreased the depression scores by increasing the frequency of contact with their children and increasing the importance of their enjoyment of life. According to the relief of depression by using Internet reasonably, policies should be designed to ensure that all ages could have easy access to the Internet.

Keywords: Internet use, depressive symptoms, older adults, digital age, China

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INTRODUCTION

Over the past decade, China's population has been aging rapidly. The number of older people aged 60 and over in China climbed to 264 million in December 2020, accounting for about 18.7% of the total population. With the continuous improvement of life expectancy and the increase in the number of elderly people, the mental health of the older people has also received attention. Depression was one of the most common mental illnesses among the elderly, and it is a recurring mental illness. The elderly often suffered the severe depression, and the prevalence of depression that does not meet the clinical diagnostic threshold was quite large in China, especially in the rural areas (1). Depression symptoms played a crucial role in the onset of dementia and other health problems of older people in later life. Thus, more attention should be paid to the depressive symptoms of the elderly.

After 2010, with the popularityof smartphones, the utilization rate of the Internet in China has increased year by year. According to the latest Statistical Report on Internet Development in China, the number of Internet users in China reached 989 million, and the penetration rate reached 70.4% in December 2020 (2). Additionally, since the COVID-19 epidemic, the Internet has brought many conveniences to life and the utilization rate of the Internet has increased sharply during the epidemic. However, due to the low level of education attainment, the decline of cognition and learning, and the difficulty in changing thinking concepts, the proportion of the older people using the Internet was low and was only 11.2% of Internet users are over the age of 60 (2). In addition, some scholars found that Internet use can contribute to mental health by increasing self-efficacy and enriching life experiences to a certain extent, as a way of reducing stress and depression levels (3). Thus, under China's context, was Internet use conducive to the mental health of older people? did using Internet promote the health level of the Chinese older people? The answer to these questions affected the formulation of Internet use policies, especially for promoting the use of the Internet among older people. Therefore, this paper explored the relationship and mechanism between Internet use and the depressive status of older people in China.

Scholars extensively researched and explored the relationship between Internet use and mental health. However, they have not reached a consistent conclusion. Some scholars believed that Internet use reduced the level of depression and was conducive to mental health. In terms of research results, Internet use enhanced people's contact with the outside world, expanded the scope of communication, increased social support, avoided social isolation, and had a positive effect on people's mental health (4–7). Trocchia and Janda (8) made a preliminary attempt to study the differences between elderly Internet users and non-users. After 12 in-depth interviews, they pointed out that the Internet had a significant happiness incentive effect on the elderly. This conclusion coincided with other scholars (9–11). Cotten et al. (12) used the Propensity Score Matching method to study the relationship between Internet use and depression in retired Americans aged 50 and over, and found that Internet use made a positive contribution to the mental health of retired older people. Shillair et al. (13) found using Internet can maintain and enrich older people's social relationships, reduce the effects of loneliness and increase life satisfaction. Confortin et al. (14) noted that the Internet can be seen as a space for older people to enjoy various information, particularly health-related information. Benvenuti et al. (15) selected 271 Italian older adults (aged 60 and over) to study and found that when the older adults used Internet, they would get positive perceptions of online social support, making them to stay closer to family and friends. For older adults with difficulties in mobility, Mcmellon and Schiffman (16) found that using the Internet would expand their social networks and maintain family ties. In addition, Cotten et al. (17) also found that older people who were unwilling to participate in social activities would also benefit from the use of the Internet.

In terms of impact mechanism, William (6) studied the relationship between technology use for social reasons and physical and mental health of older people. Through the use of five technology-based behaviors such as using e-mail, social networking sites, online video, instant messaging and using a smartphone, he found that social technology was related to higher subjective well-being and fewer depressive symptoms, and the associations were mediated by reducing loneliness. Du and Wang (18) used binary logistic regression and Propensity Score Matching to find that Internet use significantly improved the life satisfaction of Chinese older adults, in which community participation played a positive role. Cotten et al. (17) found that using the Internet could help older people overcome the obstacles of time and space to increase the frequency of social interaction, which was conducive to their mental health. Some older people maintained close contact with relatives and friends through the Internet, thus enhancing their support from family and friends, and improving their mental health (16, 19). Heo et al. (20) conducted a study using the data of the Health and Retirement Study in the United States in 2008 and found that Internet use reduced the loneliness of older people by improving social support. Another cross-sectional study also reported that using Internet was associated with greater social support, relief of loneliness, better life satisfaction and better psychological well-being (21). A Korean study (22) also confirmed the mediating role of social support, suggesting that social media use, such as the Internet, indirectly affected quality of life through social support, which in turn benefited their psychological well-being. Older adults who used online social networking sites reported that the strong sense of support from friends and the strong social connection (23). In addition, Lu and Wang (24) found that the information search and dissemination function of the Internet were the main mechanism to improve subjective welfare.

Some scholars held different views that Internet use may promote the emergence of depressive symptoms and have an adversely impact on mental health. Unhealthy Internet behavior reduced communication in real life. When a lot of time was spent on weak ties in the network, it would reduce the time spent on strong ties, destroying real relationships and negatively impacting life satisfaction. "Internet time substitution hypothesis" proposed that Internet use would occupy the time of social communication, reduce opportunities for face-to-face communication, and increase sense of isolation between people (25, 26), which was not conducive to emotional expression and maintenance of social relations, thus increasing inner loneliness and loss (27, 28). Hage et al. (29) tried to explore the relationship between online communication and social connectivity among the elderly, taking 302 older people as the research object, and found that Internet use would reduce real social participation, weakening sense of community belonging. Matsuba (30), Stepanikova et al. (31), Odaci and Elik (32), and Kitazawa et al. (33) found that excessive use of the Internet would make people addicted, produce a sense of loneliness. Elgan (34) also stated that social network addiction became a serious problem. When interacting excessively on social networks, users may experience depression and anxiety (35), because constant social comparisons and invasion of privacy leaded to negative emotions (36).

In 2020, the number of Internet applications in China grew steadily, which has affected people's daily life to a certain extent. Among them, short videos, online payment and online shopping increased most significantly, with growth rates of 12.9, 11.2, and 10.2%, respectively (2). When paying attention to the relationship between Internet and mental health, people were affected differently for different types of Internet using. Lifshitz et al. (37) found that when online social activities, instant messaging and search engines were regarded as part of leisure functions, they were related to participants' well-being, but when they were regarded as instrumental purposes, they did not show such contribution. Other scholars also pointed out that essential Internet use did not improve people's mental health, but showed higher levels of depression and anxiety (38), such as online payment and Internet financial management among the elderly. However, some scholars also pointed out that online games, short videos and other leisure methods provided by the Internet enriched people's lives (39), and social software such as Wechat, Microblog and QQ improved the level of social interaction (9, 40). Search engines could enable them to obtain information related to their hobbies and current events (4). Online platforms such as online shopping and online takeout diversified consumption patterns, which would affect people's mental health, mainly reflected in the improvement of depression.

From the above literature review, few studies focused on the impact of Internet use on depression symptoms and other mental health of Chinese older people, especially in China's context. Contrary to developed countries, the development and popularity of the Internet in China was much later. However, the current digital economy was developing faster. Therefore, the digital gap between urban and rural areas or between older people and young people in China was huge. This paper was based on the data from 2018 China Family Panel Studies (CFPS), which was representative of the current situation of Chinese social families. Most samples in the China Health and Retirement Longitudinal Study (CHARLS) were rural samples, while the samples of CFPS were balanced in urban and rural distribution. The heterogeneity of the Chinese older people group was rarely considered in the existing studies on the impact of depression symptoms and other mental health of older people. There were obvious dissimilarities in urban and rural residents, which included gender differences and education attainment. Therefore, it was necessary to analyze the impact of Internet use on depression symptoms among different population. This paper also discussed the mechanism of Internet use to further enrich the research conclusions. Further, most studies rarely considered the endogenous problem caused by self-selection when investigating the impact of Internet use on depression. Thus, the instrumental variable methods was employed to solve the endogenous problem.

MATERIALS AND METHODS

Study Population and Data Collection

2018 CFPS was used to investigate the effect of Internet use on older adults' depression symptoms. CFPS was a nationally representative and longitudinal survey conducted by the Institute of Social Science Survey of Peking University, starting in 2010. A multi-stage probability proportional to size strategy with implicit stratification was performed in the sampling process. It comprised three stages: County-level as the primary sampling unit, a community, or village for the second stage sampling unit, and the household as the final sampling unit. The CFPS survey consisted of a rich set of socioeconomic questions and information at the levels of children, adults, families, and communities (41). Human participants were approved by Peking University Biomedical Ethics Committee (IRB00001052-14010). Moreover, at the beginning of the survey, the questionnaire included the statement that the collected data would be used for scientific research. Written informed consent was obtained from each participant. For our analytic file, we used claims data from CFPS 2018, which were the latest survey data available at the time of the study. The CFPS 2018 survey collected 44,000 personal questionnaires, 22% of which was completed by telephone interviews. Given that this article studied the depression symptoms effects of the Internet use on the elderly, data including people who were under 60 years in 2018 were excluded from the study.

Depression symptoms was measured by a depression score of an eight-item version of the Center for Epidemiologic Studies (CES-D) scale in the CFPS 2018. The CES-D scale was a commonly used measure of depression symptoms in older adults (42–45) and was the only measure of depression symptoms in the CFPS. The CES-D scale consisted of eight questions about the feel of last week, namely, question N406 "I feel depressed," question N407 "I feel it takes a lot of effort to do anything," question N411 "My sleep is not good," question N412 "I feel happy," question N414 "I feel lonely," question N416 "I live happily," question N418 "I feel sad," and question N420 "I feel that life can't go on." The four options of the eight questions were hardly (< 1 day), sometimes (1–2 days), often (3–4 days), most of the time (5–7 days). They were assigned to 1, 2, 3 and 4, respectively. Among them, because of the fourth (I feel happy) and the sixth question ("I live happily)," which reflected positive emotions, the two questions were processed in reverse order, resulting in a depression score of 8–32. Higher scores indicated greater severity of depression symptoms.

We divided the study population into two groups: Internet users and non-users, according to the answers of the two questions, namely, question U201 "Do you use mobile Internet?", and question U202 "Do you use computer Internet?." The respondent was assigned to the Internet users group if they used mobile Internet or computer Internet in 2018 and the Internet non-users group if they did not surf the Internet in 2018. Moreover, we used the frequency of Internet use to replace the independent variable to further investigate the depression symptoms effect of Internet use. According to answers of question U701 "Frequency/times of using the Internet for learning," question U702 "Frequency/times of using the Internet for work," question U703 "Frequency of using the Internet for social interaction (times)," question U704 "Frequency/times of using the Internet for entertainment," and question U705 "Frequency/times of using the Internet for commercial activity, such as using online banking, online shopping." The highest frequency among them was chosen as the frequency of using the Internet, and the final assignment was 0 to 6, which means "not used," "once a few months," "once a month," "2–3 times a month," "1–2 times a week," "3–4 times a week," and "almost every day," respectively. Moreover, we examined the impact of different kind of the Internet usage on the depressive symptoms of the old adults. These variables were dummy variables formed according to questions U701, U702, U703, U704, and U705.

Internet use increased the social connections of the elderly and simultaneously allowed the elderly to have more access to the colorful world. However, due to data limitations, we only examined the frequency of contact with children in social connections and the emphasis on the joy of life. The frequency of contact with children was based on the average contact frequency of each child in question F306 "In the past 6 months, how often did you contact your child by phone, SMS, letter or email?." The value was 0–6 and the larger the value, the more times they contact. The joy of life value was obtained by answering the question M503 "the importance of having fun in life," with a value of 1–5.1 meaned not important, and five meaned very important.

However, other factors may generate bias when estimating the results. We collected the following characteristics for the study participants as covariates: age (continuous variable); sex (1 = male; 0 = female), education (0 = illiteracy, 1 = high school or lower, 2 = college or higher); Hukou (1 = non-farm; 0 = farm); marriage (1 = married/in de facto relationship, 0 = other); residence (1 = urban, 0 = rural); log of household saving per capita (lnfinc); and its square (Infinc2). These variables were selected because (1) they are highly related to the occurrence of depression symptoms and other mental problems, and (2) they are obtainable from the claims data directly or through the working definition.

Main Empirical Strategy

The ordinary least squares estimation and ordered Probit estimation were employed first within this study.

$$Depression_i = \alpha_1 + \beta_1 Internet_i + \gamma_1 Z_i + \varepsilon_i \tag{1}$$

Here, the subscript i referred to the individual. $Depression_i$ was the dependent variable related to the outcomes of depression scores. For the main independent variables, $Internet_i$ was a dummy variable equal to one for the Internet usage experimental group and zero for the non-usage control group; and vector Z_i was the covariates.

In ordinary least squares estimation, *Depression* was treated as continuous data. In the ordered probit (Oprobit) model, *Depression* was treated as a ranking variable, and it was necessary to deduce the estimator by using latent variables high likelihood estimate method.

Robustness Analysis: Impact of Frequency of Internet Usage

If the relation between Internet use and depression symptoms of older adults was robust, the different indicators to measure Internet use would have a same impact on the estimation results. Thus, the frequency of Internet use was taken as a new independent variable, and the following model was constructed to test the robustness of Internet use on depression of older adults.

$$Depression_i = \alpha_1 + \beta_1 Frequency_i + \gamma_1 Z_i + \varepsilon_i \tag{2}$$

Here, $Frequency_i$ was the frequency of individual use of the Internet, and the meaning of other variables was consistent with Equation (1).

Endogenous Problem

However, endogenous factors might bias our main results. That is, the decision to use the Internet, together with the individual's depression symptoms, may be determined or influenced by some missing or unobserved variables. Additionally, mental health status affected a person's behavior, which, in turn, may affect an individual's online behavior, creating reverse cause-and-effect problems. To overcome these problems and check the robustness of the main results, we first employed the two-stage least squares method (2SLS).

$$Internet_i = \varphi_1 + \phi_1 X_i + \lambda_1 Z_i + \varepsilon_{1i} \tag{3}$$

$$Depression_i = \varphi_2 + \phi_2 \overline{Internet_i} + \lambda_2 Z_i + \varepsilon_{2i} \tag{4}$$

Here, X_i was the instrumental variable; $\overline{Internet_i}$ was the fitted value of Equation (3).

Considering that the participants' depression scores and Internet use in this study were both discrete variables, methods based on continuous variables may be ineffective (46). Therefore, we employed the conditional mixed process method (CMP) proposed by Roodman (47) to re-estimate the model.

The CMP also belonged to the two-stage regression. As in the 2SLS model, the first stage of the CMP method was to find the instrumental variables of the main independent variable and evaluate their correlation. In the second stage, the instrumental variables were substituted into the model for regression, and the exogeneity of Internet use was verified according to the endogeneity test parameters. If the endogeneity test parameters were significantly different from 0, it indicated that the model has endogeneity problems—the estimation results of the CMP method were superior to Oprobit model. Conversely, if the endogeneity test parameters were not significantly different from 0, the Oprobit model estimation results can be referred to. The CMP method adopted simultaneous likelihood estimation in the second stage. In this study, the Internet penetration rate of the county level was taken as the instrumental variable of whether participants used the Internet, and the 2SLS and CMP methods were used, respectively.

Mediating Effect Model

This article referred to the intermediary effect test procedure proposed by Baron and Kenny (48) to explore whether the Internet use of the elderly can improve the depression status by increasing the frequency of social contact and increasing the joy of life.

$$Depression_i = \alpha_1 + \beta_1 Internet_i + \gamma_1 Z_i + \varepsilon_i \tag{5}$$

$$M_i = \alpha_2 + \beta_2 Internet_i + \gamma_2 Z_i + \varepsilon_{\mathrm{i}} \tag{6}$$

$$Depression_i = \alpha_3 + \beta_3 Internet_i + \delta M_i + \gamma_3 Z_i + \varepsilon_{\mathrm{i}} \tag{7}$$

Here, M_i was the intermediary variable. The coefficient β_1 in Equation (1) represented the total effect of the elderly's use of the Internet on depression. The coefficient β_2 in Equation (5) was the effect of Internet use on the intermediary variable. The coefficient δ in Equation (6) indicated that the effect of the intermediary variables M_i on depression after controlling Internet usage, and the coefficient β_3 represented the direct effect of Internet use on

TABLE 1 | Descriptive statistics for the sample.

	Full sample			Internet users			Internet non-users		
	N	**Mean**	**sd**	***N***	**Mean**	**sd**	***N***	**Mean**	**sd**
Depression	7,801	13.818	4.525	988	12.408	3.726	6,813	14.023	4.594
Internet	7,801	0.127	0.333	988	1	0	6,813	0	0
Frequency	7,801	0.624	1.774	988	4.924	1.917	6,813	0	0
Learn	7,800	0.044	0.206	988	0.352	0.478	_	_	_
Work	7,800	0.01	0.098	988	0.076	0.265	_	_	_
Social contact	7,801	0.093	0.29	988	0.734	0.442	_	_	_
Entertainment	7,800	0.093	0.291	988	0.736	0.441	_	_	_
Commercial activity	7,800	0.03	0.171	988	0.237	0.426	_	_	_
Age	7,801	68.192	6.325	988	65.925	5.066	6,813	68.521	6.421
Gender	7,801	0.504	0.5	988	0.603	0.489	6,813	0.49	0.5
Education	7,715	0.669	0.608	974	1.146	0.715	6,741	0.6	0.558
Illiteracy	7,715	0.38	0.485	974	0.08	0.272	6,741	0.424	0.494
High school and less	7,715	0.595	0.491	974	0.807	0.395	6,741	0.565	0.496
College and above	7,715	0.025	0.155	974	0.113	0.317	6,741	0.012	0.108
Hukou	7,792	0.301	0.459	986	0.693	0.462	6,806	0.244	0.43
Marriage	7,801	0.812	0.391	988	0.888	0.316	6,813	0.801	0.399
Residence	7,756	0.484	0.5	981	0.782	0.413	6,775	0.441	0.497
lnfinc	7,754	9.413	1.233	981	10.284	1.124	6,773	9.287	1.197
lnfinc2	7,754	90.127	21.804	981	107.013	21.196	6,773	87.682	20.784
The child contact frequency	7,212	4.271	0.688	919	4.393	0.67	6,293	4.253	0.689
The importance of having fun in life	7,789	4.166	0.986	988	4.303	0.823	6,801	4.146	1.007

depression under the control of the intermediary variables M_i. At this time, the mediation effect was equal to the indirect effect, that is, the product of coefficients $\beta_2\delta$.

The ideas of mechanism analysis were as follows: First, equation (1) was estimated, and on the basis of significant of β_1, equations (5) and (6) were further estimated, among which M_i were the mediating factors concerned in this paper. If both β_2 and δ were significant, then the mediating effect was significant. If at least one of them was not significant, further Sobel test should be conducted for the cross term $\beta_2\delta$. If the Sobel Z statistic was significant, then the mediating effect exists. If not, the indirect effect was not significant.

RESULTS

Descriptive Statistics

Table 1 provided the descriptive statistics of the sample. In the full sample, participants had an average self-reported depression score of 13.818 (out of 32, s.d. = 4.525), and about 12.7% of respondents used mobile devices or computers to access the Internet. The sample had slightly more males (50.4%) than females, with the average age of participants being 68 years old. Most of the participants had lower than high school education (97.5%). About 48.4% of participants lived in urban areas. People registering in farm (30.1%) were considerably less numerous than non-farm. Most participants were married or in de facto relationships (81.2%).

Table 1 also provided the mean of variables for Internet users and the non-users groups. Among the Internet users, 35.2% of them used the internet for learning, 7.6% for work, 73.4% for social contact, 73.6% for entertainment, 23.7% for commercial activities. The results also showed that older persons who used the Internet were more likely to have lower self-reported depression scores (mean = 12.408, s.d. = 3.726) than the non-users group (mean = 14.023, s.d. = 4.594). Moreover, compared to the non-users group, participants who used the Internet were more likely to be younger (mean = 66, s.d. = 5.066), be male (60.3%), higherly educated (mean = 1.146, s.d. = 0.715), registering in non-farm (69.3%), married (88.8%), in an urban area (78.2%), and having more household savings (mean = 10.3, s.d. = 1.124).

The Relationship Between Internet Usage and the Depressive Symptoms of Older Adults

The ordinary least squares (OLS) and Ordered Probit regression results were presented in **Table 2**. Columns (1) and (2) showed the results of the OLS method. The difference in column (2) showed the result of controlling all other variables. Columns (3) and (4) showed the results of the Ordered Probit method, and column (4) controlled all other variables. Column (2), in **Table 2**, showed that participants who used the Internet compared with Internet non-welfare residents had significantly lower depression scores by 0.3053 ($p < 0.05$). Moreover, the results in all models showed negative coefficients and were statistically significant at the 5% level, suggesting that Internet use reduced the depressive

TABLE 2 | Results of the ordinary least square and ordered probit methods.

	OLS		Ordered Probit	
	(1)	(2)	(3)	(4)
Internet	−1.6150***	−0.3053**	−0.3723***	−0.0750**
	(0.0000)	(0.0345)	(0.0000)	(0.0474)
Age		−0.0122		−0.0037*
		(0.1572)		(0.0681)
Gender		−1.1232***		−0.2829***
		(0.0000)		(0.0000)
Education		−0.3965***		−0.0891***
		(0.0003)		(0.0006)
Hukou		−0.2310		−0.0718**
		(0.1112)		(0.0423)
Marriage		−1.6656***		−0.3725***
		(0.0000)		(0.0000)
Residence		−0.4855***		−0.1231***
		(0.0001)		(0.0000)
$\mathrm{ln}finc$		0.1687		0.0515
		(0.4844)		(0.3104)
$\mathrm{ln}finc^2$		−0.0425***		−0.0106***
		(0.0018)		(0.0004)
_cons	14.0229***	20.4235***		
	(0.0000)	(0.0000)		
Province dummies	No	Yes	No	Yes
N	7,801	7,617	7,801	7,617
r2_a	0.0140	0.1304		

****, **, and * indicate significance at 1, 5, and 10%, respectively. Standard errors are presented in parentheses.*

symptoms of older persons. However, the estimated effect might still be biased because Internet use was likely to be selected and endogenous with depression. These findings should be viewed alongside further robustness checks, as described below.

Apart from using the Internet, several sociodemographic variables affected older adults' depression. We found that men tend to have lower depression scores than women ($r = 1.123$, $p < 0.01$). However, age had no statistically significant effect on mental health. People with a higher level of education reported lower depression scores. The elderly who were non-farm were more likely to have lower depression scores. Furthermore, we found a statistically significant reduction in depression scores for married and de facto relationships and those who live in urban areas. Finally, the association between household savings and depression was found to be statistically significantly positive.

Impact of Frequency and Content of Internet Usage on the Depressive Symptoms of Older Adults

Regression results of the impact of frequency and content of Internet usage on older adults' depressive symptoms were reported in **Table 3**. All the results were estimated by OLS. As shown in column (1), the average effect of more frequent Internet use can statistically significantly reduced the depression score by 0.0573 ($p < 0.05$), suggesting that the more frequently older persons use the Internet, the lower their depression scores. As shown in columns (2) to (6) different types of Internet usage have different effects on older people. Using the Internet for social contact and entertainment statistically significantly reduced the depression scores of the older adults, namely, using the Internet for social contact reduced the depression score by 0.2586 ($p < 0.1$), using the Internet for entertainment reduced the depression score by 0.4106 ($p < 0.01$). However, using the Internet to learn, work, and business activities had no statistically significant effects.

Endogenous Problems

The 2SLS and CMP methods were employed to address potential endogeneity problems. The Internet penetration rate of the county was used as an instrumental variable for the individual's Internet usage. On the one hand, the laying of network infrastructure always has regional characteristics, and personal Internet usage tended to be related to the Internet penetration rate in counties. On the other hand, whether the network infrastructure was laid in a certain area was greatly affected by the economic level and environment of the area. Therefore, the Internet penetration rate was not related to residents' depression at the micro-individual level. We used the 2SLS and CMP methods in a two-stage process. First, we estimated the effect of the Internet penetration rate at the county level on Internet use. Second, we estimated the effect of Internet use on depression by regression (47). The estimation results were reported in **Table 4**.

As shown in **Table 4**, in the first stage regression of the 2SLS model and the CMP method, the Internet penetration rate of the county was statistically significantly positively correlated with Internet usage, meeting the dependency condition of the instrumental variables. Moreover, the endogeneity test parameter atanhrho_12 in the CMP estimation was statistically significant, also indicating that Internet usage was an endogenous independent variable.

Next, the second stage regression results of the 2SLS model showed that Internet usage still had a statistically significant and reduced effect on the depression symptoms of participants after correcting for possible endogenous bias and was statistically significant at the 1% level, suggesting a very reliable causality. The results from the CMP estimation were still negative but much less so. This further confirmed the reduced effect of Internet usage on the depression symptoms of the participants. Compared to other results in this study, 2SLS point estimates showed larger impacts of Internet use on depression symptoms, while the sign of impacts was unchanged. One possible reason was that the results of the 2SLS estimations were likely to be inconsistent when the regression model was specified as a linear form, but the dependent variable was a count or dichotomous variable. More generally, 2SLS estimates may be inconsistent because they reflected the linear local average treatment effect (LATE), not the average treatment effect (ATE) for the whole population. A Durbin–Wu–Hausman test was used to check the model's endogeneity, and the null hypothesis that all explanatory variables were exogenous cannot be strongly rejected (6.4938 [$p < 0.01$]). The endogeneity problem caused no statistically

TABLE 3 | Impact of internet use frequency and the kind of internet usage using OLS.

	(1)	(2)	(3)	(4)	(5)	(6)
Frequency	−0.0573**	−0.0134				
	(0.0293)	(0.9479)				
Learn		−0.0134				
		(0.9479)				
Work			−0.1094			
			(0.7938)			
Social contact				−0.2586*		
				(0.0974)		
Entertainment					−0.4106***	
					(0.0080)	
Commercial activity						−0.0532
						(0.8274)
Age	−0.0122	−0.0099	−0.0104	−0.0115	−0.0125	−0.0104
	(0.1573)	(0.2451)	(0.2235)	(0.1824)	(0.1455)	(0.2229)
Gender	−1.1251***	−1.1282***	−1.1248***	−1.1301***	−1.1239***	−1.1255***
	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)
Education	−0.3966***	−0.4253***	−0.4243***	−0.4043***	−0.3953***	−0.4237***
	(0.0003)	(0.0001)	(0.0001)	(0.0002)	(0.0003)	(0.0001)
Hukou	−0.2314	−0.2669*	−0.2679*	−0.2432*	−0.2244	−0.2664*
	(0.1092)	(0.0638)	(0.0618)	(0.0923)	(0.1205)	(0.0638)
Marriage	−1.6669***	−1.6644***	−1.6690***	−1.6654***	−1.6678***	−1.6690***
	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)
Residence	−0.4867***	−0.4972***	−0.4964***	−0.4912***	−0.4851***	−0.4958***
	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0001)	(0.0000)
ln*finc*	0.1711	0.1945	0.1935	0.1781	0.1709	0.1935
	(0.4802)	(0.4203)	(0.4221)	(0.4618)	(0.4806)	(0.4225)
$(\ln finc)^2$	−0.0426***	−0.0445***	−0.0444***	−0.0432***	−0.0425***	−0.0444***
	(0.0019)	(0.0011)	(0.0011)	(0.0016)	(0.0019)	(0.0011)
_cons	20.4054***	20.1238***	20.1503***	20.3096***	20.4425***	20.1623***
	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)
Province dummies	Yes	Yes	Yes	Yes	Yes	Yes
N	7,617	7,617	7,616	7,617	7,616	7,616
r2_a	0.1304	0.1300	0.1297	0.1302	0.1305	0.1297

****, **, and * indicate significance at 1, 5, and 10%, respectively. Standard errors are presented in parentheses.*

significant estimation bias in our analysis, and the main results were reliable. Overall, all regressions produced similar results, although the magnitudes and significances appeared to be slightly different.

Effects by Population Groups

Given that the impact of Internet usage on mental health was likely to have differential effects in terms of individual characteristics, the whole sample was divided into subsamples according to different criteria, with two subsamples based on age (under 70 years old, or above), two subsamples based on sex (male or female), two subsamples based on residence (urban or rural), and three subsamples based on education level (illiteracy, high school and below, or college and higher). The CMP was conducted separately for these subgroups. **Table 5** displayed the estimates of the population groups.

As shown in **Table 5**, Internet usage had a heterogeneous effect on mental health among older people based on age group. Among those aged 70 or below, there was a statistically significantly lower depression score ($r = -0.2938$, $p < 0.1$). Conversely, there were no statistically significant effects for participants above 70 years, and the effects were much smaller ($r = -0.1627$, $p > 0.1$). In terms of sex, Internet use had a statistically significant negative impact on self-reported depression scores for women ($r = -0.4455$, $p < 0.05$) but not for men ($r = -0.2090$, $p > 0.1$). The positive effects of Internet usage on mental health vary by residential area. Participants in rural areas showed statistically significant lower depression scores if they used the Internet. However, for those in urban areas, the effect was much smaller.

The effects of Internet usage on depressive symptoms of old adults varied according to educational level. The effect of Internet usage on depressive symptoms was only statistically significant in the middle and low education level groups. Self-reported depression scores of older people with an education level of high school or below were lower for the Internet usage group than for the non-usage group. Moreover, the effect of Internet usage on depressive symptoms was much larger for illiterate participants. However, for those with a college education or higher, the coefficients of CMP estimation were statistically insignificant, indicating that the depressive symptoms of those with higher education would not be affectedif they used the Internet.

TABLE 4 | Results Estimated by the 2SLS and CMP Methods.

	2SLS		CMP	
	Stage I	**Stage II**	**Stage I**	**Stage II**
Internet		−2.9012***		−0.3774***
		(1.0356)		(0.1139)
Internet penetration rate of the	0.4584***		3.9455***	
county level	(0.0367)		(0.1557)	
DWH	6.4938			
atanhrho_12			0.1745***	
			(0.0632)	
Covariates	Yes	Yes	No	Yes
Province dummies	Yes	Yes	No	Yes
N	7,617		7,617	

****, **, and * indicate significance at 1, 5, and 10%, respectively. Standard errors are presented in parentheses. DWH is the estimated parameter of Durbin–Wu–Hausman test. The atanhro_12 is a parameter in the CMP model. If it is different from zero, then there are unobserved factors simultaneously affecting the dependent variable and main independent variable, suggesting the main independent variable is endogenous.*

Intermediary Mechanism

The aforementioned literature analysis found that the effect of Internet use on depression is mainly through two aspects: first, Internet use increased the connection between older adults and society, increasing social support. Second, increased entertainment can be obtained using the Internet, which would enrich the lives of older adults, reducing the depression of the elderly. Therefore, we selected the average frequency of contact with children and the self-rated importance of life pleasure as the mediating variables to analyse the mechanism of the impact of Internet use on the depressive symptoms of the elderly.

Results were reported in **Table 6**. Models 1 and 3 were the regression results of the intermediary variables used by the Internet, and models 2 and 4 were the regression results of the benchmark model after adding the intermediary variables. As

TABLE 5 | Results of the subgroups analysis (age, sex, residence).

Variables	**Age**		**Sex**		**Residence**	
	<70	**> =70**	**Male**	**Female**	**Urban**	**Rural**
Internet	−0.2938*	−0.1627	−0.2090	−0.4455**	−0.3782**	−0.7812***
	(0.1624)	(0.2484)	(0.1977)	(0.1761)	(0.1589)	(0.2205)
atanhrho_12	0.1328	0.1031	0.1161	0.2035**	0.1826*	0.3981***
	(0.0937)	(0.1372)	(0.1152)	(0.0994)	(0.0961)	(0.1063)
Results of First Stage—use Internet or not						
Internet penetration rate of the county level	2.5408***	2.5749***	2.5479***	2.5195***	2.6401***	1.8944***
	(0.2214)	(0.3691)	(0.2524)	(0.2878)	(0.2287)	(0.3598)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes
N	4,921	2,696	3,839	3,778	3,678	3,939

Variables			**Education**	
Results of the subgroups analysis (education)				
		Illiteracy	High school or less	College or more
Internet		−0.7993*	−0.3952**	−0.6619
	(0.4207)	(0.1554)	(0.5143)	
atanhrho_12		0.3878**	0.1822**	0.4735
		(0.1814)	(0.0904)	(0.3051)
Results of First Stage—use Internet or not				
Internet penetration rate of the county level		1.8105***	2.5785***	2.5558***
		(0.5212)	(0.2131)	(0.9065)
Covariates		Yes	Yes	Yes
N		2,906	4,524	187

****, **, and * indicate significance at 1, 5, and 10%, respectively. Standard errors are presented in parentheses.*

TABLE 6 | Mediating effect of children contact frequency and life fun.

	(1)	(2)	(3)	(4)
	Contact frequency	**Depression**	**Life fun**	**Depression**
Internet	0.5565***	−0.1843	0.0772**	−0.2386*
	(0.0000)	(0.2138)	(0.0205)	(0.0927)
Contact frequency		−0.1372***		
		(0.0000)		
Life fun				−0.9273***
				(0.0000)
Covariates	Yes	Yes	Yes	Yes
Province dummy	Yes	Yes	Yes	Yes
N	7,127	7,127	7,605	7,605
r2_a	0.1361	0.1372	0.0321	0.1698

****, **, and * indicate significance at 1, 5, and 10%, respectively. Standard errors are presented in parentheses.*

shown in **Table 6**, Internet use statistically significantly increased the frequency of children's contact ($r = 0.5565$, $p < 0.01$), increased the importance of the elderly's joy in life ($r = 0.0772$, $p < 0.05$), and statistically significantly reduced the depression scores of the older people through the two.

DISCUSSION

Most older adults in our sample did not use the Internet (87.3%). Although not being able to use the Internet was currently the norm among the older Chinese, rates of Internet users were rapidly increasing. Younger generations have a much greater chance of being Internet users. Demographics indicated that Internet users had a higher standard of living, tended to be younger, higher educated, registering in non-farm, married, and in urban areas. These results were consistent with previous research highlighting the relationship between socioeconomic status and Internet use (49–51).

Examination of the self-reported depression scores for Internet users and non-users provided support for the hypothesis that using the Internet reduced depressive symptoms older adults. Internet users experienced lower levels of depressive symptoms. These effects were significant after controlling for demographic variables, including economic standards of living, and after overcoming endogenous problems. These results supported previous findings linking Internet use to better health and well-being (4, 17, 52). Moreover, the frequency and kinds of Internet usage had an important impact on older adults' depressive symptoms. The more frequently older persons use the Internet, the lower their depression scores. Using the Internet for social contact and entertainment reduced the depression scores of the older adults, while using the Internet to learn, work, and business activities don't.

Furthermore, different impact emerged among Internet users and non-users based on demographic variables. Only the younger group of older adults had statistically significantly lower depression scores. It was relatively easy for the younger group of older adults to use the Internet. Therefore, they had access to various kinds of information through more frequent use and thus maintained a good connection with social affairs. However, older adults above 70 years were more likely to focus on reconciling with themselves and less likely to be interested in the outside world (53, 54). Access to the Internet was more challenging for those older adults (49, 55–60), and their enthusiasm waslacking (61, 62). Moreover, the enhancement of their learning ability and social participation through Internet use was relatively limited. Thus, the benefits of reducing depression were correspondingly limited. Further, the reducing depression effect was more apparent in older women than in older men when using the Internet. This was possibly because women were more likely to be happy from social activities. The Internet made it easier to keep in touch with friends and family. Additionally, lower depression scores were found for the lower education group and the illiterate group who used the Internet, whereas no significant differences were found for the high education level group. The variance may be attributed to the fact that people with higher education levels tend to have more social capital in the first place (63). However, for those with lower education or who for those who were illiterate, the Internet mainly provided a way to explore the world and social interaction.

The relief of depression when using the Internet was more obvious among rural residents than among urban residents. In China, this was because the Internet in urban areas developed earlier and was matured in urban. For urban residents, the Internet may be commonplace. The development and popularization of the Internet started late in rural areas and was now in a period of rapid growth, making it still a novelty. For rural residents, the mass of information, instant social media, and convenience of e-commerce provided a stronger sense of accomplishment and satisfaction compared with urban Internet users. Therefore, it was necessary to further strengthen the construction of Internet infrastructure in rural areas and make Internet use more convenient for older adults.

Furthermore, Internet use reduced the depression scores of the elderly by increasing the frequency of connection with their children and importance of their enjoyment of life. This was consistent with the findings of Cotten et al. (17), Braun (64), and Benvenuti et al. (15). Internet use helped older adults to maintain family ties and obtain more emotional support from family and friends. It also opened the eyes of the older person so that they can learn about and have a more interesting life.

Since depressive symptoms have a great impact on health in old age, we would like to propose relevant interventions measures to reduce depressive symptoms of the older adults (65, 66). Firstly, for older people themselves, it was important to share their interests and enrich their entertainment life to improve their sense of life and well-being (67), which can improve their gastrointestinal, cardiovascular and cerebrovascular discomforts and alleviate somatic discomfort (68). It can also expand the scope of social activities for older people and promote them to face life positively. Secondly, in terms of family and community, which were closely related to the lives of older people, social networks can alleviate depression in older people, especially support from family (69), and children should give older people more companionship. High frequency and quality interactions were beneficial for older people to receive material and spiritual support from family members (70). Community health service and activities for the elderly should be promoted (71). It was also necessary to establish electronic health records for older people and to realize networked management of family and community healthcare institutions, such as health education, medication and psychological counseling (72). Finally, on a social level, good social relationships affected older people's psychological well-being in terms of positive emotions such as a sense of belonging and security (73), encouraging older people to increase their contact with society and actively engage with people to address psychosocial barriers and improve emotional and physical well-being (74), which was consistent with other scholars (75, 76). The risk of depression can be reduced by encouraging older people to take an active part in voluntary activities to enhance their sense of worth and identity (77). In addition, the state should pay attention to older people's job satisfaction while delaying the retirement age, and choose satisfying jobs that take into account their own interests to further reduce the risk of depression.

CONCLUSION

In general, older people in China who used the Internet have lower depression scores than those who do not. Demographic differences in Internet use highlighted that policy should pay particular attention to the accessibility of Internet use for the vulnerable group, so as to achieve a healthy China strategy. First, accelerate the construction of Internet infrastructure and further improve the coverage of broadband networks. There is a need to improve the accessibility of Internet use for older people, especially who in rural areas. The development of the Internet in urban and rural areas is not balanced due to the gap of urban-rural development. Therefore, to improve the usage rate of the Internet in rural older people, we should realize the same network and speed in urban and rural areas and accelerate the development of the Internet in rural areas. Second, improve the attitude to Internet of older people, by cultivating their ability, reducing the sense of powerlessness. It is necessary to conduct Internet use skills training to help them become familiar and master the use of various applications, such as health management, leisure, entertainment, and learning. This will eliminate the technical threshold of Internet use, enrich the content of Internet use of older people, and improve their sense of happiness and attainment. Finally, standardize the Internet use content and improve the experience of Internet use of older people. Relevant departments should strengthen the review and supervision of relevant contents during the use of the Internet by older people, use big data to more accurately understand their potential needs. In addition, actively establish a community network environment focusing on entertainment and leisure, social chat and learning, using network technology to improve the online social participation ability and reduce the depression and loneliness of older people.

This study has some limitations. Firstly, the mediating role of social participation of all kinds has not been fully explored. Second, the amount of Internet usage time may also be relevant to the depression outcome (17), but we did not address this specific issue due to data limitation. Moreover, the sampling weights could be used in further analysis. Further examinations of the interrelationships between Internet use and depressive symptoms are encouraged in future researches.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: http://www.isss.pku.edu.cn/cfps.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CFPS was undertaken according to the guidelines laid down in the Declaration of Helsinki and all participants signed an informed consent form. Human participants were approved by Peking University Biomedical Ethics Committee (IRB00001052-14010-exemption). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SZ and H-lY conceived this research. H-lY, Z-yL, and LX were responsible for the methodology. S-qZ conducted software analyses. SZ and Y-yW conducted necessary validations. L-lT conducted a formal analysis and managed the investigation. SZ and S-qZ gathered resources, curated all data, wrote/prepared the original draft, and were responsible for project administration. LX and Z-yL reviewed, edited the manuscript, and were responsible for visualization. H-lY supervised the project and acquired funding. All authors contributed to the article and approved the submitted version.

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Developing a Predictive Model for Depressive Disorders Using Stacking Ensemble and Naive Bayesian Nomogram: Using Samples Representing South Korea

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This study provided baseline data for preventing depression in female older adults living alone by understanding the degree of their depressive disorders and factors affecting these depressive disorders by analyzing epidemiological survey data representing South Koreans. To achieve the study objective, this study explored the main risk factors of depressive disorders using the stacking ensemble machine technique. Moreover, this study developed a nomogram that could help primary physicians easily interpret high-risk groups of depressive disorders in primary care settings based on the major predictors derived from machine learning. This study analyzed 582 female older adults (≥60 years old) living alone. The depressive disorder, a target variable, was measured using the Korean version of Patient Health Questionnaire-9. This study developed five single predictive models (GBM, Random Forest, Adaboost, SVM, XGBoost) and six stacking ensemble models (GBM + Bayesian regression, RandomForest + Bayesian regression, Adaboost + Bayesian regression, SVM + Bayesian regression, XGBoost + Bayesian regression, GBM + RandomForest + Adaboost + SVM + XGBoost + Bayesian regression) to predict depressive disorders. The naive Bayesian nomogram confirmed that stress perception, subjective health, n-6 fatty acid, n-3 fatty acid, mean hours of sitting per day, and mean daily sleep hours were six major variables related to the depressive disorders of female older adults living alone. Based on the results of this study, it is required to evaluate the multiple risk factors for depression including various measurable factors such as social support.

Keywords: naive Bayesian nomogram, extreme gradient boosting (XGBoost), stacking ensemble, depressive disorders, multiple risk factors, synthetic minority oversampling technique (SMOTE)

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INTRODUCTION

South Korea has entered the aged society in 2017 at the fastest rate in the world (1). If this trend continues, it is predicted to enter the super-aged society in 2026 (1). Particularly, the number of older adults living alone is rapidly increasing in South Korea. Statistics Korea (2) reported that the increase in the female older adult population, the increased number of the older old (75 years or older), and the increase in the older adults living alone accounted for the increase in the older adults in South Korea over the past 10 years. Over the past 30 years, the proportion of older adults supported by their families while living with adult children or spouses has decreased but the proportion of older adults living alone has increased, which changed the composition of older adult households (2). The proportion of older adults living alone tended to increase (2). The number of older adults living alone was 190,000 in 1990 and increased to 1.35 million in 2017, a seven-fold increase (2). Due to the favor of the nuclear family as moving into the twenty-first century, the function of supporting older adults has been weakened and more older adults want to live in a space independent from their children in South Korea (3). As a result, it is expected that the number of older adults living alone in South Korea will continue to increase in the future.

The increase of older adults living alone draws attention because most of them are socioeconomically vulnerable (4) and 85% of them are women (2). As of 2020, the life expectancy of South Korean is 80.3 years for men and 86.3 years for women (5). As women are expected to live 6 years longer than men, it is expected that the number of female older adults living alone will increase further (5). Another problem associated with the increased number of older adults living alone is the increase in depressive disorders. The national survey by the Korea Institute for Health and Social Affairs (6) showed that 21.1% of older adults (≥65 years) had depressive symptoms. The Health Insurance Review and Assessment Service (7) also reported that 31.2% of the entire patients with depressive disorders (796,364 patients) were older adults (≥65 years). Particularly, older adults living alone are more likely to be more vulnerable to depressive disorders than those living with their families (4). Therefore, it is necessary to screen high-risk groups by identifying factors related to the depressive disorder of older adults living alone based on these results for preventing the occurrence of depressive disorders of older adults living alone.

The results of previous studies (8–11) argued that female older adults living alone tended to be psychologically atrophied and depressed because they became less socially active due to an increase in chronic degenerative diseases (11). It was also reported that female older adults living alone were more likely to be older, struggle against a disease, be less educated, and have more financial difficulties than male older adults living alone (8). These socioeconomic, personal, and environmental characteristics of female older adults living alone suggested that factors related to their depressive disorders were different from older adults living with their families. Nevertheless, most previous studies that have identified the factors related to the depressive disorders of older adults have focused on older adults living with their families (12) and only a few studies have tried to predict the depressive disorders of female older adults.

For the past 10 years, studies in the medical field have continuously tried to identify risk factors for depressive disorders using data mining techniques as well as traditional statistical analysis models (e.g., regression model) (13). Particularly, recent studies (14, 15) have used the stacking ensemble technique that predicts y-class by integrating multiple individual machine learning techniques to overcome the limitations of a single machine learning technique. It is known that stacking ensemble has higher accuracy than a single learning machine technique because it predicts again using a meta model based on the data predicted by individual algorithms (14). However, it was also reported that the prediction of a stacking ensemble model was lower than that of a single machine learning model depending on the type of algorithm of the base model and meta model (16). Consequently, it is necessary to conduct more stacking ensemble based machine learning studies to find the best-performing ensemble based predictive model for predicting depressive disorders.

When developing a model for predicting a disease using machine learning, it is important that medical personnel can understand the results derived from machine learning, in addition to predictive performance such as accuracy. Therefore, developing eXplainable Artificial Intelligence (X-AI) has become an important issue in machine learning research using medical data in recent years. This study enhanced analysis power by applying a naive Bayesian nomogram to the results derived from machine learning and tried to resolve the intrinsic issue of ensemble-based machine learning's black-box approach (the issue of difficulty in interpreting the results while increasing the accuracy of prediction).

When composing a naive Bayesian nomogram using medical data, it is assumed that all features significantly affect y-class (label). However, not all investigated features have a meaningful effect on y-class. For example, a feature may be barely related to y-class and it may act as noise in some times to make it harder to predict y-class. Therefore, it is very important to select features used in the model when constructing a nomogram. This study developed an ensemble-based predictive model and selected variables to be entered into the nomogram based on the importance of the variables derived from the predictive model as a method of choosing features constituting the naive Bayesian nomogram. As far as we are aware, this is the first study using a stacking ensemble machine technique for selecting variables to be included in the nomogram.

This study provided baseline data for preventing depression in female older adults living alone by understanding the degree of their depressive disorders and factors affecting these depressive disorders by analyzing epidemiological survey data representing South Koreans. To achieve the study objective, this study explored the main risk factors of depressive disorders using the stacking ensemble machine technique. Moreover, this study developed a nomogram that could help primary physicians easily interpret high-risk groups of depressive disorders in primary care settings based on the major predictors derived from machine learning.

METHODS

Data Source

This study analyzed the raw data of the 7th National Health and Nutrition Examination Survey, conducted from 2016 to 2018 under the supervision of the Korea Centers for Disease Control and Prevention. This study used secondary data. The National Health and Nutrition Examination Survey is a national epidemiological data supervised by the Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention. It was carried out after receiving written consent from all participants and receiving approval (No.1041107-201806-HR-011-01) from the Institutional Review Board of the Korea Centers for Disease Control and Prevention [please refer to (16) for detailed sampling and survey methods]. In summary, the 7th National Health and Nutrition Examination Survey targeted 24,269 people from 13,248 households, and the survey completion rate (participation rate) was 76.7% ($n = 18{,}614$). The health survey of the National Health and Nutrition Examination Survey consisted of medical history, activity restrictions and quality of life, physical activity, and health behavior. It was conducted by using interviews and self-interviewing method. The physical examination was composed of physical measurement, blood pressure measurement, and blood test. During the survey period, an examination team consisting of doctors and nurses visited the target area using a mobile physical examination vehicle and conducted a 1:1 checkup and health survey. A nutritional survey was performed by having a nutrition surveyor visit the home of the survey subject and conduct an interview using a food intake frequency survey method. This study selected 634 female older adults ($\geq$60 years old) who completed health surveys, blood pressure measurements, physical measurements, and blood tests as primary analysis subjects. Afterward, this study excluded 61 participants who did not respond (missed) to the Korean version of Patient Health Questionnaire-9 (PHQ-9) (17), a standardized depression screening test, and 582 patients were finally analyzed.

Measurement of Variables

The depressive disorder, a target variable, was measured using the Korean version of PHQ-9 (17). PHQ-9 is a standardized depression screening test, developed by Spitzer et al. (18), and has been used widely to diagnose mental health in primary health care centers. PHQ-9 consists of nine items corresponding to the diagnostic criteria for major depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (i.e., changes in sleep in the last 2 weeks, changes in appetite, anhedonia, feelings of guilt or worthlessness, feeling down, depressed, fatigued, or restlessness, lowered concentration, and frequency of having suicidal thoughts). It is assessed on a 4-point scale ("never," "several days," "more than a week," or "almost every day"), and the sum of scores ranges from 0 to 27. A higher score means a severer depressive disorder. Depressive disorders were defined as 10 or higher PHQ-9 points based on the results of previous studies (19, 20). Choi et al. (21) reported that the specificity of PHQ-9 was 89.9% and the sensitivity of it was 81.1%. In addition, the reliability of PHQ-9 (Cronbach's α) in this study was 0.89.

Developing a Model to Predict the Depressive Disorders of Female Older Adults Living Alone

The model for predicting the depressive disorders of female older adults living alone was composed of exploring the best predictive factors for depressive disorders using stacking ensemble (step 1) and developing a naive Bayesian nomogram that could predict high-risk groups of depressive disorders based on major variables derived from machine learning (step 2).

Exploring the Best Predictive Factors for Depressive Disorders Using Stacking Ensemble: Base Model

This study explored the key variables of depressive disorders in female older adults living alone using the stacking ensemble technique. A number of studies (14, 15, 22) have reported that the stacking ensemble model shows excellent accuracy because it compensates for the overfitting possibility, a disadvantage of a single predictive model. In other words, the goal of the stacking ensemble is to improve generalization capacity, and it has been widely used for classifying and developing predictive models using machine learning. The stacking ensemble creates a new model by combining various different machine learning models as if stacking them in layers (14). It improves the performance of the final model by taking the strengths of each model and complementing the weaknesses of each model while going through two stages [base model (single predictive model and meta model)] (14). The concept of a stacking ensemble is presented in **Figure 1**.

This stacking ensemble model used GBM, Adaboost, XGBoost, SVM, and random forest as the base model to explore the key factors of depressive disorders in female older adults living alone.

GBM is a type of boosting. Boosting refers to a method to make a more accurate model by gradually improving inaccurate models (23). It creates a model, even if its accuracy is low. Then, it makes up for the weakness of the previous model by applying a large weight to a measurement value with a large error and a small weight to a measurement value with a small error. In this process, it is important to choose an appropriate weight to be applying by measuring the prediction error for each measurement value. GBM determines the weight by using the gradient descent method. If F(x) is assumed as the predicted value of a weak model, the prediction error of each variable can be expressed as the error function L in Equation (1).

$$L\left(\boldsymbol{y},\, F\left(\mathbf{X}\right)\right) = \sum_{i=1}^{N} \left(y_i - F\left(\boldsymbol{x}_\mathbf{i}\right)\right)^2,\ \forall\, i \in N \qquad (1)$$

$$\widehat{F\left(\mathbf{X}\right)} = \underset{F}{\operatorname{arg}min}\, L(F\left(\mathbf{X}\right)) \qquad (2)$$

When the value of Equation (1) shows in Equation (2) is improved $k = 1, 2, \ldots, M$ times toward the direction of decreasing the prediction error value, the differential slope is defined as the improvement direction of F(x). In the k-th improvement, the direction of the differential slope ($g_k(x)$) is defined in Equation (3), and the magnitude of the slope (ρ_k) is defined in Equation (4).

$$g_k\left(\boldsymbol{x}_\mathbf{i}\right) = \left[\frac{\partial L(y_i, F\left(\boldsymbol{x}_\mathbf{i}\right))}{\partial F(\boldsymbol{x}_\mathbf{i})}|x\right]_{F(\boldsymbol{x}_\mathbf{i})=F_{k-1(\boldsymbol{x}_\mathbf{i})}},\ \forall\, i \in N,\ \forall\, k \in M \qquad (3)$$

$$\rho_k = \underset{\rho}{\operatorname{arg}min}\, L(F\left(\boldsymbol{x}_\mathbf{i}\right)_{k-1} - \rho g_k(\boldsymbol{x}_\mathbf{i})),\ \forall\, i \in N,\ \forall\, k \in M \qquad (4)$$

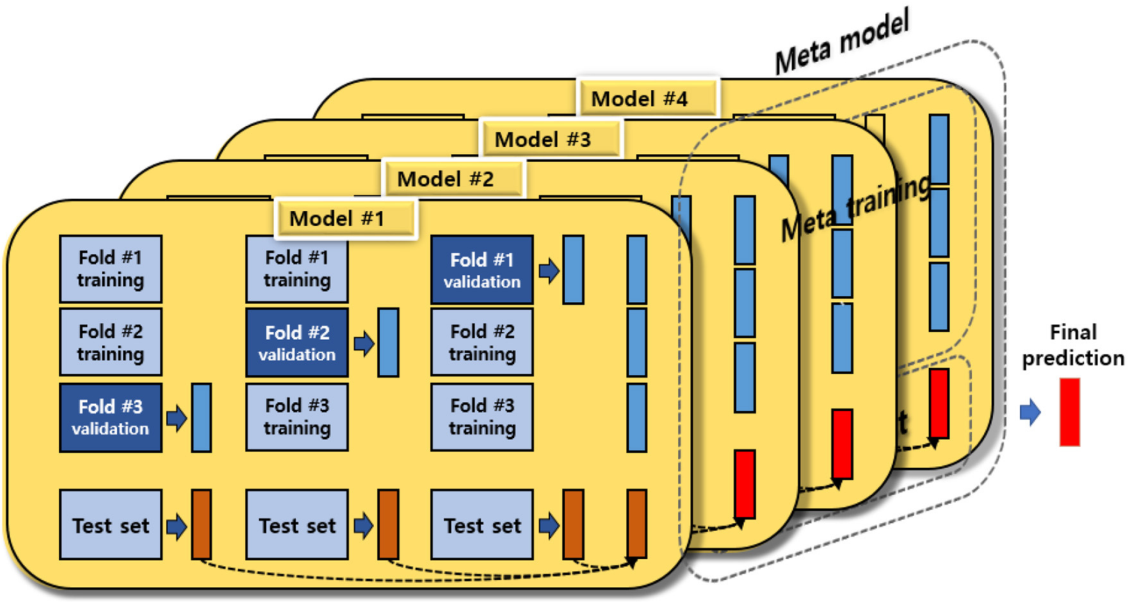

FIGURE 1 | The concept of a stacking ensemble.

If the multiplication of $g_k(x)$ and ρ_k is defined as an improvement amount, the new F(x) is improved according to Equations (5)–(7). The model is improved M times according to this algorithm to construct the final model.

$$f_k\left(\mathbf{x_i}\right) = \rho_k g_k\left(\mathbf{x_i}\right), \forall\, i \in N, \forall\, k \in M \tag{5}$$

$$F_{M-1}\left(\mathbf{x_i}\right) = \sum_{k=0}^{M-1} f_k\left(\mathbf{x_i}\right), \forall\, i \in N \tag{6}$$

$$F_M\left(\mathbf{x_i}\right) = F_{M-1}\left(\mathbf{x_i}\right) + f_M\left(x_i\right), \forall\, i \in N \tag{7}$$

The AdaBoost algorithm is to create a strong classifier by combining weak classifiers. Here, a weak classifier refers to a classifier that has slightly better predictive power than random prediction, and a strong classifier is a classifier that has close to optimal predictive power.

When the AdaBoost algorithm starts, all data have the same probability to be extracted at the beginning of learning. However, it increases the extraction probability of data that are poorly classified and decreases the extraction probability of data that are well-classified. It reiterates learning while adjusting the extraction probability of data. This is explained in Equation (8).

$$D = \left\{\left(\mathbf{x_1}, y_1\right), \left(\mathbf{x_2}, y_2\right), \ldots, \left(\mathbf{x_n}, y_n\right)\right\}, \quad \mathbf{x_i} \in R^k, y_i \in \{-1, +1\} \tag{8}$$

Let's assume that Equation (8) is a set of training data, and the extraction probability of each dataset is $w_1, w_2, \ldots, w_n$. Initially, the probability of extracting each dataset is the same. That is, $w_i^{(1)} = \frac{1}{n}, i = 1, \ldots, n$, where the number of bootstrap samples is M, and the classifier derived from each bootstrap sample group is $C_1, C_2, \ldots, and\ C_M$. Then, the miss-classification error (ϵ_m) of the classifier C_m is calculated as in Equation (9).

$$\epsilon_m = \frac{\sum_{i=1}^n w_i^{(m)} I(C_m(\mathbf{x_i}) \neq y_i)}{\sum_{i=1}^n w_i}, \quad m = 1, \ldots, M \tag{9}$$

Here, ϵ_m is a misclassification rate using the extraction probability of data for each data misclassification by the classifier C_m as a weight. The confidence of the classifier C_m (α_m) is determined as in Equation (10).

$$\alpha_m = \frac{1}{2}\ln\frac{1-\epsilon_m}{\epsilon_m}, \quad m = 1, \ldots, M, \tag{10}$$

When $w_i^{(m)}$ is the extraction probability of the mth bootstrap sample, the extraction probability of the (m+1)th bootstrap sample ($w_i^{(m+1)}$) is calculated as in Equation (11).

$$w_i^{(m+1)} = \frac{w_i^{(m)} \exp(-\alpha_m y_i C_m(x_i))}{Z_m} \tag{11}$$

Here, Z_m is a normalization constant and satisfies Equation (12).

$$Z_m = \sum_{i=1}^n w_i^{(m)} \exp\left(-\alpha_m y_i C_m\left(x_i\right)\right) \tag{12}$$

The final classifier ($C^*(\boldsymbol{x}')$) created by combining the M classifiers generated for the new test data ($\mathbf{x_i}' \in R^k$) is as Equation (13).

$$C^*(\boldsymbol{x}') = sign\left(\sum_{m=1}^M \alpha_m C_m(\boldsymbol{x}')\right) \tag{13}$$

Here,

$C^{*}(\boldsymbol{x}^{'})$ is a weighted bound formula, obtained by reflecting weights as much as the importance of each classifier (α_m).

XGBoost is an advanced version of gradient boosting. The main goal is to increase speed and the efficiency of competition. XGBoost basically uses a technique called boosting, which increases accuracy by binding weak classifiers. At this time, XGBoost tends to fill in the missing values and refers to extreme slope improvement.

The probability of predicting Z correctly for learner A is as follows.

$$Z = A(x) + Error \qquad (A)$$

When it is assumed that there is learner B that can classify "Error" precisely (Error > Error 2),

$$Error = B(x) + \ Error\ 2 \qquad (B)$$

When it is assumed that there is learner C that can classify "Error 2" more precisely (Error 2 > Error 3),

$$Error\ 2 = C(x) + \ Error\ 3 \qquad (C)$$

When (B) and (C) are applied to (A), Equation (14) is derived.

$$Z = A(x) + B(x) + C(x) + Error\ 3 \tag{14}$$

Although the accuracy of it is higher than when learner A is used alone, classifiers A, B, and C have different performances. Therefore, since they all have the same ratio ($1^{*}A + 1^{*}B + 1^{*}C$), it may increase errors by interfering with random x. In this case, weights are applied in front of each model, and the optimal weight is found by using machine learning, which is presented in Equation (15). The model of Equation (15) becomes a classifier with better performance than the model of Equation (14) (Error 3 > Error 4).

$$Z = \alpha^{*}A(x) + \beta^{*}B(x) + \gamma^{*}C(x) + Error\ 4 \tag{15}$$

SVM predicts using a supporting vector that supports decision-making. The strength of SVM is that it can find a divisional plane even if data are overlapped by expanding the dimension of predictor variables using various kernel functions, unlike linear regression. Moreover, it tends to overfit less because it uses only minimum data supporting decision-making. SVM models in a direction that minimizes the sum of reciprocals of the distance between prediction errors, divisional planes, and supporting vectors.

If the predictor variable is $x_{\mathbf{i}} (i = 1, 2, 3, \cdots, N)$, when $y_i\ (i = 1, 2, 3, \cdots, N)$ is given for each data, the coefficient β is obtained when Equation (16) is minimal.

$$\min C \sum_{i=1}^{N} \left(\xi_i + \hat{\xi}_i \right) + \frac{1}{2} \| \beta \|^2 \tag{16}$$

ϵ_i in the right term of Equations (17) and (18) indicates the tolerance range. If the difference between the actual value and the predicted value is less than ϵ_i, the error value is 0, and if it is greater than ϵ_i, the error value is imposed. Slack variables, ξ_i and $\hat{\xi}_i$, indicate how far the predicted value deviates from the sum of the measurement and the error tolerance (ϵ_i), and has a value greater than 0 depending on Equations (19) and (20). The right term in Equation (16) maximizes the distance between the coefficient β and the support vector by minimizing the magnitude of the coefficient.

$$s.t.\ t_i \le F(\boldsymbol{x}_{\mathbf{i}}) + \epsilon_i + \xi_i,\ \forall\ i \in N \tag{17}$$

$$t_i \ge F(\boldsymbol{x}_{\mathbf{i}}) + \epsilon_i + \hat{\xi}_i,\ \forall\ i \in N \tag{18}$$

$$\xi_i \ge 0,\ \forall\ i \in N \tag{19}$$

$$\hat{\xi}_i \ge 0,\ \forall\ i \in N \tag{20}$$

Random forest is a supervised learning model (24). It consists of a number of decision trees capable of both classification and regression (24). It is designed to overcome the overfitting problem of decision trees (24). It reiterates random sampling of predictors and observations to create multiple decision trees. After obtaining prediction categories from numerous decision trees, it determines the final category prediction using a majority vote method. It can iteratively make independent decision trees by giving randomness to the decision tree formation, and it is possible to reduce prediction error using this method. A bootstrapping technique is used for selecting predictors and observations randomly.

Meta Model

This study used Bayesian regression for the meta model. The regression algorithm increases the reliability of the base model while maximizing the stability of the model (25). Previous studies (25, 26) also reported that the predictive performance such as accuracy was improved compared to a single predictive model, when regression was used for the meta model. Therefore, this study used the regression algorithm for the meta model. Finally, this study developed five single predictive models (GBM, RandomForest, Adaboost, SVM, XGBoost) and six stacking ensemble models (GBM + Bayesian regression, RandomForest + Bayesian regression, Adaboost + Bayesian regression, SVM + Bayesian regression, XGBoost + Bayesian regression, GBM + RandomForest + Adaboost + SVM + XGBoost + Bayesian regression) to predict depressive disorders in female older adults living alone (**Figure 2**).

Testing the Predictive Performance of Stacking Ensemble Model

Since the number of people with a disease is smaller than that of those without a disease, a binary classifier is generally likely to cause a class imbalance issue. This study also found that the ratio of older adults without depression to those with depression was 87.5:12.5 and showed an imbalance problem. Therefore, this study resolved the imbalance issue of binary datasets using the synthetic minority oversampling technique (SMOTE) method. SMOTE is an oversampling technique that generates synthesis data using the k-nearest neighbor algorithm. In other words, it means a method of generating new data between a near minority class and random minority class

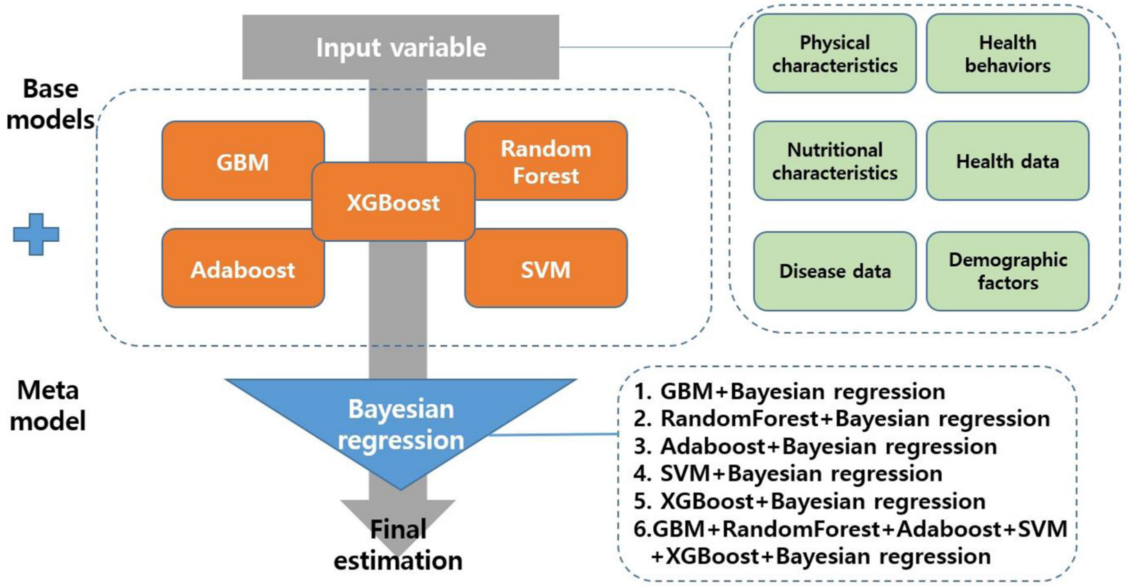

FIGURE 2 | Process flow diagram for depressive disorders of female older adults living alone.

TABLE 1 | The procedure for performing SMOTE.

SMOTE algorithm	
Step 1	It calculates K-nearest neighbors for x_i, a sample, belonging to a minority class.
Step 2	It randomly selects one neighbor ($\hat{x}_i$) among the K-nearest neighbors, obtained in step 1, to calculate the Euclidian distance from the sample x_i.
Step 3	It generates a new sample (x_{new}) by multiplying the Euclidian distance obtained in step 2 with a random value between 0 and 1 and then adding it to the original sample. $x_{new} = x_i + (\hat{x}_i - x_i) \times \delta, \quad \delta \in [0,\ 1]$
Step 4	The new sample (x_{new}) generated in step 3 is added to the training data.

data. SMOTE first selects random data from a minority class and then sets a k-nearest neighbor in the next data. In the next step, synthesis data are generated between the random data and the random k-nearest neighbor. This procedure is repeated until the minority class and the majority class have the same ratio. The procedure for performing SMOTE is presented in **Table 1**.

The predictive performance of the developed 11 machine learning models was tested using the leave-one-out cross-validation (LOOCV) method. LOOCV is a validation method that complements the shortcoming of the validation set approach, which is likely to produce different results when a different random set is drawn. LOOCV produced models N times. When creating each model, only one sample was excluded and the test set performance of it was calculated using the excluded samples. Afterward, it calculates the mean of N performance (**Figure 3**). When each sample is used as a test set, the mean squared error (MSE) of ith sample is MSE$_i$: $MSE_i = (y_2 - \hat{y}_2)^2$ (Equation 21).

$$CV_{(n)} = \frac{1}{n}\sum_{i=1}^{n} MSE_i \tag{21}$$

This study used F1-score, accuracy, recall, and precision as indices to evaluate predictive performance. The equation of each evaluation index is presented below.

True positive (TP) = It is actually a depressive disorder r, and the predicted outcome is a depressive disorder.
False negative = It is actually a depressive disorder, but the predicted outcome is normal.
False positive = It is actually normal, and the predicted outcome is a depressive disorder.
True negative = It is actually normal, and the predicted outcome is normal.
Recall = TP/(TP + FN)
Precision = TP/TP + FP
Accuracy = TP + TN/TP + TN + FP + FN
F1-score = 2*(precison*recall)/(precision+recall)

This study assumed that the model with the highest F1-score was the model with the best accuracy in predicting depressive disorders of female older adults living alone. If the F1-scores of two models are the same, the model with the higher recall was defined as a better model.

Developing Nomogram Based on Naive Bayesian Technique

This study developed a naive Bayesian nomogram with reference to Možina et al. (27) so that clinicians could easily interpret

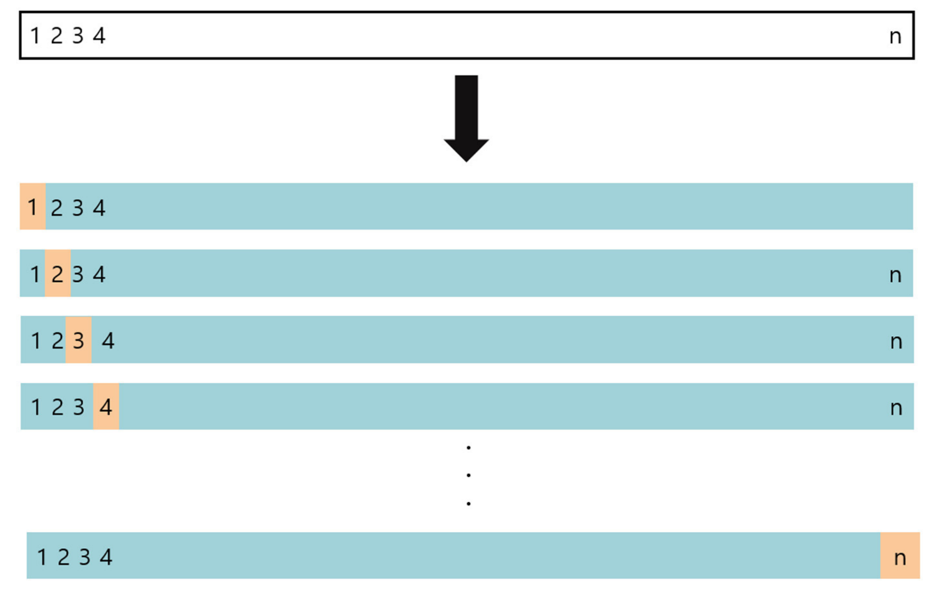

FIGURE 3 | The concept of the LOOCV method.

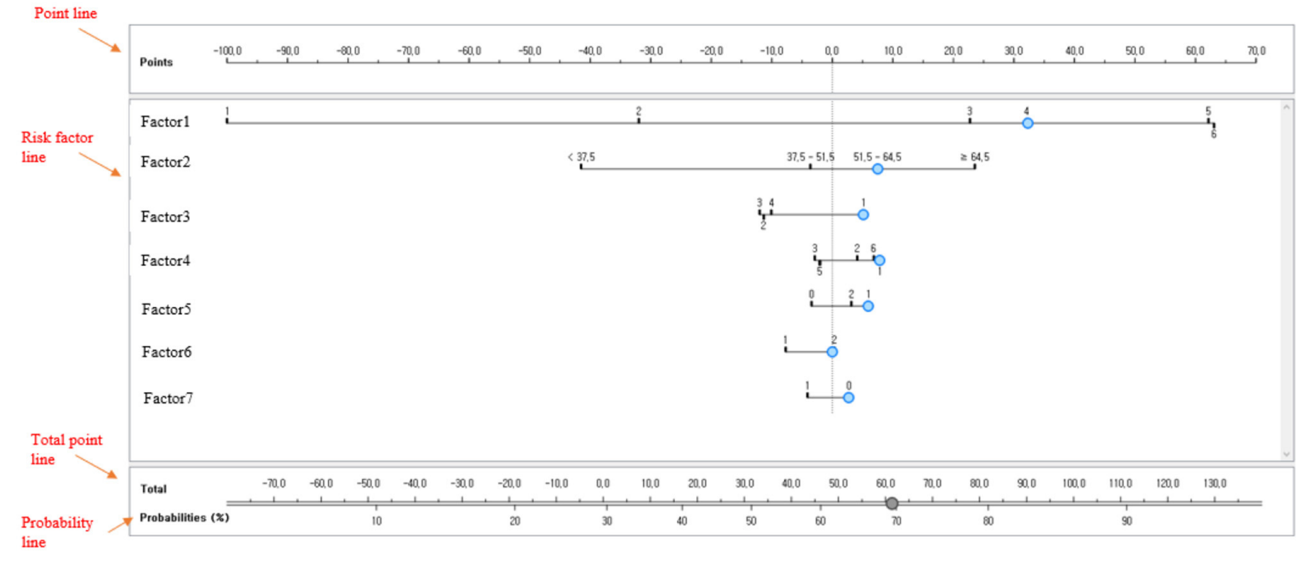

FIGURE 4 | Example of a naive Bayesian nomogram.

the prediction (predicted probabilities) using the major variables derived from the final model for predicting depressive disorders. In general, a nomogram consists of 4 types of lines. First, a point line is presented. The score line is a line placed at the top of the nomogram to derive a score corresponding to the class of each risk factor. In the naive Bayesian nomogram, positive numbers are interpreted as risk factors and negative numbers are understood as preventive factors. Second, a risk factor line is presented. The number of risk factor lines is equal to the number of risk factors affecting depressive disorder. Third, the total point line refers to the sum of the scores of individual risk factors and is located at the bottom of the nomogram. Fourth, a probability line is presented. The probability line is the final sum of the nomogram scores calculated by adding up multiple risk factors. It is placed at the bottom of the nomogram to calculate the occurrence probability of depressive disorders in female older adults living alone. **Figure 4** shows an example of a naive Bayesian nomogram.

TABLE 2 | Data, measurement unit of female older adults living alone in South Korea, mean ± SD/*n* (%).

Characteristics	*n* (%)
Age	72.9 ± 6.20
Alcohol consumption	
No	214 (37.2)
Yes	364 (62.8)
Binge drinking	
No	535 (92.7)
Yes	42 (7.3)
Smoking	
No	552 (90.6)
Yes	54 (9.4)
Whether or not to receive national basic livelihood security	
No	456 (78.5)
Yes	125 (21.5)
Perception of subjective body type	
Very thin	43 (7.4)
Slightly skinny	55 (9.5)
Average	226 (39.1)
Slightly obese	192 (33.2)
Very obese	62 (10.7)
Control weight over the past year	
Try to lose weight	176 (30.4)
Try to maintain weight	72 (12.5)
Try to gain weight	33 (5.7)
Never tried to control weight	297 (51.4)
Monthly mean household income	
<KRW 1.5 million	514 (88.6)
≥KRW 1.5 million	66 (11.4)
Education level	
Middle school graduation or below	503 (86.4)
High school graduation or above	78 (13.4)
Level of stress awareness	
I feel stressed very much	30 (5.2)
I feel stressed a lot	82 (14.2)
I feel stressed a little	246 (42.7)
I hardly feel stressed	218 (37.8)
Obesity by body mass index (BMI, kg/m^2)	
Underweight (<18.5 kg/m^2)	14 (2.5)
Normal weight (≥18.5 kg/m^2 and < 23 kg/m^2)	228 (40.1)
Pre-obesity stage (≥23 kg/m^2 and <25 kg/m^2)	193 (33.9)
Stage 1 obesity (≥25 kg/m^2 and <30 kg/m^2)	104 (18.3)
Stage 2 obesity (≥30 kg/m^2 and <35 kg/m^2)	29 (5.1)
Stage 3 obesity (≥35 kg/m^2)	1 (0.2)
Mean frequency of having breakfast per week for the past year	
5–7 times per week	480 (88.9)
3–4 times per week	25 (4.6)
1–2 times per week	13 (2.4)
Rarely	22 (4.1)
Moderate-intensity physical activity	
Yes	13 (2.2)
No	569 (97.8)
Subjective health status	
Good	79 (13.6)
Okay	271 (46.6)
Bad	232 (39.9)
Hypertension	
Normal	94 (16.2)
Prehypertension	102 (17.5)
Hypertension	386 (66.3)
Diabetes	
Normal	243 (45.3)
Impaired fasting glucose	148 (27.6)
Diabetes	145 (27.1)
Hypertriglyceridemia	
No	423 (87.4)
Yes	61 (12.6)
Hypercholesterolemia	
No	318 (59.3)
Yes	218 (40.7)
Waist Circumference (cm)	84.6 ± 9.8
N-3 fatty acid intake per day (g)	1.35 ± 1.8
N-6 fatty acid intake per day (g)	5.47 ± 6.7
Vitamin c intake per day(g)	50.1 ± 57.6
Energy intake per day (Kcal)	1,416.8 ± 603.9
Water intake per day (g)	693.5 ± 497.7
Protein intake per day (g)	45.6 ± 25.0
Cholesterol intake per day (g)	113.6 ± 174.9
Carbohydrate intake per day (g)	254.6 ± 109.0
Calcium intake (mg)	386.6 ± 264.8
Vitamin A intake per day (ug)	432.9 ± 483.4
Usual hours of sitting per day	9.0 ± 4.0
Usual hours of sleep per day	
<5	49 (8.5)
5–6	72 (12.4)
6–7	108 (18.7)
7–8	159 (27.5)
8–9	116 (20.0)
>9	75 (13.0)
Depressive disorders	
No	509 (87.5)
Yes	73 (12.5)

This study used the following notation to describe the content for convenience.

$A = \{a_1, a_2, \ldots, a_m\}$: A set of features used to represent a dataset

$C = \{0, 1\}$: The label of a class; where 0 denotes another class and 1 denotes the target class.

$D = \{d_1, d_2, \ldots, d_n\}$: A set of patient data

$d_i = (\upsilon_{i1}, \upsilon_{i2}, \ldots, \upsilon_{im}, c_i)$: **i**th data.
υ_{ij} refers to the value of a feature (a_j)
c_i represents a class.
N_j: j-th generated nomogram
$E_{N_j}(d_i)$: The value evaluate the degree of data (d_i) belonging to the target class by using nomogram N_j
$(d_{(1)}, d_{(2)}, \ldots, d_{(n)})$: A sequence of a data set D in the increasing order of $E_{N_j}(d_i)$
$D_P = \{d_k \mid c_k = c, d_k \in D\}$: A subset of D belonging to the target class c
$D_N = \{d_k \mid c_k \neq c, d_k \in D\}$: A subset of D not belonging to the target class c

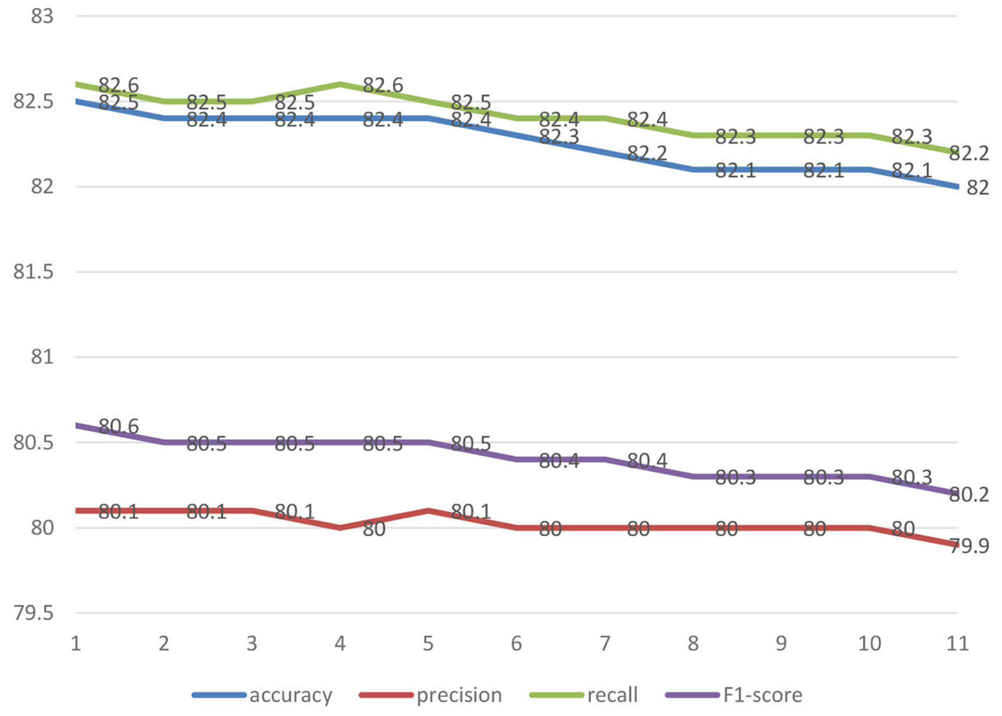

FIGURE 5 | The comparison of 11 machine learning models (accuracy, precision, recall, F1-score) for predicting the depressive disorders of female older adults living alone.

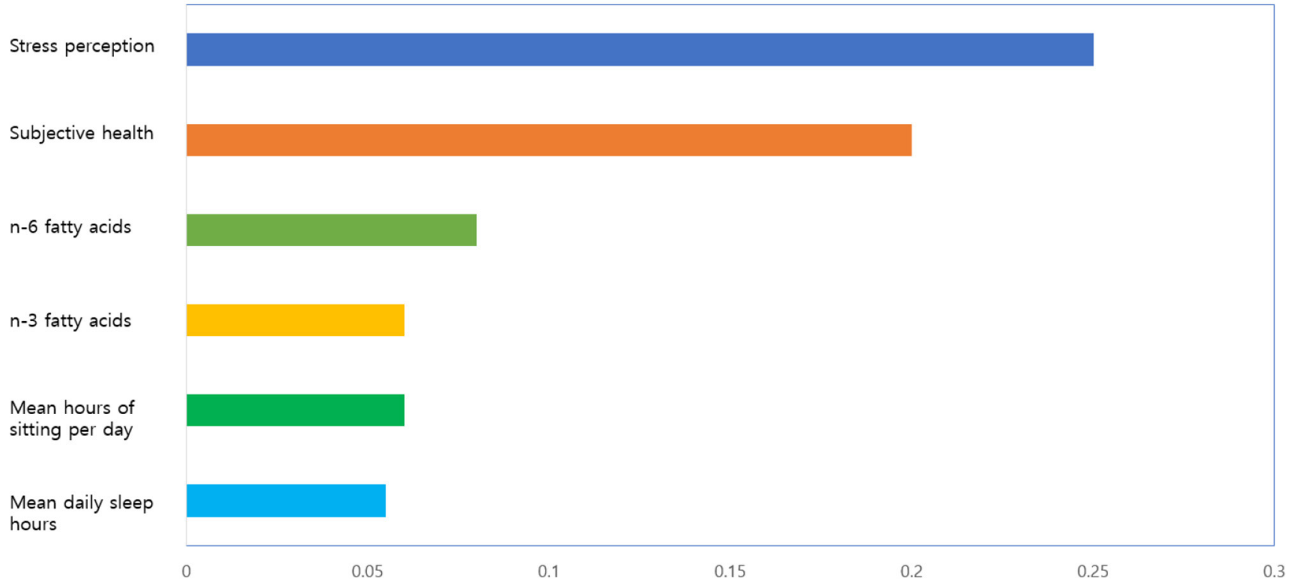

FIGURE 6 | The feature importance (best 6) of final model.

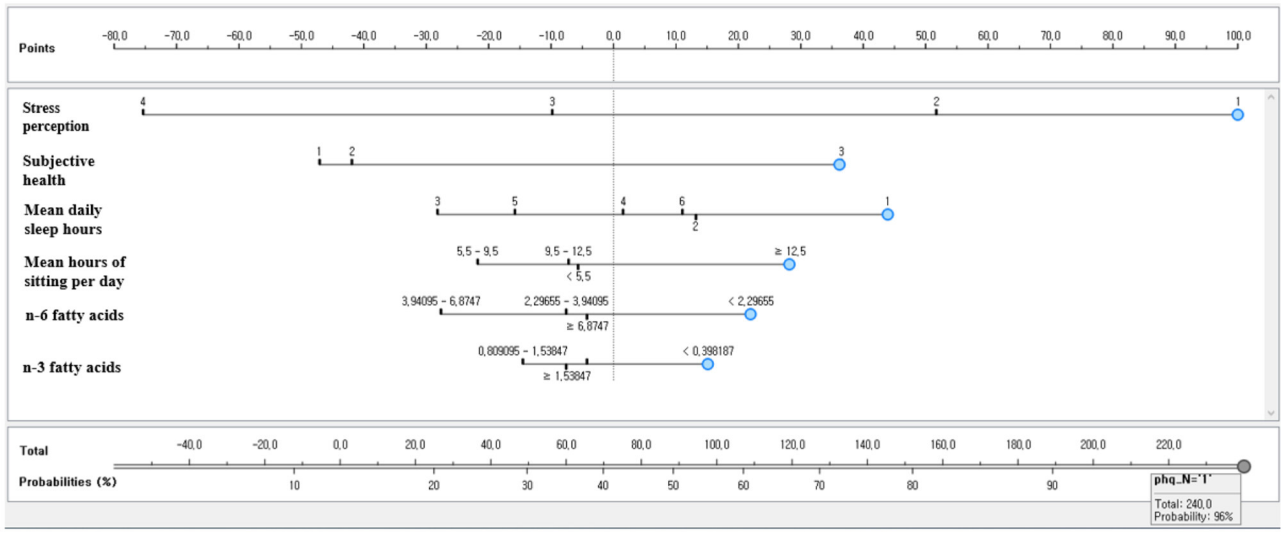

FIGURE 7 | The naive Bayesian nomogram for predicting the depressive disorders of female older adults living alone in South Korea.

$n_P = |D_P| : \ Number\ of\ data\ in\ D_P n_N = |D_N| : \ Number\ of\ data\ in\ D_N$

$p_j^P(\upsilon) = \frac{\{d_i | a_i^j = \upsilon,\ d_i \in D_P\}}{n_P}$: Relative frequency of data in which the jth features in Dp has a value υ

$p_j^N(\upsilon) = \frac{\{d_i | a_i^j = \upsilon,\ d_i \in D_N\}}{n_N}$: Relative frequency of data in which the jth features in DN has a value υ

The characteristics of the naïve Bayesian classifier was used to construct a nomogram using the naive Bayesian technique. The naive Bayesian classifier determines the probability of a specific class by applying the Bayesian theorem under the assumption that data features or events are independent of each other. Using the assumption of feature independence, the posterior probability (P(c|X)), which is the probability that an entity X =(a_1,a_2,…,a_m) belongs to class c, is calculated as follows.

$$p(c|X) = \frac{P(a_1, a_2, \ldots, a_m|c)\, P(c)}{P(X)} = \frac{P(c) \prod_i P(a_i|c)}{P(X)} \quad (22)$$

A nomogram can also be considered as a model for evaluating how well an entity fits a particular class. When c is the target class of the nomogram and c is a class other than c, P(c|X) indicates the probability that an entity X does not belong to class c. The odds ratio (Odds) for these two probabilities can be expressed as follows using Equation (23).

$$Odds = \frac{P(c|X)}{P(\overline{c}|X)} = \frac{P(c) \prod_i P(a_i|c)}{P(\overline{c}) \prod_i P(a_i \lceil c)} \quad (23)$$

log *it* is defined as the logarithm of *Odds*.

The logit for $(c|)$ can be expressed as the following.

$$\log it\ P(c|X) = logit\ P(c) + \sum_i \log \frac{P(a_i|c)}{P(a_i \lceil c)} \quad (24)$$

$$= logit\ P(c) + \sum_i \log OR(a_i)$$

The above Equation (24) shows that the logit value of $P(c|X)$ can be expressed as the sum of the log $OR(a_i)$ of each feature value. Since the final probability value can be expressed as the sum of the evaluation values of each feature value, this property is similar to the method of interpreting the nomogram. Consequently, by using the above properties of the naive Bayesian classifier, a nomogram can be generated through the following process.

1. For the given data D, calculate the relative frequencies ($p_i^P(\upsilon_j)$ and $p_i^N(\upsilon_j)$) of the value (υ_j) of each feature (a_i) in the target class c and the relative class c.
2. Calculate the log OR for the value (υ_j) of each feature (a_i).

$$\log OR(\upsilon_j) = log \frac{p_i^P(\upsilon_j)}{p_i^N(\upsilon_j)}$$

3. Evaluation Function ($E(d_i)$) for Data di Is Defined by $\sum_j logOR(\upsilon_{ij})$, While Treating $logOR(\upsilon_j)$ as the score for the corresponding feature a_i.

$$E(d_i) = \sum_{a_j \in SAT} \log OR(\upsilon_{ij}),\ \log OR(\upsilon_{ij}) = \log_{10} \frac{p_j^P(\upsilon_{ij})}{p_j^N(\upsilon_{ij})} \quad (25)$$

4. Find the maximum (max) and minimum (min) for all possible feature value combinations.

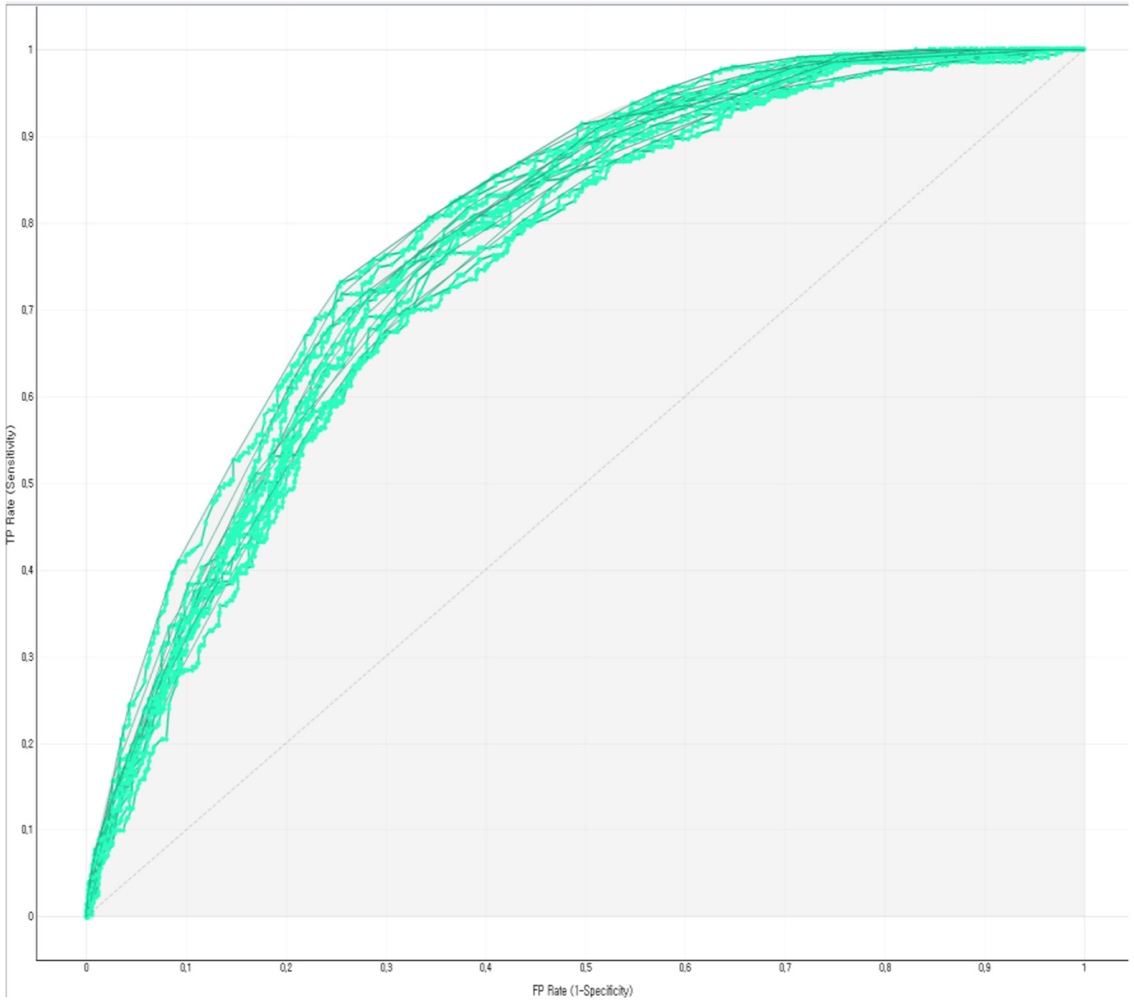

FIGURE 8 | ROC of the Bayesian nomogram for predicting the depressive disorders of female older adults living alone.

5. Determine the probability ($p(c|d_i)$) for the interval [min, max] that the data d_i belongs to the target class c using the following equation.

$$p\left(c|X\right) = \left[1 + e^{-\log itP(c)-E(d_i)}\right]^{-1} \tag{26}$$

6. Prepare a graph for the nomogram using the logOR for each feature and the probability for the interval (min, max).

The accuracy of the final nomogram was checked using general accuracy, the area under the curve (AUC), and calibration plot, which visually confirms the agreement between predicted probability and observed probability in the nomogram, using the LOOCV.

RESULTS

The Data, Measurement Unit of Female Older Adults Living Alone in South Korea

The mean age of the 582 subjects was 72.9 ± 6.20 years, and the prevalence of depressive disorders was 12.5% (**Table 2**). The majority of the subjects experienced drinking during their lifetime (62.8%), did not experience binge drinking in the past year (92.7%), were not smokers (90.6%), had a mean monthly household income of less than KRW 1.5 million (88.6%), tried to lose weight in the past year (30.4%), were older adults who did not engage in moderate-intensity physical activity (97.8%), were middle school graduates or below (86.4%), were unemployed (69.0%), had normal weight (39.1%), ate breakfast 5–7 times per week on average for the past year (88.9%), had ordinary subjective health (46.6%), did not have diabetes (45.3%), did not have hypertension (66.3%), did not have hypertriglyceridemia (59.3%), did not have hypercholesterolemia

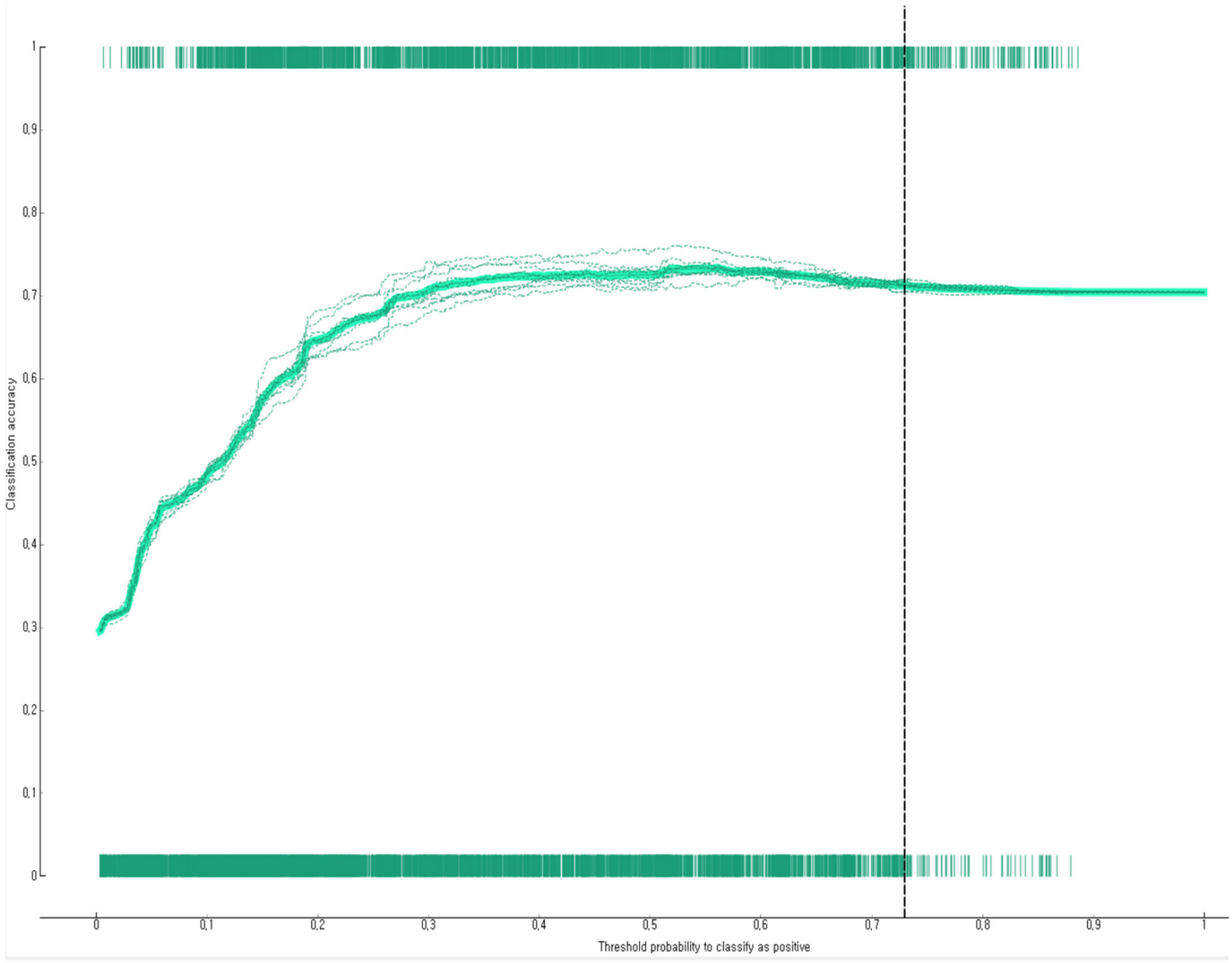

FIGURE 9 | Classification accuracy of the Bayesian nomogram for predicting the depressive disorders of female older adults living alone.

(87.4%), and slept 7–8 h per day (27.5%). The subjects sat 9.0 ± 4.0 h per day on average. Moreover, they ate 1.35 ± 1.8 g of n-3 fatty acid and 5.47 ± 6.7 g of n-6 fatty acid. Since only one older adult had class 3 obesity (0.2%), "class 3 obesity" was reclassified as "class 2 obesity or high" in the development of the predictive model.

Comparing the Accuracy of Models Predicting the Depressive Disorders of Female Older Adults Living Alone

Figure 5 shows the comparison of 11 machine learning models (accuracy, precision, recall, F1-score) for predicting the depressive disorders of female older adults living alone. The analysis results showed that the prediction performance of "GBM + RandomForest + Adaboost + SVM + XGBoost + Bayesian regression" was the best (accuracy = 82.52%, precision = 80.13%, recall = 82.60%, and F1-score = 80.62%).

1 = GBM + RandomForest + Adaboost + SVM + XGBoost + Bayesian regression; 2 = GBM + Bayesian regression 3. Adaboost + Bayesian regression; 4 = XGBoost + Bayesian regression; 5 = RandomForest + Bayesian regression; 6 = SVM + Bayesian regression; 7 = GBM; 8 = Adaboost; 9 = RandomForest; 10 = XGBoost; 11 = SVM.

Exploring the Major Predictors of the Depressive Disorders of Female Older Adults Living Alone

Figure 6 presents the feature importance of GBM + RandomForest + Adaboost + SVM + XGBoost + Bayesian regression model, the final model. This study calculated the importance of a variable using mean decrease in impurity (MDI) Importance. MDI is an index for calculating the importance of a variable, built in as a default of scikit-learn. When each variable is split, it defines the mean of the decrease of impurity as the importance. The function is as shown in Equation (27). The decrease of impurity is calculated while considering the number of observations in each node. A higher value indicates that the

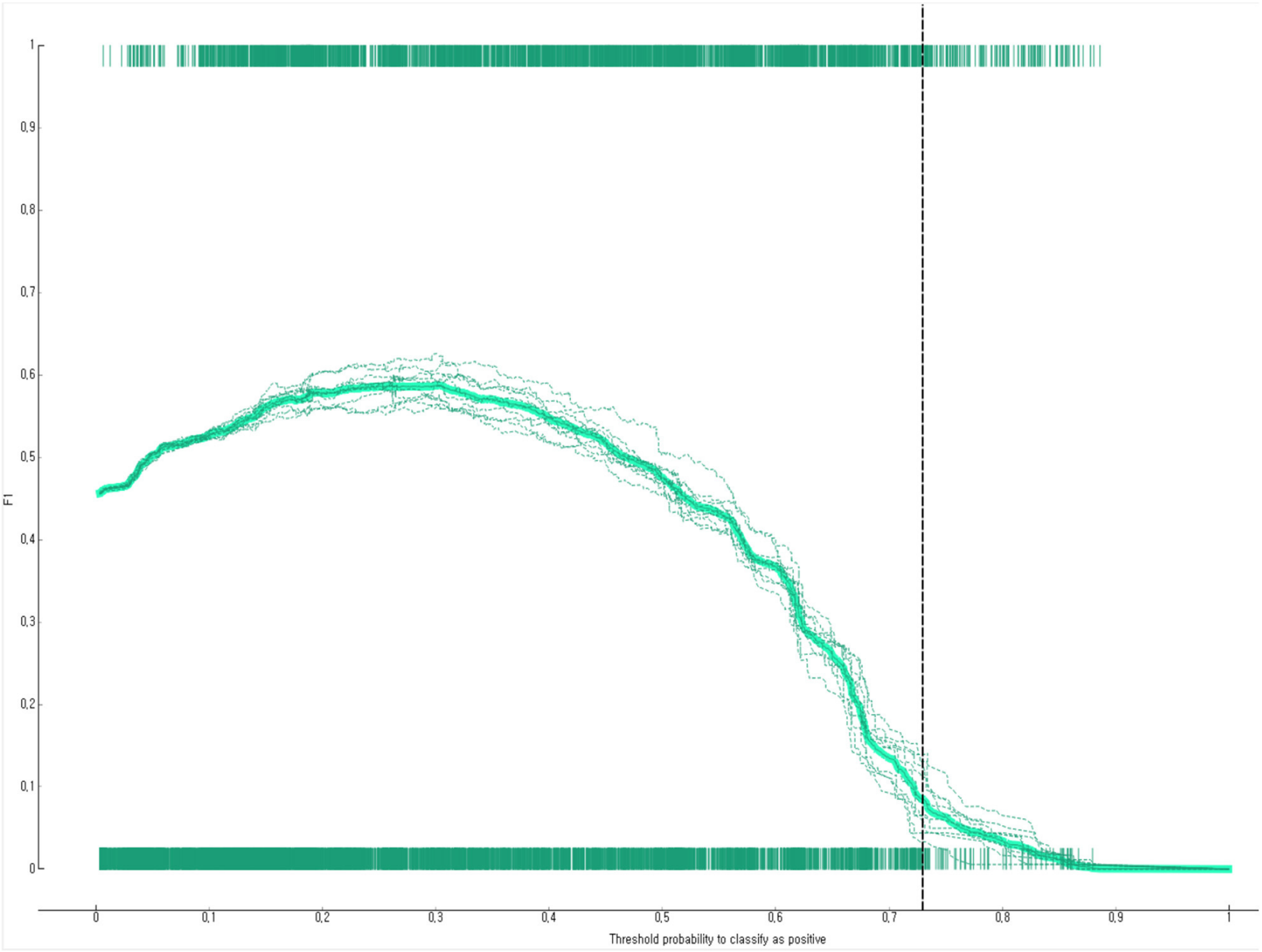

FIGURE 10 | F1-score of the Bayesian nomogram for predicting the depressive disorders of female older adults living alone.

importance is higher.

$$\Delta i(t) = i(t) - \frac{N_{tl}}{N_t} i(t_l) - \frac{N_{tr}}{N_t} i(t_r) \tag{27}$$

$i(t)$: impurity of node t (entropy, gini index, variance, …)

N_t: number of observations at node t

The model confirmed that stress perception, subjective health, n-6 fatty acids, n-3 fatty acids, mean hours of sitting per day, and mean daily sleep hours were six major variables related to the depressive disorders of female older adults living alone. Among them, stress perception was the most important factor in the final model.

Development of a Nomogram for Predicting the Depressive Disorders of Female Older Adults Living Alone

Figure 7 shows the naive Bayesian nomogram for predicting the depressive disorders of female older adults living alone in South Korea. Stress perception level showed the highest influence among the risk factors of depressive disorders for female older adults living alone. Female older adults living alone who perceived stress a lot were most vulnerable to depressive disorders. For example, the developed Bayesian nomogram predicted that female older adults living alone who perceived a lot of stress, perceived that their subjective health was bad, slept <5 h per day on average, sat 12.5 h or more per day on average, ate <2.29 g of N6 fatty acid, and ate <0.39 g of N3 fatty acid had the 96% probability of having a depressive disorder (**Figure 6**).

The prediction performance of the developed Bayesian nomogram was validated using classification accuracy, AUC, F-1 score, precision, recall, and calibration plot. The results of LOOCV showed that the AUC (**Figure 8**), classification accuracy (**Figure 9**), F-score (**Figure 10**), precision, and recall of the nomogram developed in this study were 0.77, 0.73, 0.71, 0.71, and 0.73, respectively. This study compared the prediction probability and observation probability of a group with depressive disorders and a group without depressive disorders using calibration plot and the chi-square test (**Figure 11**) to find that there was no significant difference between them ($P = 0.583$).

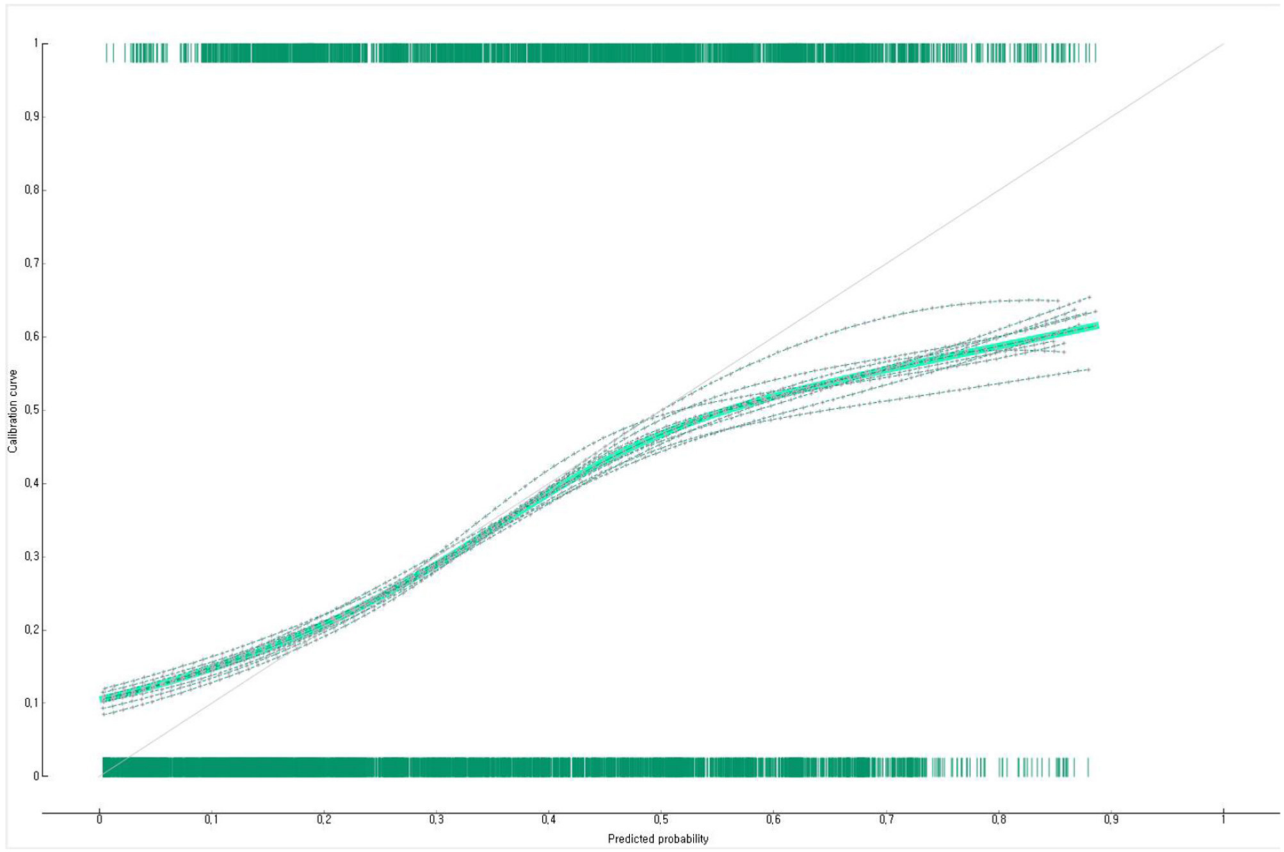

FIGURE 11 | Calibration plot of the Bayesian nomogram for predicting the depressive disorders of female older adults living alone.

DISCUSSION

This study identified factors related to the depressive disorders of female older adults living alone using stacking ensemble machine and confirmed that stress perception, subjective health, n-6 fatty acids, n-3 fatty acids, mean sitting hours per day, and mean sleeping hours per day were key risk factors related to the depressive disorders of female older adults living alone.

It is generally believed that the prevalence of depressive disorders increases when the older adult population perceives stress more (28, 29), is less frequently involved in physical activity (30), has poorer subjective health (31, 32), and experiences sleep disturbance more (33). Nevertheless, there was a limitation in identifying multiple risk factors for depressive disorders because most previous studies (28–33) that explored risk factors for depressive disorders did not examine factors related to depressive disorders while distinguishing older adults living family and those living alone and were limited to identifying individual risk factors using regression analysis. This study evaluated multiple risk factors for depressive disorders in female older adults living alone by developing the Bayesian nomogram. The results showed that female older adults living alone would have a very high-risk probability (96%) of depressive disorders when they perceived stress a lot, perceived their subjective health as poor, slept <5 h per day on average, sat 12.5 h or more per day on average, ate <2.29 g of N6 fatty acid per day, and ate <0.39 of N3 fatty acid per day. Therefore, it is necessary to find the high-risk group of depression with these multiple risk factors among female older adults living in the community and continuously monitor them at the community level to prevent depressive disorders.

Older adults have a strong tendency to complain of stress or physical (abnormal) symptoms first rather than directly complaining about depressive symptoms to their family members or neighbors (34). If the symptoms perceived by older adults belonging to a high-risk group for depression are neglected, the depressive symptoms may be worsened, leading to suicide attempts in extreme cases (35). In particular, neglecting the chronic depressive symptoms of older adults can be a major cause of suicidal thoughts or suicide attempts (36). It is necessary to screen high-risk groups of depression early and to provide them with emotional and psychological therapy because female older adults living alone may experience family separation and domestic abuse after bereavement (37). Nevertheless, only a few studies have identified multiple risk factors for predicting the depressive disorders of female older adults living alone. This study proposed a stacking ensemble machine approach and a Bayesian nomogram as methods to identify multiple risk factors for a disease. Based on the results of this study, it is required to evaluate the multiple risk factors for depression including various measurable factors such as social support.

The advantages of this study were that this study explored the risk factors of depressive disorders from various aspects including sociodemographic factors, health habits, health status, and nutritional factors by using epidemiological data representing South Korean older adults and this study developed a nomogram allowing people to visually and easily identify high-risk groups of depressive disorders. The limitations of this study are as follows. First, this study treated older adults living alone as a single group without classifying them into different types according to causes. However, older adults living alone can be divided into those living alone due to unavoidable circumstances such as bereavement and those living alone due to divorce or separation. These two groups may have different depressive characteristics. Future studies are necessary to identify risk factors for depressive disorders according to the type of older adults living alone. Second, this study could not identify the severity or type of depressive symptoms because this study analyzed the prevalence of depressive disorders in older adults living in the community based on the depression screening test, mainly used in epidemiological investigations. Follow-up studies are needed to classify the types of depressive disorders using medical diagnosis and to explore risk factors according to depression type based on this. Third, although depressive disorders can be affected by social networks such as family relationships, friendship, and social support, this did not evaluate the social networks of older adults living alone. Fourth, the food intake frequency survey is based on the subject's subjective memory, and this method has a possibility of a recall bias. Fifth, this study used the SMOTE, a method widely used to resolve data imbalance. Although SMOTE has the advantage that it does not lose information, it may be disadvantageous in predicting the data of new cases because it reflects only the characteristics between the minority data in the modeling set. Therefore, future studies are required to process imbalance data with improved SMOTE, such as adaptive synthetic sampling, when analyzing data with severe imbalance. Sixth, since it is a cross-sectional study, even risk factors for depression cannot be understood as a causal relationship. Additional longitudinal studies are required to prove causality.

CONCLUSIONS

The results of this study implied that it would be necessary to continuously evaluate complex risk factors such as stress perception, subjective health, n-6 fatty acids, n-3 fatty acids, mean daily sitting hours, and mean daily sleeping hours for detecting the depressive symptoms of female older adults living alone in the community as soon as possible. It is difficult for patients to recognize the symptoms of senile depression in the early stage because these symptoms are mild. To make it worse, older adults living alone rarely visit a doctor's office due to depressive symptoms actively, or they tend to visit a doctor's office after depressive symptoms are already severe. Therefore, the Bayesian nomogram developed in this study can be usefully used to detect and manage the depressive disorders of older adults living alone in primary care at an early stage. Furthermore, it is required to continuously manage high-risk groups at the community level as well as to discover the high-risk groups of depression for older adults living alone based on multiple risk factors.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of these data. Data was obtained from Korea Institute for Health and Social Affairs and are available (from the Korea Institute for Health and Social Affairs/https://www.kihasa.re.kr/en) with the permission of Korea Institute for Health and Social Affairs. Requests to access these datasets should be directed to the Korea Institute for Health and Social Affairs/https://www.kihasa.re.kr/en.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University (Protocol Code 20180042 and date: 2018.07.01). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HB designed the paper, was involved in study data interpretation, preformed the statistical analysis, and assisted with writing the article.

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Depression, Anxiety and Sleep Alterations in Caregivers of Persons With Dementia After 1-Year of COVID-19 Pandemic

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Background: Social isolation due to COVID-19 pandemic has an important psychological impact particularly in persons with dementia and their informal caregivers.

Aim: To assess frequency and severity of long-term stress-related symptoms in caregivers of patients with dementia 1-year after the beginning of COVID-19 pandemic and to identify predictors of psychological outcomes.

Methods: Eighty-five caregivers were involved in a longitudinal study with 1-year follow-up during pandemic in Italy. At baseline in April 2020 a telephone interview assessed socio-demographic characteristics of caregivers and self-perception of distress symptoms. After 1 year, between March and April 2021, the same standardized interview was delivered to the caregivers' sample. In addition, scales assessing levels of depression and anxiety (DASS-21), sleep disturbances (PSQI) and coping strategies (COPE-NVI) were administered to the caregivers and to 50 age and sex-matched non-caregivers subjects. Linear regression analysis was performed to investigate the power of baseline variables to predict long-term psychological outcomes.

Results: After 1 year of pandemic frequency of caregivers' stress-related symptoms increased respect to baseline: depression (60 vs. 5, 9%; $p < 0.001$), anxiety (45, 9 vs. 29, 4%; $p = 0.035$), irritability (49, 4 vs. 24, 7%; $p < 0.001$), and anguish (31, 7 vs. 10, 6%; $p < 0.001$). Frequency of severe depression was higher in caregivers than in non-caregivers ($p = 0.002$) although mean levels of depression were comparable in the two groups. Long-term higher depression was predicted by a model built on baseline information ($r^2 = 0.53$, $p < 0.001$) where being female ($t = -3.61$, $p < 0.001$), having lower education ($t = -2.15$, $p = 0.04$), presence of feelings of overwhelm ($t = 2.29$, $p = 0.02$) and isolation ($t = 2.12$, $p = 0.04$) were significant predictors. Female sex was also predictive of anxiety ($t = -2.7$, $p = 0.01$) and poor sleep quality ($t = -2.17$, $p = 0.03$).

Discussion: At 1 year follow-up caregivers of patients with dementia reported higher prevalence of all stress-related symptoms respect to the acute phase of lockdown, particularly depression. Long-lasting stressful conditions may cause exhaustion of resilience factors and increased depression. Planning interventions should support caregivers to enable them to continue with their role during pandemic.

Keywords: dementia, COVID, lockdown, burden, caregivers, depression

INTRODUCTION

Italy was the first European country declaring in March 2020 a national lockdown to contain contagion after pandemic of the new Coronavirus SARS-Cov2, forcing the population into social restrictions, with individuals being allowed to leave home only for limited and recognized necessities. The experience of lockdown is often unpleasant for different level of stressors as social separation, loss of freedom, perception of uncertainty and boredom, with negative psychological effects including post-traumatic stress symptoms, confusion, and anger in normal population (1). Evidence of lockdown from previous viral outbreaks reported a substantial impact on general mental health, as anxiety, mood alterations and post-traumatic stress symptoms (2–4). During COVID-19 pandemic, post-traumatic stress symptoms (37, 1%), depressive symptoms (17, 3%), anxiety (20, 8%) (5), changes in appetite, reduced libido (6), and altered sleeping patterns (6, 7) were revealed in the general population. Among stressors associated with negative psychological impact during lockdown, female gender (5, 6, 8), lower levels of education (8), story of previous psychiatric illness, and being a care worker (1) were most relevant.

Elderly people with cognitive decline and their caregivers had negative outcomes from the experience of social isolation imposed by pandemic. Even in non-pandemic context, family members caring for individuals with dementia often describe this experience as "enduring stress and frustration" and the term caregiver burden is most often used to describe this phenomenon (9). Indeed, the contextual experience of caring a person with dementia lead to psychologically stressful and physically exhausting tasks, with significant expenditure of time, energy, and money over potentially long periods of time (10, 11).

During pandemic, direct outcomes of restrictive measures induces a substantial change in patients with dementia and caregivers' daily routine, with reductions of physical and cognitive activities change in lifestyle and in the management of the disease (12, 13). Increment of behavioral disturbances as agitation, sleep disorders, hallucinations, wandering, anxiety, apathy, and depression occurred in patients with dementia (14–16). Caregiver distress and psychological well-being exacerbated (17), possibly acting in a vicious loop with mutual increase of psychiatric burden (15) and caregiver burden (18, 19). These significant social stressors, together with worsening of patient's cognitive, behavioral and motor deficits (14, 15), increased caregiver stress perception during COVID-19 pandemic (17).

Studies during the first lockdown in Italy investigated caregiver stress perception with telephone surveys, demonstrating the presence of stress-related symptoms reported by 65,9% of caregivers including anxiety, helplessness, anguish, irritability, abandonment, and feelings of depression (14, 15). Other studies in Italy (17, 19, 20) and Spain (12, 16) had similar results, all highlighting that lockdown led to warning psychological response in caregiver of patients with dementia during the first months of pandemic. After the first lockdown in March 2020, a new decree-law in force since October 8 confirmed the previous containment measures, and from November 6 containment for differentiated scenarios and curfew were established. Lockdown periods, partial limitations of social life and worries of contamination due to ongoing pandemic endured until a vaccination campaign was started at the beginning of 2021.

To our knowledge, no studies are available assessing long-term psychological effects of pandemic in caregivers of persons with dementia. The aim of this study was to longitudinally investigate the long-term psychological impact of restrictive measures in caregivers of patients with dementia assessed in March 2020, at the beginning of social isolation due to COVID-19 pandemic, and 1 year later (March 2021). In details, presence and severity of depression, anxiety, change of sleep quality, caregiver burden and coping strategies after 1 year of pandemic will be assessed, and their demographic, social and psychological predictors at the beginning of lockdown will be evaluated.

METHODS

Participants

A total of 151 individuals, 101 informal caregivers of persons with dementia and 50 subjects without caregiving duties were enrolled in this study.

Caregivers were all family members or careers of patients with cognitive decline regularly attending the Memory Clinic of the Neurology Unit at the Hospital of Padua. Of the 101 caregivers assessed at baseline in March 2020 (T1), 16 caregivers were not assessed at follow-up (T2) performed in March 2021 and therefore the final sample of informal caregivers considered for statistical analyses consisted of 85 subjects with both T1 and T2 evaluations. Reasons for drop out from the longitudinal study were: withdrawn of consent ($n = 6$), loss of contacts ($n = 8$), institutionalization or death of their care receiver ($n = 2$). Fifty non-caregivers subjects were evaluated only in March 2021. Non-caregivers were selected from volunteers of charities and social services or referred from general practitioners. Inclusion criteria were: living at home in the last year; functional independency; age within in the range similar to that of caregivers. Exclusion criteria were: presence of neurological or psychiatric disorders; caring for a person with physical or mental disability; having had COVID infection with hospitalization in the last year. Psychiatric and psychopathological history was screened before starting the phone interview with a short anamnestic questionnaire investigating possible neurological (i.e., Parkinson's disease, stroke, epilepsy) or psychiatric (i.e., anxiety, depression) disorders and/or the use of psychotropic drugs.

None of the subjects involved in the study was affected by COVID-19 infection in the period of observation.

MATERIALS AND METHODS

This is a longitudinal study with 1-year follow-up and two-time points assessments. At baseline participants were interviewed during the first COVID-19 lockdown in March 2020 (T1) assessing socio-demographic characteristics of the caregiver, continuity of therapeutic care, self-perception of distress symptoms such as anxiety, insomnia, irritability, and specific variables of wellbeing such as working conditions, cohabitation, and social support. Methodology of this phone-based interview has been already published (14). After one-year from baseline a second follow-up assessment (T2) was performed through a telephone interview administrated to all participants by the same experimenter (TB) between the 22nd March and 24th April 2021. The follow-up assessment consisted of two parts: (1) a semi-structure interview using the same questionnaires administered at T1 enquiring on changes of socio-demographic characteristics, self-perception of distress symptoms, global health and COVID-19 infection; (2) standardized questionnaires and scales to assess presence and severity of depression, anxiety, sleep changes, caregiver burden and coping abilities. The degree of depression and anxiety was assessed with the Depression, Anxiety and Stress Scale (DASS-21); sleep quality with the Pittsburgh Sleep Quality Index (PSQI), the caregiver burden with the Caregiver Burden Inventory (CBI) and coping strategies with the Coping Orientation to Problems Experienced – Nuova Versione Italiana (COPE-NVI).

DASS-21 (21, 22) was used for the assessment of depression (dysphoria, hopelessness, devaluation of life, lack of interests and incentive, low self-esteem, and anhedonia), and anxiety (somatic and subjective symptoms of anxiety, autonomic arousal, and situational anxiety) symptoms. Each subscale consists of seven items rated on a 4-points Likert scale (from 0 "*never*" to 3 "*nearly always*"). The total score for each sub-scale is given by the sum of its items multiplied by two, where higher values correspond to a higher and more severe alteration. Recommended cut-off scores for severity levels were considered as following: depression = normal 0–9, mild 10–13; moderate 14–20, severe >21; anxiety = normal 0–7, mild 8–9; moderate 10–14, severe >15 (23).

A modified version of PSQI (23, 24) was used for assessing the following four domains of sleep/wake disorders: (1). Sleep quality subjective perception; (2); Habitual sleep efficiency (including sleep duration as sleep time/bedtime). The range of scores for both variables is between 0 and 3 for, respectively "very bad" and "very good"; (3). Use of sleeping medications and 4; Daytime dysfunctions (i.e., daytime sleepiness, or lack of energies during the day). The range of scores for these two last variables is between 0 and 3, where 0 indicates low frequencies, as "not during the past month" and 3 indicates high frequencies ("more than 3 times a week").

CBI (25, 26) explores five burden domains: time-dependence burden, developmental burden, physical burden, social burden, and emotional burden. Due to time-dependent constrains of a telehone interview, from CBI we chose to explore the following three domains: (1). "Time-dependence burden," due to time and energy spent for the constant vigilance and sense of responsibility – "*My care receiver is dependent on me*" or "*I don't have a minute's break from my caregiving chores*"; (2). "Developmental burden," relying to the sense of failure in development and guilty with respect to peers due to failure of role expectations of becoming caregiver - items like "*Why did this happen to me*?" or "*I expected that things would be different at this point in my life*" and (3). "Emotional burden," describing caregivers' negative feelings toward care receivers, which may result from the patient's unpredictable and often bizarre behavior - items like, "*I resent my care receiver*" and "*I feel angry about my interactions with my care receiver*." Each factor consisted of five items rated on a 5-points Likert scale (from 0 "never" to 4 "nearly always"). The social burden and physical burden were not investigated considering the confounding variables introduced during pandemic as far as social restrictions and physical symptoms.

COPE-NVI (27) was administered to assess the ability to manage traumatic events or stressful situations. In particular, we investigated four dimensions: (1). Social support (tendency to seek understanding, support and information from others); (2). Avoidance strategies (tendency to use behavioral and mental denial and detachment); (3). Positive attitude (tendency to adopt a positive acceptance and reinterpretation of events) and (4). Problem orientation (tendency to use active planning strategies). Each domain is rated on a 4-points Likert scale from 1 "*usually I did not do it*" to 4 "I almost always do it." The total score for each scale is given by the sum of its items, where higher values refer to a greater tendency to use that specific coping strategy.

Non-caregivers controls were assessed only at T2 with DASS-21, PSQI and COPE-NVI questionnaires. All the questionnaires were administered with the same chronological order in the two groups.

All participants were asked for a prior consent, guaranteeing them total anonymity in the processing of data.

Statistical Analysis

Answers to the telephonic survey were first analyzed using frequency analysis to assess differences and longitudinal changes (i.e., T1 vs. T2) in caregivers.

Then, long-term psychological effects of pandemic were analyzed by comparing caregivers and non-caregivers across a series of scales administered in T2. Notably, despite significant differences between caregivers and non-caregivers in the education level, we did not use education as covariate since its impact on DASS-21, PSQI and COPE-NVI scores has been shown negligible (22, 23, 27).

Specifically, we investigated the impact of being a caregiver (i.e., Factor 1) by comparing caregivers and non-caregivers, and the impact of being in a pandemic (i.e., Factor 2) by comparing non-caregivers and normative data, which were collected from non-caregivers and not during a pandemic. Finally, the comparison between caregivers and normative data allowed us to study the cumulative effect of such factors (i.e., the impact of being a caregiver during a pandemic). Bonferroni correction for multiple comparison was applied.

Notably, in all comparisons t-tests were used after checking the reliability of the results also with non-parametric statistics (i.e., Mann-Whitney test).

Finally, we aimed to find baseline predictors of worse psychological outcome in T2. To this end, we first compared *via t*-test the level of DASS-21-Depression scores (T2) of caregivers who answered "Yes" or "No" to the first survey items (T1) regarding the presence of insomnia (sleep disturbances), depression and anxiety. Then, we built a series of stepwise linear regression models based on demographic features (i.e., caregiver's sex, age and education, patient's age and sex) and T1 survey responses to predict T2 more relevant psychological scores (PSQI-Sleep Quality, DASS-21-Depression and DASS-21-Anxiety), which were checked for normality of residuals by means of the Shapiro-Wilk test.

The prediction was realized with a leave-one-out cross-validation (LOOCV) design and its accuracy was evaluated as the correlation between actual and predicted score values. All analyses were ran using R software version 3.6.2.

RESULTS

Socio-Demographic Characteristics

Caregivers and non-caregivers controls were matched for age (caregivers: mean = 62 ± 14,6; non-caregivers: M = 62 ± 11,2 years; $p = 0.869$) and gender (female, caregivers: 69,4%, $n = 59$; non-caregivers: 64%, $n = 32$; $p = 0.492$) while education level was higher for non-caregivers (caregivers: mean = 11,6 ± 4,3; non-caregivers: mean = 13,06 ± 3,9 years; $p = 0.023$). The majority of caregivers were spouses (57,6%, n = 49) and cohabitant with the patient (67,1%, $n = 57$). Patients cared by caregivers recruited in the study (mean age 74,62 ± 11,3) were affected by dementia with different etiology: 51 with Alzheimer's Disease, 26 with dementia with Lewy Body, 6 with Frontotemporal Dementia, 2 with Vascular Dementia. Severity of cognitive impairment measured with the Clinician Dementia Rating (CDR) scale was mild in the majority of patients having CDR 1 in 60% ($n = 51$) of cases, CDR 2 (moderate stage) in 19% ($n = 16$) and CDR 3 (severe) in 21% ($n = 18$).

At T2, 81,2% ($n = 69$) of caregivers did not change work status during pandemic while 18,8% ($n = 16$) did it, such as implementation of remote working (9,4%, $n = 8$), loss of employment (4,7%, $n = 4$) and increase in the amount of work (4,7%, $n = 4$). Difficulties with the continuity of care were reported more frequently at T2 than T1 (38,8 vs.17,7%; $p = 0.006$). 15% ($n = 13$) needed the help of a formal caregiving.

Change of Frequency of Self-Reported Stress Related Symptoms

After 1 year of pandemic almost all caregivers (96,5%, $n = 82$) reported at least one stress-related symptom. Depression and perception of sadness were the most prevalent complaints, been reported by 60% ($n = 51$) of participants, followed by feelings of irritability (49,4%, $n = 42$), anxiety (45,9%, $n = 39$), insomnia (40%, $n = 34$), isolation (41,2%, $n = 35$), overwhelm (37,6%, $n = 32$), anguish (31,8%, $n = 27$) and abandonment (25,9%, $n = 22$). The 37,6% ($n = 32$) of the caregivers reported feeling of calmness.

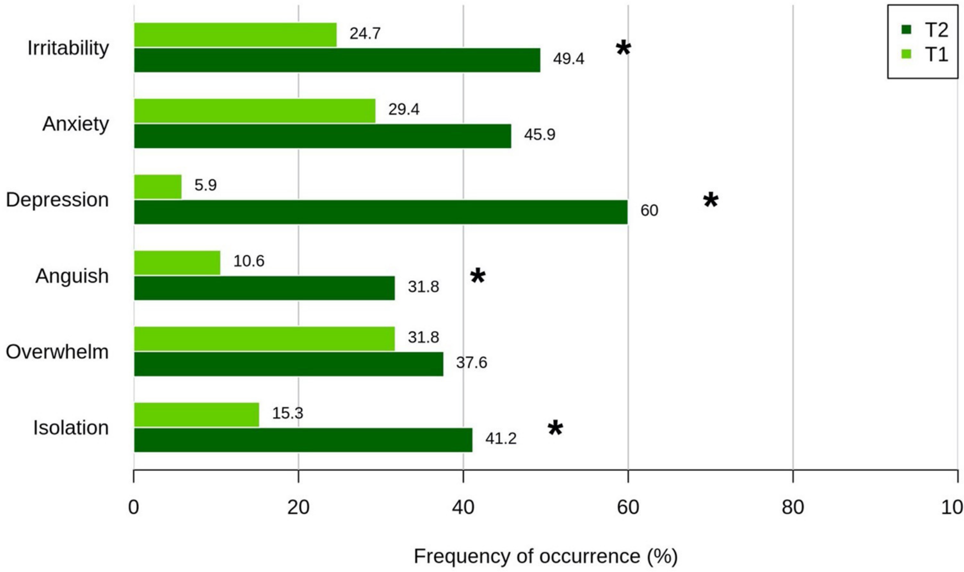

FIGURE 1 | Frequency of stress-related symptoms reported by caregivers during the first lockdown (T1, March 2020; light green) and 1 year after first restrictions (T2, March-April 2021, dark green). T1 and T2 proportion of answers were compared by means of a series of McNemar's χ^2 tests for paired comparisons. *Bonferroni-corrected significant difference.

The frequency of stress-related symptoms was increased at T2 respect to T1 (**Figure 1**). A significant difference surviving Bonferroni correction between T2 and T1 was found particularly for depression ($\chi^2(1) = 42{,}188$, $p < 0.001$), isolation ($\chi^2(1) = 14{,}7$; $p < 0.001$), irritability ($\chi^2(1) = 11{,}429$; $p < 0.001$), and anguish ($\chi^2(1) = 11{,}115$, $p < 0.001$). Anxiety was reported more frequently at T2 (45,9%) than T1 (29,4%) but difference did not survive multiple comparisons correction ($\chi^2(1) = 4{,}46$; uncorrected $p = 0.0.35$).

Psychological Long-Term Effects of Social Restrictions

In **Table 1** and **Figure 2A** are shown results obtained from the comparison of mean scores from scales assessing depression, anxiety, sleep abnormalities and coping strategies in caregivers and non-caregivers groups at T2.

Both caregivers and non-caregivers showed higher mean scores compared to non-pandemic normative data in the DASS-21-Depression and Anxiety scale (23) and worse sleep disturbances scores at the Sleep Quality Perception and Habitual Sleep Efficacy subitems of PSQI questionnaire (26). Higher levels of depression and more frequent use of sleep inducers were detected in caregivers compared to non-caregivers although differences did not survive multiple comparisons correction. Regarding COPE-NVI performances, caregivers showed lower scores in all coping dimensions. Taken together, these results suggest that a common feature shared by both caregivers and non-caregivers played a main role as stressor.

In the attempt to disentangle the relative contribution of different stressors, we identified two factors, namely being caregiver (Factor 1) and living in a pandemic situation (Factor 2). To this end, we selectively compared by means of a series of *t*-tests caregivers and non-caregivers both each other and with normative data, across the DASS-21, PSQI and COPE-NVI scales. Specifically, the role of Factor 1 was investigated by comparing caregivers and non-caregivers, while Factor 2 was highlighted by comparing non-caregivers with normative data (assuming that the normative sample for all scales was composed by individuals without caregiving duties and not dealing with a pandemic). Moreover, we evaluated the possible cumulative effect of both factors on stress symptoms (i.e., Factor 1 + Factor 2 = being a caregiver in a pandemic). The results of this analysis are reported in (**Figure 2B**), and showed that being a caregiver (Factor 1) was not the main driver of stress symptoms. Indeed, caregivers and non-caregivers scores were highly similar. On the other hand, living in a pandemic (Factor 2) contributed to increase anxiety, depression and sleep abnormalities ($p < 0.001$), and the combination of the two factors (being a caregiver in pandemic) showed a cumulative effect on the same symptoms as well as on sleep efficacy ($p < 0.001$). This suggests that being a caregiver further increased psychological outcomes of the pandemic especially regarding of sleep changes.

Forty-nine percent of caregivers ($n = 42$) had DASS-21-Depression scores above the cut-off levels for normality (>9) compared to 38% ($n = 19$) of non-caregivers, having more frequently extremely severe levels of depression compared to non-caregivers ($\chi^2(1) = 9.11$, $p = 0.0025$) (**Figure 3**). Regarding DASS-21-Anxiety, 32% ($n = 27$) of caregivers had scores above normal cut-off levels (>7) respect to 30% ($n = 15$) of non-caregivers. Caregivers had prevalent moderate and severe degrees of anxiety and non-caregivers had prevalent mild levels of anxiety (**Figure 3**).

Caregiver burden was higher during pandemic respect to normative values in the non-pandemic scenario (21) in all the three CBI-domains investigated, especially for time-dependence burden.

Results from correlation analysis between the variables detected at T2 for each group (caregivers and non-caregivers) are shown in (**Supplementary Figure 1**).

TABLE 1 | Descriptive measures (mean ± SD) of each questionnaires' component with caregivers and non-caregivers' comparisons. Descriptive measures (mean ± SD) for each component were shown by normative data (22, 23, 26).

Variables assessed at T2	Caregivers ($n = 85$) *Mean ± SD*	Non-caregivers ($n = 50$) *Mean ± SD*	*P (uncorrected.)*	*Normative data*
DASS-21-depression	11.96 ± 11.19	8.40 ± 7.07	0.025	3.5 ± 3.2
DASS-21–anxiety	5.94 ± 7.66	5.56 ± 5.07	0.73	2.4 ± 2.6
PSQI–sleep quality	1.19 ± 0.73	1.12 ± 0.52	0.53	0.80 ± 0.13
PSQI–habitudinal sleep efficiency	0.96 ± 1.16	0.62 ± 0.94	0.23	0.40 ± 0.31
PSQI–use of sleeping medication	0.76 ±1.29	0.24 ± 0.74	0.003	0.10 ± 0.10
PSQI–daytime dysfunction	0.60 ± 0.83	0.44 ± 0.64	0.22	0.60 ± 0.27
CBI–time dependence burden	10.84 ± 6.49	-	-	6.98 ± 5.89
CBI–developmental burden	7.94 ± 6.28	-	-	7.08 ± 5.89
CBI–emotional burden	3.04 ± 3.07	-	-	2.02 ± 3.04
COPE-NVI–social support	24.18 ± 7.94	25.74 ± 7.69	0.26	27.7 ± 8.4
COPE-NVI–avoidance strategies	21.27 ± 5.54	22.44 ± 6.83	0.31	23.5 ± 5.1
COPE-NVI–positive attitude	31.13 ± 8.04	32.96 ± 8.86	0.23	30.9 ± 6
COPE-NVI–problem orientation	32.84 ± 8.15	33.82 ± 8.44	0.51	32 ± 6.7

DASS-21, Depression, Anxiety and Stress Scale; PSQI, Pittsburgh Sleep Quality Index; CBI, Caregiver Burden Inventory; COPE-NVI, Coping Orientation to the Problem Experienced-Nuova Versione Italiana.

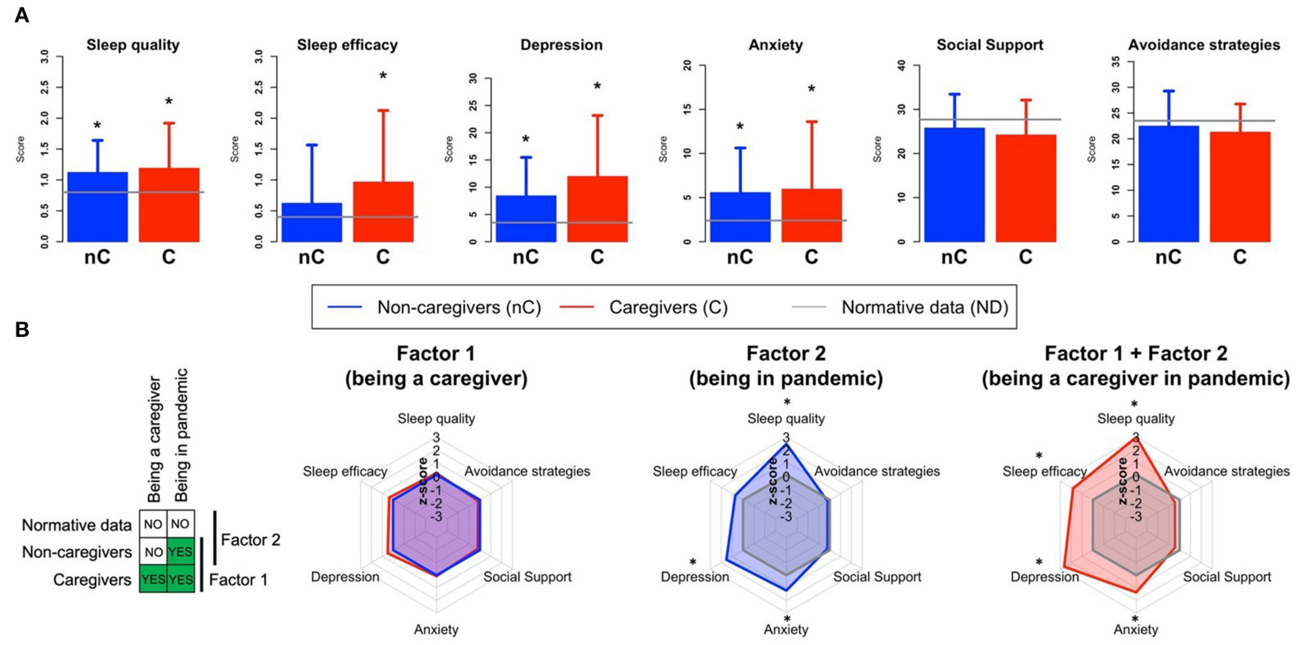

FIGURE 2 | (A) Comparisons between caregivers (C), non-caregivers (nC) for PSQI-Sleep Quality Perception, PSQI-Sleep Efficiency, DASS-Depression, DASS-Anxiety, COPE-NVI-Social Support and COPE-NVI-Avoidance Strategies scores. Dashed lines indicated normative data (ND) level for each component. Higher values for the PSQI quality perception and efficiency scores mean worse performance (bad quality perception and bad habitual efficiency). *significant difference with the normative data. **(B)** Radar plots show the results of the investigation of the role of different components of caregivers' stress on depression, anxiety, sleep abnormalities and coping strategies in T2. Factor 1 (being a caregiver) was analyzed by comparing caregivers and non-caregivers (both in pandemic). Factor 2 (being in a pandemic) was investigated by comparing non-caregivers with normative data (i.e., not collected during a pandemic). Finally, we investigated both Factor 1 and Factor 2 (being a caregiver in pandemic) by comparing caregivers and normative data. The radar plots show the comparison between two groups, with one group used as reference (i.e., the scores of one group were z-scored on the reference group). For Factor 1 the non-caregivers were the reference group, for Factor 2 and 3 we used the normative data as reference.

Within the caregivers' group, higher DASS-21 Depression scores correlated with higher CBI-developmental burden (r(85) = 0.66, $p < 0.05$) and emotional burden (r(85) = 0.57, $p < 0.05$). Depression levels were positively associated with higher levels of avoidance coping strategies both in caregivers (r(85) = 0.62 $p < 0.05$) and in non-caregivers (r(85) = 0.48 $p < 0.05$). Only in the caregivers' group higher depression scores correlated with higher anxiety (r(85) = 0.55, $p < 0.05$).

Baseline Predictors of Long-Term Psychological Outcomes

Self-reported perception of insomnia, depression and anxiety at T1 were significantly associated with DASS-depression symptoms at T2 ($p < 0.001$) (**Figure 4**).

We built a series of linear regression models from T1 variables to predict depression, sleep quality and anxiety at T2. Specifically, one model was built for each variable with the aim of highlighting the best set of T1 predictors of T2 symptoms.

The model best predicting depression at T2 included female sex ($p < 0.001$) low education level ($p = 0.04$), feelings of being overwhelm ($p = 0.02$) and isolated ($p = 0.04$) among all demographic, socio-relational, psychological, and COVID-19 care related variables selected from the baseline survey ($p < 0.001$) (**Table 2**).

Female sex was also predictive of worse sleep quality ($p = 0.01$) and higher anxiety ($p = 0.03$). Several psychological, burden-related and social variables explained anxiety 1 year after the first restrictions (**Table 2**).

Finally, we used the models described above to predict depression, anxiety and sleep quality scores at T2 with a Leave-One-Out Cross-Validation (LOOCV) design. The results showed that the model-predicted scores significantly correlated with actual scores in all cases (all $p < 0.001$), and again, the strongest correlation (i.e., prediction accuracy) observed was for depression ($r = 0.53$, $p < 0.001$) (**Supplementary Figure 2**).

DISCUSSION

Self-perceived of psychological stress-related symptoms were significantly increased after 1 year of COVID-19 pandemic in comparison with the frequency detected in the first lockdown phase. Ninety-six percent of caregivers reported at least one stress-related symptom, with depression being the most frequently reported 1 year after the beginning of pandemic, followed by irritability, anxiety, and sleep alterations. *Ad-hoc*

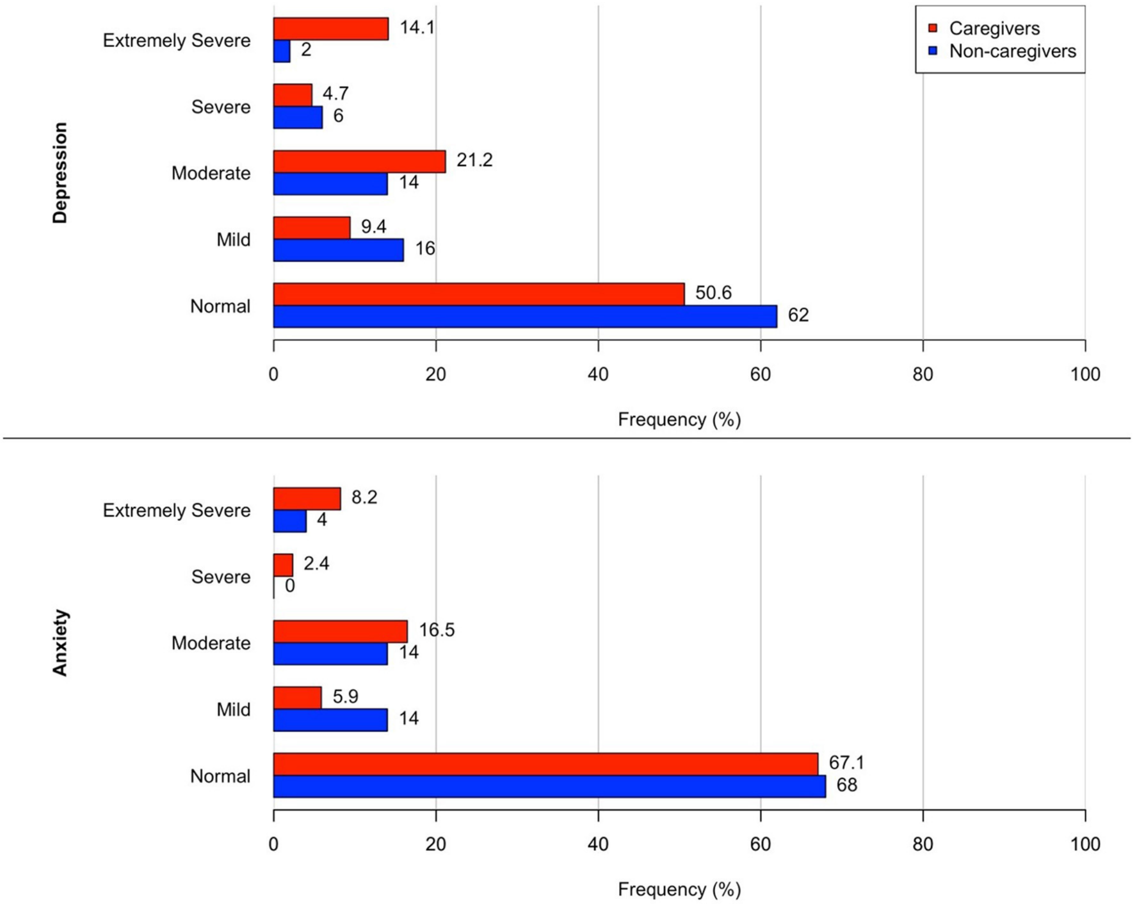

FIGURE 3 | Frequency distribution of DASS-21 Anxiety and Depression levels of severity in caregivers (red) and non-caregivers (blue) 1 year after first restrictions (T2, March-April 2021), Recommended cut-off scores for severity levels were considered as following: depression = normal 0–9, mild 10–13, moderate 14–20, severe > 21; anxiety = normal 0–7, mild 8–9, moderate 10–14, severe > 15 (23).

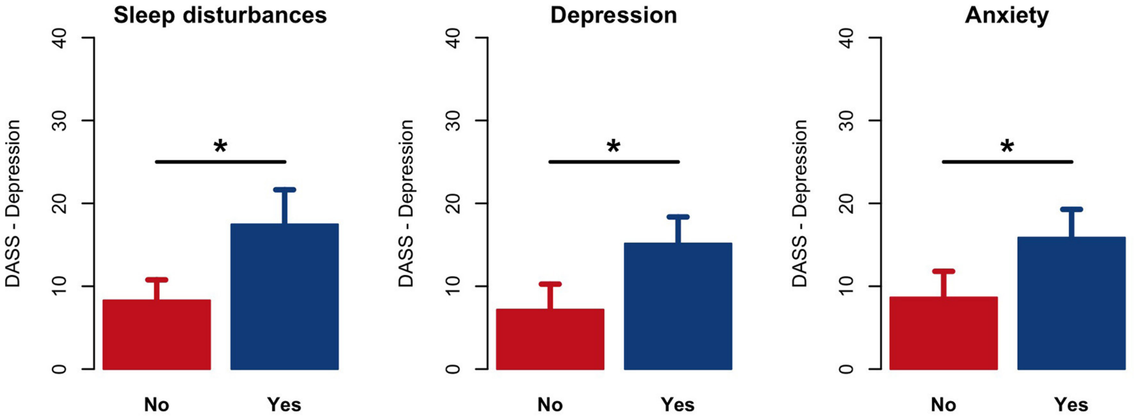

FIGURE 4 | Comparison results of DASS-21-Depression scores at T2 between those caregivers who answered "Yes" or "No" to the first survey items (T1) regarding the presence of insomnia (sleep disturbances), depression and anxiety. *$p < 0.001$.

TABLE 2 | Variables included in the predictive model for depression, sleep quality and anxiety levels at T2.

Predictors	Depression				Sleep quality				Anxiety			
	Beta	***SE***	***t***	***p***	***Beta***	***SE***	***t***	***p***	***Beta***	***SE***	***t***	***p***
Sex (caregiver)	−0.19	0.05	−3.61	<0.001	−0.19	0.05	−3.61	<0.001	−0.11	0.05	−2.17	0.03
Education (caregiver)	−0.01	0.01	−2.15	0.04	−0.01	0.01	−2.15	0.04	−0.01	0.01	−2.39	0.02
Isolation	0.17	0.08	2.12	0.04	0.17	0.08	2.12	0.04	-	-	-	-
Overwhelm	0.14	0.06	2.29	0.02	0.14	0.06	2.29	0.02	0.11	0.05	2.16	0.03
Distress	0.13	0.08	1.53	0.13	0.13	0.08	1.53	0.13	-	-	-	-
Care continuity	−0.1	0.06	−1.66	0.1	−0.1	0.06	−1.66	0.1	-	-	-	-
Irritability	-	-	-	-	-	-	-	-	0.18	0.06	2.94	<0.001
Life change–time	-	-	-	-	-	-	-	-	0.23	0.07	3.46	<0.001
Other people	-	-	-	-	-	-	-	-	0.13	0.05	2.79	0.01
Relation change–worse	-	-	-	-	-	-	-	-	−0.19	0.09	−2.14	0.04
Social support	-	-	-	-	-	-	-	-	0.09	0.05	1.99	0.05
Life change–relation	-	-	-	-	-	-	-	-	−0.15	0.09	−1.62	0.11

Predictive power of the model for depression F[6,78] = 8.54, $p < 0.001$, $R^2 = 0.35$; sleep quality: F[9,75] = 4.94, $p < 0.001$, $R^2 = 0.29$; and anxiety: F[6,78] = 1.45, $p < 0.001$, $R^2 = 0.24$.

scales showed increased levels of depression and worse sleep quality in both caregivers and non-caregivers, with higher frequency of severe degree of depression in caregivers. Increased levels of depressive symptoms were predicted by female sex, lower education, perception of isolation, and overwhelm at the beginning of pandemic.

Psychological Outcomes After 1 Year of Pandemic

The large prevalence of stress in family caregivers of patients with dementia has been observed during the first restrictions due to COVID-19 in Italy (14, 15, 17). This study highlighted evidence of a long-term psychological impact of isolation in dementia caregivers, with further increment of stress-related symptoms, particularly depression.

While only 5,9% of caregivers reported feelings of depression at the first lockdown in March 2020, the frequency of subjective depressive symptoms highly increased to 60% at 1-year follow-up. Self-perception of having depressive symptoms was confirmed by higher scores at DASS-Depression scale detected in almost 50% of caregivers (24). Increased levels of depression were also detected in 38% of persons not involved in caregiving, highlighting pandemic as a common stressor in the general population. During the first lockdown increased levels of depression were found in the general populations (6, 28, 29). Mild/severe levels of depression increased up to 32,3% in the last week of restrictions in Italy, compared to 15,4% before lockdown (6). Both caregivers and non-caregivers had also higher scores at the DASS-21-Anxiety at T2 compared to non-pandemic normative data without significant difference between the two groups.

Frequency distribution of self-perception of stress-related psychological symptoms changed from acute to long-term stage of pandemic. After 1-year of social isolation due to pandemic, depressive symptoms were more frequent than anxiety symptoms. This observation could be interpreted as persisting effects of a stressful situation. According to the General Adaptation Syndrome (30), the human reaction to an extreme stress situation occurs through three different stages. Firstly, the alarm reaction stage refers to the initial symptoms experienced in a stressful condition and involves a "fight-or-flight" response. This is a physiological response to stress that prepares the system either to flee or to protect itself in dangerous situations. Secondly, in the resistance stage the subject tries to manage and adapt to the negative effects of the prolonged stress. Finally, when the stress factors become chronic, the exhaustion takes place. Considering the COVID-19 pandemic a chronic stressor, after a first phase of alarm with a greater prevalence in caregivers of perceived anxiety, the exposure to prolonged uncertainty may have induced a phase of exhaustion with higher prevalence of depressive symptoms respect to the first phase of alarm with greater prevalence of perceived anxiety.

Caregivers and non-caregivers showed worse sleep quality perception and sleep efficacy than in normal conditions (25). Although caregivers had worse sleep quality than non-caregivers, differences did not survive correction for multiple comparison. Prior non-pandemic literature showed that dementia caregivers had poorer perceived sleep quality and shorter sleep duration than non-caregivers (31). Cellini and colleagues (7) showed that sleep-wake rhythms markedly changed in the Italian population during the first lockdown, with people spending more time in bed, but also reporting a lower sleep quality (7). Alteration in sleep quality and sleep efficacy was associated with an increased feeling of expansion of time. Several studies (32–35) during the first lockdown showed that one of the main consequences of restrictive measures was an alteration in people's relationship to time. Time seemed to pass far more slowly compared to before the lockdown. Moreover, since people suffering from depression already found that time passes slower than other people (36), lockdown could have increased this perception even more.

Baseline Predictors of Long-Term Psychological Outcomes

Caregivers' stress responses are mediated by a variety of factors relating to both socio-demographic and psychological variables such as gender, kinship ties (9), self-efficacy and coping strategies (37). In our study depression, poor sleep quality and anxiety were predicted by lower education and female sex. Being a female caregiver is considered an important risk factor for health problems, depressive symptoms and caregiver burden (9, 38). Being female is also a risk factor of negative psychological impact during COVID-19 lockdown (5, 6). Women could get overloaded with additional family, household and working activities under restrictions (6).

Among psychological variables, presence of feelings of overwhelm at the beginning of pandemic was the best predictors of long-term depression and anxiety, while feelings of isolation and sleep alterations were predictors of subsequent depression. Increased anxiety was predicted by changes regarding socio-relational variables, such as the amount of time needed for assistance, decreased quality in the relationship with the care-receiver, need of support. These predictive factors, which affect mood and sleep over the long term, should be taken in consideration for prevention strategies in caregivers of people with dementia.

Caregivers Burden and Coping Strategies

Caregivers had higher levels in time dependence burden, developmental/psychological burden and emotional burden during the COVID-19 pandemic, indicating that the restrictive measures might have charged caregivers with additional challenges and responsibilities affecting the caregiver burden in normal condition (18, 39).

Higher levels of developmental/psychological burden and emotional burden were positively associated with higher depression. The significant relationship between developmental burden and depression is consistently reported in literature (40, 41). The developmental/psychological dimension of caregiver burden is associated with depression to a greater extent than other types of caregiver burden (42), and caregivers who feel deprived of doing things were more likely prone to depression (41). Regarding the emotional burden, past studies failed to find significant associations with depression (40, 41).

It is known that subjects tend to respond to increasing burden and stressful events with three different types of internal coping strategies: emotion-focused strategies (acceptance, emotional support, humor, positive reframing, and religion), problem-focused strategies (active coping, instrumental support, and planning) and dysfunctional coping (behavioural disengagement, denial, self-distraction, self-blame, substance use) (43). Within the caregivers' group, increased levels of depression and anxiety were closely related with dysfunctional coping strategies in pandemic. These findings are consistent with previous research in caregivers underlying an association between stress-coping strategy focused on avoidance and levels of depression, anxiety, and burden (44–48). Avoidance coping can be useful during the first phase of an uncontrollable stressful situation, as protective and defensive strategy. Yet, with the chronicity of the stressful situation, this strategy is less used with increasing risk of depression (22, 49).

Social support represents another external component of coping (50). Caregivers tend to use less social support strategies and avoidance strategies (22). Social support is often negatively correlated with depressive symptoms in elderly, and in caregivers of patients with Alzheimer's disease (51). Furthermore, despite social support is generally considered a protective factor for depression (52), female caregivers usually tend to refuse other's help, isolating themselves (53), with a possible increasing of subjective burden perception (9).

Our results indicate that maintaining lower social support due to persistence of restrictions and dysfunctional coping strategies are risk factor for developing of depressive symptoms in caregivers of persons with dementia.

Study Limitations

There are a few limitations of this study to be considered. First, the study started during the acute phase of pandemic and collection of data using *ad-hoc* scales assessing behavioral features such as depression, anxiety, sleep alteration, and coping strategies of a stressful events was not feasible. Therefore, these measures were only available at follow-up time-point and direct comparison between baseline and follow-up assessments was not allowed. Nonetheless, we could analyze other baseline variables obtained within a large survey performed in the acute pandemic stage allowing to investigate predictive demographic, social and psychological features of worse mental health outcomes in caregivers. Secondly, we did not assess correlations between severity of patients' behavioral and psychological burden and symptoms of caregivers distress. Finally, although the present study did not acquire information about caregivers' mental state before the pandemic outbreak, the administration of the interview in two different periods during pandemic allowed to track changes of psychological well-being during a chronic stressor in add-on to the burden due to caregiving.

CONCLUSION

In accordance with some recent studies (6, 7, 14, 15, 19), we confirm long-term psychological stress-related symptoms including depression, anxiety, and sleep quality disorders in caregivers of persons with dementia during COVID-19 restrictions in Italy. Self-perceptions of higher levels of depression, anxiety and poor sleep quality and sleep efficacy were confirmed by standardized questionnaires. Depression was more frequent after 1 year of pandemic that at the beginning of lockdown suggesting that chronic exposure to stressful events may have led to exhaustion of psychological resources. Female caregivers and those with lower education have the higher risk of depression.

Providing information about effective coping strategies together with "how to cope" may be useful to deal and cope with emergent issues (54). To this purpose, a combined support intervention targeting multiple levels of the stress/health model could produce a significant improvement in both caregiver burden and wellbeing, focusing on reducing caregivers' loneliness and on psychoeducational interventions to relieve anxiety, enhance awareness and healthy behaviors and reduce family conflicts, promoting the active listening, and mutual support between family members (55).

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Azienda Ospedaliera of Padova (Italy). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CB: designed the study and wrote the manuscript. TB: collected data and wrote the draft. MZ: revised the draft. IR: supervised the study and revised the draft. SM: collected the data. AZ: analyzed the data and revised the draft. AC: designed the study, analyzed the data, and revised the manuscript. 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.2022.826371/full#supplementary-material

Supplementary Figure 1 | Correlation matrices within the caregiver' group (left) and the non-caregivers' group (controls; right) between the components of each standardized questionnaire administered. White spaces indicate that there is no correlation.

Supplementary Figure 2 | Correlation between the sleep quality, depression and anxiety's scores predicted by the model vs. the scores really obtained at T2 ($p < 0.001$).

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CAG Repeats Within the Non-pathological Range in the HTT Gene Influence Personality Traits in Patients With Subjective Cognitive Decline: A 13-Year Follow-Up Study

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Objective: *HTT* is a gene containing a key region of CAG repeats. When expanded beyond 39 repeats, Huntington disease (HD) develops. *HTT* genes with <35 repeats are not associated with HD. The biological function of CAG repeat expansion below the non-pathological threshold is not well understood. In fact higher number of repeats in HTT confer advantageous changes in brain structure and general intelligence, but several studies focused on establishing the association between CAG expansions and susceptibility to psychiatric disturbances and to other neurodegenerative disease than HD. We hypothesized that *HTT* CAG repeat length below the pathological threshold might influence mood and personality traits in a longitudinal sample of individuals with Subjective Cognitive Decline.

Methods: We included 54 patients with SCD. All patients underwent an extensive neuropsychological battery at baseline, *APOE* genotyping and analysis of *HTT* alleles. We used the Big Five Factors Questionnaire (BFFQ) and Hamilton Depression Rating Scale (HDRS), respectively, to assess personality traits of patients and depression at baseline. Patients who did not progress to Mild Cognitive Impairment (MCI) had at least 5-year follow-up time.

Results: In the whole sample, CAG repeat number in the shorter *HTT* allele was inversely correlated with conscientiousness (Pearson $= -0.364$, $p = 0.007$). There was no correlation between HDRS and CAG repeats. During the follow-up, 14 patients [25.93% (95% C.I. = 14.24–37.61)] progressed to MCI (MCI^{+}) and 40 [74.07% (95% C.I. = 62.39–85.76)] did not (MCI^{-}). When we performed the same analysis in the MCI^{+} group we found that: CAG repeat length on the shorter allele was inversely correlated with energy (Pearson $= 0.639$, $p = 0.014$) and conscientiousness (Pearson $= -0.695$, $p = 0.006$). CAG repeat length on the longer allele was inversely correlated with conscientiousness (Pearson $= -0.901$, $p < 0.001$) and directly correlated with emotional stability (Pearson $= 0.639$, $p = 0.014$). These associations were confirmed also by multivariate analysis. We found no correlations between BFFQ parameters and CAG repeats in the MCI$^-$ group.

Discussion: Personality traits and CAG repeat length in the intermediate range have been associated with progression of cognitive decline and neuropathological findings consistent with AD. We showed that CAG repeat lengths in the *HTT* gene within the non-pathological range influence personality traits.

Keywords: subjective cognitive decline (SCD), mild cognitive impairment (MCI), Huntington (disease), Alzheimer's disease, HTT CAG repeat, personality, intermediate alleles, big five questionnaire

INTRODUCTION

Huntingtin (*HTT*) is a gene coding for a soluble peptide which is widely expressed during development, being essential for embryogenesis (1), and plays crucial roles in axonal trafficking, regulation of gene transcription, and cell survival in post developmental life (2). *HTT* contains a key region of CAG repeats which is translated into a corresponding polyglutamine stretch (3). The expansion of CAG triplet beyond 40 repeats leads to the dysfunction and death of neurons in the striatum and in other brain regions, causing Huntington's disease (HD) (4), a neurodegenerative disorder characterized by cognitive, motor and psychiatric disturbance (5).

Several studies showed that carriers of *HTT* CAG repeats in the pathological range (HD carriers) had a defined personality profile, characterized by higher conscientiousness, lower emotional stability (6) and lower social cognition (7) as compared to controls.

However, there are only a few studies exploring the effect of CAG repeats in the non-pathological range on personality traits and mood. Killoran et al. showed that the individuals with a number of CAG repeats in the range of the so-called intermediate alleles (IA) (27–35 CAG repeats) were more likely to experience trouble with motivation, to have thoughts of suicide and generally reported more mood and behavior problems than those with <27 repeats (8). Other authors showed that IAs of *HTT* are associated with higher prevalence of neurodegenerative conditions, such as Alzheimer's disease (AD) (9) and to the non-fluent variant of primary progressive aphasia (10). IA proportion has been reported to be significantly increased in AD patients (8) as compared to healthy controls and *HTT* levels were increased in neuronal cells in the hippocampus of AD cases (11). Alzheimer-type lesions, in turns, were found more frequently in autopsy of HD patients [from 67 (12) to 80% (13)] as compared to healthy controls. Finally, a recent work by our group found that *HTT* CAG expansions influence neuropsychological functions in individuals experiencing Subjective Cognitive Decline (SCD) or Mild Cognitive Impairment (MCI) (14).

Therefore, in the present study we hypothesized that *HTT* CAG repeat length below the pathological threshold might influence mood and personality traits in a longitudinal sample of individuals with SCD.

MATERIALS AND METHODS

Participants and Clinical Assessment

We included 54 consecutive patients who complained memory disorder and self-referred to the Center for Alzheimer's disease and Adult Cognitive Disorders of Careggi Hospital in Florence. Inclusion criteria were: (1) complaining of cognitive decline with a duration of $\geq$ 6 months; (2) normal functioning on the Activities of Daily Living and the Instrumental Activities of Daily Living scales (15); (3) unsatisfied criteria for dementia or MCI at baseline (16, 17). Exclusion criteria were: (1) history of head injury, current neurological and/or systemic disease, symptoms of psychosis, major depression, alcoholism or other substance abuse. No patient had family history of Huntington disease.

The local ethics committee approved the protocol of the study. All participants gave written informed consent. All procedures involving experiments on humans have been done in accordance with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accordance with the Helsinki Declaration of 1975. Specific national laws have been observed.

At baseline, all participants underwent: (1) comprehensive family and clinical history, general and neurological examination; (2) extensive neuropsychological battery including assessment of cognitive complaints, depressive symptoms, and premorbid intelligence; (3) brain MRI or CT scan; (4) peripheral blood collection to analyze Apolipoprotein E (*APOE*) and *HTT* genotypes. A positive family history of dementia was defined as one or more first-degree relatives with documented cognitive decline. Disease duration was defined as the time from the onset of symptoms to the first neurological or neuropsychological evaluation.

All patients underwent clinical and neuropsychological follow-up every 12 or 24 months. Progression to MCI and conversion to AD were defined according to the National Institute on Aging-Alzheimer's Association (16, 17).

Neuropsychological Assessment

All patients underwent an extensive neuropsychological assessment, consisting of: global measurements (Mini-Mental State Examination), tasks exploring verbal and spatial working memory (Digit Span; Corsi Tapping Test), verbal long-term memory (Five Words and Paired Words Acquisition; Recall after 10 min; Recall after 24 h; 15 Words of Rey Babcock Short Story Immediate and Delayed Recall), language [Token Test; Category Fluency Task, Phonemic Fluency Test (15)],visual-spatial abilities (Rey-Osterrieth Complex Figure copy), visual-spatial long-term memory [Rey-Osterrieth Complex Figure test (18)], attention/executive function [Dual Task (19), and Trail Making Test (20)], everyday memory (Rivermead Behavioral Memory Test) (18). All raw test scores were adjusted for age, education and gender according to the correction factor reported in validation studies for the Italian population (15, 18–22).

Cognitive complaints were explored using a survey based on the Memory Assessment Clinics-Questionnaire (MAC-Q) (23).The presence and severity of depressive symptoms was evaluated by the 22-item Hamilton Depression Rating Scale (HRSD) (24). Premorbid intelligence, as a cognitive reserve proxy, was assessed at by *Test di Intelligenza Breve* (TIB, i.e., Brief Intelligence Test) (25), an Italian version of the National Adult Reading Test (NART) (26).

Personality Traits

Personality traits were assessed by the Big Five Factors Questionnaire (BFFQ), a self-administered inventory following a widely accepted five-traits personality model (27). The five dimensions of the BFFQ are: (1) emotional stability: the resilience to unpleasant emotions like anger, anxiety, depression, self-pity and worry; (2) energy: being active, assertive, energetic, enthusiastic, outgoing, and talkative; (3) conscientiousness: the degree of organization, persistence, and motivation in goal-directed behavior; (4) agreeableness: the quality of interpersonal orientation to compassion, including adjectives like appreciative, forgiving, generous, kind, sympathetic, and trusting; (5) openness to culture and experience: active imaginations, aesthetic sensitivity, intellectual curiosity, wide variety of interests. Each of the five dimensions of personality consists of two sub-dimensions defined in turn by 24 items. Subjects rated their level of agreement on a five-point scale ranging from "strongly agree" to "strongly disagree".

HTT and *APOE* Genotyping

Subjects' DNA was isolated from peripheral blood using a standard automated method (QIAcube, QIAGEN). *APOE* genotypes were investigated by High Resolution melting Analyses (HRMA) (28). Two sets of PCR primers were designed to amplify *APOE* regions encompassing rs7412 [NC_000019.9:g.45412079C>T] and rs429358 (NC_000019.9:g.45411941T>C). Patients who were carriers of the ε4 allele (one or two *APOE*ε4 alleles) were classified as *APOE*$\varepsilon 4^+$, while patients who were not carriers of ε4 allele (no *APOE*ε4 alleles) were classified as *APOE*$\varepsilon 4^-$.

HTT CAG repeat expansion was determined by a polymerase chain reaction amplification assay, using fluorescently labeled primers (29). The size of the fragment was determined by capillary electrophoresis using SeqStudio Genetic Analyzer (ThermoFisher) and the GeneMapper version 4.0 software (Applied Biosystems). A set of *HTT* CAG alleles, whose lengths were confirmed by DNA sequencing, was used to provide size standards. Patients who were carriers of the intermediate allele [at least one *HTT* allele with CAG-repeat sizes of 27–35 repeats (5)] were classified as IA^+, while patients who were not carriers were classified as IA^-.

Statistical Analysis

We tested for normality by the Shapiro-Wilk test. Patient groups were characterized by using means and standard deviations, median and interquartile range (IQR), frequencies or percentages and 95% confidence interval (95%C.I.) for continuous distributed variables, continuous non-normally distributed variables and categorical variables, respectively. Depending on the distribution of our data, we used *t*-test or non-parametric Mann-Whitney-U Tests for between-groups comparisons, Pearson's correlation coefficient or non-parametric Spearman's ρ (rho) to evaluate correlations between groups' numeric measures, and chi-square tests to compare categorical data. We calculated the size effect by Cohen's *d* for normally distributed numeric measures, η^2 for Mann-Whitney-U Test and Cramer's *V* for categorical data. We used backward linear regressions as multivariate analyses. Bonferroni correction was applied to correct for multiple comparisons dividing 0.05 by the numbers of variables included in each analysis (adjusted statistical significance levels are reported in the caption of each table). All statistical analyses were performed with SPSS software v.25 (SPSS Inc., Chicago, USA) and the computing environment R 4.0.3 (R Foundation for Statistical Computing, Vienna, 2013).

RESULTS

Demographic and Clinical Features at Baseline, Frequency Distributions of CAG Repeats and Comparison Between IAs^- and IAs^+

Our sample included 37 male and 13 females. Mean age at baseline was 60.80 (± 7.33). All the patients were Caucasian. Median CAG repeats lengths were 18.00 (IQR 4.00, range: 12–29) in the shorter allele and 21.00 (4.00, range: 16–31) in the longer allele. The most common *HTT* alleles had 18 (shorter alleles) and 18, 21 and 22 (longer alleles) CAG-repeats (**Figure 1**). Six out of 54 patients [11.11% (95% CI 2.73–19.49)] were carriers of intermediate alleles of *HTT* gene (IAs^+). Among these, one patient was homozygous for IA (29 and 31 CAG-repeats). There was no significant difference in disease duration, family history of AD, sex, years of education, TIB, MMSE, HDRS and BFFQ score between IAs^- and IAs^+. There was no difference in any neuropsychological test score between IAs^- and IAs+.

Patients were followed-up for a median time of 13 years. During the follow-up, 14 patients [25.93% (95% C.I. = 14.24–37.61)] progressed to MCI (MCI^+) and 40 patients [74.07% (95% C.I. = 62.39–85.76)] did not progress to MCI (MCI^-) with a mean follow-up time of 15.29 (IQR 4.44). Follow-up time of $MCI^-$was significantly longer than mean progression time of

MCI$^+$ [8.35 (IQR 6.33), $p < 0.001$, $\eta^2 = 0.27$] years. There was no difference in proportion of IA between MCI$^-$and MCI$^+$ ($p = 0.661$).

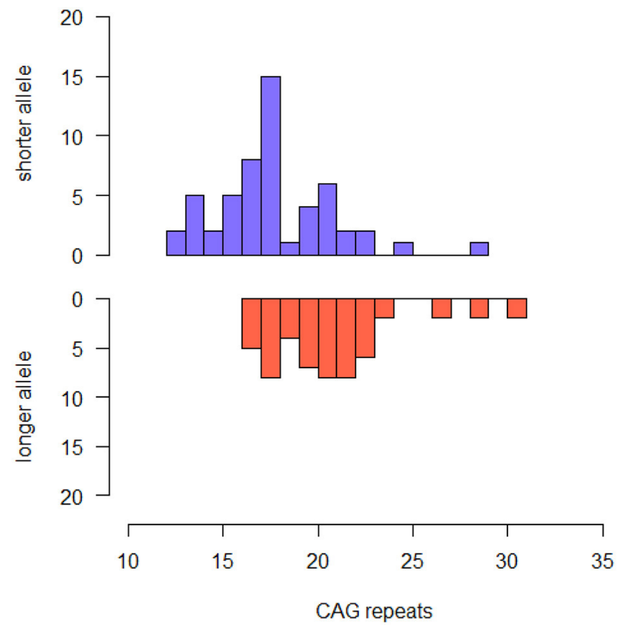

FIGURE 1 | Histogram describing the frequency of CAG repeat lengths of shorter and longer alleles in the whole sample.

At baseline no significant differences were found with respect to disease duration, family history of AD, sex, years of education, TIB, MMSE, HDRS and BFFQ score between MCI$^-$and MCI$^+$ (**Table 1**).

Correlations Between Personality Traits, Demographic and Genetic Features

In the whole sample, energy was directly correlated with conscientiousness (Pearson = 0.318, $p = 0.019$) and openness (Pearson = 0.614, $p < 0.001$). Emotional stability was directly correlated with conscientiousness (Pearson = 0.357, $p = 0.008$) and inversely correlated with HDRS (Pearson = −0.30, $p = 0.028$). Openness was significantly higher in man than in women (51.47 ± 10.51 vs. 4481 ± 9.80, $p = 0.028$, Cohen's $d = 0.66$). BFFQ scores were not associated with demographic features, neuropsychological scores and *APOE* genotype.

CAG repeat number in the shorter allele was inversely correlated with conscientiousness (Pearson = −0.364, $p = 0.007$). There was no correlation between CAG repeat numbers and HDRS scores.

We performed this analysis in the MCI$^-$ and MCI$^+$ groups separately. In the MCI$^+$ group CAG-repeat length on the shorter allele was inversely correlated with conscientiousness (Pearson = −0.695, $p = 0.006$, **Figure 2A**) and energy (Pearson = −0.694 $p = 0.006$, **Figure 2B**); CAG repeat length on the longer allele was inversely correlated with conscientiousness (Pearson = −0.901, $p < 0.001$, **Figure 2C**) and directly correlated with emotional stability (Pearson = 0.639, $p = 0.014$, **Figure 2D**). We found no

TABLE 1 | Baseline features in the whole group and comparison between MCI$^-$ and MCI$^+$.

	SCD	MCI$^-$	MCI$^+$
N [% (95% C.I.)]	54	40 [74.07 (62.39–85.76)]	14 (25.93 [14.24–37.61])
Age at baseline, mean (SD)	60.80 (7.33)	59.99 (7.63)	63.11 (6.073)
Age at onset, mean (SD)	56.13 (9.09)	54.73 (9.67)	60.14 (5.75)
Disease duration, median (IQR)	3.33 (5.09)	3.58 (4.02)	2.72 (1.30)
Follow-up time, median (IQR)	15.29 (4.67)	**15.29 (4.44)*****	**8.35 (6.33)*****
Sex (women/men)	37/13	26/14	11/3
Family history of dementia, % (95% C.I.)	51.85% (38.52–65.18)	52.50% (37.02–67.98)	50.00% (23.81–76.19)
Years of education, median (IQR)	12.50 (8)	12.58 (4.41)	11 (5.97)
TIB, median (IQR)	113.09 (4.57)	113.11 (4.49)	113.04 (20.29)
CAG repeat (shorter allele), median(IQR)	18.00 (4)	18.00 (4)	17.50 (4)
CAG repeat (longer allele), median(IQR)	21.00 (4)	21.00 (4)	19.50 (7)
APOE $\varepsilon4^+$, % (95% C.I.)	31.71% (17.46–45.95)	17.50% (5.72–29.28)	42.86% (16.93–68.78)
IA$^+$ % (95% C.I.)	11.11% (2.73–19.49)	66.67% (28.95–104.39)	33.33% (−4.39–71.05)
MMSE, median (IQR)	29.00 (1)	30.00 (1)	29.00 (1)
HDRS, median (IQR)	25.00 (6.00)	25.00 (6.00)	26.50 (7.75)
MAC-Q, mean (SD)	25.84 (2.57)	25.84 (2.54)	25.81 (2.79)
Energy, mean (SD)	45.50 (10.24)	46.55 (10.42)	42.50 (9.42)
Friendship, mean (SD)	49.80 (9.12)	48.80 (9.27)	52.64 (8.33)
Conscientiousness, mean (SD)	46.83 (9.86)	45.75 (10.24)	49.93 (8.23)
Emotional Stability, mean (SD)	49.28 (10.52)	48.05 (10.04)	52.79 (11.45)
Openness, mean (SD)	46.91 (10.41)	47.20 (10.34)	46.07 (10.80)

Demographic data. Values quoted in the table are mean (SD), median (IQR), percentages (95% C.I.), or frequencies. Age at baseline, age at onset, follow-up time, disease duration are expressed in years. Statistical significance received a Bonferroni adjustment and being accepted at the $p < 0.003$ and $p < 0.016$ for categorical variables ($^{***}p < 0.001$, $\eta^2 = 0.27$). TIB: MMSE, Mini Mental State Examination; HDRS, Hamilton Depression Rating Scale; MAC-Q, Memory Assessment Clinics-Questionnaire.

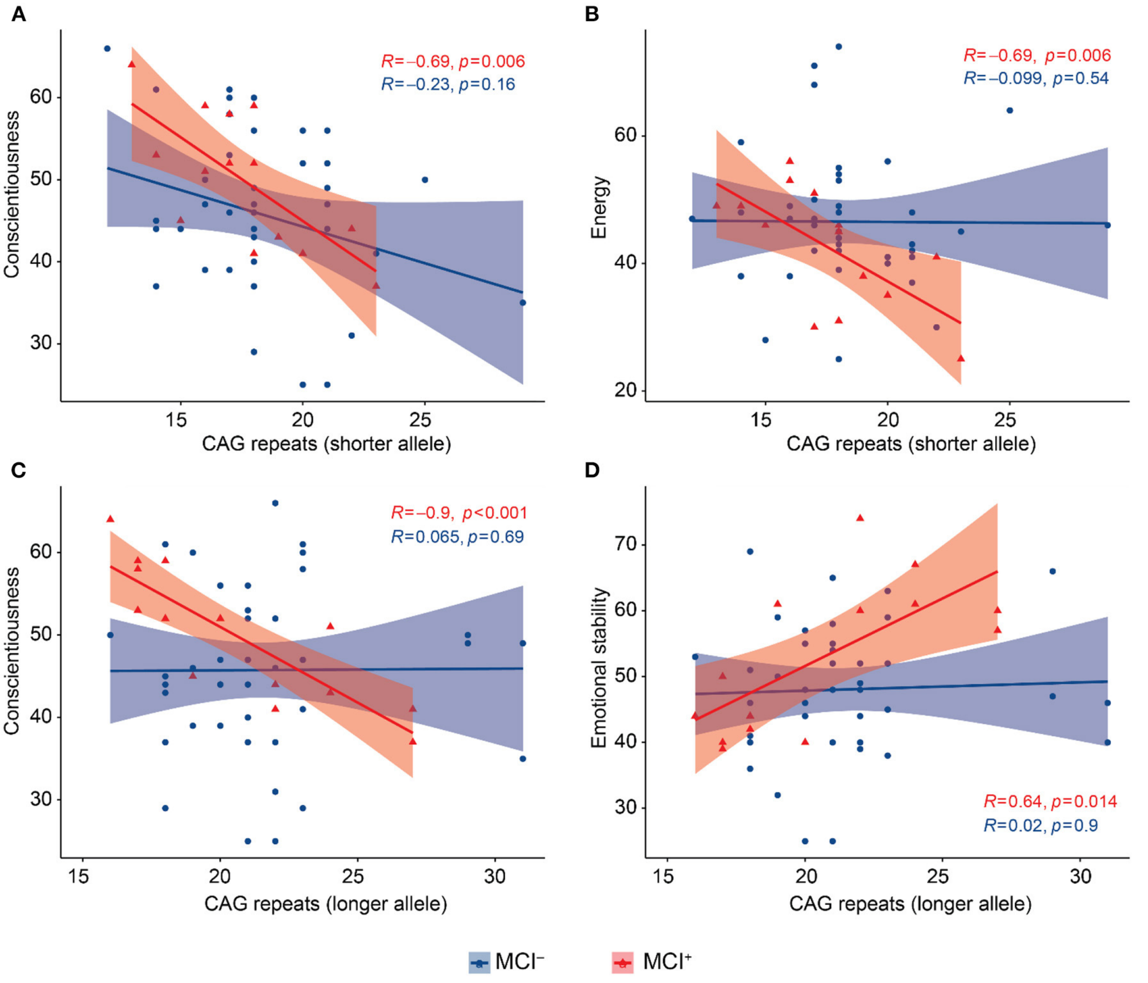

FIGURE 2 | Scatter plots with lines of best fit (95% C.I.) showing the relationship between CAG repeat lengths and BFFQ dimensions in MCI$^-$ and MCI$^+$. Pearson correlation coefficient (R) and level of significance (p) are reported (statistical significance at the $p < 0.05$). **(A)** CAG repeat length on the shorter allele was inversely correlated with conscientiousness in MCI$^+$. **(B)** CAG repeat length on the shorter allele was inversely correlated with energy in MCI$^+$. **(C)** CAG repeat length on the longer allele was inversely correlated with conscientiousness in MCI$^+$. **(D)** CAG repeat length on the longer allele was directly correlated with emotional stability in MCI$^+$.

correlations between BFFQ parameters and CAG repeats in the MCI$^-$ group. There was no association between HDRS score and CAG repeat length neither in MCI$^-$ nor in MCI$^+$ group.

Multivariate Analysis and Regression Models

To ascertain that the associations between personality traits and CAG repeat lengths were independent from confounding factors, we performed multiple regression analyses in the MCI$^+$ group. Energy, emotional stability and conscientiousness were considered as dependent variables one at a time. CAG repeat numbers in the shorter and longer allele were both considered as independent variables. Variables that have been found to be associated with personality traits have been considered as covariates. There was no evidence of multicollinearity among covariates, as assessed by tolerance values >0.10. Energy remains significantly associated with CAG repeat length on the *HTT* shorter allele [$B = -2.33$ (95%CI = −4.02:−6.4), $p = 0.011$]; emotional stability remains significantly associated with CAG repeats on the *HTT* longer allele [$B = 2.30$ (95%CI = 1.26:3.34), $p = 0.001$] and with HDRS [$B = -1.49$ (95%CI = −2.24:−0.73), $p = 0.001$]; conscientiousness remains significantly associated with *HTT* longer allele [$B = -1.46$ (95%CI = −2.26:−0.66), $p = 0.002$] (**Table 2**).

Discussion

In the present study we explored the association between CAG repeat lengths in the *HTT* gene with personality traits and mood in a sample of SCD patients followed-up for a median time of 13 years. As the main result we found that the length of CAG repeats in the *HTT* gene within the non-pathological range are associated with personality traits in SCD patients who progressed to MCI but not in patients who remained stable. In particular, lower level of conscientiousness and energy and

TABLE 2 | Multiple regression model.

Energy	***B***	**95% C.I. for B**		**β**	***P***
		Lower	**Upper**		
(Constant)	83.42	53.36	113.49	–	<0.001
***HTT* shorter**	**−2.33**	**−4.02**	**−6.4**	**−0.66**	**0.011**
Conscientiousness					
(Constant)	100.32	82.35	118.281	–	< 0.001
HTT shorter	−1.07	−2.19	−0.05	−0.34	0.059
***HTT* longer**	**−1.46**	**−2.26**	**−0.66**	**−0.66**	**0.002**
Emotional stability					
HTT shorter	1.35	−0.09	2.78	0.45	0.063
***HTT* longer**	**2.30**	**1.26**	**3.34**	**0.94**	**0.001**
HDRS	**−1.49**	**−2.24**	**−0.73**	**−0.74**	**0.001**
Conscientiousness	0.368	0.07	0.66	0.34	0.020

Unstandardized Regression Coefficients (B) and 95% Confidence Intervals (95% C.I.), standardized coefficient (β) and p-value (p), are reported. Statistical significance received a Bonferroni adjustment and was accepted at the $p < 0.012$ (in bold characters).

higher level of emotional stability were correlated with higher number of CAG repeats. These associations were independent from possible confounding variables and were not influenced by depressive symptoms measured by HDRS. An association between *HTT* variants and personality traits was shown by Larsen et al. (6). Interestingly, these authors found opposite associations: HD carriers and healthy first-degree relatives (individuals at risk for HD) had greater conscientiousness and lower emotional stability as compared to controls. However, they did not find any difference between HD carriers and non-carriers at risk for HD, concluding that there is no direct effect of the *HTT* gene on personality traits. The discrepancies with our results could be due to the different populations considered. Larsen et al. enrolled both HD carriers and HD non-carriers with family history for HD while none of the individuals included in our sample had family history for HD. It is known that HD symptoms and onset are influenced also by modifier genes other than *HTT* (30, 31). Therefore, we could speculate the opposite effect of *HTT* in individuals at risk and not at risk for HD might follow a polygenic effect.

Moreover, Larsen et al. did not report CAG repeat numbers of the control group. So, we do not know if the effect on personality traits is due to the higher number of CAG repeats or to the family history for HD. We aim to test these hypotheses in future studies on larger samples.

To the best of our knowledge there are no previous reports showing an effect of *HTT* CAG repeat length on personality traits in non-HD patients. Even more importantly, our results showed that his effect may depend on the pathological background of the SCD.

SCD is an heterogeneous condition including normal aging, psychiatric conditions, neurologic and medical disorders, substance use, and medication (32). Longitudinal data allowed us to isolate patients whose memory symptoms were more probably due to a neurodegenerative condition underlying SCD. In other words, it is probable that the SCD of patients who progressed to MCI was due to a degenerative disease already active at the SCD stage.

We already showed that CAG repeat lengths in *HTT* may differently influence neuropsychological performances according to cognitive status of subjects (14). In more detail, we showed that a higher number of GAC repeats in the non-pathological range was associated with higher scores in tasks assessing executive function, memory, visual–spatial ability and language in SCD patients but to lower scores in the same cognitive domain in MCIs. Therefore, we might speculate that the effect found in this study of *HTT* variants both on cognitive function and on personality traits may be evident only when a pathological process occurs. In other words, as mutant *HTT* leads to a defined personality profile in HD patients, the number of CAG repeats in *HTT* influence personality traits and neuropsychological function also in patients with a probable neurodegenerative process underlying a subjective or objective cognitive decline.

The biological substrate of this effect might lie in the interaction of *HTT* protein with a number of proteins with a role in microtubule-based axon trafficking (33, 34). In particular, wild-type Hintingtin protein specifically enhances the vesicular transport of Brain Derived Natriuretic Factor (BDNF) (35), a neurotrophic factor involved in synaptic connections (36), neural growth (37), synaptic plasticity (38), and essential for long-term potentiation underlying hippocampus-related memory (14, 39). PolyQ tracts in Huntingtin protein stabilize interactions (40), according to a non-linear relation with the best function reached at an intermediate number of CAG repeats and then showing a progressive decrease (41). We might speculate that the interaction between Huntingtin and BDNF or the effect of this interaction on axonal trafficking may depend not only on the length of PolyQ tracts, but also on a possible pathological process underlying the progression from SCD to MCI. We think that our results could represent first clinical evidence to further explore this mechanism.

It would be interesting to know if this effect changes over time, for instance, collecting BFFQ data also at the end of the follow-up and in patients without SCD.

The relationships of personality traits with SCD and risk of progression of cognitive decline have been already reported by previous works with different results. Lower conscientiousness has been associated with higher complaints about their memory in SCD (42). Prospective studies indicate that individuals who score higher on conscientiousness have a slower rate of cognitive decline and reduced risk of developing dementia, even in the presence of AD neuropathology (43, 44). Conscientiousness is even associated with less amyloid deposition in cognitively normal aging (45). Low emotional stability has been reported as a risk factor for clinical AD and memory deficit has been associated with a faster rate of cognitive decline (46), while higher emotional stability seems to moderate the effect of the *APOEε4* on cognitive function and risk of dementia (47). On the contrary, in a previous study we showed that higher emotional stability was linked to higher risk of progression from SCD to MCI.

We are not aware of studies showing association of energy with SCD and progression to objective cognitive impairment. Nevertheless, it is well recognized that patients with AD dementia showed a reduction of social life, tendency to social isolation, loss of motivation or reduced initiative (48).

Interestingly, recent studies showed that carriers of IAs had higher β-amyloid burden and developed MCI more frequently than non-carriers of IAs (49).

Taking this evidence together, we could speculate that CAG repeat number in *HTT* gene might be one of the genetic factors mediating the effect of conscientiousness, emotional stability and energy on neurodegeneration and progression of cognitive decline. We aim to better explore this hypothesis in further studies, first of all expanding our sample size. Indeed, the small sample size is the first limitation of the present work, in particular when we classified patients according to the progression to MCI (only 14 patients were MCI^+). Moreover, only six patients were carriers of the IA. A larger sample would allow us to assess for personality trait differences between IA^- and IA^+. Another limitation is the lack of a control group. Finally, as it is a single-center study, there may be biases regarding assessment and diagnosis procedures and inclusion of only Caucasian participants.

However, this study has some remarkable strengths: this is the first study assessing the correlation of CAG repeat lengths with personality traits in patients without family history of HD. This may lead to the exclusion of a polygenic effect of modifier genes which are involved in HD symptoms and onset in individuals with family history for HD. The second strength is the very long, median follow-up time. In fact, follow-up time in the MCI^- is much longer than the time of conversion of MCI^+. This information allows us to minimize the possible underestimation of progression to MCI.

Conclusions

We showed that length of CAG repeats in the *HTT* gene within the non-pathological range might influence personality traits in SCD patients who will progress to MCI. Low level of conscientiousness, low level of energy and high level of emotional stability are associated with a higher number of CAG repeats. Both personality traits and CAG repeat length in the intermediate range have been associated with progression of cognitive decline and neuropathological findings consistent with AD. If confirmed by further studies on larger samples, our results may be the key to reveal the missing link among *HTT* gene, personality traits and neurodegenerative process.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS, BN,VB, and SM: conceptualization. VM, SM, SB, SP, AI, VB, and LB: methodology. SM: statistical analysis. VM, VB, SM, FE, CM, GG, and SP: investigation. VB, SM, SB, and CF: resources. SM, GG, CM, and TF: data curation. VM, SM, and VB: writing—original draft preparation. VM, SM, BN, and VB: writing—review and editing. VB, BN, and SS: supervision and project administration. VB and BN: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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CASE REPORT
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Case Report: Treatment of Delusions of Theft Based on the Assessment of Photos of Patients' Homes

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Background: The occurrence of behavioral and psychological symptoms of dementia is affected by individualized context. However, details regarding delusion of theft have been poorly documented. This report describes a useful assessment to understand the environmental context of delusion through two cases of Alzheimer's disease (AD).

Familial interview was conducted to assess the phenomenological features. Photos of patients' homes were used to increase the assessment accuracy and check the individualized environmental contexts; this is known as Photo Assessment of Living Environment (PA-LE).

Case Description: Case 1 was of an 88-year-old woman whose Mini-Mental State Examination (MMSE) score was 23/30. She believed that one neighbor stole her wallet and stored it on a shelf in the living room. She sometimes placed it in other places, such as under the bed as safekeeping. The delusion often occurred when getting ready to go shopping. PA-LE confirmed that the room and shelf were not cluttered, although the incorrect storage place seemed to be hard-to-find.

Case 2 was of a 78-year-old woman. The MMSE score was 20/30. She believed that some neighbors stole her garden items. The delusion was limited to her garden, yet the items were varied. Auditory hallucinations exacerbated her belief that the neighbors intruded the garden. PA-LE confirmed that the garden was cluttered with several duplicated items. Moreover, the patient inaccurately remembered the condition of the garden.

Non-pharmacological approaches were tailored to the patients' environmental and psychological states, referring to the interview and PA-LE. This included environmental adjustment or increasing self-esteem. Antipsychotics were also prescribed. Environmental and psychological triggers of delusion were improved by the interventions, and the patients had uneventful courses without active delusions.

Conclusion: Evaluating patients' homes using photos could detect the environmental context of delusion of theft among patients with AD and assist in the management.

Keywords: case report, delusion of theft, Alzheimer's disease, assessment, environmental factor

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INTRODUCTION

Behavioral and Psychological Symptoms of Dementia (BPSD) are clinically important symptoms in people with dementia and frequently occur in their clinical course (1). BPSD often cause negative outcomes, including early hospital admission, significant care burden, and decrease in the quality of life (2–4). In the non-pharmacological intervention as first-line treatment for BPSD, understanding the mechanism that caused each of the BPSD is of critical importance (5). Notably, the occurrence of BPSD is well-known to be involved in highly individualized contexts (6), such as the living environment or relationship with the caregiver. Generally, it would be difficult to accurately assess these individualized contexts using only the existing standard assessment scale (7).

Delusion of theft is one of the most common BPSD in patients with Alzheimer's disease (AD). The mechanism of delusion of theft has been well-identified (8); however, details of individualized contexts and specific methods have not yet been thoroughly documented. As one example, it is conceivable that cluttered rooms could induce the failure experience of misplacing things, potentially increasing the risk for delusions of theft. However, such environmental contexts have been too highly individual to implement a general assessment or intervention.

This case report preliminarily shows an overview of the new assessment method through interviews using photographs of the homes of two AD inpatients. We believe that this method will be useful for visually assessing individualized environmental contexts and describing the phenomenological features of delusions of theft to develop individualized intervention plans.

CASE DESCRIPTION

Parts of personal information were anonymized to protect patients' privacy. Written informed consent from both patients was obtained for the publication of this case report.

The Japanese version of the 12-item Neuropsychiatric Inventory (NPI-12) was used to assess BPSD (9). The NPI-12 includes 12 domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating. A composite score of all domains was calculated by multiplying the frequency and severity within each domain as follows: 1–4 (4 = most frequent) and 1–3 (3 = most severe), respectively. The total score ranges from 0 to 144, with higher scores indicating more severe neuropsychiatric symptomology.

We conducted the new method of "Photo Assessment of Living Environment (PA-LE)" to identify environmental context involved in delusion of theft. The photos of the outdoors, indoors, and home appliances were prepared by the patients' families according to the photographic place guidance. The guidance consisted of seven sheets describing how to photograph the exterior and indoor environment, including the bedroom, living room, kitchen, and closet, and home appliances, such as the refrigerator and washing machine. The guidance also included the house layout. Additionally, the places and objects that seemed to be associated with the delusion of theft were photographed. Familial interviews were conducted to identify the phenomenological features of the delusion of theft. In this interview, questions associated with the delusion of theft, including the frequency, person, item, time, and location were asked (**Table 1**), while observing the photo of the patient's home. Photos depicting the state of their homes were used to increase interview accuracy and not overlook the important findings. We also assessed the psychosocial aspects such as self-esteem, daily life at home, or life history from the patient or the family.

Non-pharmacological and pharmacological treatments, i.e., antipsychotics, were provided. Non-pharmacological treatment involved identifying several targets tailored to the patient's psychological and environmental state, while also contextualizing the delusion of theft based on a comprehensive perspective such as the interview assessments, PA-LE, and the neuropsychological tests. Non-pharmacological treatments to address these targets were planned and implemented to (a) increase self-esteem, (b) decrease the triggers of delusion, (c) replace the time spent on delusional thinking with other activities, and (d) provide pleasure in their daily lives. **Table 2** shows the details of contents and background of planning in non-pharmacological intervention.

Case 1

An 88-year-old woman was admitted to our psychiatric ward for delusions. She lived alone, and much of the housework was done by her family. She had engaged in volunteer activities, such as helping the local community, for over 20 years. However, she was unable to continue to volunteer due to community changes and the chairman's replacement that resulted in hostility against the neighbors. Her self-esteem likely decreased as a result. Four years ago, she began to suspect that her properties were stolen by a neighbor. This led to increasing problems with the neighbors and involvement of the police.

On admission, the patient's Mini-Mental State Examination (MMSE) score was 23/30. The logical memory scores in the Wechsler Memory Scale-Revised (WMS-R) were 2 for immediate and 0 for delayed recall. The Frontal Assessment Battery (FAB) score was 17/18. Addenbrooke's Cognitive Examination III (ACE-III) score was 74/100 and sub-domain scores were as follows: attention, 16/18; fluency, 11/14; visuospatial, 16/16; memory, 10/26; and language, 21/26. Neuropsychological tests mainly revealed partial disorientation to time and place with mild to moderate amnesia. The total NPI-12 score was 24/144. The rated symptoms and their respected scores were as follows: delusions, 12; hallucinations, 2; agitation/aggression, 4; elation/euphoria, 3; and night-time behaviors, 3. Brain magnetic resonance imaging (MRI) showed diffuse cortical atrophy prominently in the bilateral parietal but relatively sparing the medial temporal lobes with bilateral hippocampal sulcus remnant (**Figure 1A**). Florbetapir F 18 positron emission tomography (PET) showed amyloid depositions mainly in the frontal cortex (**Figure 1B**). In the cerebrospinal fluid testing, phosphorylated tau at epitope 181 (p-tau) and total tau (t-tau) were 103 and 830 pg/mL, respectively. These results were suggestive of AD pathology (10).

TABLE 1 | Delusion features assessed using interviews and photographs.

	Case 1	Case 2
Age (years)	88	79
Sex	Female	Female
Diagnosis	AD†	AD†
Duration of delusion (years)	4	1
MMSE‡	23/30	20/30
Living arrangement	Alone	With daughter and granddaughter
Delusion of theft features		
Frequency	Unknown	Almost daily
Who stole	One specific neighbor	Some neighbors
What was stolen	Wallet and passbook	Various garden items
Where the delusion occurred	Living room	Garden
When the delusion occurred	Unspecified	Midnight
Why the patient thought that their objects are stolen	Inability to find the wallet before going shopping	Hearing digging sounds and footsteps in the middle of the night
How the patient dealt with the theft	Complaints to the neighbor, police notification, surveillance cameras installed, and specific windows were blockaded	Neighbor notification, police notification, surveillance cameras installed, and garden fences were added

†Alzheimer's disease. ‡Mini-Mental State Examination.

TABLE 2 | The content and background of non-pharmacological intervention.

Case 1	Case 2
(a) Increase self-esteem Avoiding identification of her failures such as losing valuables was encouraged, since she tended to have high levels of self-reliance from the familiar interview. We also offered her family the specific place that they should put her valuables back based information of the PA-LE (**Figures 1C,D**)	***(a) Increase self-esteem*** Based on the interview with her and family, the change in household roles was likely to affect her self-esteem. We proposed her family that they gave her several roles in the family. We also advised the family to avoid denying her false beliefs, in order not to decrease her self-esteem
(b) Decrease the triggers of delusion Inability to find the wallet before going shopping was inferred as one of the triggers of delusion by the interview of phenomenon regarding delusion. As such, we encouraged the family to get ready and go shopping with her	***(b) Decrease the triggers of delusion*** The cluttered garden was presumed to exacerbate her failure experience that she could not find own properties based on information of the PA-LE. Based on the information of PA-LE, we proposed to her family that they reduced the objects, especially duplicate items and items that she has not been using for a while in the garden (**Figure 2C**) and limited the specific storage place of garden items (**Figure 2D**) in consultation with her
(c) Replace the time spent on delusional thinking with other activities Based on the familial interview of daily life, she tended to have less opportunities of engaging in meaningful activities since much of housework was done by others. We encouraged the family to involve her in several housework such as washing or sweeping, tasks that she could perform.	***(c) Replace the time spent on delusional thinking with other activities*** Based on the interview regarding the phenomenon of delusion, her delusion tended to occur with auditory hallucination in the middle of the night. We encouraged the family to increase her daytime activity such as attending an adult day care, in order to decrease night awakening
(d) Provide pleasure in their daily lives She actively engaged and enjoyed interaction with other inpatients of same age during her hospital stay. We encouraged her and her family to talk to individuals of the same age as part of group therapy in an adult day care after discharge	***(d) Provide pleasure in their daily lives*** She took care of her garden at home and enjoyed a horticulture program during hospital stay. We encouraged her to engage in gardening more proactively and safely as a leisure activity, while decreasing the duplicated and not-necessary items and limiting the storage place of garden items

The features of delusions were assessed through interviews and photographs of the patient's home (**Table 1**). Familial interviews revealed that she strongly believed that one specific neighbor stole her wallet and passbook. The delusion often occurred when she could not find her wallet in the shelf while getting ready to go shopping. The time of the day describing the theft was unspecified and the frequency of delusions was unknown because she lived alone. The delusional misidentification syndrome was not exhibited. The items she accused of being stolen were usually stored on a shelf in the living room, while she sometimes kept these items in incorrect places (where she thought were safer), such as under the bed. **Figure 1** shows the photos of the rooms and places associated with these delusions through PA-LE (**Figures 1C,D**). The photos revealed that the shelf and living room she frequently used were not cluttered, and it seemed to be easy to find her wallet. In contrast, the incorrect storage places, such as under the bed, might have been hard to find the wallet in, although the place was not cluttered.

Risperidone (0.5 mg/day) was prescribed. A few days later, delusional thinking and agitation improved relatively; however, the original delusion of theft remained for about 7 weeks from the start of an atypical antipsychotic till discharge. For further management of delusion, upon discharge, we provided her caregivers with instructions regarding non-pharmacological interventions which included the following (**Table 2**): (a) To increase the patient's self-esteem, avoid pointing out failures, such as losing valuables, and consider putting them back in their usual place by the family based on the information of the PA-LE (**Figures 1C,D**). (b) To decrease triggers of delusion, encourage the family to get ready and go shopping with her. (c) To decrease the time spent for delusional thinking, leave her several housework such as washing or sweeping she could perform. Finally, (d) to increase pleasure in her daily life, encourage talking with individuals of the same age as part of group therapy in an adult day care.

The patient had an uneventful course without active delusions during the post-discharge period. The guidance we provided altered the family's attitude toward her and increased her daily activities, such as engagement in leisure activities and attending an adult day care. Her family also tried to help her with shopping to avoid her failure experience. She spent much of her daily time in arranging the garden as a pleasurable role. One year after discharge, she continued living alone without major problems.

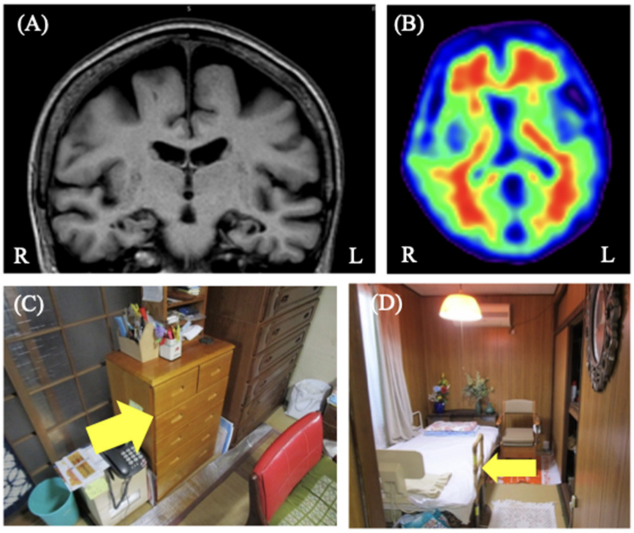

FIGURE 1 | Case 1 images. **(A)** Brain magnetic resonance T1-weighted image showed diffuse cortical atrophy but relative sparing of the medial temporal lobes with bilateral hippocampal sulcus remnant. **(B)** Florbetapir 18 positron emission tomography showing positive results. **(C,D)** These are the images of the patient's home. She usually stored her valuables such as wallet in yellow arrowed shelf **(C)**. She sometimes hid her valuables under the yellow arrowed bed **(D)**. We proposed to her family that they put her valuables back to usually stored place if they found them in unusual places.

Case 2

A 78-year-old woman was admitted to our psychiatric ward for treatment of delusions. She lived with her oldest daughter and granddaughter. She had worked in a public hall, where she interacted with local people. In the past 10 years, she lost numerous relatives, including her husband and sister. Her daughter had also recently changed her long-term job. These events led her to feel anxious. In the past year, her daughter and granddaughter performed most of the housework because the patient suffered an upper arm fracture. Since then, she began to suspect that her garden items, which she used for leisure activities, were stolen by the neighbors. This led to increasing problems with the neighbors and involvement of the police.

On admission, her MMSE score was 20/30. The logical memory scores in the WMS-R were 3 for immediate recall and 0 for delayed recall. The FAB score was 9/18. ACE-III score was 65/100 and sub-domain scores were as follows: attention, 14/18; fluency, 8/14; visuospatial, 14/16; memory, 6/26; and language, 23/26. Neuropsychological tests mainly revealed partial disorientation to time and place with mild to moderate amnesia, decreased attention function, and constructional disability. The total NPI-12 score was 58/144. The rated symptoms and their respective scores were as follows: delusions, 12; hallucinations, 12; depression, 8; anxiety, 8; apathy, 8; disinhibition, 6; and night-time behaviors, 4. Brain MRI showed diffuse cortical atrophy, which was relatively prominent in the bilateral hippocampal and parietal lobes (**Figure 2A**). Florbetapir PET showed amyloid depositions more in the posterior temporal and occipital lobes (**Figure 2B**). In the cerebrospinal fluid testing, phosphorylated tau at epitope 181 (p-tau) and total tau (t-tau) were 64 and 316 pg/mL, respectively. These results were suggestive of AD pathology (10). Neurological examination was unremarkable. The patient had a history of hypertension, dyslipidemia, and left cerebral aneurysm. She was diagnosed with probable AD according to the National Institute on Aging-Alzheimer's Association 2011 criteria (11).

The features of delusions were assessed through interviews and photos (**Table 1**). The familial interview revealed that the patient believed that some of her neighbors stole her garden items, such as flowerpots and trowels. This delusion was only associated with her garden, whereas the type of items suspected to be stolen varied. Her family also reported that she experienced hearing noises from the garden, such as digging sounds and footsteps in the middle of the night. These were not proven to be accurate, and the patient did not have any hearing impairment. The auditory hallucinations were likely to exacerbate her belief that some neighbors intruded into her garden. Therefore, the delusion often occurred at midnight. The delusional misidentification syndrome was not exhibited. **Figure 2** shows the photos of the garden and items associated with these delusions through PA-LE (**Figures 2C,D**). The photos revealed that the garden was cluttered and there were many items with duplicates. There were also several storage places of her garden items. The patient was unable to accurately remember their location and the quantity of the garden items.

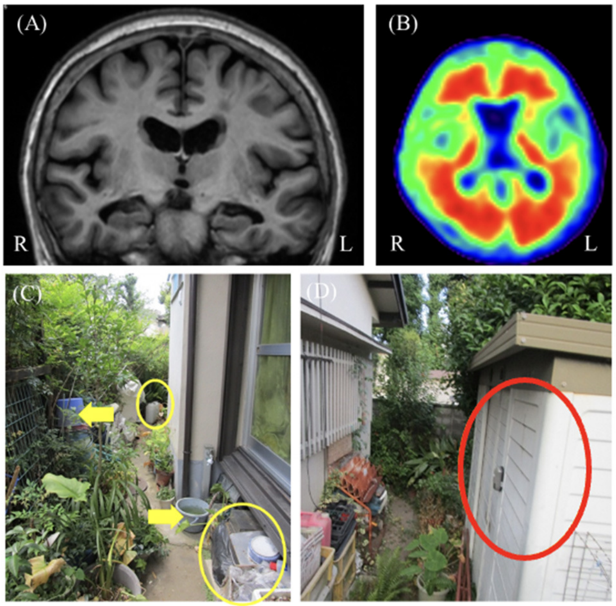

FIGURE 2 | Case 2 images. **(A)** Brain magnetic resonance T1-weighted image showed bilateral hippocampal atrophy. **(B)** Florbetapir positron emission tomogrpahy showing positive results. **(C,D)** These images show the patient's cluttered garden. The yellow circled items were the examples of things she has not been used in a while. The yellow arrowed ones were the examples of duplicated items. We proposed to her family that they reduced these items after consulting with her **(C)**. The red circled storage was one of the several storage places of her garden items. We proposed to her and the family that they limitedly stored the garden items in just this place **(D)**.

Risperidone (0.5 mg/day) was prescribed. A few days later, the patient developed mild upper limb rigidity, whereas her mood and delusional thinking remained mostly unchanged. It was continued as an outpatient treatment to monitor the progress of the treatment effect. The original delusion of theft remained for 5 days from the start of an atypical antipsychotic till discharge. For the further management of delusion, upon discharge, we provided her caregivers the with the following instructions regarding non-pharmacological interventions (**Table 2**): (a) To increase her self-esteem, give her several roles in the family, and avoid denying her false beliefs. (b) To decrease the triggers of delusion, reduce the objects such as duplicate items and items that she has not been using for a while in the garden (**Figure 2C**) and limit the specific storage place of garden items (**Figure 2D**) with her consultation. (c) To decrease the time spent on delusional thinking, increase her daytime activity such as attending the adult day care, in order to decrease night awakening. Finally, (d) to improve pleasure in daily life, encourage her and the family to engage in gardening more proactively and safely as a leisure activity, while decreasing the duplicated and not-necessary items and limiting the storage place of garden items. After discharge, the patient lived in both her oldest and second daughter's homes in turns.

The patient had an uneventful course without active delusions in her second daughter's home. However, a new delusion that her granddaughter stole her item occurred in the oldest daughter's home, although her original delusion was not exacerbated. According to the guidance we provided, the cluttered garden was partially improved by herself and her family member, and she attended the adult day care. There was also the patient's comment "Now that we've cleaned up some of the stuff in the garden, it's not stolen at all." One year after discharge, former behavioral problems, such as those with the neighbor or police notifications, did not occur. Delusions of theft seemed to have reduced to tolerable or acceptable levels.

DISCUSSION

This case report described two patients with AD and delusions of theft who were evaluated through familial interviews and photographs of their homes, revealing the phenomenological features of delusion of theft with the living environments. Moreover, we noted that several individualized features of the environments, such as a non-unified and hard-to-find storage space, or cluttered places, may have partially exacerbated the false belief that the patients' own properties were stolen by someone. In addition, the non-pharmacological interventions that were tailored to the patients' environmental and psychological states were likely to show partial improvement of delusion, assisting them to continue living in the community.

Delusion of theft is caused by interactions among various factors, including gender, cognitive deficit, loneliness, negative feelings, defense mechanisms, and brain dysfunction (8, 12, 13). Understanding the phenomenological features with several individualized environmental contexts found through our report may assist in interpreting the complex personal experiences of these patients and implementing individualized non-pharmacological interventions. Tible et al. (14) reported that qualitative phenomenological approach could help interpret the behavioral symptoms of patients with dementia. Considering that what was thought to be stolen and the situation around it were relatively limited, the failure experience associated with memory impairment may have been an important trigger in the patient in Case 1 of our report. Symptoms in the patient in Case 2 may have been partially caused by environmental factors, such as disorganized or duplicated items, although auditory hallucinations could have also contributed to these delusions. Additionally, the two AD patients seemed to have responded positively to the non-pharmacological interventions that were tailor-made based on the assessment of their individual contexts, although the effect of the non-pharmacological intervention could not be clearly distinguished from that of the pharmacological intervention. A possible explanation for this result is that the intervention altered several environmental and psychological triggers associated with delusion of theft according to each individual's context of events. In recent years, environmental factors, such as home environment or environmental stimulation, have received considerable attention as modifiable factors related to BPSD for the development of effective interventions (15, 16).

A qualitative study showed that interviews with photos can help understand the daily life of people with dementia (17). This supports the concept used in our case report. The photos of patients' homes provide more information about the actual state of their daily life than the interview assessments. Interestingly, Ramsdell et al. (18) have reported that interview assessments resulted in an underestimation of the degree of identified problems of people with dementia compared with home-visiting assessments. They also indicated that the potential risk for problems in daily life can be checked through observation of the patient's living environment. This indication agrees with our experience with PA-LE. For instance, if there had been no visual data of the patients' homes based on PA-LE, the hard-to-find storage place or significant cluttering in the garden, such as those that would potentially exacerbate the failure experience associated with memory impairment, would not have been confirmed in detail. Incorporating visual information of the patients' living environments into the general assessment of delusions of theft likely contributed to a more accurate understanding of the individualized environmental context for the patients' delusions.

To our knowledge, this case report is the first to reveal the phenomenological features of delusions of theft using individualized environmental contexts based on familial interviews and photographs of patients' homes. The findings of this case report will help understand the individualized environmental contexts for not only delusions but also other BPSD and provide effective management tailored to the environmental and psychological state of each patient.

In conclusion, interview assessments with photographs of the patients' homes helped identify the phenomenological features of the environmental contexts for the delusions of theft in patients with AD. PA-LE may be useful for understanding the individualized environmental context of delusions. Future prospective studies involving larger populations are required to reveal the effects of environmental factors on delusions of theft. A careful design that could clearly identify how much improvement is due to non-pharmacological intervention instead of pharmacological therapy will be useful to determine an effective intervention tailored according to these factors.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any images or data included in this article. Parts of personal information were anonymized to protect patients' privacy.

AUTHOR CONTRIBUTIONS

DI and YS: treated the patient during admission, while MI, YS, and DT: conducted the outpatient treatment. DI: wrote the first draft. HK, MH, YN, YS, DT, and MI: offered advice for interpretation of the result and participated in the discussion. All authors contributed to the article and approved the submitted version.

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Clinical Perception and Treatment Options for Behavioral and Psychological Symptoms of Dementia (BPSD) in Italy

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Background: Behavioral and psychological symptoms of dementia (BPSD) have a high prevalence, and their presence is associated with a severe impact in terms of social costs. However, dedicated clinical tools or biomarkers to detect these symptoms are lacking. Thus, BPSD management in clinical settings is challenging. The aim of this study was to investigate the perception and the treatment strategies for BPSD in Italian centers working in the dementia field.

Methods: A multicenter, national survey was developed by BPSD Study Group of the Italian Neurological Society for Dementia (SINDEM). The survey consisted of a semi-structured questionnaire that was e-mailed to SINDEM members, dementia centers part of the national network of memory clinics (Centers for Cognitive Deterioration and Dementia [CDCD]), and clinicians working in dementia care settings. The questions were focused on (1) perceived global frequency and relevance of BPSD; (2) tools used to assess BPSD; (3) pharmacological treatment for psychosis, apathy, agitation, aggression, depression, anxiety, sleep, and nutrition disturbances; (4) non-pharmacological treatments; (5) drugs side effects.

Results: One-hundred and thirty-six clinicians participated in this study. Seventy-nine participants worked in a CDCD and 57 in other settings. The perceived frequency of BPSD was 74%. BPSD are detected by means of a clinical assessment for 96.3% or a caregiver interview for 97%. For psychosis treatment the first choice was atypical antipsychotics (83.3%), followed by typical antipsychotic (8.9%) and antidepressants (4.8%). For agitation, atypical antipsychotics were the first-choice treatment in 64% of cases and antidepressants in 16.1%. For aggression, the most used drugs were atypical antipsychotics (82.9%). For anxiety, 55.2% use antidepressants, 17.9% use atypical antipsychotics, and 16.9% use benzodiazepines. Interestingly, most of the centers apply non-pharmacological treatments for BPSD. Some differences emerged comparing the responses from CDCD and other care settings.

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Conclusion: The survey results revealed many differences in BPSD perception, treatment options, and observed side effect according to the clinical setting. This variability can be explained by the absence of clear guidelines, by differences in patients' characteristics, and by clinical practice based on subjective experience. These results suggest that producing guidelines for the pharmacological treatment of BPSD is a major need.

Keywords: BPSD (behavioral and psychological symptoms in dementia), psychosis, BPSD management, dementia, apathy

INTRODUCTION

According to the original definition, behavioral, and psychological symptoms of dementia (BPSD) are "a heterogeneous set of psychological reactions, psychiatric symptoms and anomalous behaviors that appear in patients with dementia, of any etiology" (1). BPSD have been grouped in different clusters according with the characteristics of the examined populations or based on the settings in which subjects were evaluated. In a large cohort of newly diagnosed untreated patients with Alzheimer's disease (AD), evaluated with a 10-items version of the Neuropsychiatric Inventory (NPI) (2), a factor analysis identified five BPSD clusters, i.e., psychosis (delusions and hallucinations), affective syndrome (anxiety and depression), apathy, psychomotor syndrome (irritability, aberrant motor behavior, and agitation), and mania (euphoria and dis-inhibition). A longitudinal study focusing on BPSD in AD reported three clusters, i.e., psychotic syndrome (hallucinations, delusions), affective syndrome (depression, anxiety, irritability, agitation), and a behavior syndrome (euphoria, dis-inhibition, apathy, aberrant motor behavior) (3). In another study conducted in institutionalized non-demented elderly with the full 12-items NPI, neuropsychiatric clusters were defined in a slightly different fashion: affective (depression, anxiety, night-time behaviors), hyperactive (agitation, irritability, appetite abnormalities), psychotic (delusions and hallucinations), manic (euphoria and dis-inhibition), and apathetic (apathy and aberrant motor behavior) syndromes (4). A systematic review of the studies on BPSD in AD highlighted that the most inconsistent results for BPSD syndrome clustering concerned "sleep and nighttime behavior disorders" and "appetite and eating disorders" (5). These differences may depend on some factors such as age, severity of disease, heterogeneity of subjects' characteristics, and pharmacological treatments.

Some BPSD are part of the diagnostic core criteria for different forms of dementia (6, 7), and they can also appear before cognitive symptoms and overt dementia. In this case BPSD can be considered prodromal symptoms of dementia, according to the definition of Mild Behavioral Impairment (MBI), a condition which consists of the occurrence of BPSD in subjects without cognitive impairment or in patients with mild cognitive impairment (MCI) (8). Furthermore, specific neuropsychiatric syndromes can predict cognitive and functional decline progression in MCI patients with BPSD: manic syndrome has been found to be associated with a higher risk of cognitive decline, whereas affective syndrome has been found to predict functional decline (9).

BPSD prevalence is high and their presence is associated with severe caregivers' burden and a greater rate of institutionalization with a major impact in terms of social costs (10–13).

Despite their high prevalence, there are only a few dedicated clinical tools (scales/questionnaires) or biomarkers to detect these symptoms, and this may alter the BPSD perceived prevalence. Criteria have been established for apathy, depression, and psychosis, mainly in AD (14–17), with the aim to facilitate the enrollment in clinical trials.

Moreover, little is known about the neurobiological basis of BPSD and research on specific biomarkers associated with BPSD is lacking. Consequently, treatments tailored for BPSD do not exist. Also, in the scientific community no agreement has been reached on practice recommendations for BPSD, although non-pharmacological treatments are indicated as first-line, whereas pharmacological treatment are proposed as second-line options (18).

In clinical settings the management of BPSD is challenging and requires experience in the field and large competencies (19, 20). In this wide blunt context regarding BPSD diagnosis, detection, and treatment, it would be important to better characterize BPSD and harmonize the clinical and instrumental tools dedicated to these symptoms. As a first step to attain this goal, in this study the BPSD Study Group of the Italian Neurological Society for Dementia (SINDEM) aimed at investigating the clinical perception and the adopted treatment strategies for BPSD in Italian centers working in the dementia field.

MATERIALS AND METHODS

A multicenter national survey was developed by the BPSD Study Group of the Italian Neurological Society for Dementia (SINDEM). The survey consisted of a semi-structured questionnaire that was e-mailed to SINDEM members and dementia centers part of the national network of memory clinics, (Centers for Cognitive Deterioration and Dementia [Centri per i Disturbi Cognitivi e Demenze, CDCD]). To extend the number of participants, we also asked colleagues to email the questionnaire to other neurologists or geriatricians involved in dementia care in different settings. In the survey, the participants were asked to specify in which type of setting they worked. The questionnaire included either closed (yes/no) or multiple-choice responses. The questions were focused on (1) perceived global frequency and relevance of BPSD; (2) tools used to assess BPSD; (3) pharmacological treatment for psychosis, apathy, agitation, aggression, depression, anxiety, sleep, and eating disturbances; (4) non-pharmacological treatments; and (5) drugs side effects. In some questions participants were asked to order by frequency the observed symptoms or the drugs used to treat the symptoms. Multiple-choice questions investigated what techniques or biomarkers were used in clinical practice to investigate BPSD, including structural (CT or MRI) or functional neuroimaging (FDG-PET), along with genetic, blood, and cerebrospinal fluid (CSF) analyses. Finally, the participants were asked whether they could be interested in new scales and biomarkers for BPSD. The questionnaire answers were anonymous to let responders feel free to express their opinions. However, an email was sent to possible responders, to leave them the opportunity to declare their participation in the survey. This was done in order to allow participants to disclaim their interest in initiatives of the BPSD SINdem study group and to express suggestions and comments for a possible follow-up of the study. Among the 56 responders who disclaimed their participation, 49 were neurologists, 5 geriatricians, 1 psychiatrist, 1 was both neurologist and psychiatrist, and 2 were psychologists. Their experience ranged from 5 to 40 years (mean and standard deviation: 24.4 ± 11). Thirty-four had already performed some kind of research about BPSD and most of them were aware of BPSD guidelines. The questionnaire responses were first analyzed globally and then separately for responders working in CDCD and those working in other type of settings.

RESULTS

One-hundred and thirty-six specialists participated in this study. Seventy-nine participants worked in a CDCD and 57 in other settings (e.g., general hospital wards, long-term care facilities, public outpatient services). The perceived frequency of BPSD was 74% and the importance of these symptoms was judged to be 88 over 100. BPSD are evaluated by means of a caregiver interview for 97% or by clinical assessment for 96.3%; dedicated tools are used by 72% of participants. Eighty-one percent use the complete NPI, 11.2% use NPI-questionnaire (NPI-Q), 1.6% use the Informant-based Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), and 6% other scales. The responders reported as most frequent symptoms agitation (37%), apathy (27.2%), and depression (22.5%) followed by psychosis (5.7%) and aggression (3.8%). Eighty-one percent of responders used drugs to counteract apathy, specifically antidepressants (SSRI 62.2% and SNRI 17.7%), but also dopaminergic drugs. For psychosis the first-choice treatments were atypical antipsychotics (83.3%), followed by typical antipsychotic (8.9%), and antidepressants (4.8%). For agitation, atypical antipsychotics were the first-choice treatment in 64% of cases and antidepressants in 16.1%. For aggression, the far most used drugs were atypical antipsychotics (82.9%); as a second line 36.6% used typical antipsychotics and

TABLE 1 | Answer differences in CDCD vs. non-CDCD setting; values ae expressed as percentages.

	CDCD (*n* = 79)	NON-CDCD (*n* = 57)
How frequently do you observe BPSD?	73	75
How important are BPSD in your clinical practice?	88	87
How do you evaluate BPSD?		
Clinical evaluation	97.4	94.8
Information by caregivers	97.4	96.5
Dedicated tools	75.6	68.9
Which assessment tool do you use?		
NPI	80.2	82.7
NPI-Q	15.07	5.8
BEHAVE-AD	1.3	1.9
Others	2.7	9.6
Which BPSD is more frequent (1st place)?		
Agitation	31.8	44
Apathy	28.7	25
Depression	27.1	16.6
Psychosis	4.3	7.7
Aggression	4	3.5
Do you usually treat apathy?		
Yes	87.3	73.6
No	12.6	26.3
Do you think AChEIs are effective for BPSD?		
Yes	66.7	62.5
No	33.3	37.5
Do you think memantine is effective for BPSD?		
Yes	70.9	60.4
No	29.1	39.6
What are the most frequent adverse event to antipsychotics?		
Parkinsonism	31.1	38.2
Confusion/sedation	62.5	57.4
Vascular	0	2.1
Cardiac	1.4	0
Paradoxical effect	4.4	1.9
What are the most frequent adverse event to antidepressants?		
Ataxia	3	4.4
Confusion/sedation	44.4	44
Nausea	35.6	21.6
Cardiac	1.5	8.2
Paradoxical effect	11.6	8.5
What are the most frequent adverse event to benzodiazepines?		
Ataxia	4.6	11.1
Confusion/sedation	84	75.9
Paradoxical effect	12.9	13
Do you usually prescribe drugs for BPSD in monotherapy or in polytherapy?		
Monotherapy	84.8	68.4
Polytherapy	8.6	24.5
Do you use non-pharmacological treatments for BPSD?		
Yes	65.9	65.5
No	34.1	34.5

(Continued)

TABLE 1 | Continued

	CDCD (*n* = 79)	NON-CDCD (*n* = 57)
Which non-pharmacological treatments do you use?		
Occupational therapy	43.6	53.7
Cognitive stimulation	45.5	58.5
Validation	10.9	4.9
Gentle care	14.6	29.3
Person centered care	14.6	17.1
Counseling	89.1	82.9
Do you perform diagnostic exams specific for BPSD?		
Yes	27.9	21.4
No	34.2	35.7
What procedures do you perform for BPSD?		
MRI	61.1	59
CT	66.7	61.5
FDG-PET	31.5	28.2
EEG	61.1	59
Other functional neuroimaging	13	7.7
Blood exams	85.2	82.1
Lumbar puncture	20.4	23.1
Would you be interested in clinical scale specific for BPSD?		
Yes	94.9	91.4
No	5.1	8.6
Would you be interested in biomarkers specific for BPSD?		
Yes	91.1	82.8
No	8.9	17.2

16.9% antidepressants. For depression most participants used antidepressants (85.2%); less frequent was the use of atypical antipsychotics (10.2%). For anxiety, 55.2% used antidepressants in the first instance, almost 17.9% use atypical antipsychotics, and 16.9% benzodiazepines, which were the second choice in 28.3% of the cases. For sleep and eating disorders, 62.9% and 60.4% of participants, respectively, used non pharmacological treatments as first choice interventions. For BPSD treatment 78.1% of the responders preferred a monotherapy and 15.3% a combination of treatments. In their opinion, 64.2% of the responders reported that acetyl-cholinesterase inhibitors (ACHeI) are effective for BPSD treatment and 66.6% reported the same for memantine. The most common reported side effects with antipsychotics were sedation/confusion (59.8%) and parkinsonism (34.6%). Interestingly, even if almost all responders were medical doctors and not psychologists, non-pharmacological approaches were reported to be used to treat BPSD, including caregiver counseling and education (86.4%), cognitive stimulation (51%), occupational therapy (47.9%), and gentle and person-centered care (20.8%). Blood tests are the most frequent exams to investigate BPSD (84.04%); neuroimaging such as CT and MRI is used in 60 and 64% of the centers. However, other exams are also used to this aim: 60% of participants use EEG, 29.7% FDG-PET, and 21.2% CSF analysis. Most responders expressed their interest in developing a new specific scale to evaluate BPSD (93.4%) and in specific biomarkers for BPSD (87.6%). Some differences emerged comparing the responses from CDCD and those from other care settings, specifically in BPSD treatment and reported treatments side effects. See **Tables 1**, **2** and **Figures 1**, **2** on this point.

DISCUSSION

In this study, we present the results from a survey involving a large number of Italian specialists in the field of dementia concerning the general recognition, management, and opinions on BPSD.

Overall, the responders perceive the importance of BPSD and most of them assess these symptoms through a caregiver inquiry and dedicated tools. The most reported symptoms were agitation, apathy, and depression. Indeed, apathy is described to be the most common BPSD in dementia (21) and often occurs in early disease stage, whereas agitation is most common in later stages: it is probable that this kind of occurrence influences the subjective perception of these two symptoms, making them the most frequently perceived. Moreover, apathy and depression have been found to be predictive of MCI conversion to AD (22) and they can appear in the prodromal stage of dementia. Nevertheless, the perceived prevalence of these symptoms is lower than reported in the literature: thus, it would be important to improve the knowledge and awareness of BPSD among specialists working in this field. Although there are no specific recommendations for treatment of apathy, and it is well-known that apathy is different from depression (23), and most of the centers prescribe antidepressants to treat this symptom. It would be useful to investigate whether this strategy has some efficacy evidence in clinical practice, above all when we consider that antidepressants, and especially SSRI, can cause emotional blunting (24). Some responders prescribe dopaminergic treatments as well: this kind of therapy could have a more solid scientific basis (25). AChEIs and memantine were generally considered effective in the treatment of BPSD. In fact, it is well-known that AChEIs reduce psychotic symptoms in Lewy Body Dementia (26), but an effect on BPSD has been also advocated in AD (27). Even if medical agencies have reduced the impact of these medications on BPSD highlighting a small cost efficacy ratio, a survey on the management of BPSD and prescribing practices in the UK found that AChEIs were considered the second most appropriate pharmacological choice for psychosis after quetiapine (28), and recent studies have shown the effects of combination therapy on reducing dis-inhibition symptoms (29) and on improving all NPI domains except euphoria and apathy (30). For the control of aggression, most responders use atypical and typical antipsychotics as their first choice and, as a second line, antidepressants as well. Agitation and aggression appear to be symptoms difficult to treat, with physicians attempting different pharmacological classes to reduce symptoms. For anxiety, most used drugs were antidepressants followed by atypical antipsychotics and benzodiazepines. Some choices can appear unconventional, such as the use of antipsychotics as the first line for anxiety, but they can be explained by the clinician's

TABLE 2 | A comparison of first choice treatment options for neuropsychiatric symptoms between centers for cognitive disorders and dementia (CDCD) and other settings.

		Anti-depressants	Atypical antipsychotics	Typical antipsychotics	Benzo-diazepines	Anti-epileptics	Dopaminergics	Non-pharmacological interventions
Aggression	CDCD	1.5	***83.7***	6.9	2.9	2.9	-	-
	Others	4	***81.5***	8.2	2	4	-	-
Agitation	CDCD	15.1	***64***	5.5	1.4	8.2	-	-
	Others	17.7	***64.2***	8	1.9	10.2	-	-
Anxiety	CDCD	***57.5***	14.5	3.1	18.3	18.4	-	-
	Others	***51***	22.6	4.2	15.4	8.2	-	-
Apathy	CDCD	***92.2***	-	-	-	-	4.5	-
	Others	***85.3***	-	-	-	-	9.1	-
Depression	CDCD	***86.7***	13	1.5	-	-	-	-
	Others	***83***	6.4	2	4.4	2.1	-	-
Nutrition disorders	CDCD	14.7	16.2	3.1	1.5	-	-	***61.6***
	Others	18.9	18.4	-	0	-	-	***60***
Psychosis	CDCD	5.6	***84.4***	8.5	-	-	-	-
	Others	3.9	***81.8***	9.6	1.9	6	-	-
Sleep disorders	CDCD	12.6	13	1.5	9.9	-	-	***68.1***
	Others	11.3	23.1	0	13.2	-	-	***59.6***

Data are expressed as percentages (CDCD: n. 79; other settings: n. 57). Bold values indicate the first choices.

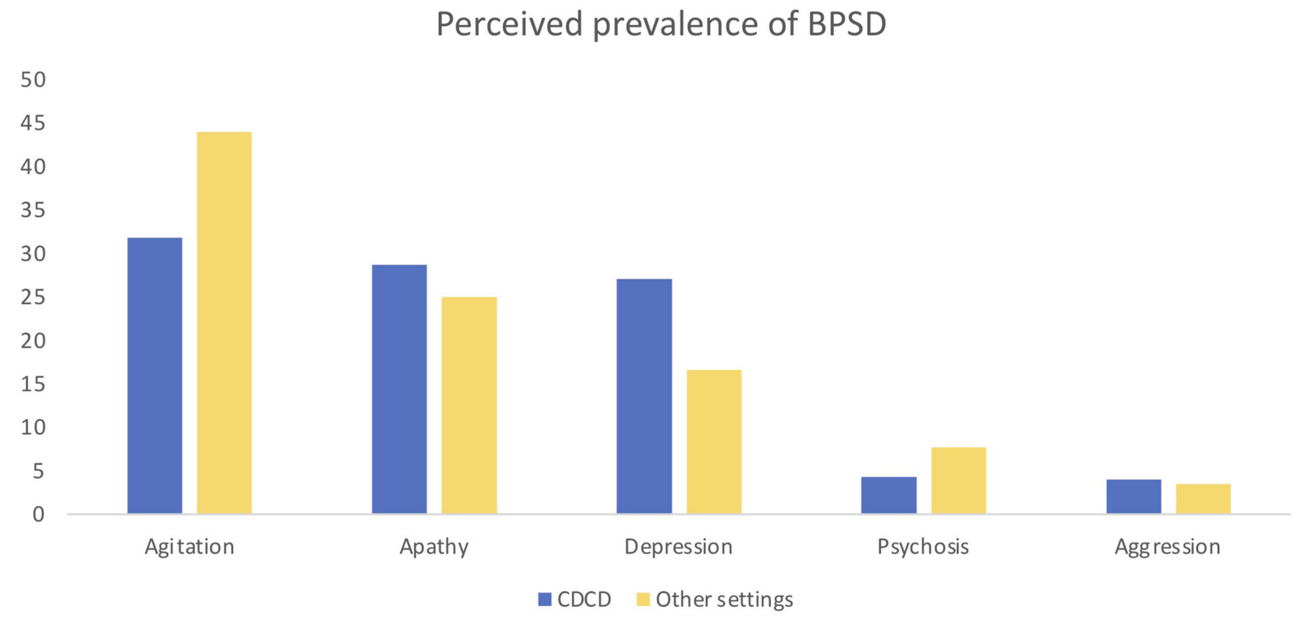

FIGURE 1 | Answer differences between CDCD and non-CDCD setting: perceived prevalence of BPSD.

attempt to avoid the use of benzodiazepines in dementia patients for their well-known side effects such as confusion and sedation. Moreover, anxiety in dementia can often be the epiphenomenon of restlessness or unmotivated fears or even psychotic beliefs.

It is worth noting that most of the centers apply non-pharmacological treatments for BPSD, especially caregiver counseling and education, and cognitive stimulation as well. Italian specialists on dementia seem therefore to be aware that most guidelines recommend a non-pharmacological approach as the first-line treatment for BPSD, even if there is no consensus on the best technique to be used (18).

When the responses to the survey were analyzed comparing the different settings, and in particular when comparing CDCD and other settings, some differences in BPSD perception, treatment options, and observed side effect were found. First, agitation was perceived as most common in other settings

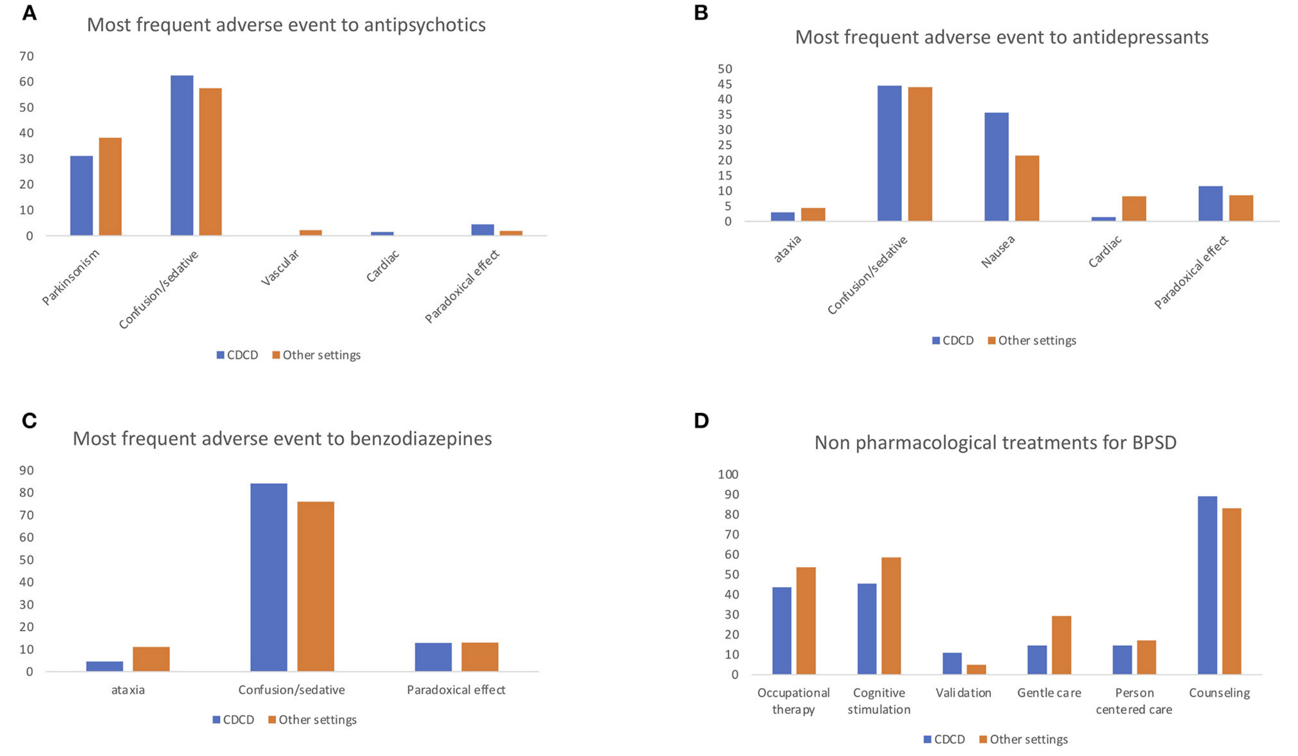

FIGURE 2 | Answer differences between CDCD and non-CDCD setting: perceived most frequent side effects of antipsychotics **(A)**, antidepressants **(B)**, benzodiazepines **(C)**, and use of non-pharmacological approach to treat BPSD **(D)**.

compared to CDCD, while apathy and depression were perceived as less frequent. Moreover, apathy was treated more frequently in CDCD than in the other settings, and the use of serotonin and norepinephrine reuptake inhibitors (SNRI) to this aim was higher than in the other settings. In anxiety treatment the atypical antipsychotics were more used in other clinical settings than in CDCD. For sleep disorders, specialists working in CDCD tend to use non-pharmacological treatment more than in other settings, while specialists working in other settings more often use atypical antipsychotics. The variability related to the work setting is also reflected in reported side effects. Atypical antipsychotics were reported to cause parkinsonism more frequently in other settings than in CDCD. Benzodiazepines were reported to produce ataxia more frequently in other settings then in CDCD. These data could depend on different possible factors: in a general hospital, where an acute confusional state is often superposed to dementia and where the care setting is not adapted to the special needs of people with dementia, larger doses of antipsychotics and benzodiazepines could be used than in the specialized CDCD setting. In day care centers, there are many people with dementia in the moderate-severe phase, when agitation, aggression, and sleep disorders are more frequent. Therefore, neuroleptics and benzodiazepines could be used more frequently and at larger dosage. Non-pharmacological therapy is used in both settings but, while specialists working in CDCD mainly prefer the caregiver counseling, in other settings cognitive stimulation and occupational therapy are used more often. This difference could be due to organization difficulties: CDCD are ambulatory patients services, while day care centers or long-term facilities are residential settings where it is easier to organize formal and/or group therapies for patients. Another difference was the interest in the new biomarker development which was more conspicuous in CDCD than in other settings. This could be due to the fact that CDCD are the main reference in Italy for diagnosis and treatment of dementia: biomarker development could facilitate these tasks. Biomarkers could include structural and functional neuroimaging correlates or cerebro-spinal fluids (CSF) biomarkers. Findings on neural correlates associated with neuropsychiatric syndromes have been summarized in a review by Rosenberg et al. (31). The authors reported that structural and functional alterations associated with agitation may be related to alterations in the regions involved by the AD core pathology and also to brain regions associated with emotional regulation (amygdala) and salience (insula), while apathy was found to be associated with structural and functional alterations in regions such as the anterior cingulate cortex and amygdala. Delusions were instead associated with alterations in frontal and temporal regions (31–35). Moreover, research on CSF biomarkers suggest that elevated CSF tau might be associated with agitation (36) and with psychosis in AD (37, 38). Improving research on BPSD biomarkers could help to better characterize these symptoms and could help to develop new treatment strategies.

The variability in the responses about BPSD treatment can obviously be explained also by the absence of clear guidelines, in addition to differences in patients' characteristics and clinical practice based on subjective experience. However, some general principles are generally shared by Italian specialists, such as using antipsychotics in the lowest dose sufficient to control symptoms, with close monitoring for adverse effects.

The fact that most of the centers involved in the survey use NPI to detect neuropsychiatric symptoms deserves considerations. Indeed, NPI has some limitations. Specifically, it does not allow investigation of the detailed phenomenology of each BPSD, nor does it investigate symptoms according to BPSD clusters. Moreover, the NPI questions refer just to a specific time period (previous 4 weeks). However, according to the hypothesis that BPSD may represent a patient's trait and not only a patient's state, information about patient's BPSD history can be missed. A further important aspect is that the NPI is administered to caregivers and it can be influenced by the personal caregiver's perception and burden. Thus, NPI lacks a direct observation of the patients by the clinicians. It would be helpful to validate and standardize a scale to investigate BPSD comprising both caregiver's perception and patient's observation, which might also be useful to detect drugs effects in clinical trials targeting BPSD.

The differences outlined by our survey underline that for clinicians the choice of the right drug for a specific BPSD and therapy-tailoring is challenging.

A study that applied a standard methodology such as the Appraisal of Guidelines Research and Evaluation (39), an instrument for the quality assessment of clinical practice guidelines, compared the existing guidelines for BPSD treatment with the aim to detect recommendations with great impact. The authors reported that, while some agreement exists on the use as first choice of non-pharmacological treatment, and on the antipsychotics, overall research in BPSD management is lacking, and they highlighted the need of formulating specific guidelines (18).

This study has some limitations. Since the survey investigated many aspects of BPSD management, to warrant a high proportion of responses, it was not possible to include too many or too detailed questions, such as drug dosages, treatment durations, or specific tools used to assess BPSD in different types of dementia or disease stage. Future studies are needed to investigate these aspects. Another limitation is that some care settings were in fact excluded or underrepresented such as the homecare, geriatric wards, and long-term care facilities (as there were more neurologists than geriatricians among the responders). It would be also important to investigate BPSD perception and management in context different from those specialized in dementia field, such as primary care. Since the survey reported data based on clinicians' impressions, quantitative data about BPSD management were not collected. Moreover, it was not possible to investigate in more detail non-pharmacological treatments, although many of the centers reported them as first choice for BPSD. Further studies focusing on these aspects are also warranted.

Our results suggest that producing guidelines focusing on management and pharmacological treatment of BPSD is a major need. Specific practice recommendations in existing dementia guidelines should be formulated to clarify for each BPSD which drug should be used as first line and second line at which dosage and possibly for how long. Moreover, it would be important to specify if some drugs are more effective in specific forms of dementia, and whether it is better to use them in monotherapy or in polytherapy. Specific guidelines could help in an effort to harmonize BPSD management and provide clear recommendation for clinicians in the dementia field.

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.

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AUTHOR CONTRIBUTIONS

FD'A, LT, MZ, SP, and EF: conceptualization and writing—review and editing. FD'A, LT, and EF: methodology and formal analysis. Sindem BPSD Study Group: resources. FD'A: writing—original draft preparation. EF: supervision. All authors contributed to the article and approved the submitted version.

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Frailty and Incident Depressive Symptoms During Short- and Long-Term Follow-Up Period in the Middle-Aged and Elderly: Findings From the Chinese Nationwide Cohort Study

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Objective: Prefrailty and frailty are two common conditions among older individuals. Recent studies have reported the association between frailty and depressive symptoms, but whether those conditions could predict depressive symptoms is still inconsistent in a few longitudinal studies. In our study, we aimed to estimate the cross-sectional and longitudinal associations between frailty and incident depressive symptoms in a nationally representative sample of community-dwelling middle-aged and older Chinese adults.

Method: Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS), which included 17,284 adults aged $\geq$ 45 years. Participants were followed every two years using a face-to-face, computer-aided personal interview (CAPI) and structured questionnaire. We excluded participants with no follow-up data. The numbers of individuals who completed the baseline surveys were 2,579 and follow-up surveys were 839 for the short-term (2 years from 2011 to 2013) and 788 for the long-term (4 years from 2011 to 2015). In addition, Frailty was measured by the Fried criteria and depressive symptoms were estimated by the Chinese version of the Center for Epidemiologic Studies-Depression scale (CES-D). Logistic regression was used to analyze the odds ratio (OR), and 95% confidence interval (CI) for the cross-sectional associations of frailty and its components with depressive symptoms in the participants at baseline. Cox proportional hazards analysis was conducted using the hazard ratio (HR), and 95% confidence interval (CI) for the prospective associations of baseline frailty and pre-frailty and its component in the participants without depressive symptoms at baseline.

Results: At baseline, 57.93% of participants had depressive symptoms and 55.84% had pre-frail and 11.63% had frailty. In the cross-sectional analysis, both pre-frailty (OR = 5.293, 95%CI 4.363–6.422) and frailty (OR = 16.025, 95%CI 10.948–23.457) were associated with depressive symptoms. In the longitudinal analysis, frailty [HR = 1.395 (0.966–2.013)] and pre-frailty [HR = 2.458 (0.933, 6.479)] were not significantly associated with incident depressive symptoms in a full-adjusted model among participants free of baseline depressive symptoms during the short-term. However, frailty [HR = 1.397 (1.017, 1.920)] and pre-frailty [HR = 2.992 (1.210, 7.397)] were significantly associated with incident depressive symptoms during the short term. In the components of frailty, slowness [HR = 1.597 (1.078, 2.366)] was associated with an increased risk of depressive symptoms onset during the short-term. Weakness [HR = 2.08 (1.055, 4.104)] and exhaustion [HR = 1.928 (1.297, 2.867)] were associated with increased risk of depressive symptoms onset during the short-term.

Conclusion: Among the middle-aged and older adults, frailty, pre-frailty did not predict depressive symptoms during 2 years of follow-up, when accounting for the potential confounders, slowness considered alone predicted depressive symptoms. Additionally, frailty, pre-frailty predicted depressive symptoms during 4 years of follow-up, when accounting for the potential confounders, weakness and exhaustion considered alone predicted depressive symptoms.

Keywords: cohort study, depressive symptoms, frailty, incidence, middle-aged and elderly

INTRODUCTION

The depressive symptom is a common medical disorder condition among middle-aged and elderly adults with a prevalence of 37.84% in China (1). Depressive symptom severity is related to serious results such as sadness, disability, increasing the burden of patients, family, and society (2, 3). Frailty, defined by a clinical syndrome of increased vulnerability to stressors, is characterized by loss of physiologic reserve among older age, which is associated with disability, hospitalization, and death (4). The most well-known biological syndrome model of frailty is characterized as exhaustion, weakness, low physical activity, slowness, and weight loss (pre-frailty as the presence of one or two of these components, and frailty as the presence of three or more components) (5). Most studies included adults aged ≥65years, the proportions of 10.7% for frailty and 41.6% for prefrailty (6). A meta-analysis including 240 studies reported that the prevalence of frailty was 11-13% among the aged ≥50 adults, and the prefrailty was 45–48% (7). Cross-sectional analysis of 18,227 selected community-dwelling individuals 50 years of age and older in Europe in 2004 found that prevalence of frailty was 4.1%, and prefrail was 37.4% (8). 2006–2010 Bus Santé study including participants aged 50 and more showed that 28.7% and 7.8% presented one frailty indicator, and two or more frailty indicators, respectively (9). Other studies reported that the prevalence of frailty was 61.6% in the middle-aged diabetic population (10), and 6.1% in HIV-infected individuals.

Mounting evidence demonstrates that frailty could be associated with depression. The current meta-analysis sought to estimate the strength of the relationship between frailty and depression. A recent meta-analysis conducted with fourteen studies (10 cohort studies and 4 cross-sectional studies) by Chu et al. (11) found that older adults aged 65 years or older, with depression, are more prone to frailty than are those without depression (OR = 2.99, 95%CI 2.19–4.08). Furthermore, older males with depression were at a higher risk for frailty than older females with depression (female: OR = 2.25, 95%CI 1.54–3.27; male: OR = 4.76, 95%CI 3.61–6.27). Another meta-analysis performed for the 24 studies by Soysal et al. (12) found that (I) people with depression were at increased odds of having frailty (OR = 4.07, 95%CI 1.93–8.55), and (II) older adults with frailty were at increased odds of having depression (OR = 2.64, 95%CI: 1.59–4.37), and (III) frailty at the baseline increased the risk of incident frailty by about 272% (HR = 3.72, 95%CI 1.95–7.08); and (IV) frailty at the baseline increased the risk of incident depression by about 90% (HR = 1.90, 95%CI 1.55–2.32). In

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Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CAPI, Computer-Aided Personal Interview; HRs, Hazard Ratios; OR, Odds Ratio; BMI, Body Mass Index; M, Mean; SD, Standard Deviation; CIs, Confidence Intervals; CESD, Chinese version of the Center for Epidemiologic Studies-Depression scale; CRP, C-Reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; GDS-15, Geriatric Depression Scale; NSFC, The National Natural Science Foundation of China; NIA, National Institute on Aging; WB, World Bank.

addition, the other three meta-analysis studies (13–15) also tested the association between frailty and depression and supported for a bidirectional association between depression and frailty. Although the meta-analysis included cohort studies and cross-sectional studies and highlighted the potential adverse effect of frailty on depression, no considerations of the components effect of frailty on depression over several years in different studies were made. Moreover, the meta-analysis only included Western participants, and no considerations of other ethnicities, such as Asians. Thus, further studies among the middle-aged and elderly in Asian nations are needed to identify whether the relationship between frailty and incidence of depression in Asian participants.

To address these gaps, we used 4 years of longitudinal data from the nationally-representative sample of community-dwelling Chinese participants aged ≥45 years and explored to examine the relationship between frailty and incidence of depressive symptoms during the short- (2 years) and long-term (4 years) internals. Furthermore, our study explores the stability of the association between components of frailty and depressive symptoms by controlling potential confounders.

MATERIALS AND METHODS

Study Participants

We obtained the data from The China Health and Retirement Longitudinal Study (CHARLS). The CHARLS began in 2011 with a cohort of 17,284 participants ≥45 years (Wave1). Subsequently, data collection was conducted in 2013 (Waves2), 2015 (Waves3). CHARLS was a nationally representative longitudinal survey of the mid-aged and elderly population in China along with their spouses. The respondents will be followed every 2 years using a face-to-face, computer-aided personal interview (CAPI) and structured questionnaire. The current study used data from participants who participated in Wave1, Waves2, and Waves3. We excluded individuals who met any of the following criteria at baseline (1) Chinese version of the Center for Epidemiologic Studies-Depression scale (CESD-10) ≥10 scores, (2) no components of frailty data, (3) no age/sex/educational levels/marital status/current smoking/alcohol drinking/exercise/chronic diseases/live place/activities data. In addition, we excluded participants with no follow-up data. The numbers of individuals who completed both the baseline were 2,579 individuals, and follow-up surveys were 839 for the short-term (2 years from 2011 to 2013), and 788 for the long-term (4 years from 2011 to 2015).

Depressive Symptom

The Chinese version of the Center for Epidemiologic Studies-Depression scale (CES-D) (16–19) was used to measure depressive symptoms in the study. The CES-D consists of 10 items, and each item uses a 4-point Likert scale [from 0 "Rarely or none of the time (<1 day)" to 3 "Most or all of the time (5–7 days)"] to reflect the severity of a particular symptom during the past week. The total score ranges from 0 to 30, with a higher total score indicating more severe depressive symptoms. We used harmonized criteria cutoff values to define depressive symptom-total score ≥10. The Chinese version of the CES-D has shown adequate reliability and validity in the middle-aged and elderly. In our study, the Cronbach alpha coefficient was 0.86 and the construct validity was 0.62 (1).

Frailty Assessment

Frailty was evaluated through the widely used criteria originally proposed by Fried et al. (5), modified with the information available in the CHARLS. In the definition, frailty contained five components of exhaustion, weakness, low physical activity, weight loss, and slowness. In our study, the five components of frailty were evaluated and defined as follows: (1) **Exhaustion:** exhaust was present if the participant answered "Most or all of the time" or "Occasionally or a moderate amount of the time" for either of the Chinese version of the Center for Epidemiologic Studies-Depression scale (CES-D) questions (20): "I felt everything I did was an effort during last week" or "I could not get going during last week." This component was constructed identically to the originally proposed by Fried et al. (5). (2) **Weakness:** weakness was measured using the self-reported item "having difficulty in Lifting or carrying weights over 10 jin, like a heavy bag of groceries" (21). (3) **Low physical activity:** CHARLS defined WALK as walking those participants might do solely for recreation, sport, excise, or leisure at work and at home, walking to travel from place to place, and any other walking. Low physical activity was considered to be present if the participants had no physical activity or WALK at least 10 min at a time during a usual week. This component was different from that proposed by Fried et al. (5), but similar treatment variables have been used before to evaluate the low physical activity (22). (4) **Weight loss:** the weight loss was defined as the unintentional loss of 5 or more kilograms in the last year (21) or current body mass index (BMI) $\leq$ 18.5 kg/m^2 (23). (5) **Slowness:** these questions asked the participants to report whether they have difficulty with walking 100 meters or climbing several flights of stairs without resting, which was similar to that used in other studies (21). Those participants who had difficulty with performing the walking or climbing were categorized as slowness. In our study, robustness was defined as the absence of any component, pre-frailty as the presence of one or two of these components, and frailty as the presence of three or more components.

Body Measurement

Body measure index (BMI) was defined as the body mass (kg) divided by the square of the body height (m). BMI were divided into 4 categories: underweight (BMI $<$ 18.5 kg/m^2), normal (18.5–24 kg/m^2), overweight (24–28 kg/m^2), and obese (≥28 kg/m^2) (24–26).

Covariates

Age, sex (male, female), educational levels, marital status, current residence, current smoking, alcohol drinking, chronic diseases, activities at baseline, and entry wave (Wave 1, 2, 3) were incorporated as covariates in the present research. (1) Age was classified into four categories: below 45–54, 55–64, 65–74, and above 75 yr old. (2) Educational levels including illiterate (no formal education), less than elementary school (did not finish primary school but capable of reading or writing, graduate from sishu/home school, elementary school, or middle school), high school, and above vocational school (graduate from two/three-year college/associate degree, graduate from post-graduate, doctoral degree/Ph. D). (3) Marital status was categorized into two groups: the single (divorced, and never married, widowed, or separated) and married. (4) Current residence including rural and urban. (5) Current smoking including current smoker, former-smoker and never smoked. (6) Alcohol drinking including never drinker, less than once a month, and more than once a month. (7) Activities (interacted with friends/ provided help to family, friends, or neighbors who do not live with you and who did not pay you for the help/went to a sport, social, or other kind of club/played Ma-jong, played chess, played cards, or went to community club/took part in a community-related organization/done voluntary or charity work/cared for a sick or disabled adult who does not live with you and who did not pay you for the help/attended an educational or training course/stock investment /used the Internet) were dichotomized as ever (at least once a month) vs. never. (8) Chronic diseases, including (1) hypertension, (2) cancer or malignant tumor (excluding minor skin cancers), (3) diabetes or high blood sugar, (4) chronic lung diseases, (5) dyslipidemia, (6) liver disease (except fatty liver, tumors, and cancer), (7) kidney disease (except for tumor or cancer), (8) stroke, (9) heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems, (10) stomach or other digestive disease (except for tumor or cancer), (11) memory-related disease, (12) emotional, nervous, or psychiatric problems, (13) arthritis or rheumatism, (14) asthma were reported by the respondents (diagnosed by a doctor). According to previous standard (1, 27), a continuous variable is used to reflect the presence of chronic health conditions among 14 common chronic diseases which ranges from 0 to 14. The numbers of the condition of the chronic disease were classified into three categories: 0, 1–2, and 3–14. The categories have been widely used in our previous studies (1, 24–26, 28–31).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS version25.0 (IBM Corp., Armonk, NY). Categorical variables were expressed as frequencies and percentages and compared using the χ^2 test. Logistic regression was used to analyze the odds ratio (OR), and 95% confidence interval (CI) for the cross-sectional associations of frailty and its components with depressive symptoms in the participants at baseline. Depressive symptoms were analyzed as binary dependent variable (no-depressive symptoms and depressive symptoms), and covariates were sequentially entered into the regression models. Model 1 included frailty or its components only, model 2 additionally included socio-demographic characteristics (age, sex, educational levels, marital status, current residence), and model 3 further included health behaviors and condition (current smoking, alcohol drinking, activities, chronic diseases), and model 4 additionally included body measure (BMI). Cox proportional hazards analysis was conducted using the hazard ratio (HR), and 95% confidence interval (CI) for the prospective associations of baseline frailty and pre-frailty and its component in the participants without depressive symptoms at baseline. Covariates were modeled by methods identical to those in cross-sectional analysis. A two-sided P-value of <0.05 was considered a statistically significant level.

RESULTS

Table 1 shows the baseline characteristics of participants according to the level of depressive symptoms. The mean age of participants was 61.06 (SD ± 10.12); 38.31% were male; 16.01% were single; 91.74% were living in rural. 9.00% were former smoking, and 24.58% were current smoking; 7.10% were drinking less than once a month, and 19.35% were drinking more than once a month; 49.24% were taking activities; 51.38% had 1–2 chronic diseases, and 27.14% had 3–14 chronic diseases. The frequency of depressive symptoms was 57.93%. The differences among participants with or without depressive symptoms were observed in the distribution of age subgroups, sex, educational levels, marital status, living place, cigarette smoking, alcohol consumption status, and chronic diseases.

Table 2 shows the baseline characteristics of participants according to the level of frailty. A total of 2,579 robust individuals (32.53%), pre-frail (55.84%), and frailty (11.63%) at baseline were included in the cross-sectional analysis. The differences among components of frailty were observed in the distribution of age subgroups, sex, educational levels, marital status, living place, alcohol consumption status, taking activities, chronic diseases, and BMI categories.

Table 3 shows baseline characteristics classified according to the subsequent onset of depressive symptoms. In the short-term (2 years from 2011 to 2013), participants who developed depressive symptoms were more likely to be female and to live in rural. They tended to be never smoking. In the long-term (4 years from 2011 to 2015), participants who developed depressive symptoms were also more likely to be female and to take no activities.

Table 4 shows the cross-sectional relationship between frailty and depressive symptoms at baseline. Both pre-frailty (OR = 5.293, 95%CI 4.363–6.422) and frailty (OR = 16.025, 95%CI 10.948–23.457) were significantly associated with depressive symptoms after adjusting for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, and BMI (adjusted model 4). In the frailty component, after adjusting for the full set of covariates, exhaust (OR = 12.094, 95%CI 9.864–14.827), weakness (OR = 2.058, 95%CI 1.526–2.775), weight loss (OR = 1.526, 95%CI 1.167–1.995), and slowness (OR = 1.849, 95%CI 1.521–2.247) were associated with prevalent depressive symptoms. However, low physical activity (OR = 1.227, 95%CI 0.973–1.548) was not associated with prevalent depressive symptoms.

Table 5 shows the prospective associations between baseline frailty and depressive symptoms at 2- and 4-years follow-up survey in the participants without depressive symptoms

TABLE 1 | Baseline characteristics of participants according to the level of depressive symptoms in CHARLS Waves 2011 (*N*, %).

Variables	All participants (2,579)	No-depressive symptoms (1,085)	Depressive symptoms (1,494)	*t*/χ^2	*P*-value
Age (years)	61.06 ± 10.12	61.67 ± 10.29	60.61 ± 9.98	2.623	0.006
Age groups (years)					
45–54	727 (28.19)	298 (27.47)	429 (28.71)	10.074	0.018
55–64	948 (36.76)	370 (34.10)	578 (38.69)		
65–74	620 (24.04)	287 (26.45)	333 (22.29)		
≥75	284 (11.01)	130 (11.98)	154 (10.31)		
Sex					
Male	988 (38.31)	499 (45.99)	489 (32.73)	46.761	0.000
Female	1,591 (61.69)	586 (54.01)	1,005 (67.27)		
Education					
Illiterate	890 (34.51)	328 (30.23)	562 (37.62)	44.975	0.000
Less than elementary school	1,517 (58.82)	647 (59.63)	870 (58.23)		
High school	102 (3.96)	62 (5.71)	40 (2.68)		
Above vocational school	70 (2.71)	48 (4.42)	22 (1.47)		
Marital status					
Single	413 (16.01)	153 (14.1)	260 (17.40)	5.094	0.024
Married	2,166 (83.99)	932 (85.9)	1,234 (82.60)		
Current residence					
Rural	2,366 (91.74)	973 (89.68)	1,393 (93.24)	10.526	0.001
Urban	213 (8.26)	112 (10.32)	101 (6.76)		
Current smoking					
No	1,713 (66.42)	675 (62.21)	1,038 (69.48)	16.487	0.000
Former smoke	232 (9.00)	118 (10.88)	114 (7.63)		
Current smoke	634 (24.58)	292 (26.91)	342 (22.89)		
Alcohol drinking					
No	1,897 (73.56)	771 (71.06)	1,126 (75.37)	9.220	0.010
Less than once a month	183 (7.10)	74 (6.82)	109 (7.30)		
More than once a month	499 (19.35)	240 (22.12)	259 (17.34)		
Taking activities					
No	1,309 (50.76)	528 (48.66)	781 (52.28)	3.281	0.070
Yes	1,270 (49.24)	557 (51.34)	713 (47.72)		
Chronic diseases (counts)	1.76 ± 1.49	1.55 ± 1.42	1.92 ± 1.53	1.932	0.000
Chronic diseases groups (counts)					
0	554 (21.48)	282 (25.99)	272 (18.21)	42.020	0.000
1–2	1,325 (51.38)	572 (52.72)	753 (50.40)		
3–14	700 (27.14)	231 (21.29)	469 (31.39)		
BMI (kg/m^2)					
BMI categories	23.70 ± 4.09	23.86 ± 4.08	23.58 ± 4.09	0.214	0.078
<18.5	200 (7.75)	68 (6.27)	132 (8.84)	6.808	0.078
18.5–24	1,253 (48.58)	530 (48.85)	723 (48.39)		
24–28	789 (30.59)	348 (32.07)	441 (29.52)		
≥28	337 (13.07)	139 (12.81)	198 (13.25)		

at baseline. Firstly, in crude analysis, pre-frailty and frailty were not significantly associated with incident depressive symptoms during the short-term [pre-frail: HR = 1.316 (0.959, 1.805); frailty: HR = 2.162 (0.945, 4.948)]. Secondly, in crude analysis, the frailty [HR = 1.386 (1.019, 1.885)] and pre-frailty [HR = 2.492 (1.054, 5.893)] were significantly associated with incident depressive symptoms during the long-term. Thirdly, after adjusting for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, and BMI, frailty [HR = 1.395 (0.966, 2.013)] and pre-frailty [HR = 2.458 (0.933, 6.479)] were not significantly associated with incident depressive symptoms during the short-term. Lastly, after adjusting for the full set of covariates, the HR for pre-frailty was 1.397 (95%CI 1.017–1.920)

TABLE 2 | Baseline characteristics of participants according to the level of frailty in CHARLS Waves2011.

Variables	All participants (2,579)	Robust (839)	Pre-frail (1,440)	Frailty (300)	F/χ^2	P-value
Age (years)	61.06 ± 10.12	60.11 ± 9.84	60.61 ± 9.88	65.83 ± 10.79	39.506	0.000
Age groups (years)						
45–54	727 (28.19)	263 (31.35)	425 (29.51)	39 (13)	81.216	0.000
55–64	948 (36.76)	317 (37.78)	528 (36.67)	103 (34.33)		
65–74	620 (24.04)	185 (22.05)	347 (24.1)	88 (29.33)		
≥75	284 (11.01)	74 (8.82)	140 (9.72)	70 (23.33)		
Sex						
Male	988 (38.31)	347 (41.36)	556 (38.61)	85 (28.33)	15.990	0.000
Female	1,591 (61.69)	492 (58.64)	884 (61.39)	215 (71.67)		
Education						
Illiterate	890 (34.51)	245 (29.2)	494 (34.31)	151 (50.33)	71.495	0.000
Less than elementary school	1,517 (58.82)	505 (60.19)	872 (60.56)	140 (46.67)		
High school	102 (3.96)	47 (5.6)	49 (3.4)	6 (2)		
Above vocational school	70 (2.71)	42 (5.01)	25 (1.74)	3 (1)		
Marital status						
Single	413 (16.01)	108 (12.87)	240 (16.67)	65 (21.67)	13.740	0.001
Married	2,166 (83.99)	731(87.13)	1,200 (83.33)	235 (78.33)		
Current residence						
Rural	2,366 (91.74)	745 (88.8)	1,338 (92.92)	283 (94.33)	14.890	0.001
Urban	213 (8.26)	94 (11.2)	102 (7.08)	17 (5.67)		
Current smoking						
No	1,713 (66.42)	565 (67.34)	932 (64.72)	216 (72)	9.004	0.061
Former smoke	232 (9)	77 (9.18)	127 (8.82)	28 (9.33)		
Current smoke	634 (24.58)	197 (23.48)	381 (26.46)	56 (18.67)		
Alcohol drinking						
No	1,897 (73.56)	594 (70.8)	1,058 (73.47)	245 (81.67)	16.428	0.002
Less than once a month	183 (7.1)	71 (8.46)	93 (6.46)	19 (6.33)		
More than once a month	499 (19.35)	174 (20.74)	289 (20.07)	36 (12)		
Taking activities						
No	1,309 (50.76)	361 (43.03)	769 (53.4)	179 (59.67)	33.617	0.000
Yes	1,270 (49.24)	478 (56.97)	671 (46.6)	121 (40.33)		
Chronic diseases (counts)	1.76 ± 1.49	1.43 ± 1.33	1.83 ± 1.47	2.38 ± 1.77	50.520	0.000
Chronic diseases categories						
0	554 (21.48)	229 (27.29)	287 (19.93)	38 (12.67)	80.684	0.000
1–2	1,325 (51.38)	457 (54.47)	732 (50.83)	136 (45.33)		
3–14	700 (27.14)	153 (18.24)	421 (29.24)	126 (42)		
BMI (kg/m^2)	23.70 ± 4.09	24.00 ± 4.05	23.61 ± 4.00	23.26 ± 4.55	4.289	0.014
BMI categories						
<18.5	200 (7.75)	37 (4.41)	118 (8.19)	45 (15)	41.081	0.000
18.5–24	1,253 (48.58)	409 (48.75)	703 (48.82)	141 (47)		
24–28	789 (30.59)	284 (33.85)	434 (30.14)	71 (23.67)		
≥28	337 (13.07)	109 (12.99)	185 (12.85)	43 (14.33)		

and for frailty was 2.992 (95%CI 1.210–7.397) during the long-term.

Table 6 shows the association between components of frailty and incident depressive symptoms not depressed at baseline. Firstly, in crude analysis, depressive symptoms risk was increased for the slowness [HR = 1.519 (1.046, 2.204)] during the short-term. However, weakness, weight loss, exhaustion, and low activity were not significantly associated with incident depressive symptoms [weakness: HR = 1.334 (0.694, 2.566), weight loss: HR = 1.631 (0.983, 2.705), exhaustion [HR=1.410 (0.944, 2.104), low activity: HR = 0.972 (0.604, 1.563)]. Secondly, in crude analysis, depressive symptoms risk was increased for the weakness [HR = 2.205 (1.146, 4.243)] and exhaustion [HR = 1.853 (1.264, 2.716)] during the

TABLE 3 | Baseline characteristics classified according to subsequent onset of depressive symptoms.

Variables	**2011→ 2013 Incidence rate (*N* = 839,%)**	***P1***	**2011→ 2015 Incidence rate (*N* = 788,%)**	***P2***
Age (years)		0.313		0.121
45–54	8.34		11.17	
55–64	8.82		11.93	
65–74	7.39		7.74	
≥75	1.67		1.27	
Sex		0.000		0.000
Male	9.42		11.04	
Female	16.81		21.07	
Education		0.204		0.245
Illiterate	8.46		10.41	
Less than elementary school	15.49		18.91	
High school	1.67		1.65	
Above vocational school	0.6		1.14	
Marital status		0.124		0.671
Single	23.6		28.43	
Married	2.62		3.68	
Current residence		0.025		0.853
Rural	24.67		29.06	
Urban	1.55		3.05	
Current smoking		0.004		0.136
No	18.59		21.95	
Former smoke	1.43		2.28	
Current smoke	6.2		7.87	
Alcohol drinking		0.258		0.081
No	19.55		24.62	
Less than once a month	1.31		2.03	
More than once a month	5.36		5.46	
Taking activities		0.590		0.008
No	12.75		17.51	
Yes	13.47		14.59	
Chronic diseases (counts)		0.126		0.752
0	5.6		8.5	
1–2	15.14		17.13	
3–14	5.48		6.47	
BMI (kg/m^2)		0.525		
<18.5	1.79		1.78	0.344
18.5–24	13.71		16.12	
24–28	7.75		9.39	
≥28	2.98		4.82	

long-term. However, slowness, weight loss, and low activity were not significantly associated with incident depressive symptoms [slowness: HR = 1.006 (0.687, 1.474), weight loss: HR = 0.986 (0.574, 1.693), low activity: HR = 1.478 (0.941, 2.32)]. Thirdly, after adjusting for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, and BMI, the HR for slowness was 1.597 (95%CI 1.078, 2.366) during the short-term. However, weakness, weight loss, exhaustion, and low activity were not significantly associated with incident depressive symptoms [weakness: HR = 1.186 (0.602, 2.334), weight loss: HR = 1.510 (0.895, 2.548), exhaustion: HR = 1.353 (0.897, 2.041), low activity: HR = 1.023 (0.627, 1.668)]. Lastly, adjusting for the full set of covariates, the HR for weakness was 2.080 (95%CI 1.055, 4.104) and for exhaustion was 1.928 (95%CI 1.297, 2.867) during the long-term. However, slowness, weight loss, and low activity were not significantly associated with incident depressive symptoms [slowness: HR = 0.998 (0.670, 1.487), weight loss: HR = 0.992 (0.568, 1.735), low activity: HR = 1.582 (0.988, 2.533)].

DISCUSSION

Previous studies have reported differences in the relationship between frailty and the incidence of depressive symptoms. Furthermore, the results in the association among the mid-aged and elderly in China have been sparse. Our study describes the cross-sectional and longitudinal associations between pre-frailty/frailty/components of frailty and depressive symptoms. Firstly, it is confirmed that pre-frailty/frailty/components of frailty (exhaust, weakness, weight loss, and slowness) at baseline was related to depressive symptoms; Secondly, pre-frailty/frailty at baseline was not significantly associated with the onset of depressive symptoms after 2 years of follow-up. Among specific criteria, slowness was a significant independent predictor of future depressive symptoms. Lastly, pre-frailty/frailty at baseline was significantly associated with the onset of depressive symptoms after 4 years of follow-up. Among specific criteria, weakness and exhaustion were significant independent predictors of future depressive symptoms.

Although several meta-analysis studies (11–15) included cohort studies and cross-sectional studies and highlighted the potential adverse effect of frailty on depression, no considerations of the components effect of frailty on depression over several years in different studies were made. Moreover, the meta-analysis only included Western participants, and no considerations of other ethnicities, such as Asians. Thus, further studies among the middle-aged and elderly in Asian nations are needed to identify whether the relationship between frailty and incidence of depression in Asian participants. Several findings from longitudinal studies have found that factors similar to components of frailty, such as physical activity (32, 33), fatigue (34–36) and mobility impairment (37) appear to increase the risk for developing depressive symptoms in the older adult. Findings from the present longitudinal data in our study indicate that preferability/frailty is associated with increased risk of incident depressive symptoms after 4 years of follow-up in the middle-aged and elderly aged 45–96 years was in line with the previous studies conducted in the United Kingdom (22), Japan (38), Italians (39), and mainland China (22, 40–42), although the measurements of the frailty phenotype, the population and the years of follow-up were different. Interestingly, we did not find a significant association between baseline

TABLE 4 | Odds ratios (ORs) and 95% confidence interval (CIs) for depressive symptoms at baseline associated with frailty and components of frailty at baseline.

***N* = 2,579**	**Model 1 OR (95%CI)**	**Wald, df**	***P*-value**	**Model 2 OR (95%CI)**	**Wald, df**	***P*-value**	**Model 3 OR (95%CI)**	**Wald, df**	***P*-value**	**Model 4 OR (95%CI)**	**Wald, df**	***P*-value**
Frailty status												
Robust (839)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Pre-frail (1,440)	5.413 (4.493, 6.522)	315.891,1	0.000	5.539 (4.572, 6.710)	305.97,1	0.000	5.32 (4.385, 6.453)	287.728,1	0.000	5.293 (4.363, 6.422)	285.437,1	0.000
Frailty (300)	15.942 (11.07, 22.96)	221.346,1	0.000	17.445 (11.958, 25.45)	220.146,1	0.000	16.228 (11.091, 23.743)	205.974,1	0.000	16.025 (10.948, 23.457)	203.67,1	0.000
P-trend	4.696 (4.020, 5.487)	379.743,1	0.000	4.852 (4.131, 5.698)	370.504,1	0.000	4.668 (3.970, 5.489)	347.338,1	0.000	4.642 (3.947, 5.46)	343.942,1	0.000
Weakness												
No (2,301)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Yes (278)	2.395 (1.802, 3.182)	36.251,1	0.000	2.266 (1.688, 3.043)	29.6,1	0.000	2.089 (1.55, 2.816)	23.426,1	0.000	2.058 (1.526, 2.775)	22.387,1	0.000
Slowness												
No (1,875)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Yes (704)	1.969 (1.638, 2.367)	51.916,1	0.000	1.979 (1.634, 2.398)	48.715,1	0.000	1.833 (1.508, 2.227)	37.154,1	0.000	1.849 (1.521, 2.247)	38.066,1	0.000
Weight loss												
No (2,285)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Yes (294)	1.688 (1.301, 2.189)	15.556,1	0.000	1.677 (1.287, 2.185)	14.669,1	0.000	1.575 (1.206, 2.058)	11.11,1	0.001	1.526 (1.167, 1.995)	9.533,1	0.002
Exhaustion												
No (1,360)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Yes (1,219)	12.185 (10.014, 14.828)	623.315,1	0.000	12.511 (10.218, 15.319)	598.182,1	0.000	12.177 (9.934, 14.927)	578.921,1	0.000	12.094 (9.864, 14.827)	574.89,1	0.000
Low activity												
No (2,188)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
Yes (391)	1.169 (0.938, 1.457)	1.929,1	0.165	1.201 (0.955, 1.509)	2.458,1	0.117	1.208 (0.959, 1.523)	2.565,1	0.109	1.227 (0.973, 1.548)	2.994,1	0.084

Model 1, unadjusted; Model 2, adjusted for age, sex, educational levels, marital status, live place; Model 3, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases; Model 4, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, BMI.

preferability/frailty and the longitudinal onset of depressive symptoms after 2 years of follow-up. The phenomenon could be explained by the cumulative effect, which showed a significant association between preferability/frailty and the longitudinal onset of depressive symptoms over long-term exposure (4 years of follow-up).

With regard to the components of frailty, we found slowness was related to increased risk of incident depressive symptoms after 2 years of follow-up in older adults without baseline depressive symptoms. Moreover, weakness and exhaustion were significantly associated with the onset of depressive symptoms after 4 years of follow-up. However, the findings are partly in accordance with previous studies. Veronese et al. (23) using data from 4,077 representative of people living in England aged 50 years and over, found that slowness (slow gait speed) considered alone predicted depression. Collard et al. (39) launched another similar study to discuss the association and found that Low physical activity was associated with incident depressive symptoms. Chu et al. (42) conducted a population-based cohort study including 1,788 older adults aged 70–84 years in Rugao, Jiangsu Province, China and found that weakness (lower grip strength) was associated with incident depressive symptoms. Several hypotheses could be used to explain the differences between our study and the previously mentioned studies in the literature. First, methodological differences (evaluation tools for depressive symptoms and frailty, length of follow up and confounders) reported in these studies may play an important role. For example, 10-item Epidemiologic Studies-Depression scale for evaluating depressive symptoms was used in our study, but 20-item Epidemiologic Studies-Depression scale and 15-item Geriatric Depression Scale (GDS-15) in other studies (23, 39, 42). Second, the different results reflect that the association may be influenced by cultural background. Furthermore, it is likely adaption of revised Fried's criteria (5) used in our study may influence our result. The mechanisms underline the relationship between frailty and incidence of depressive symptoms is still unknown. Frail individuals may develop depressive symptoms through impaired function, lack of social community, and lower physical activity (42). Several hypotheses could explain the significant relationship between slowness and the onset of depressive symptoms (2 years of follow-up). Firstly, slowness might be an early marker of a depressed mood (43). Secondly, slowness and depressive symptoms shared some risk and pathogenic factor that might affect the onset of depressive symptoms (23). Thirdly, individuals with slowness might be socially isolated, and could be more depressive symptoms (44). Finally, individuals with slowness might have lower physical activity, and might increase the risk of future depressive symptoms (45). However, weakness and exhaustion were significantly associated with the onset of depressive symptoms after 4 years of follow-up. Long exposure to the frailty, individuals with weakness and exhaustion may impair posterior aspects of brain (40, 46), and increased low-grade inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), or tumor necrosis factor-α(TNF-α), and mediated the risk of depressive symptoms. Interventions designed to prevent

TABLE 5 | Association between frailty and incident depressive symptoms not depressed at baseline.

Follow-up period		**Model 1 HR (95%CI)**	**Wald, df**	***P*-value**	**Model 2 HR (95%CI)**	**Wald, df**	***P*-value**	**Model 3 HR (95%CI)**	**Wald, df**	***P*-value**	**Model 4 HR (95%CI)**	**Wald, df**	***P*-value**
2011→ 2013	Frailty status												
***N* = 839**	Robust (471)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Pre-frail (343)	1.316 (0.959, 1.805)	2.9,1	0.089	1.366 (0.991, 1.882)	3.624,1	0.057	1.380 (0.957, 1.989)	2.972,1	0.085	1.395 (0.966, 2.013)	3.155,1	0.076
	Frailty (25)	2.162 (0.945, 4.948)	3.332,1	0.068	2.207 (0.943, 5.168)	3.326,1	0.068	2.487 (0.948, 6.519)	3.431,1	0.064	2.458 (0.933, 6.479)	3.308,1	0.069
	P-trend	1.366 (1.041, 1.793)	5.046,1	0.025	1.404 (1.064, 1.853)	5.756,1	0.016	1.443 (1.053, 1.978)	5.2,1	0.023	1.451 (1.057, 1.990)	5.316,1	0.021
2011→ 2015	Frailty status												
***N* = 788**	Robust (447)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Pre-frail (319)	1.386 (1.019, 1.885)	4.33,1	0.037	1.450 (1.06, 1.983)	5.417,1	0.020	1.400 (1.018, 1.923)	4.295,1	0.038	1.397 (1.017, 1.920)	4.249,1	0.039
	Frailty (22)	2.492 (1.054,5.893)	4.326,1	0.038	2.939 (1.208, 7.153)	5.644,1	0.018	3.036 (1.231, 7.487)	5.815,1	0.016	2.992 (1.210, 7.397)	5.63,1	0.018
	P-trend	1.443 (1.103, 1.886)	7.178,1	0.007	1.525 (1.159, 2.006)	9.08,1	0.003	1.494 (1.130, 1.976)	7.94,1	0.005	1.489 (1.126, 1.969)	7.775,1	0.005

Model 1, unadjusted; Model 2, adjusted for age, sex, educational levels, marital status, live place; Model 3, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases; Model 4, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, BMI.

TABLE 6 | Association between components of frailty and incident depressive symptoms not depressed at baseline.

Follow-up period		Model 1 HR (95%CI)	Wald, df	*P*-value	Model 2 HR (95%CI)	Wald, df	*P*-value	Model 3 HR (95%CI)	Wald, df	*P*-value	Model 4 HR (95%CI)	Wald, df	*P*-value
2011→ 2013	Weakness												
***N* = 839**	No (795)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (44)	1.334 (0.694, 2.566)	0.747,1	0.387	1.29 (0.662, 2.516)	0.56,1	0.454	1.224 (0.623, 2.403)	0.343,1	0.558	1.186 (0.602, 2.334)	0.243,1	0.622
	Slowness												
	No (679)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (160)	1.519 (1.046, 2.204)	4.828,1	0.028	1.617 (1.101, 2.376)	5.995,1	0.014	1.549 (1.048, 2.288)	4.829,1	0.028	1.597 (1.078, 2.366)	5.454,1	0.020
	Weight loss												
	No (766)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (73)	1.631 (0.983, 2.705)	3.592,1	0.058	1.632 (0.976, 2.73)	3.488,1	0.062	1.587 (0.944, 2.667)	3.042,1	0.081	1.510 (0.895, 2.548)	2.38,1	0.123
	Exhaustion												
	No (705)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (134)	1.410 (0.944, 2.104)	2.82,1	0.093	1.394 (0.928, 2.093)	2.556,1	0.110	1.352 (0.897, 2.037)	2.079,1	0.149	1.353 (0.897, 2.041)	2.082,1	0.149
	Low activity												
	No (738)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (101)	0.972 (0.604, 1.563)	0.014,1	0.907	1.006 (0.619, 1.634)	0.001,1	0.982	0.997 (0.612, 1.625)	0,1	0.991	1.023 (0.627, 1.668)	0.008,1	0.929
2011→ 2015	Weakness												
***N* = 788**	No (750)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (38)	2.205 (1.146, 4.243)	5.61,1	0.018	2.098 (1.078, 4.083)	4.755,1	0.029	2.103 (1.068, 4.142)	4.625,1	0.032	2.080 (1.055, 4.104)	4.467,1	0.035
	Slowness												
	No (639)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (149)	1.006 (0.687, 1.474)	0.001,1	0.975	1.047 (0.708, 1.547)	0.052,1	0.820	0.992 (0.667, 1.477)	0.002,1	0.969	0.998 (0.670, 1.487)	0.000,1	0.993
	Weight loss												
	No (722)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (66)	0.986 (0.574, 1.693)	0.003,1	0.958	0.994 (0.575, 1.72)	0,1	0.984	1.017 (0.585, 1.77)	0.004,1	0.951	0.992 (0.568, 1.735)	0.001,1	0.979
	Exhaustion												
	No (656)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (132)	1.853 (1.264, 2.716)	9.997,1	0.002	1.961 (1.326, 2.898)	11.394,1	0.001	1.936 (1.302, 2.877)	10.674,1	0.001	1.928 (1.297, 2.867)	10.542,1	0.001
	Low activity												
	No (698)	Ref (1.000)			Ref (1.000)			Ref (1.000)			Ref (1.000)		
	Yes (90)	1.478 (0.941, 2.32)	2.878,1	0.090	1.618 (1.016, 2.576)	4.113,1	0.043	1.566 (0.979, 2.505)	3.495,1	0.062	1.582 (0.988, 2.533)	3.652,1	0.056

Model 1, unadjusted; Model 2, adjusted for age, sex, educational levels, marital status, live place; Model 3, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases; Model 4, adjusted for age, sex, educational levels, marital status, live place, current smoking, alcohol drinking, activities, chronic diseases, BMI.

depressive symptoms may be useful in reducing frailty among middle-aged and older adults.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study has several strengths. The study was based on a nationwide population-based cohort study, which included participants aged ≥45 years. It compared the effect of frailty and its components across two different intervals on the depressive symptom. Previous studies used only a set single interval to identify the relationship between frailty and depressive symptom. It helped us to understand the short- and long-term effects of frailty on the incidence of depressive symptoms. Several limitations in our study should be noted. The depressive symptom was self-reported in the three waves when it was subjectively measured. This may have a reporting bias. It is known that people tend to underreport their mental illness in the research. Many participants were excluded for the missing data, and further research should focus more on a set of complete material.

CONCLUSIONS

Among middle-aged and older adults, frailty, pre-frailty did not predict depressive symptoms during 2 years of follow-up, when accounting for the potential confounders, slowness considered alone predicted depressive symptoms. Additionally, frailty, pre-frailty predicted depressive symptoms during 4 years of follow-up, when accounting for the potential confounders, weakness and exhaustion considered alone predicted depressive symptoms.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Approval for this study was given by the Medical Ethics Committee of Wannan Medical College (Approval Number 2021–3). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL and LZ: conceived and designed the research. LZ: wrote the article and analyzed the data. HL, LZ, XY, GX, J-lL, L-lG, LY, CW, TY, DZ, HW, JL, YLe, LS, XL, YH, HC, ML, and YLi: revised the article. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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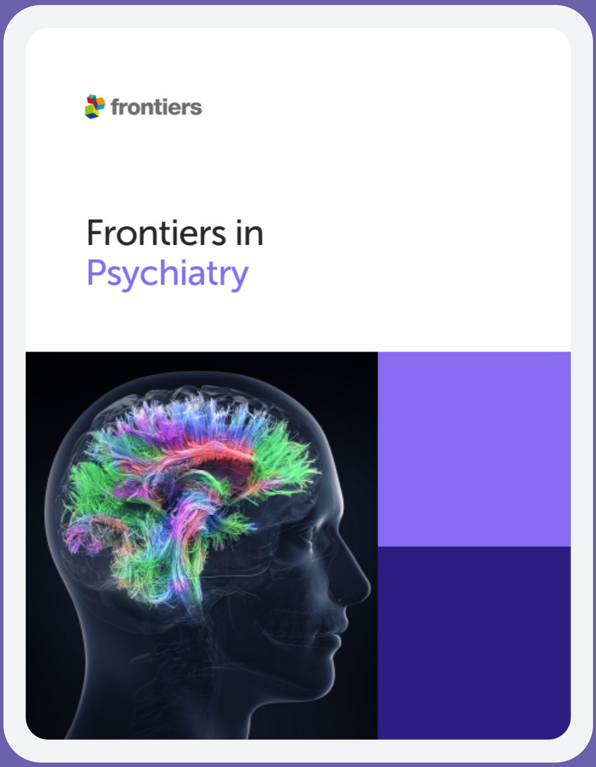
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