Differential associations between depressive symptom-domains with anxiety, loneliness,

and cognition in a sample of community older Chinese adults: A multiple indicators

multiple causes approach

Tianyin Liu<sup>1</sup>, PhD

https://orcid.org/0000-0003-1196-5345

Man-Man Peng<sup>2</sup>, PhD

Frankie H. C. Wong<sup>3</sup>, MSc

https://orcid.org/0000-0001-9072-769X

Dara K. Y. Leung<sup>4</sup>, PhD

https://orcid.org/0000-0002-7255-2790

Wen Zhang<sup>5</sup>, PhD

https://orcid.org/0000-0002-8166-2879

Gloria H. Y. Wong<sup>1</sup>, PhD

https://orcid.org/0000-0002-1331-942X

Terry Y. S. Lum<sup>1,4</sup>, PhD

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<sup>1</sup> Department of Social Work and Social Administration, The University of Hong Kong, Hong Kong, China

<sup>2</sup> Institute of Advanced Studies in Humanities and Social Sciences, Beijing Normal University, Zhuhai, China

<sup>3</sup> Philip Merrill College of Journalism, University of Maryland, College Park, Maryland, USA

<sup>4</sup> Sau Po Centre on Ageing, The University of Hong Kong, Hong Kong, China

<sup>5</sup> School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong,

China

\*Address correspdonence to: Tianyin Liu. E-mail: tianyin@hku.hk

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#### Abstract

**Background and Objectives:** Depressive symptoms are common in older adults, and often co-occur with other mental health problems. However, knowledge about depressive symptom-domains and their associations with other conditions is limited. This study examined depressive symptom-domains and associations with anxiety, cognition, and loneliness.

**Research Design and Methods:** A sample of 3795 participants aged 60 years and older were recruited from the community in Hong Kong. They were assessed for depressive symptoms (Patient Health Questionnaire-9 [PHQ-9]), anxiety (Generalized Anxiety Disorder 7-item), loneliness (UCLA 3-item) and cognition (Montreal Cognitive Assessment 5-minute protocol). Summary descriptive statistics were calculated, followed by confirmatory factor analysis (CFA) of PHQ9. Multiple indicators multiple causes (MIMIC) analysis was used to examine the associations between mental health conditions in the general sample and subgroups based on depressive symptom severity.

**Results:** A four-factor model based on the Research Domain Criteria (RDoC) showed the best model fit of PHQ-9 ( $\chi^2$ /df = 10.63, RMSEA = 0.05, CFI = 0.96, TLI = 0.93). After adjusting for demographics, four depressive symptom-domains were differentially associated with anxiety, loneliness, and cognition across different depression severity groups. The Negative Valance Systems and Internalizing domain (*NVS-I*; guilt and self-harm) were consistently associated with anxiety ( $\beta$ =0.45, 0.44) and loneliness ( $\beta$ =0.11, 0.27) regardless of depression severity (at risk/mild vs moderate and more severe, respectively, all *p*<0.001).

**Discussion and Implications:** The consistent associations between the *NVS-I* domain of depression with anxiety and loneliness warrant attention. Simultaneous considerations of depressive symptom-domains and symptom severity are needed for designing more personalized care.

## Clinical Trial Registration: NCT03593889

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Keywords: Mental health, Quantitative research methods, Depression and Anxiety, Common mental health issues, Research Domain Criteria

## **Translational Significance**

Depressive symptoms are common in older adults and are heterogeneous with multiple symptom-domains. This study investigated depressive symptom-domains among communitydwelling older Chinese in Hong Kong, and examined their association with anxiety, loneliness, and cognition. We found four depressive symptom-domains in this sample, and people with different depressive symptom-domains have differential possibilities to demonstrate co-occurrent anxiety, loneliness, and cognitive decline. Those with feelings of inappropriate guilt and suicidal ideation were more likely to show anxiety symptoms and loneliness as well. A more fine-grained assessment of depression is needed for personalized care.

#### Introduction

Depression is a common mental health condition in older people with a global prevalence of 13.3% (95% CI: 8.4-20.3%) (Abdoli et al., 2021), and it is associated with a high rate of mortality and a significant risk of dementia (Baldwin et al., 2006). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) describes nine major depressive disorder (MDD) symptoms, including (1) anhedonia, (2) depressive mood, (3) sleep difficulties, (4) fatigue, (5) appetite/weight symptoms, (6) feelings of inappropriate guilt/worthlessness, (7) diminished concentration, (8) psychomotor problems, and (9) selfharm/suicidal ideation (APA, 2013). The diagnostic criteria of MDD concern not only the number of symptoms but also frequency, duration and/or severity, reflecting the conceptualization of depression along a spectrum, with increasing severity varying from nonsymptomatic to showing subclinical symptoms to having MDD (Ayuso-Mateos et al., 2010). Although the causes and very nature of depression remain subject to debate, it is widely acknowledged that depression is a heterogeneous condition with multiple symptom-domains and subtypes, and two persons with an MDD diagnosis may share no single symptom (Chen et al., 2000; Fried & Nesse, 2015). People may experience depressive symptoms but fall short of the diagnostic threshold for MDD, and among them, the depressive symptoms may also present in heterogeneous patterns (Chen et al., 2000).

### Prevention of Depression in Subclinical and At-Risk Populations

Traditionally, research and intervention for depression have focused on the clinical population, but more efforts have been devoted to the reduction of symptoms and risk factors because numerous studies have documented the benefits of early intervention and prevention of depression in subclinical and at-risk populations (Cuijpers et al., 2014; Rebar et al., 2015). Subclinical, or subthreshold, depression is when an individual displays clinically relevant, i.e., moderate and more severe, depressive symptoms, but standard diagnostic criteria are not

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met (Rodríguez et al., 2012). It is more prevalent than MDD in the community, associated with increased risk for MDD, decreased health-related quality of life, and mortality rates in older people (Chachamovich et al., 2008; Cuijpers et al., 2013; Lee et al., 2019). Even without clinically relevant depressive symptoms, older adults face multiple risk factors for depression, including biological (chronic health condition, cognitive impairment, and functional limitations), psychological (external locus of control, dysfunctional coping, negative self-image and psychopathology), and social factors (smaller network size, stressful events, and living alone) (Vink et al., 2008). Following stressful events such as retirement, death of loved ones, and functional decline, it is common for older people to develop depressive symptoms such as sleep disturbance, loss of interest, and depressed mood (Maier et al., 2021).

Increasing evidence supports differential preventive strategies for mental health in atrisk/with mild depressive symptoms and subclinical populations. Selective prevention is effective in promoting mental well-being and preventing mental disorders in those at-risk or with mild symptoms, and indicated prevention is effective in shifting the trajectories towards less debilitating outcomes or delaying the onset of mental disorders among those with moderate and more severe depressive symptoms (Arango et al., 2018). In the case of late-life depression, selective prevention focuses on people with established susceptibility based on risk factors such as social isolation and bereavement, where group-based psychoeducation and behavioral activation approaches are typically used; and indicated prevention focuses on those already living with clinically relevant symptoms, where more targeted intervention is prescribed (Almeida, 2014; Reynolds et al., 2012). These strategies have proven effective and cost-effective, and given the trend of population aging and the shortage of mental health workforce, it is crucial to develop more targeted and cost-effective risk-reduction strategies for different populations (Reynolds et al., 2012).

### **Depressive Symptom-Domains**

The Patient Health Questionnaire-9 (PHQ-9) is one of the depression screening instruments comprising items that map onto the DSM diagnostic criteria for depressive symptoms (Kroenke et al., 2001). Some studies using the PHQ-9 provided support for one single underlying factor of depressive symptoms (Cameron et al., 2008; Keum et al., 2018); however, many more studies suggested multiple domains of depressive symptoms detectable by the PHQ-9, mostly two-factor structure (cognitive-affective and somatic) (Chilcot et al., 2013; Petersen et al., 2015).

Despite the utility of the DSM, it may not reflect the recent advances in understanding mental disorders based on behavioral dimensions and neurobiological measures (Dillon et al., 2014). To address this limitation, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) initiative to provide a new framework for psychopathology research rooted in a dimensional approach to mental health (Insel et al., 2010). A recent study drew on the RDoC matrix and used factor and qualitative analysis to map the PHQ-9 items, and identified a four-factor model: Negative Valence Systems and Externalizing (*NVS-E*; anhedonia and depression), Negative Valence Systems and Internalizing (*NVS-I*; guilt and self-harm), Arousal and Regulatory Systems (*ARS*; sleep, fatigue and appetite) and Cognitive and Sensorimotor Systems (*CSS*; concentration and psychomotor); the authors suggested that recognizing these phenotypes may provide a step towards developing more personalized care depending on varying patterns of depressive symptoms (Gunzler et al., 2020).

#### Associations with Anxiety, Loneliness and Cognition

There are abundant empirical research and theories on the associations between depressive symptoms and other mental health conditions in older adults. Among the common mental health issues in older people, this study focused on anxiety, loneliness, and cognition because these three conditions have high rates of co-existence or complex relationship with depressive symptoms, are preventable or manageable if identified early, and would lead to worse mental health outcomes and lower quality of life if left untreated (Cacioppo et al., 2006; Kalin, 2020; Kaup et al., 2016).

Many studies focused on associations between two conditions. For depression and anxiety, a worldwide survey reported that 45.7% of individuals with lifetime depression had a history of one or more anxiety disorders (Kessler et al., 2015), and a review suggested that the high co-occurrence may be due to shared structural and functional brain alterations in circuits involving emotion regulation and cognitive control (Kalin, 2020). For depressive symptoms and loneliness, a longitudinal study revealed reciprocal influences between loneliness and depressive symptomatology, signalling a synergistic effect of depressive symptoms and loneliness to diminish well-being in older adults (Cacioppo et al., 2006). For depressive symptoms are risk factors for cognitive decline or dementia (Byers & Yaffe, 2011), some suggested that older adults may develop depressive symptoms in reaction to cognitive decline (Jajodia & Borders, 2011); and others theorized that both conditions might reflect a similar neurodegenerative process (Panza et al., 2010).

Research in the recent two decades is taking a more holistic approach to examine the complex associations between more than two mental health issues, for understanding the complex mental health needs of older people may help tailor integrated and personalized interventions. Among these studies, cognition is often the central focus and much attention is

given to improving or maintaining cognitive health. For example, one study examined the association of anxiety, depression, and worry symptoms on cognitive performance in older adults and found that worry symptoms had the highest contribution in predicting cognition; in contrast, anxiety and depressive symptoms had few unique associations with cognitive performance (de Vito et al., 2019). Another study examined the behavioral mechanisms between loneliness, depression, and cognition and found that loneliness and depression may associate with fewer health-promoting and cognitive-stimulating behaviors, e.g., fewer physical, social, and cognitive activities, leading to cognitive impairment according to the "use it or lose it" hypothesis (Salthouse, 2006).

In summary, depressive symptoms are heterogeneous and with multiple domains, and they are associated with other preventable or manageable mental health conditions in older adults. So far, despite abundant research on the associations between depression, anxiety, loneliness, and cognition in older people, depression took less of a central focus; little is known about the depressive symptom domains in older people and whether and how different symptom domains are associated with other mental health conditions in a community sample. It is also of clinical relevance to differentiate the relationships between these mental health conditions in predominately healthy but with some risks or mild symptoms and in subclinical populations with moderate and more severe symptoms, because the related management strategies of depressive symptoms also differ for these two populations (Kok & Reynolds, 2017). Characterizing depressive symptom-domains and their associations with other common mental health conditions in different depressive symptom severity groups among older people may improve diagnostic accuracy and inform more personalized care planning. The aims of the present study were threefold: (1) to examine the depressive symptomdomains, (2) to investigate the associations between depressive symptom-domains and other common mental health conditions, including anxiety, loneliness, and cognition, and (3) to

compare the associations between at-risk population and subclinical population in community-dwelling older adults in Hong Kong.

### Methods

### **Participants**

Participants were community-dwelling older adults at risk of depression or with subclinical depressive symptoms who participated in a collaborative stepped care with peer support program offered by non-governmental organizations (NGOs) in Hong Kong, registered with ClinicalTrials.gov (NCT03593889) (Liu et al., 2022). The inclusion criteria of this study were: (1) aged 60 years or older; (2) at risk for depression, defined as had no depressive symptoms (PHQ-9 total score <5) but at least one risk factor of late-life depression, including reported loneliness, lack of social interaction, lack of meaningful or enjoyable daily activities, chronic pain, more than four common chronic diseases and/or recent bereavement; or (3) had mild to moderately severe depressive symptoms (5< PHQ-9 total score <20). The exclusion criteria were: (1) known history of autism, intellectual disability, schizophrenia spectrum disorder, bipolar disorder, Parkinson's disease or dementia/significant cognitive impairment; (2) significant suicidal risk measured using PHQ-9 item 9 (self-harm/suicidal ideation), and follow-up risk assessment; and (3) declined to participate or difficulty in communication. The analysis used screening data for admission to the program collected by trained social workers between January 2018 and September 2019 from 3795 community-dwelling older adults. Written informed consent was obtained from all participants.

#### Measures

Depressive symptoms were measured using the validated Chinese version of the PHQ-9, which has a high internal consistency (Cronbach's  $\alpha = 0.91$ ) (Yeung et al., 2008). Responses to each item in the PHQ-9 are rated on a four-point Likert scale from 0 (not at all) to 3 (nearly every day). The total score of the PHQ-9 ranges from 0 to 27, with a higher score representing a more severe degree of depression. A classification system is commonly used to interpret PHQ-9 score, with a predefined cutoff score of 10 as a dichotomous scoring system for differentiating clinically relevant depressive symptoms (Kroenke et al., 2001). Since this study used a community sample with no depression diagnosis, we categorized those who scored 0–9 on the PHQ-9 as the "at-risk/mild" and those who scored 10 and above as "moderate and more severe" depressive symptom groups. This categorization has service implications because the corresponding preventive care approaches could differ for these two groups.

Anxiety was measured by the Chinese version of the seven-item Generalized Anxiety Disorder (GAD-7) questionnaire, which has a good internal consistency (Cronbach's  $\alpha = 0.89$ ) (Tong et al., 2016). Each item is rated on a four-point Likert scale from 0 (not at all) to 3 (nearly every day), the total score ranges from 0 to 21, and a higher score indicates more severe depressive symptoms (Spitzer et al., 2006).

Loneliness was measured by the locally adapted three-item UCLA Loneliness Scale (UCLA-3) with a high internal consistency (Cronbach's  $\alpha = 0.87$ ) (Liu et al., 2020). It consists of three items: lack of companionship, feeling left out, and isolated over the past two weeks. The locally adapted Chinese version has four possible responses for each item from 0 (never) to 3 (often). The total score ranges from 0 to 9 points, with a higher score indicating a higher degree of perceived loneliness (Hughes et al., 2004).

Cognition was measured by the Chinese version of the Montreal Cognitive Assessment 5-minute protocol (MoCA-5), which has an acceptable level of reliability (Cronbach's  $\alpha = 0.79$ ) (Wong et al., 2015). Five domains were tested: attention, verbal learning and memory, executive function, language, and orientation. The sum score of the MoCA-5 ranges from 0 to 30, with a higher score indicating better cognitive function.

Participants' demographic characteristics, including age (years), sex (male or female), education level (highest attainment), marital status (married/cohabit or otherwise) and living arrangement (living alone or otherwise), were also collected.

#### **Data Analysis**

First, descriptive statistics were used to summarize demographic variables and responses to clinical measures. Little's Missing Completely at Random (MCAR) test was conducted to identify the mechanism of missing data (Newgard & Haukoos, 2007). Results suggested that data was probably not missing at random; missing data patterns and handling procedures were reported in Supplementary Table 1. Multiple imputations were therefore used to handle the missing data (Sterne et al., 2009). Second, the internal consistencies of the PHQ-9, GAD-7, UCLA-3, and MoCA-5 were evaluated using Cronbach's alpha. Third, Confirmatory Factor Analyses (CFA) were conducted to test and compare three depressive symptom-domain models derived from the literature: single-factor, two-factor (somatic and cognitive-affective), and four-factor model mapped onto RDoC.

After evaluating the measurement model with CFA, we used the Multiple Indicators Multiple Causes (MIMIC) model to measure the associations of depressive symptomdomains with anxiety, loneliness, and cognitive function. The MIMIC model is a specific application of Structural Equation Model (SEM) that involves latent variables with usual multiple indicators, and simultaneously predicted by observed variables (Jöreskog &

Goldberger, 1975). Compared to traditional SEM, a MIMIC model allows the simultaneous evaluation of the effect of the covariates on the factor indicators, providing a better insight into the relations between measured items, latent variables, and covariates. Three MIMIC models were tested: a general model of the total sample and two models by depression severity groups. The model fit of the CFA and MIMIC models was determined with the following commonly used indicators: chi-square  $(\chi^2)$ /degree of freedom (df) ratio, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Goodness-of-fit Index (GFI), the standardized root mean square residual (SRMR) and a non-centrality-based index, the Root Mean Square Error of Approximation (RMSEA). The usual rule of thumb for model fit indices is that  $\gamma^2/df$  equals or below 5, CFI, TLI, and GFI values greater than 0.90, SRMR and RMSEA values below 0.08 indicate an acceptable fit (Marsh & Hocevar, 1985), while  $\chi^2$ /df equals or below 2, CFI, TLI, and GFI values greater than 0.95, SRMR and RMSEA below 0.06 indicate good model fit (Hu & Bentler, 1999). Supplementary Table 1 summarizes the details of the statistical analyses and results. Sensitivity analyses using nonimputed data were performed and reported in supplementary materials (Supplementary Tables 2 and 3). Statistical analyses were conducted using SPSS (24.0) and AMOS (24.0) statistical software.

## **Ethics Statement**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Human Research Ethics Committee (HREC) of the University of Hong Kong.

#### Results

### **Descriptive statistics**

Table 1 shows the sample's descriptive statistics (N = 3795) and the missing value pattern of each variable. The total percentage of missing data was 8.48%, with highest missing rate of 4.91% in MoCA scores, and missing data were addressed using multiple imputations (Supplementary Table 1). Participants had a mean age of 77.34 years (SD = 8.74), and most were female (77.60%). They scored 4.43 (SD = 4.57) on the GAD-7, 3.98 (SD = 2.96) on the UCLA-3, 20.56 (SD = 5.32) on the MoCA-5, and 6.44 (SD = 4.00) on the PHQ-9 on average. In terms of responses to individual items of the PHQ-9, symptoms having a relatively higher score were sleep problems (Mean = 1.40, SD = 1.04), fatigue (Mean = 1.21, SD = 0.92), and depressed mood (Mean = 1.07, SD = 0.92); the average scores of all other symptoms were lower than one. We separated the analyses by depression severity (at risk/mild [PHQ-9  $\leq$  9] vs moderate and more severe [PHQ-9  $\geq$  10]) and compared the two groups; results are summarized in Table 1.

### CFA of the PHQ-9

Reliability analyses suggested that all measures had satisfactory to good internal consistency (PHQ-9: Cronbach's  $\alpha = 0.70$ ; GAD-7: 0.90; UCLA-3: 0.88; MoCA-5: 0.62) (Tavakol & Dennick, 2011). Table 2 shows the factor loadings and model-fitting indices of four proposed PHQ-9 symptom-domains. Compared to the other two models, the four-factor model based on RDoC had the best model fit to the observed data ( $\chi^2/df = 10.63$ , SRMR = 0.02, RMSEA = 0.05, GFI = 0.99, CFI = 0.96, TLI = 0.93), and the correlations between the four factors ranged between 0.62 to 0.78 (Figure 1). Although the relative chi-square is larger than 5, likely to be driven by the large sample size, all other model fitting indices suggest good

model fitting. Sensitivity analyses with original (non-imputed) data revealed similar results that the four-factor model based on RDoC had the best model fit ( $\chi^2/df = 9.24$ , SRMR = 0.03, RMSEA = 0.05, GFI = 0.99, CFI = 0.96, TLI = 0.93).

#### **MIMIC models**

Table 3 shows the regression weights between clinical variables and model-fitting indices of three MIMIC models; Figure 2 summarizes the standardized regression weights of significant associations between key variables under examination (see Supplementary Figure 1 for details concerning all variables). The results of Model 1 with the overall sample suggested acceptable model fitting  $(\chi^2/df = 6.68, \text{SRMR} = 0.02, \text{RMSEA} = 0.04, \text{GFI} = 0.99, \text{CFI} = 0.99$ 0.97, TLI = 0.92). Among the basic demographics, only education level had a negative association with the NVS-I domain ( $\beta = -0.07$ ), and others had no association with any depressive symptom-domain. Anxiety (GAD-7) showed a positive association with all four domains (all p < 0.001), among which the strongest was with the CSS domain ( $\beta = 0.63$ ). Loneliness (UCLA-3) was positively related to three symptom-domains (all p < 0.001) but not the ARS. Note that living alone and loneliness were not related, nor was living alone associated with any depressive symptom-domain, suggesting that subjective appraisal of feeling lonely was conceptually different from living alone. Cognition (MoCA-5) was negatively associated with NVS-E ( $\beta = -0.17$ , p < 0.001) and CSS ( $\beta = -0.12$ , p < 0.001), but not NVS-I or ARS domains. Sensitivity analysis revealed similar results: the overall model fit was acceptable ( $\chi^2/df = 6.18$ , SRMR = 0.02, RMSEA = 0.04, GFI = 0.99, CFI = 0.97, TLI = 0.93), anxiety was positively associated with all four domains, and cognition was negatively associated with NVS-E and CSS domains. The only difference was that loneliness was

positively related to all four domains in the non-imputed sample, although the association with *ARS* domain was weak ( $\beta = 0.09$ , all p < 0.05).

In Model 2, with those at-risk or with mild depressive symptoms, the model fit indices indicated acceptable model fitting ( $\chi^2/df = 6.34$ , SRMR = 0.03, RMSEA = 0.04, GFI = 0.99, CFI = 0.94, TLI = 0.86). Similar to the results of Model 1, anxiety (GAD-7) was positively associated with all four depressive symptom-domains (all *p* < 0.001), and the degrees of association were similar between those with *NVS-E* ( $\beta$  = 0.47), *NVS-I* ( $\beta$  = 0.45), and *CSS* ( $\beta$ = 0.45). Loneliness (UCLA-3) was positively associated with three symptom-domains (all *p* < 0.001) but not the *ARS*. Cognition (MoCA-5) had negative associations with *NVS-E* ( $\beta$  = -0.17, *p* < 0.001) and *CSS* ( $\beta$  = -0.34, *p* < 0.001). Sensitivity analysis results were similar: the overall model fit was slightly better ( $\chi^2/df$  = 5.31, SRMR = 0.03, RMSEA = 0.04, GFI = 0.99, CFI = 0.96, TLI = 0.90), anxiety was positively associated with all four depressivesymptom domains, cognition with *NVS-E* and *CSS* domains; and the only difference was that loneliness was positively associated with all four domains as well, although the association with *ARS* domain was weak ( $\beta$  = 0.10, all *p* < 0.05).

In Model 3, with participants having moderate or more severe depressive symptoms, the model fitting indices suggested good model fitting ( $\chi^2/df = 1.04$ , SRMR = 0.03, RMSEA = 0.01, GFI = 0.99, CFI = 0.99, TLI = 0.99). Anxiety (GAD-7) was positively associated with *NVS-E* ( $\beta = 0.29$ ), *NVS-I* ( $\beta = 0.44$ ) and *CSS* ( $\beta = 0.60$ ), all p < 0.001. Loneliness (UCLA-3) was only positively associated with *NVS-I* ( $\beta = 0.27$ , p < 0.001), but not other symptomdomains. Cognition (MoCA-5) was not associated with any depressive symptom-domain. Sensitivity analysis again revealed similar results: the overall model fit was good ( $\chi^2/df =$ 1.07, SRMR = 0.03, RMSEA = 0.01, GFI = 0.99, CFI = 0.99, TLI = 0.99); anxiety was positively and strongly associated with *NVS-E* and *NVS-I*, not with *ARS*; loneliness was only

#### Discussion

This study contributes to current knowledge by investigating the depressive symptomdomains and examining their associations with anxiety, loneliness, cognition, and demographic risk factors across groups with different depressive symptom severity. It is the first study of this kind to be conducted among community-dwelling older Chinese, and the results may have service implications as the symptom profiles derived from readily available measurements can help to inform more personalized care. For older people in the community, screening for multiple mental health conditions are needed, and depressive symptom severity and symptom-domains may be both considered in service planning. Other than the wellestablished selective and indicated prevention for at-risk/mild symptom and subclinical groups, individuals with anhedonia and depressive mood are more likely to benefit from comprehensive preventive care such as group exercise, healthy lifestyle intervention, and active engagement in community affairs; and individuals with feelings of inappropriate guilt and self-harm thoughts may require more indicated prevention such as group compassionfocused therapy that improves self-esteem and peer group that builds social network.

First, our findings add evidence to the heterogeneity of depression in a community sample and support the four-factor structure of depression based on the RDoC framework (Gunzler et al., 2020). The high correlation between the four factors indicates that screening and monitoring the community population for depression using the total score of PHQ-9 is likely useful in most circumstances. However, monitoring different depressive symptom-domains must not be overlooked, as individuals with similar levels of depression severity

may present with different symptom profiles. We found that community-dwelling older Chinese reported more symptoms in the *ARS* domain (sleep, fatigue and appetite), which is consistent with the literature that older Chinese are more likely to somatize psychological distress or find it easier to express somatic complaints (Hybels et al., 2011). Therefore, it is important not to dismiss somatic complaints when assessing depression in older Chinese adults.

Second, we found that anxiety, loneliness, and cognition were differentially associated with depressive symptom-domains. In the overall sample, anxiety was positively associated with all four depressive domains, and the CSS domain (concentration and psychomotor) was mostly affected. It has been well-documented that the comorbidity between anxiety and depression is high in older adults (Lamers et al., 2011). Our finding contributed to the literature that anxiety is more likely to affect the cognitive domain of depression than other domains. There are two plausible mechanisms to explain this association. For one, the attentional control theory proposes that individuals with an elevated level of anxiety would have attentional biases towards threatening stimuli, which may lead to difficulty filtering information from working memory and affect the monitoring of ongoing activities (Bar-Haim et al., 2007). Consequentially, the emotional information acquired from biased attention to threatening stimuli would retain in thoughts and may lead to impaired concentration on other upcoming events (Eysenck et al., 2007). Alternative to the attentional control theory, anxiety could also be a psychological reaction to an individual's subjective cognitive decline, which could be an early manifestation of neurodegenerative disorders (Liew, 2020). A further cognitive examination may be needed for those exhibiting comorbid depression and anxiety to identify appropriate intervention approaches.

Loneliness was positively associated with three depressive symptom-domains, strongest in the *NVS-E* (anhedonia and depression), but not the *ARS* domain. The close

association between loneliness and depression has been well established in older people (Lee et al., 2021), and our findings add to the literature that loneliness is more likely to affect the external negative valence system but less related to somatic domains of depression. Research has highlighted that older people are vulnerable to experiencing loneliness (Gardiner et al., 2020), and interventions to reduce loneliness could prevent or reduce depression in older adults (Fakoya et al., 2020). Assessing loneliness may also act as a screening tool to identify depression among older adults, especially in contexts with a more substantial stigma toward mental disorders (Liu et al., 2020).

Cognition was negatively associated with *NVS-E* and *CSS* but not the other two depressive symptom-domains. The significant association between global cognition assessed by MoCA-5 and *NVS-E* is consistent with one recent review on the commonalities between cognition, anhedonia, and brain insulin resistance, drawing from pathophysiological evidence (Hamer et al., 2019). Brain insulin resistance has long been hypothesized as the missing link between MDD and dementia, because of insulin's role in regulating cognitive function, dopamine function, reward, and emotional behavior (Kleinridders & Pothos, 2019). Besides pharmacotherapy that targets insulin signaling, exercise is effective in mitigating depressive symptoms, including anhedonia, maintaining cognitive capacities, and improving insulin signaling (Toups et al., 2017). Cognition was not related to *ARS* or *NVS-I*, suggesting that global cognition may have little impact on somatic symptoms or how individuals relate to their emotional state.

Third, we also found that anxiety, loneliness, and cognitive functioning were differentially associated with depressive symptom-domains across different depression severity groups. The pattern observed in the at-risk/mild depressive symptom group was similar to that of the general population, and this is likely because the at-risk/mild symptom group formed 83% of the total sample, which also reflects a higher demand for selective prevention of late-life depression in the community. The complex associations between four depressive symptom-domains and other mental health conditions may contribute to misdiagnosis or ignorance of symptoms in the at-risk/mild depressive symptom group, suggesting the importance of screening for multiple mental health issues and more finegrained examination. In the moderate and more severe depressive symptom (subclinical) group, anxiety was still significantly associated with NVS-I and CSS, loneliness was only associated with NVS-I, and cognition was no longer associated with any depressive symptomdomain. The fewer associations between depressive symptom-domains and loneliness and the absence of connections between depressive symptom-domains with cognition may imply the distinction of subclinical depression from other mental health conditions. Although literature suggested older adults may develop depressive symptoms in reaction to cognitive decline (Jajodia & Borders, 2011), we did not find any association between global cognition and depressive symptom-domains among those with subclinical depression, presumably, because this is a community sample without apparent cognitive impairment. More fine-grained assessments of cognition and multiple assessments over time are needed to unveil the complex relationship between cognition and depression. Nevertheless, the consistent association between anxiety, loneliness and NVS-I across different severity groups may suggest the crucial roles of anxiety and loneliness concerning how individuals evaluate themselves and their emotional state and risk for self-harm. This finding may also imply that to address the NVS-I domain of depression and to reduce self-harm risk, efforts can be made to increase individuals' social connectedness and reduce loneliness and anxiety.

Fourth, only a few demographic factors in this study were associated with different depressive symptom-domains; even for those with a significant association, the effect was small. Some of these findings are consistent with the literature; for example, education was negatively associated with depressive symptoms (Peyrot et al., 2015), and older age was not

associated with a higher prevalence of depression in a Chinese community sample (Li et al., 2011). Other findings may fuel the discussions about the roles of certain demographic factors. Female sex was not associated with depressive symptom-domains other than in the subclinical population with NVS-I domain, which is inconsistent with the majority of the literature that women are at higher risk for depression (Maier et al., 2021). We speculate that for those at risk or with mild symptoms, the effect of sex became insignificant after multiple factors were considered. Marital status was not associated with any depressive symptomdomain, likely because how we measured it, and some studies suggested that only "never being married" was associated with a higher incidence of depression (Conde-Sala et al., 2019). Lastly, although living alone is documented to be a risk factor for depression (Lim & Kua, 2011), in our sample, it was not associated with any of the depressive symptom-domain. While living alone may predispose an individual to more loneliness and depression, older adults living alone in Hong Kong reported more social contact than their peers who lived with others, and the two groups showed similar levels of social and productive activities (Lou & Ng, 2012). Our sample was recruited from community centers, which provide space for social gatherings and regularly organize events for older adults, all adding to the protective factors of their mental health. Alternatively, it was also possible that for the "hidden older people", who are disengaged from the community and not recruited in this study, living alone may further elevates the risk of social isolation and in turn, be associated with poor mental health (Chau et al., 2014).

## **Limitations and Future Directions**

Several limitations should be noted when interpreting the findings of this study. First, given its cross-sectional design, the study could not demonstrate variance in the impact of anxiety, loneliness, or cognition on depressive symptoms within an individual over time. Second, the PHQ-9 was used as a screening tool among community-dwelling older adults without a clinical diagnosis. Therefore, the current findings might not be generalizable to clinical populations of older adults. Third, the majority of the current sample was at risk or with mild depressive symptoms, which might influence the results of the MIMIC model in the overall population. Four, the current sample is community-dwelling older Chinese recruited through NGOs in Hong Kong, a more developed region than most of the cities in Mainland China, and boasts a mixture of traditional Han Chinese, ethnic Southeastern Chinese, and Western culture. Therefore, the findings from this sample may not be generated to the overall older Chinese, a much more diverse population with different subcultures and lifestyles. Five, this study only included a few risk factors, and some important factors, such as physical health, were not collected. Future investigations could consider multiple and repeated measures of depression, including more documented risk factors such as physical health condition and comparing the domains of depressive symptoms between the general older adult population and clinical samples.

### Conclusion

To sum up, the findings of this study confirmed the utility of the RDoC framework in understanding depressive symptom-domains in community-dwelling older Chinese, and the differential associations between different depressive symptom-domains and anxiety, loneliness, and cognition may inform more personalized care. Individuals with anhedonia and depressive mood (*NVS-E*) may also exhibit anxiety symptoms, cognitive problems, and feelings of loneliness, especially among those at risk of or with mild depressive symptoms. Therefore, they are more likely to benefit from comprehensive preventive care, e.g., group exercise and healthy lifestyle intervention. For individuals with feelings of inappropriate guilt and self-harm thoughts (*NVS-I*), anxiety symptoms and loneliness are likely to co-occur regardless of depressive symptom severity, which may infer higher resistance and relapse if the intervention targets depressive symptoms only. More indicated prevention and treatment addressing meaning in life, self-worthiness, and expanding social network are needed for those with *NVS-I* domain symptoms. Finally, for individuals who report more somatic or cognitive complaints (*ARS* and *CSS* domains), their depression may be masked or overlooked if no symptom is reported in the *NVS* domain; more fine-grained assessment is needed, and intervention for their mental well-being may consider their anxiety level as well.

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## **Conflict of Interest**

We have no conflict of interest to declare.

## **Data Availability**

The data, analytical methods, and materials that support the findings of this study are available from the corresponding author upon reasonable request. The study reported in the manuscript was pre-registered with ClinicalTrials.gov (NCT03593889).

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### References

- Abdoli, N., Salari, N., Darvishi, N., Jafarpour, S., Solaymani, M., Mohammadi, M., & Shohaimi, S. (2021). The global prevalence of major depressive disorder (MDD) among the elderly: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2021.10.041
- Almeida, O. P. (2014). Prevention of depression in older age. *Maturitas*, 79(2), 136-141. https://doi.org/10.1016/j.maturitas.2014.03.005
- Arango, C., Díaz-Caneja, C. M., McGorry, P. D., Rapoport, J., Sommer, I. E., Vorstman, J. A., McDaid, D., Marín, O., Serrano-Drozdowskyj, E., Freedman, R., & Carpenter, W. (2018). Preventive strategies for mental health. *The Lancet Psychiatry*, 5(7), 591-604. https://doi.org/10.1016/S2215-0366(18)30057-9
- Ayuso-Mateos, J. L., Nuevo, R., Verdes, E., Naidoo, N., & Chatterji, S. (2010). From depressive symptoms to depressive disorders: the relevance of thresholds. *The British Journal of Psychiatry*, 196(5), 365-371. https://doi.org/10.1192/bjp.bp.109.071191
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Publishing. https://doi.org/10.1176/appi.books.9780890425596
- Baldwin, R. C., Gallagley, A., Gourlay, M., Jackson, A., & Burns, A. (2006). Prognosis of late life depression: a three gear cohort study of outcome and potential predictors. *International Journal of Geriatric Psychiatry*, 21(1), 57-63. https://doi.org/10.1002/gps.1424
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & Van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin*, 133(1), 1-24. https://doi.org/10.1037/0033-2909.133.1.1
- Byers, A., Yaffe, K. Depression and risk of developing dementia. *Nature Review Neurology*, 7, 323–331 (2011). https://doi.org/10.1038/nrneurol.2011.60
- Cacioppo, J. T., Hughes, M. E., Waite, L. J., Hawkley, L. C., & Thisted, R. A. (2006). Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychology and Aging*, 21(1), 140. https://doi.org/10.1037/0882-7974.21.1.140
- Cameron, I. M., Crawford, J. R., Lawton, K., & Reid, I. C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *British Journal of General Practice*, 58(546), 32-36. https://doi.org/10.3399/bjgp08X263794
- Chachamovich, E., Fleck, M., Laidlaw, K., & Power, M. (2008). Impact of major depression and subsyndromal symptoms on quality of life and attitudes toward aging in an international sample of older adults. *The Gerontologist*, 48(5), 593-602.
   https://doi.org/10.1093/geront/48.5.593
- Chau, P. H., Gusmano, M. K., Cheng, J. O., Cheung, S. H., & Woo, J. (2014). Social vulnerability index for the older people—Hong Kong and New York City as examples. *Journal of Urban Health, 91,* 1048-1064. https://doi.org/10.1007/s11524-014-9901-8
- Chen, L.-S., Eaton, W. W., Gallo, J. J., & Nestadt, G. (2000). Understanding the heterogeneity of depression through the triad of symptoms, course and risk factors: a longitudinal, population-based study. *Journal of Affective Disorders*, 59(1), 1-11. https://doi.org/10.1016/S0165-0327(99)00132-9
- Chilcot, J., Rayner, L., Lee, W., Price, A., Goodwin, L., Monroe, B., Sykes, N., Hansford, P., & Hotopf, M. (2013). The factor structure of the PHQ-9 in palliative care. *Journal of Psychosomatic Research*, 75(1), 60-64.

https://doi.org/10.1016/j.jpsychores.2012.12.012

- Conde-Sala, J. L., Garre-Olmo, J., Calvó-Perxas, L., Turró-Garriga, O., & Vilalta-Franch, J. (2019). Course of depressive symptoms and associated factors in people aged 65+ in Europe: A two-year follow-up. *Journal of Affective Disorders*, 245, 440-450. https://doi.org/10.1016/j.jad.2018.10.358
- Cuijpers, P., Koole, S. L., van Dijke, A., Roca, M., Li, J., & Reynolds, C. F. (2014). Psychotherapy for subclinical depression: meta-analysis. *The British Journal of Psychiatry*, 205(4), 268-274. https://doi.org/10.1192/bjp.bp.113.138784
- Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2013).
   Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. *The British Journal of Psychiatry*, 202(1), 22-27. https://doi.org/10.1192/bjp.bp.112.112169
- de Vito, A., Calamia, M., Greening, S., & Roye, S. (2019). The association of anxiety, depression, and worry symptoms on cognitive performance in older adults. *Aging, Neuropsychology, and Cognition*, 26(2), 161-173. https://doi.org/10.1080/13825585.2017.1416057
- Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and pleasure: An RDOC□inspired examination of threat responses and reward processing in anxiety and depression. *Depression and Anxiety*, 31(3), 233-249. https://doi.org/10.1002/da.22202
- Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion*, 7(2), 336.
- Fakoya, O. A., McCorry, N. K., & Donnelly, M. (2020). Loneliness and social isolation interventions for older adults: a scoping review of reviews. *BMC Public Health*, 20(1), 1-14. https://doi.org/10.1186/s12889-020-8251-6
- Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR\* D study. *Journal of Affective Disorders*, 172, 96-102. https://doi.org/10.1016/j.jad.2014.10.010
- Gardiner, C., Laud, P., Heaton, T., & Gott, M. (2020). What is the prevalence of loneliness amongst older people living in residential and nursing care homes? A systematic review and meta-analysis. *Age and ageing*, 49(5), 748-757. https://doi.org/10.1093/ageing/afaa049
- Gunzler, D., Sehgal, A. R., Kauffman, K., Davey, C. H., Dolata, J., Figueroa, M., Huml, A., Pencak, J., & Sajatovic, M. (2020). Identify depressive phenotypes by applying RDOC domains to the PHQ-9. *Psychiatry Research*, 286, 112872. https://doi.org/10.1016/j.psychres.2020.112872
- Hamer, J. A., Testani, D., Mansur, R. B., Lee, Y., Subramaniapillai, M., & McIntyre, R. S. (2019). Brain insulin resistance: A treatment target for cognitive impairment and anhedonia in depression. *Experimental Neurology*, 315, 1-8. https://doi.org/10.1016/j.expneurol.2019.01.016
- Hu, L. t., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural equation modeling*, 6(1), 1-55. https://doi.org/10.1080/10705519909540118
- Hughes, M. E., Waite, L. J., Hawkley, L. C., & Cacioppo, J. T. (2004). A short scale for measuring loneliness in large surveys results from two population-based studies. *Research on Aging*, 26(6), 655-672. https://doi.org/10.1177/0164027504268574
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, 167(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

- Jajodia, A., & Borders, A. (2011). Memory predicts changes in depressive symptoms in older adults: A bidirectional longitudinal analysis. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 66B*(5), 571-581. https://doi.org/10.1093/geronb/gbr035
- Jöreskog, K. G., & Goldberger, A. S. (1975). Estimation of a model with multiple indicators and multiple causes of a single latent variable. *Journal of the American statistical Association*, 70(351a), 631-639. https://doi.org/10.1080/01621459.1975.10482485
- Kalin, N. H. (2020). The critical relationship between anxiety and depression. American Journal of Psychiatry, 177(5), 365-367. https://doi.org/10.1176/appi.ajp.2020.20030305
- Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., Smagula, S. F., Rubin, S. M., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA psychiatry*, 73(5), 525-531. https://doi.org/10.1001/jamapsychiatry.2016.0004
- Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., Bunting, B., Demyttenaere, K., Florescu, S., de Girolamo, G., Gureje, O., He, Y., Hu, C., Huang, Y., Karam, E., Kovess-Masfety, V., Lee, S., Levinson, D., Medina Mora, M. E., Moskalewicz, J., ... Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiology and Psychiatric Sciences*, 24(3), 210-226. https://doi.org/10.1017/S2045796015000189
- Kessler, R. C., & Wang, P. S. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annual Review of Public Health*, 29, 115–129. https://doi.org/10.1146/annurev.publhealth.29.020907.090847
- Keum, B. T., Miller, M. J., & Inkelas, K. K. (2018). Testing the factor structure and measurement invariance of the PHQ-9 across racially diverse US college students. *Psychological Assessment*, 30(8), 1096. https://doi.org/10.1037/pas0000550
- Kleinridders, A., & Pothos, E. N. (2019). Impact of brain insulin signaling on dopamine function, food intake, reward, and emotional behavior. *Current Nutrition Reports*, 8(2), 83-91. https://doi.org/10.1007/s13668-019-0276-z
- Kok, R. M., & Reynolds, C. F. (2017). Management of depression in older adults: A review. Jama, 317(20), 2114-2122. https://doi.org/10.1001/jama.2017.5706
- Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine*, 16(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x
- Lee, S. L., Pearce, E., Ajnakina, O., Johnson, S., Lewis, G., Mann, F., Pitman, A., Solmi, F., Sommerlad, A., Steptoe, A., Tymoszuk, U., & Lewis, G. (2021). The association between loneliness and depressive symptoms among adults aged 50 years and older: a 12-year population-based cohort study. *The Lancet Psychiatry*, 8(1), 48-57. https://doi.org/10.1016/S2215-0366(20)30383-7
- Lee, Y. Y., Stockings, E. A., Harris, M. G., Doi, S. A. R., Page, I. S., Davidson, S. K., & Barendregt, J. J. (2019). The risk of developing major depression among individuals with subthreshold depression: a systematic review and meta-analysis of longitudinal cohort studies. *Psychological Medicine*, 49(1), 92-102. <u>https://doi.org/</u>10.1017/S0033291718000557
- Li, Y., Chen, C., Tu, H., Cao, W., Fan, S., Ma, Y., Xu, Y., & Hua, Q. (2012). Prevalence and risk factors for depression in older people in Xi' an China: A community based study. *International Journal of Geriatric Psychiatry*, 27(1), 31-39. https://doi.org/10.1002/gps.2685
- Liew, T. M. (2020). Subjective cognitive decline, anxiety symptoms, and the risk of mild

cognitive impairment and dementia. *Alzheimer's Research & Therapy*, *12*(1), 107. https://doi.org/10.1186/s13195-020-00673-8

- Lim, L. L., & Kua, E.-H. (2011). Living alone, loneliness, and psychological well-being of older persons in Singapore. *Current Gerontology and Geriatrics Research*, 2011, 673181. https://doi.org/10.1155/2011/673181
- Liu, T., Leung, D. K. Y., Lu, S., Kwok, W.-W., Sze, L. C. Y., Tse, S. S. K., Ng, S. M., Wong, P. W. C., Lou, V. W. Q., & Tang, J. Y. M. (2022). Collaborative community mental health and aged care services with peer support to prevent late-life depression: study protocol for a non-randomised controlled trial. *Trials*, 23(1), 1-13. https://doi.org/10.1186/s13063-022-06122-1
- Liu, T., Lu, S., Leung, D. K., Sze, L. C., Kwok, W. W., Tang, J. Y., Luo, H., Lum, T. Y., & Wong, G. H. (2020). Adapting the UCLA 3-item loneliness scale for communitybased depressive symptoms screening interview among older Chinese: a crosssectional study. *BMJ Open*, 10(12), e041921. https://doi.org/10.1136/bmjopen-2020-041921
- Maier, A., Riedel-Heller, S. G., Pabst, A., & Luppa, M. (2021). Risk factors and protective factors of depression in older people 65+. A systematic review. *PloS one*, *16*(5), e0251326. https://doi.org/10.1371/journal.pone.0251326
- Marsh, H. W., & Hocevar, D. (1985). Application of confirmatory factor analysis to the study of self-concept: First-and higher order factor models and their invariance across groups. *Psychological Bulletin*, *97*(3), 562. https://doi.org/10.1037/0033-2909.97.3.562
- Newgard, C. D., & Haukoos, J. S. (2007). Advanced statistics: missing data in clinical research—part 2: multiple imputation. *Academic Emergency Medicine*, *14*(7), 669-678. https://doi.org/10.1111/j.1553-2712.2007.tb01856.x
- Peyrot, W. J., Lee, S. H., Milaneschi, Y., Abdellaoui, A., Byrne, E. M., Esko, T., de Geus, E. J., Hemani, G., Hottenga, J. J., Kloiber, S., Levinson, D. F., Lucae, S., Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (Corporate Collaborator), Martin, N. G., Medland, S. E., Metspalu, A., Milani, L., Noethen, M. M., Potash, J. B., Rietschel, M., ... Social Science Genetic Association Consortium Corporate Collaborator (2015). The association between lower educational attainment and depression owing to shared genetic effects? Results in~ 25 000 subjects. *Molecular Psychiatry*, 20(6), 735-743. https://doi.org/10.1038/mp.2015.50
- Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A. M., Imbimbo, B. P., Santamato, A., Vendemiale, G., Seripa, D., Pilotto, A., Capurso, A., & Solfrizzi, V. (2010). Late-life depression, mild cognitive impairment, and dementia: Possible continuum? *The American Journal of Geriatric Psychiatry*, 18(2), 98-116. https://doi.org/10.1097/JGP.0b013e3181b0fa13
- Petersen, J. J., Paulitsch, M. A., Hartig, J., Mergenthal, K., Gerlach, F. M., & Gensichen, J. (2015). Factor structure and measurement invariance of the Patient Health Questionnaire-9 for female and male primary care patients with major depression in Germany. *Journal of Affective Disorders*, 170, 138-142. https://doi.org/10.1016/j.jad.2014.08.053
- Reynolds, C. F., 3rd, Cuijpers, P., Patel, V., Cohen, A., Dias, A., Chowdhary, N., Okereke, O. I., Dew, M. A., Anderson, S. J., Mazumdar, S., Lotrich, F., & Albert, S. M. (2012). Early intervention to reduce the global health and economic burden of major depression in older adults. *Annual Review of Public Health*, *33*, 123-135. https://doi.org/10.1146/annurev-publhealth-031811-124544
- Rebar, A. L., Stanton, R., Geard, D., Short, C., Duncan, M. J., & Vandelanotte, C. (2015). A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-

clinical adult populations. *Health Psychology Review*, *9*(3), 366-378. https://doi.org/10.1080/17437199.2015.1022901

- Rodríguez, M. R., Nuevo, R., Chatterji, S., & Ayuso-Mateos, J. L. (2012). Definitions and factors associated with subthreshold depressive conditions: A systematic review. *BMC Psychiatry*, 12, 1-7. <u>https://doi.org/10.1186/1471-244X-12-181</u>
- Salthouse, T. A. (2006). Mental exercise and mental aging: Evaluating the validity of the "use it or lose it" hypothesis. *Perspectives on Psychological Science*, 1(1), 68-87. https://doi.org/10.1111/j.1745-6916.2006.00005.x
- Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Archives of Internal Medicine, 166(10), 1092-1097. https://doi.org/10.1001/archinte.166.10.1092
- Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A. M., & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*, 338. https://doi.org/10.1136/bmj.b2393
- Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International Journal* of Medical Education, 2, 53. https://doi.org/10.5116/ijme.4dfb.8dfd
- Tong, X., An, D., McGonigal, A., Park, S.-P., & Zhou, D. (2016). Validation of the Generalized Anxiety Disorder-7 (GAD-7) among Chinese people with epilepsy. *Epilepsy Research*, 120, 31-36. https://doi.org/10.1016/j.eplepsyres.2015.11.019
- Toups, M., Carmody, T., Greer, T., Rethorst, C., Grannemann, B., & Trivedi, M. H. (2017). Exercise is an effective treatment for positive valence symptoms in major depression. *Journal of Affective Disorders*, 209, 188-194. https://doi.org/10.1016/j.jad.2016.08.058
- Vink, D., Aartsen, M. J., & Schoevers, R. A. (2008). Risk factors for anxiety and depression in the elderly: A review. *Journal of Affective Disorders*, *106*(1-2), 29-44. https://doi.org/10.1016/j.jad.2007.06.005
- Wong, A., Nyenhuis, D., Black, S. E., Law, L. S., Lo, E. S., Kwan, P. W., Au, L., Chan, A. Y., Wong, L. K., & Nasreddine, Z. (2015). Montreal Cognitive Assessment 5-minute protocol is a brief, valid, reliable, and feasible cognitive screen for telephone administration. *Stroke*, 46(4), 1059-1064. https://doi.org/10.1161/strokeaha.114.007253
- Yeung, A., Fung, F., Yu, S.-C., Vorono, S., Ly, M., Wu, S., & Fava, M. (2008). Validation of the Patient Health Questionnaire-9 for depression screening among Chinese Americans. *Comprehensive Psychiatry*, 49(2), 211-217. https://doi.org/10.1016/j.comppsych.2006.06.002



Variable <sup>a</sup>		Subgroups based on depressive symptoms severity				
	Overall	At risk/mild	Moderate and more	t/χ <sup>2</sup>		
	(n = 3795)	[PHQ9 0-9] (n=	severe [PHQ9≥10] (n			
		3146)	= 649)			
Age, mean (SD), years	77.34 (8.74)	77.52 (8.72)	76.48 (8.81)	-2.77***		
Sex, female, n (%)	2,946 (77.60)	2,436 (77.40)	510 (78.60)	0.38		
Married/cohabit, n (%)	1,497 (39.90)	1,264 (40.18)	233 (35.91)	22.86***		
Education, level, n (%)						
No formal education	1,089 (28.70)	901 (28.64)	188 (28.97)	11.00		
Bok Bok Zaai <sup>b</sup>	189 (4.98)	167 (5.31)	22 (3.39)			
Primary school	1,404 (37.00)	1,153 (36.65)	251 (38.67)			
Middle school	555 (14.63)	477 (15.16)	78 (12.02)			
High school	351 (9.25)	291 (9.25)	60 (9.24)	•		
Diploma	64 (1.69)	48 (1.53)	16 (2.47)			
Bachelor's degree	59 (1.56)	49 (1.56)	10 (1.54)			
Living alone, n (%)	1,574 (41.48)	1,315 (41.80)	259 (39.91)	0.79		
GAD-7 scores, mean (SD)	4.43 (4.57)	3.57 (3.87)	8.58 (5.35)	$27.92^{***}$		
UCLA-3 scores, mean (SD)	3.98 (2.96)	3.72 (2.88)	5.26 (3.00)	12.34***		
MoCA-5 scores, mean (SD)	20.56 (5.32)	20.65 (5.23)	20.14 (5.73)	$2.13^{*}$		
PHQ-9 scores, mean (SD)	6.44 (4.00)	5.08 (2.60)	13.03 (2.94)	69.33***		
Responses to PHQ-9 items						
1. Anhedonia	0.89 (0.92)	0.68 (0.77)	1.87 (0.95)	34.30***		
2. Depressed mood	1.07 (0.92)	0.89 (0.83)	1.96 (0.82)	$29.88^{***}$		
3.Sleep	1.39 (1.04)	1.24 (1.00)	2.15 (0.92)	21.52***		
4.Fatigue	1.20 (0.92)	1.03 (0.83)	2.06 (0.87)	$28.54^{***}$		
5.Appetite	0.26 (0.62)	0.14 (0.43)	0.81 (0.98)	27.67***		
6.Guilt	0.52 (0.81)	0.31 (0.58)	1.53 (0.98)	42.69***		
7.Concentration	0.65 (0.78)	0.52 (0.66)	1.25 (1.00)	23.07***		
8.Psychomotor	0.25 (0.56)	0.16 (0.41)	0.68 (0.89)	22.93***		
9.Self-harm	0.21 (0.52)	0.11 (0.33)	0.71 (0.86)	29.75***		

# Table 1. Basic and clinical characteristics of participants

Notes. GAD-7=Generalized Anxiety Disorder-7; PHQ-9=Patient Health Questionnaire-9; MoCA-5=Montreal Cognitive Assessment 5-minute protocol; SD=standard deviation; UCLA-3=UCLA 3-item loneliness scale.

<sup>a</sup> Missing data pattern of the variables are summarized in Supplementary Table 1.

<sup>b</sup> bok bok zaai: one to three years informal education provided by private institutions in Cantonese speaking regions, gradually disappearing since the New Culture Movement in China in the 1910s. \*p<0.05; \*\*\* p<0.001.

Table 2. Fac	tor loadings and	model-fitting ind	ices of three theory	y-based PHO-9 structures

Variable	Loadings	Model fit						
		$\chi^2/df$	р	SRMR	RMSEA	GFI	CFI	TLI
One-factor		563.48 /27 = 20.87	< 0.001	0.03	0.07	0.97	0.89	0.85
Factor 1: Depression								
1. Anhedonia	0.61							
2. Depression	0.66							
3. Sleep	0.32							
4. Fatigue	0.43							
5. Appetite	0.37							
6. Guilt	0.61							
7. Concentration	0.40							
8. Psychomotor	0.33							
9. Self-harm	0.51							
Two-factor		442.89 /26 = 17.03	< 0.001	0.03	0.07	0.97	0.91	0.88
Factor 1: Somatic symptoms								
3. Sleep	0.44							
4. Fatigue	0.58							
5. Appetite	0.40							
Factor 2: Cognitive-affective								
symptoms								
1. Anhedonia	0.62							
2. Depression	0.67							
6. Guilt	0.61							
7. Concentration	0.40							
8. Psychomotor	0.33							
9. Self-harm	0.51							
Four-factor		223.16 /21 = 10.63	< 0.001	0.02	0.05	0.99	0.96	0.93
Factor 1: Negative valence								
systems & externalizing								
1. Anhedonia	0.67							
2. Depression	0.74							
Factor 2: Negative valence								
systems & internalizing								
6. Guilt	0.70							
9. Self-harm	0.57							
Factor 3: Arousal & regulatory								
systems								
3. Sleep	0.43							
4. Fatigue	0.58							
5. Appetite	0.41							
Factor 4: Cognitive &								
sensorimotor systems								
7. Concentration	0.44							
8. Psychomotor	0.38							

Notes. CFI=comparative fit index; *df:* degree of freedom; GFI=goodness-of-fit index; PHQ-9=patient health questionnaire – 9 items; RMSEA=root mean square error of approximation; SRMR=standardized root mean square residual; TLI=Tucker-Lewis index.

<sup>a</sup> The criteria for a good model fit are:  $\chi^2/df \le 5.0$ , SRMR < 0.0 8, RMSEA < 0.08, GFI > 0.90, CFI > 0.90, TLI > 0.90.

		Model 1: Overall		Model 2: A	Model 2: At-risk/mild		Model 3: Moderate and	
Pathway	VS	(N = 3795)		(n = 3146)		more sever	e(n = 649)	
•		β	SE	β	SE	β	SE	
Measure	ment Model: Depress	ive symptom-	domains			<u>,</u>		
NVS-E	Anhedonia	0.63***	0.02	0.49***	0.04	0.35***	0.20	
	Depression	$0.78^{***}$	0.04	$0.77^{***}$	0.08	0.79***	0.49	
NVS-I	Guilt	$0.70^{***}$	0.03	$0.46^{***}$	0.04	0.54***	0.09	
	Self-harm	$0.57^{***}$	0.02	$0.46^{***}$	0.05	0.37***	0.10	
ARS	Sleep	0.45***	0.03	0.36***	0.05	0.43***	0.21	
	Fatigue	$0.58^{***}$	0.06	$0.55^{***}$	0.16	0.42**	0.32	
	Appetite	$0.40^{***}$	0.04	0.13***	0.04	-0.08	0.17	
CSS	Concentration	$0.44^{***}$	0.04	0.34***	0.04	0.24***	0.22	
	Psychomotor	0.38***	0.04	$0.10^{***}$	0.04	0.29***	0.30	
Factor I	ntercorrelations							
NVS-E	NVS-I	0.54***	0.01	0.29***	0.003	0.22*	0.01	
1110 1	ARS	0.42***	0.01	0.03	0.004	-0.02	0.01	
	CSS	0.47***	0.01	0.45***	0.004	-0.35	0.01	
NVS-I	ARS	$0.47^{***}$	0.01	-0.13*	0.01	-0.34*	0.02	
11101	CSS	0.63***	0.01	-0.33*	0.01	0.05	0.02	
ARS	CSS	0.05	0.01	0.54***	0.01	-0.52	0.02	
Structur	al Model: Depressive	symptom-doi	nains	0.01	0.01	0.02	0.02	
NVS-E	Age, years	-0.03	0.001	-0.04	0.001	-0.01	0.002	
1110 1	Sex. female	-0.02	0.02	0.004	0.02	-0.07	0.04	
	Education level	0.02	0.01	0.01	0.01	0.01	0.01	
	Married/cohabit	0.01	0.02	-0.02	0.02	0.02	0.03	
	Live alone	0.02	0.02	0.02	0.02	0.04	0.04	
	GAD-7	0.54***	0.003	$0.47^{***}$	0.003	0.29***	0.005	
	UCLA-3	0.29***	0.004	0.33***	0.003	0.15	0.007	
	MoCA-5	-0.17***	0.002	-0.17***	0.002	-0.20	0.003	
NVS-I	Age, years	-0.04	0.001	-0.01	0.001	-0.03	0.004	
	Sex. female	-0.04	0.03	-0.01	0.02	-0.14*	0.08	
	Education level	-0.07***	0.01	-0.10*	0.01	-0.11	0.03	
	Married/cohabit	0.04	0.02	-0.01	0.02	0.13*	0.07	
	Live alone	0.00	0.03	-0.02	0.02	0.01	0.07	
	GAD-7	0.55***	0.003	0.45***	0.003	$0.44^{***}$	0.007	
	UCLA-3	0.11***	0.004	0.11***	0.003	0.27***	0.011	
	MoCA-5	-0.04	0.003	0.02	0.001	-0.13	0.003	
ARS	Age, years	-0.02	0.001	0.01	0.001	-0.07	0.004	
	Sex. female	0.02	0.03	0.06	0.03	0.03	0.07	
	Education level	-0.02	0.01	-0.01	0.01	-0.03	0.02	
	Married/cohabit	-0.02	0.02	-0.08*	0.02	0.04	0.06	
	Live alone	-0.003	0.02	-0.02	0.02	0.04	0.06	
	GAD-7	0.48***	0.003	0.30***	0.004	0.11	0.006	
	UCLA-3	0.07	0.004	0.09*	0.004	-0.21	0.011	
	MoCA-5	-0.04	0.002	0.03	0.002	-0.08	0.004	
CSS	Age, years	-0.08	0.001	-0.12*	0.001	-0.22	0.003	
222	Sex, female	-0.02	0.02	-0.03	0.03	-0.06	0.06	
	Education level	-0.01	0.01	0.03	0.01	-0.09	0.02	
	Married/cohabit	0.04	0.02	-0.02	0.02	0.02	0.05	
	Live alone	0.06	0.02	$0.12^*$	0.03	0.12	0.06	

 Table 3. Regression weights and model-fitting indices of three multiple indicators multiple causes (MIMIC) models

GAD-7	0.63***	0.003	$0.45^{***}$	0.003	$0.60^{***}$	0.008	
UCLA-3	$0.14^{***}$	0.004	0.31***	0.004	-0.08	0.009	
MoCA-5	-0.12***	0.002	-0.34***	0.002	-0.03	0.004	
Model fit <sup>a</sup>							
$\chi^2/df$	407	.24/61 = 6.68	386.95	5/61 = 6.34	63.67	7/61 = 1.04	
р		< 0.001	<	0.001		0.38	
SRMR		0.02		0.03		0.03	
RMSEA		0.04		0.04		0.01	
GFI		0.99		0.99		0.99	
CFI		0.97		0.94		0.99	
TLI		0.92		0.86		0.99	

Notes. CFI=comparative fit index; *df*=degree of freedom; NVS-E=Negative valence systems & externalizing; NVS-I=Negative valence systems & internalizing; ARS=Arousal & regulatory systems; CSS=Cognitive & sensorimotor systems; GAD-7=Generalized Anxiety Disorder-7; GFI=goodness-of-fit index; PHQ-9=Patient Health Questionnaire-9; MoCA-5=Montreal Cognitive Assessment 5-minute protocol; RMSEA=root mean square error of approximation; SRMR=standardized root mean square residual; TLI=Tucker-Lewis index; UCLA-3=UCLA 3-item loneliness scale.

<sup>a</sup> The criteria for a good model fit are:  $\chi^2/df \le 5.0$ , SRMR< 0.08, RMSEA < 0.08, GFI > 0.90, CFI > 0.90, TLI > 0.90.

\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001

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### Figures

Figure 1. Confirmatory factor analysis (CFA) models of depression symptom-domains: (a) one factor, (b) two-factor (somatic, cognitive-affective), and (c) four-factor (based on RDoC framework).

Notes. Standardized regression weights were reported.

Figure 2. Multiple indicator multiple cause (MIMIC) models for depression symptom-domains, anxiety, loneliness, cognition and demographics in (a) Model 1 - overall sample (N=3795), (b) Model 2 - at risk/mild (n=3146), and (c) Model 3 - moderate and more severe depressive symptoms (n=649).

Notes. NVS-E=Negative valence systems & externalizing; NVS-I=Negative valence systems & internalizing; ARS=Arousal & regulatory systems; CSS=Cognitive & sensorimotor systems. Only standardized regression weights significant at the p < 0.001 level were reported, unstandardized regression weights and measurement errors were omitted for clarity.

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Figure 2

