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Mediating Role of Homebound Status between Depressive Symptoms and Cognitive Impairment among Community-Dwelling Older Adults: A Cross-Sectional Study

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Mediating Role of Homebound Status between Depressive Symptoms and Cognitive
Impairment among Community-Dwelling Older Adults: A Cross-Sectional Study

Peer review only

Title: Mediating Role of Homebound Status between Depressive Symptoms and Cognitive Impairment among Community-Dwelling Older Adults: A Cross-Sectional Study

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Abstract

Objective: Depressive symptoms are known predictors of cognitive impairment in older adults. However, the pathway through which depressive symptoms lead to cognitive impairment is not well understood. This study aimed to investigate whether homebound status (defined as usually unable to leave home unassisted) mediates the association between depressive symptoms and cognitive impairment in community-dwelling older adults in the United States.

Design: A secondary analysis of cross-sectional data.

Setting(s): Communities in the United States.

Participants: Community-living older adults (N=7,537) from the 2011 National Health and Aging Trends Study (NHATS), a nationally representative survey of Medicare Beneficiaries in the United States.

Main outcome measures: Participants' cognitive impairment status was classified using a composite measure. Depressive symptoms were assessed using Patient Health Questionnaire-2. Homebound status was determined by the frequency, difficulty, and needing help of getting outdoors. We used logistic regression and the Paramed command in STATA to analyze whether homebound mediated the association between depressive symptoms and cognitive impairment.

Results: Participants were on average, 77.7 years old, female (58.3%), and non-Hispanic white (68.1%). About 26% of the participants were classified as having cognitive

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6 impairment, 16% reported depressive symptoms, and 25% were homebound. Depressive
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9 symptoms (adjusted OR, 1.60; 95% CI, 1.36-1.89) and homebound status (adjusted OR, 1.58;
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11 95% CI, 1.34-1.86) were independently associated with cognitive impairment. Homebound
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14 significantly mediated 12.5% of the total effect between depressive symptoms and cognitive
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17 impairment, with significant indirect effect (OR, 1.07; 95% CI, 1.04-1.10), direct effect (OR,
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19 1.61; 95% CI, 1.36-1.91) and total effect (OR, 1.72; 95% CI, 1.46-2.03).
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21

22 **Conclusions:** This study supports a mediating role for homebound status in the relationship
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24 between depressive symptoms and cognitive impairment. Interventions to promote outdoor
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26 mobility should be studied for their ability to delay cognitive impairment for older adults
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28 with depressive symptoms.
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36 **Keywords:** homebound; depressive symptoms; cognitive impairments; older adults;
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Strengths and limitations of this study

- This study is the first attempt to investigate the mediating role of homebound status in the association between depressive symptoms and cognitive impairments in community-dwelling older adults.
- Homebound status partly mediated the relationship between depressive symptoms and cognitive impairment.
- The strength of the study included a large sample size, the use of nationally representative data and adjustment for potential confounders including demographics and health-related factors.
- The cross-sectional design does not examine causality.
- All indicators were self-reported retrospectively which may cause recall bias and report errors.

Introduction

Cognitive impairment causes disabilities in older adults' physical and psychological functions and is a major public health concern.^{1,2} Cognitive impairment includes mild cognitive impairment and dementia.³ Approximately 25% of U.S. adults aged 50 and over suffer from cognitive impairment and this rate increases with age,³ bringing a huge economic burden to families and society.⁴ Older adults with cognitive impairments have a high and growing demand for long-term care, which poses a significant challenge for nurse. Thus, it is imperative for nurses and health workers to identify casual pathways and develop effective strategies to prevent and slow the progression of cognitive impairment in older adults.

Depressive symptoms are common in older adults and are associated with physical disability,⁵ social isolation,⁶ and cardiovascular diseases,⁷ all of which have been identified as contributors to declines in cognition.^{8,9} A systematic review concluded that depressive symptoms are an independent risk factor for dementia.¹⁰ In addition, multiple systematic reviews found that depressive symptoms are associated with the progression of mild cognitive impairment to dementia.¹¹⁻¹³ Despite these well-established associations between depressive symptoms and cognitive impairment, the mediating mechanisms of the association remain unclear.

In this paper we examined homebound status as a potential mediator between depressive symptoms and cognitive impairment. Being homebound, defined as limited at home, is closely related to depression and cognitive impairment. Homebound older adults

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6 have consistently been found to experience depression in high numbers; in one population-
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8 based study 59% of older adults who had not left their homes in the previous month had
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10 positive depressive symptoms.¹⁴⁻¹⁷ Prior research have also found cognitive impairment more
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12 prevalent in the homebound population than the non-homebound population.^{18,19} The
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14 confluence of mental health, physical, and social impairments that result in homebound
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16 status,²⁰ may lead to cognitive impairment and should be better understood as a potential
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18 target of intervention. For example, previous studies have shown that older adults with
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20 depressive symptoms were more likely to have physical impairments and loss of interest or
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22 energy in social participation,^{5,21} resulting in homebound status.^{19,20} Rates of physical activity
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24 and social participation, well-known protective factors against cognitive impairment,²² are
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26 low in homebound older adults and may contribute to the higher rates of cognitive
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28 impairment in this population.²⁰
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39 Homebound status can be improved using assistive devices, modifying the home
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41 environment, and accessing transportation.¹⁵ It is therefore important to investigate the
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43 potential of homebound status as a target of interventions to improve cognitive function.
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45 However, to the best of our knowledge, no study has attempted to investigate whether
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47 homebound status mediates the association between depressive symptoms and cognitive
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49 impairment. The purpose of this study was to examine whether homebound status mediates
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51 the association between depressive symptoms and cognitive impairment in a nationally
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53 representative sample of community-dwelling older adults in the U.S. We hypothesized that
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6 homebound status is a significant mediator between depressive symptoms and cognitive
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9 impairment in community-dwelling older adults.

10 11 12 **Methods**

13 14 **Design and Sample**

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17 We used the first round (2011) of data from the National Health and Aging Trends
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19 Study (NHATS), a nationally representative longitudinal cohort study of older adults in the
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21 United States who are Medicare beneficiaries aged 65 and older.²³ The NHATS study began
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23 in 2011 and aimed to understand the disability trends of older adults in late life. In the initial
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25 round, a total of 7,609 participants who lived in the community completed the sample person
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27 interview. We excluded 72 participants who had incomplete data on depressive symptoms,
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29 homebound or cognitive function, for a resulting analysis sample size of 7,537. These
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31 excluded participants were older, living alone with less education, were less likely to perform
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33 vigorous activities, had stroke, and tended to have more activities of daily living (ADL)
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35 impairments, visual impairment, and auditory impairment, compared to those who had
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37 complete data. The NHATS was approved by the Johns Hopkins Bloomberg School of Public
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39 Health Institutional Review Board, and the NHATS investigators obtained informed consent
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41 form NHATS participants. The current analyses were deemed exempt from review by the
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43 Xiangya School of Nursing Ethic Committee of Central South University.

44 45 46 **Measurement**

47 48 49 ***Dependent variables***

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6 Cognitive function was determined by a previously modified validated algorithm
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8 including a diagnosis from physicians (self-reported) and assessment of cognitive function in
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10 3 domains (memory, orientation, and executive function).²⁴ Participants were classified into
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12 three groups as follows: participants with a diagnosis of dementia, a score on the AD8
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14 Dementia Screening Interview provided by proxy respondents, or scores ≤ 1.5 Standard
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16 Deviation (SDs) below the mean in at least 2 of 3 cognitive performance tests were classified
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18 as having *probable dementia*; participants were classified as *possible dementia* if they scored
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20 ≤ 1.5 SDs below the mean in 1 cognitive performance test; all other participants were
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22 classified as having *no dementia*. We considered participants with a classification of probable
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24 dementia or possible dementia as having cognitive impairment; we considered participants
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26 with a classification of no dementia as without cognitive impairment. The NHATS dementia
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28 definition (defined as probable or possible dementia) has shown high sensitivity (85.7%) and
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30 specificity (83.7%) compared to a structured in-home clinical measurement in the landmark
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32 Aging, Demographics, and Memory Study.²⁴ For the purposes of terminology consistent with
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34 the cognitive impairment instrument, the term “cognitive impairment” was used throughout
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36 this article to replace dementia.
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49 ***Independent variable***

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52 Depressive symptoms were measured using the Patient Health Questionnaire-2
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54 (PHQ-2), a well-validated screening instrument for depression status.²⁵ Participants were
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56 asked: “Over the last month, how often have you: 1) had little interest or pleasure in doing
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6 things; 2) felt down, depressed, or hopeless.” Responses were recorded on a 4-point Likert
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9 scale (scored 0-3) with total scores ranging from 0 to 6. A higher score suggested more
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11 depressive symptoms. Following the recommendation from previous studies, we used a cut-
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13 off of 3 and higher to determine depressive symptoms. The cut-off of 3 has a sensitivity of
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15 0.79 and a specificity of 0.86 for any type of depressive disorder.²⁵
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19 ***Mediator***

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22 Based on the measurement developed by Ornstein and colleagues, homebound status
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24 was measured using four questions based on the reported frequency of outdoor mobility.¹⁵
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26 First, participants were asked about the frequency of going outside, and response options
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28 were on a 5-point Likert scale: never; rarely (≤ 1 day per week); some days (2-4 days per
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30 week); most days (5-6 days per week); and every day. Participants reporting going outside at
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32 least 2 days per week were asked whether they needed help from others to go outside. Those
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34 who reported needing help were also asked about the frequency of going outside
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36 independently. Those who reported ever going outside by themselves were asked whether
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38 they had any difficulties leaving home independently. Participants were classified as
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40 homebound if they never left home, or left home with any difficulties and assistance. All
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42 other participants were classified as non-homebound.
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52 ***Covariates***

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55 Demographic and health-related characteristics that are common risk factors for
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57 depression, homebound status, and cognitive impairment were included as covariates in
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6 analyses.

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9 Demographic characteristics included age,³ sex (male/female),²⁶ race/ethnicity (non-
10 Hispanic white, non-Hispanic Black, Hispanic, and other),²⁷ education (less than high school,
11 high school, college or vocational school and bachelor or higher),²⁸ and living arrangement
12 (alone, with spouse/partner only, with others only, with spouse/partner and with others).²⁹

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19 Health-related characteristics included smoking status (never smoker and
20 current/former smoker);⁸ whether they performed vigorous activities last month (yes/no);³⁰
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body mass index (BMI) (normal/obesity [≥ 30 kg/m²]);⁸ visual impairment (yes/no);³¹
auditory impairment (yes/no);³² diagnoses of hypertension (yes/no),⁸ diabetes (yes/no),⁸ and
stroke (yes/no);³³ number of activities of daily living impairments;³⁴ whether the subjects
were hospitalized in the last 12 months (yes/no).³⁵

Statistical Analysis

Demographic and health-related characteristics were described using frequencies,
proportions, means, and standard deviations (SDs). Chi-square test and two sample t-test
were used to test the differences between groups with and without cognitive impairment for
categorical and continuous variables, respectively. Using Baron and Kenny's method for
mediation,³⁶ we assessed the associations among depressive symptoms, homebound status,
and cognitive impairment in four logistic regression models. The first model assessed the
direct relationship between the independent variable depressive symptoms and the dependent
variable cognitive impairment. The second model examined whether depressive symptoms

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6 were associated with the hypothesized mediator homebound status. The third model
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9 evaluated the association between the hypothesized mediator homebound status and cognitive
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12 impairment. The fourth model estimated the association between the independent variable
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15 depressive symptoms and the dependent variable cognitive impairment upon inclusion of the
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18 hypothesized mediator homebound status to the model. All models were adjusted for
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21 demographics and health-related factors.

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23 Because all the associations in the above models were significant, we were able to
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26 further test homebound status as a mediator following Baron and Kenny's approach and
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29 using the Paramed command in Stata.³⁶ This procedure estimates the natural direct effects,
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32 natural indirect effects, and marginal total effects in the presence of exposure-mediator
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35 interaction. The product of direct and indirect effects was expressed as the total effect. We
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38 estimated direct and indirect effects using logistic regression models and performed a
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41 bootstrapping analysis with 1000 replications both with and without adjusting for covariates.
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44 The proportion of effect mediated by homebound status was calculated as the log of the
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47 indirect effect divided by the log of the total effect.

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49 Sensitivity analyses were performed to test the robustness of the findings. We
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52 excluded any data provided by proxy respondents (n=583) and reran the analysis (see
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55 supplementary table 1, 2 & 3). Odds ratio (ORs) and 95% confidence intervals (CI) were
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58 reported. Missing values on covariates ranged from 0.1% (stroke) to 3.5% (BMI). Given the
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large sample size, no particular technique was used to handle missing data. *P* values less than

0.05 indicated statistical significance. All analyses were performed in Stata version 15.0.³⁷

Patient and public involvement

No patients were involved in the development of the question, design or data interpretation.

Results

Characteristics of all participants and their comparisons by cognitive status are presented in Table 1 (N = 7,537). The mean age of the participants was 77.7 years old. Fifty-eight percent were female and 68% were non-Hispanic white. About 26% of the participants had cognitive impairment, 16% reported depressive symptoms and 25% were homebound. Compared to participants with no cognitive impairment, those with cognitive impairment were more likely to be older and less educated, have ADL, visual and auditory impairments, and have comorbidities of diabetes and stroke, and have been hospitalized ($P < .001$ for all comparisons). The prevalence of depressive symptoms and homebound status were significantly higher for those with cognitive impairment than those without (27.4% vs. 12.0% for depression status, and 48.1% vs. 16.7% for homebound).

Table 1. Characteristics of community-dwelling older adults, stratified by cognitive impairment status

Characteristics	Total (N=7,270- 7,537) ^a	Cognitive impairment (n=1,849- 1,988)	No cognitive impairment (n=5,421- 5,549)	<i>P</i> values
Age, M ± SD	77.7 ± 7.9	81.8 ± 7.8	76.2 ± 7.3	<.001
Sex, n (%)				.800
Female	4397 (58.3)	1155 (58.1)	3242 (58.4)	
Male	3140 (41.7)	833 (41.9)	2307 (41.6)	
Race/ethnicity, n (%)				<.001

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White, non-Hispanic	5137 (68.1)	1119 (56.3)	4018 (72.4)	
Black, non-Hispanic	1648 (21.9)	563 (28.3)	1085 (19.5)	
Hispanic	449 (6.0)	191 (9.6)	258 (4.7)	
Other	303 (4.0)	115 (5.8)	188 (3.4)	
Education, n (%)				<.001
Less than high school	2020 (27.1)	906 (46.6)	1114 (20.3)	
High school	2056 (27.6)	492 (25.3)	1564 (28.4)	
Some college or vocational school	1801 (24.2)	307 (15.8)	1494 (27.1)	
College or higher	1570 (21.1)	240 (12.3)	1330 (24.2)	
Living arrangement, n (%)				<.001
Alone	2435 (32.4)	680 (34.3)	1755 (31.7)	
With spouse/partner only	3036 (40.5)	538 (27.2)	2498 (45.2)	
With others only	1351 (18.0)	568 (28.7)	783 (14.2)	
With spouse/partner and with others	684 (9.1)	195 (9.8)	489 (8.9)	
Smoking status, n (%)				<.001
No	3721 (49.4)	1064 (53.7)	2657 (47.9)	
Yes	3807 (50.6)	919 (46.3)	2888 (52.1)	
Vigorous activity, n (%)				<.001
No	4970 (66.0)	1652 (83.2)	3318 (59.8)	
Yes	2563 (34.0)	333 (16.8)	2230 (40.2)	
BMI, n (%)				<.001
Normal (<30 kg/m ²)	5316 (72.1)	1479 (80.0)	3837 (70.8)	
Obesity (≥30 kg/m ²)	1954 (28.9)	370 (20.0)	1584 (29.2)	
Visual impairment, n (%)				<.001
No	6684 (89.1)	1540 (78.2)	5144 (93.0)	
Yes	819 (10.9)	429 (21.8)	390 (7.0)	
Auditory impairment, n (%)				<.001
No	5716 (75.8)	1356 (67.7)	4371 (78.8)	
Yes	1821 (24.2)	643 (32.3)	1178 (21.2)	
Hypertension, n (%)				.367
No	2467 (32.8)	634 (32.0)	1833 (33.1)	
Yes	5061 (67.2)	1350 (68.0)	3711 (66.9)	
Diabetes, n (%)				<.001
No	5631 (74.7)	1407 (70.9)	4224 (76.1)	
Yes	1903 (25.3)	578 (29.1)	1325 (23.9)	
Stroke, n (%)				<.001
No	6655 (88.4)	1613 (81.2)	5042 (90.9)	
Yes	876 (11.5)	373 (18.8)	503 (9.1)	
Number of ADL impairments, M ± SD	1.3 ± 0.9	1.8 ± 1.1	1.2 ± 0.6	<.001
Hospitalization, n (%)				<.001
No	5770 (76.6)	1350 (68.0)	4420 (79.7)	

Yes	1759 (23.4)	634 (32.0)	1125 (20.3)	
Depressive symptoms, n (%)				<.001
No	6328 (83.0)	1444 (72.6)	4884 (88.0)	
Yes	1209 (16.0)	544 (27.4)	665 (12.0)	
Homebound, n (%)				<.001
No	5652 (75.0)	1032 (51.9)	4620 (83.3)	
Yes	1885 (25.0)	956 (48.1)	929 (16.7)	

Abbreviations: M, mean; SD, standard deviations; BMI, body mass index; ADL, activity of daily living.

^a Please note that the sample size has a range because missing values on covariates ranged from 0.1% (stroke) to 3.5% (BMI). Given the large sample size, no particular technique was used to handle missing data.

Table 2 presents the results of the associations among cognitive impairment, depressive symptoms, and homebound status in accordance with the Baron and Kenny approach to study mediation. After adjusting for demographics and health-related factors, compared to participants without depressive symptoms or homebound status, those with depressive symptoms (adjusted OR, 1.67; 95% CI, 1.42-1.97) or homebound status (adjusted OR, 1.65; 95% CI, 1.40-1.94) had higher odds of cognitive impairment. Depressive symptoms were also a significant risk factor for homebound status (adjusted OR, 2.00; 95% CI, 1.67-2.40). Additionally, both homebound status (adjusted OR, 1.58; 95% CI, 1.34-1.86) and depressive symptoms (adjusted OR, 1.60; 95% CI, 1.36-1.89) were statistically significantly associated with cognitive impairment when they were both included as independent variables in the same model.

Table 2. Results of logistic regression analyses of associations among depressive symptoms, homebound status and cognitive impairment

Independent variable(s)	Effect size for association, OR (95% CI) ^b			
	Dependent Variable			
	Model 1: Cognitive Impairment	Model 2: Homebound Status	Model 3: Cognitive Impairment	Model 4: Cognitive Impairment

Depressive symptoms	1.67 (1.42-1.97) ***	2.00 (1.67-2.40) ***	NA	1.60 (1.32-1.89) ***
Homebound status	NA	NA	1.65 (1.40-1.94) ***	1.58 (1.34-1.86) ***

Abbreviations: OR, odds ratio; NA, not applicable.

^a * $P < .05$, ** $P < .01$, *** $P < .001$

^b All models adjusted for demographics (age, sex, education, race/ethnicity, living arrangement) and health-related characteristics (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization).

Table 3 and Figure 1 show the indirect contribution of being homebound in the relationship between depressive symptoms and cognitive impairment. Homebound status statistically significantly mediated this relationship. It partially explained the relationship; the contribution of being homebound was 40.4% of the association between depressive symptoms and cognitive impairment in the unadjusted model (Model 1), and this proportion decreased to 12.5% after adjusting for all covariates (Model 3).

Table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment

	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)	Model 3 ^d OR (95% CI)
Natural direct effect	1.93 (1.68-2.22) ***	1.88 (1.61-2.18) ***	1.61 (1.36-1.91) ***
Natural indirect effect	1.56 (1.48-1.64) ***	1.33 (1.27-1.39) ***	1.07 (1.04-1.10) ***
Marginal total effect	3.01 (2.61-3.46) ***	2.49 (2.15-2.90) ***	1.72 (1.46-2.03) ***
Proportion mediated ^a	40.4%	31.3%	12.5%

^a Proportion mediated by homebound status were calculated as the log of the indirect effect divided by the log of the total effect.

^b Model 1: independent variables of interest

^c Model 2: Model 1+ demographic covariates (age, sex, education, race/ethnicity, living arrangement)

^d Model 3: Model 2 + health-related covariates (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization)

[Insert Figure 1 about here]

Results from a sensitivity analysis suggested that homebound status statistically

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6 significantly mediated the association between depressive symptoms and cognitive
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9 impairment (adjusted OR, 1.05; 95% CI, 1.02-1.08), even after excluding data from proxy
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11 respondents (supplementary table 3, additional information see supplementary table 1 and 2).
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14 **Discussion**

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17 We examined the mediating role of homebound status in the association of
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19 depressive symptoms and cognitive impairment using a nationally representative sample of
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21 community-dwelling older Americans. Our study found that depressive symptoms and
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23 homebound status were independently associated with cognitive impairment. Moreover, more
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25 than 10% of the effect of depressive symptoms on cognitive impairment was mediated by
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27 homebound status, suggesting that one of the ways the depression status contributes to
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29 cognitive impairment is through the decreased mobility outside the home that defines
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31 homebound status. Our findings shed light on homebound status as a target of intervention to
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33 prevent and slow cognitive impairment in later life.
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41 Our results showed that depressive symptoms and homebound status were each
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43 independently associated with a greater risk of cognitive impairment; findings are consistent
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45 with previous studies.^{13,18} Depression is a well-established predictor of cognitive impairment;
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47 however we found a similar magnitude of association between homebound status and
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49 cognitive impairment as between depression symptoms and cognitive impairment, after
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51 accounting for demographic and health-related factors. This result was inconsistent with a
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53 cross-sectional study by Meng et al., which suggested that cognitive impairment was more
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6 strongly associated with homebound status compared with depressive symptoms.³⁸ Possible
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8 explanations for different results are the different measures of homebound status, differences
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10 in the covariates included, and cultural difference between the U.S. and China. Meng et al.'s
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12 study included older adults from a rural province in China, with a smaller sample size (N =
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14 720) and adjusted for sociodemographic variables only.³⁸
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20 The mediation findings of this study may be explained through several potential
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22 mechanisms. Depressed older adults often experience loss of interest and social connection,²²
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24 and have no energy to participate in outside activities, which for some leads to reduced
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26 mobility and becoming homebound.^{15,19,39} There is robust evidence that physical activity and
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28 social participation are effective strategies to prevent cognitive impairment,²² and that
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30 homebound older adults are less likely to benefit from these strategies. Homebound status
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32 may also mediate the effects of depression on cognitive impairment via other mechanisms
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34 such as nutrition disorders, social isolation, and hospitalization,^{19,40} all of which have been
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36 associated with both depression and homebound status. The results of two previous studies
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38 (one cross-sectional⁴¹ and one prospective⁴²) found that functional disability mediated the
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40 relationship between depression status and cognitive impairment, and offer additional support
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42 to our mediation findings. Although homebound status is not equivalent to functional
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44 disability, there are overlapping characteristics between homebound older adults and those
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46 with functional disability; older adults with functional disability frequently report difficulty
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48 going outside regularly and are at increased risk of being homebound.⁴³
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6 The study has important implications for nursing practice and research. Our findings
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9 suggest the utility of efforts to improve cognitive function by reducing the effect of
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11 depressive symptoms and homebound status. For example, interventions that support
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13 depressed older adults to maintain ideal outdoor mobility through health education,
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15 psychosocial interventions, and creating a safe and convenient environment, may serve to
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17 decrease risk of cognitive impairment. Some interventions have shown their potential to
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19 reduce depressive symptoms and improve cognitive impairments in depressed older adults,
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21 such as physical exercise.^{21,44,45} Yet, existing interventions are geared toward improving other
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23 outcomes of home-dwelling older adults, instead improving the status of homebound. The
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25 Centers for Medicare & Medicaid Service has suggested to improve health services for
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27 homebound older adults who receive health care at home.⁴⁶ We did not find studies of
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29 mobility interventions to reduce cognitive impairment among homebound older adults and
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31 suggest this as an area of future inquiry. Moreover, our findings suggest the utility of efforts
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33 to improve cognitive function by reducing the effect of depressive symptoms and homebound
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35 status. By recognizing the associations of depressive symptoms and homebound with
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37 cognitive impairment, nurses can screen people who are at high risk of cognitive impairment
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39 or have cognitive impairment more easily by examining their depressive symptoms and
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41 homebound status profiles in their routine practice. Last but not the least, for older adults
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43 with depressive symptoms or who are homebound, nurses can focus on whether these older
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45 adults have additional risk factors for cognitive impairment, such as physical inactivity,
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6 obesity, and social isolation, all of which are common in depressed or homebound older
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8 adults. Proactively managing these modifiable risk factors is beneficial to delay the onset of
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10 cognitive impairment and diagnose it early.
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14 To the best of our knowledge, this study is the first to explore the mediation role of
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16 homebound status in the relationship between depressive symptoms and cognitive
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18 impairments in older adults. The strength of the study included a large sample size, the use of
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20 nationally representative data and adjustment for potential confounders including
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22 demographics and health-related factors. However, several limitations of the study should be
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24 noted. The cross-sectional design does not examine causality. The PHQ-2 was not a
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26 diagnostic tool for depression, but for screening purposes. Although the PHQ-2 is a well-
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28 validated tool with acceptable specificity and sensitivity, measurement errors and
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30 misclassifications may still occur. All indicators were self-reported retrospectively which
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32 may cause recall bias and report errors. Particularly, when we assessed homebound status, a
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34 month recall time may be too long for participants or their proxies to recall accurately.
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44 **Conclusion**

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46 Based on a nationally representative sample of older adults in the U.S., we found
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48 that depressive symptoms and homebound status were associated with cognitive impairment,
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50 and homebound status partially mediated the relationship between depressive symptoms and
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52 cognitive impairment. Therefore, for future public health policy on preventing cognitive
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54 impairment in depressed older adults, homebound status should be taken into account.
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Author contributions

Wenting Peng: Concept and design, analysis, drafting of the initial manuscript and revision.

Christina E. Miyawaki: Critical feedback and revision of the manuscript.

Safiyah M. Okoye: Critical feedback and revision of the manuscript.

Wenru Wang: Critical feedback and revision of the manuscript.

Yuqian Luo: Revision of the manuscript.

Cen Mo: Revision of the manuscript.

Minhui Liu: Supervision, validation, interpretation of data and critical revision of the manuscript.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval

NHATS was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB # 00002083). NHATS participants completed written informed consent prior to being interviewed. The current analyses were deemed exempt from review by the Xiangya School of Nursing Ethic Committee of Central South University. The study was conducted according to the guidelines of the Declaration of Helsinki.

Data availability statement

The NHATS data analyzed in the current study are available for research purposes at www.nhats.org.

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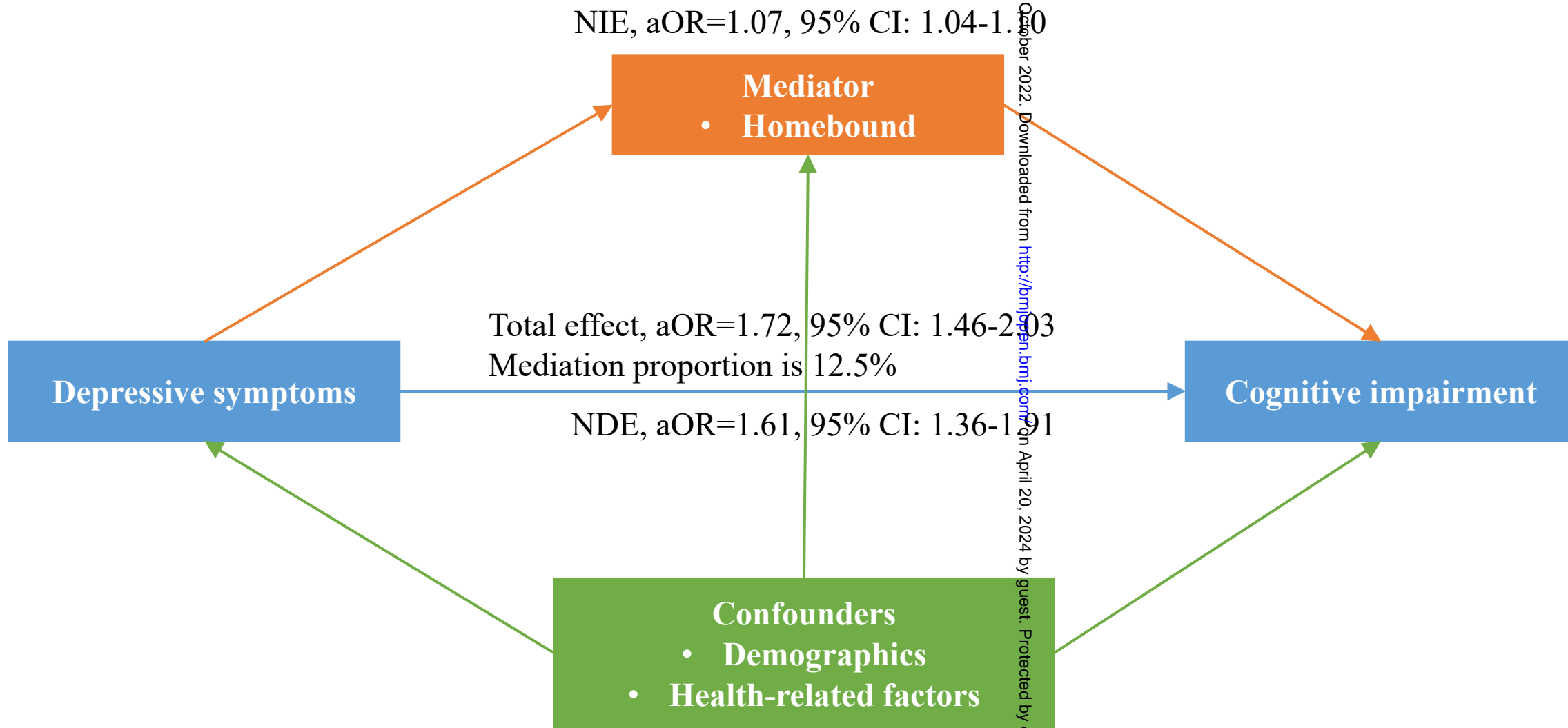
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<https://www.cms.gov/newsroom/press-releases/cms-improve-home-health-services-older-adults-and-people-disabilities>

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Figure 1. Mediation model of homebound status between depressive symptoms and cognitive impairment.



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Abbreviations: OR, odds ratio; NIE, natural indirect effect; NDE, natural direct effect.

The figure depicts that homebound status significantly mediated the relationship between depressive symptoms and cognitive impairment (NIE, aOR; 95% CI, 1.04, 1.10), with significant direct effect of depressive symptoms (NDE, aOR=1.61; 95% CI, 1.36, 1.91) and significant total effect (aOR,1.72; 95% CI, 1.46, 2.03) after adjusting for all covariates.

Supplement

Supplementary table 1. Characteristics distribution stratified by self-reported cognitive status, M \pm SD, N (%)

Supplementary table 2. Results of logistic regression analysis of associations among depressive symptoms, homebound and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Supplementary table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Supplementary table 1. Characteristics distribution stratified by self-reported cognitive status

Characteristics	Total (N=6,746- 6,978)	Cognitive impairment (n=1,416-1,530)	Nocognitive impairment (n=5,330-5,448)	<i>P</i> values
Age, M ± SD	77.2 ± 7.7	81.2 ± 7.7	76.1 ± 7.3	<.001
Sex, n (%)				.800
Female	4051 (58.1)	858 (56.1)	3193 (58.6)	
Male	2927 (41.9)	672 (43.9)	2255 (41.4)	
Race/ethnicity, n (%)				<.001
White, non-Hispanic	4847 (69.5)	878 (57.4)	3969 (72.9)	
Black, non-Hispanic	1483 (21.2)	421 (27.5)	1062 (19.5)	
Hispanic	253 (3.6)	84 (5.5)	169 (3.1)	
Other	395 (5.7)	147 (9.6)	248 (4.5)	
Education, n (%)				<.001
Less than high school	1760 (25.5)	686 (45.6)	1074 (19.9)	
High school	1905 (27.6)	370 (24.6)	1535 (28.4)	
Some college or vocational school	1734 (25.1)	255 (17.0)	1479 (27.4)	
College or higher	1509 (21.8)	191 (12.7)	1318 (24.3)	
Living arrangement, n (%)				<.001
Alone	2315 (33.3)	575 (37.8)	1740 (32.1)	
With spouse/partner only	2913 (41.9)	447 (29.3)	2466 (45.5)	
With others only	1104 (15.9)	359 (23.6)	745 (13.7)	
With spouse/partner and with others	615 (8.9)	142 (9.3)	473 (8.7)	
Smoking status, n (%)				<.001
No	3382 (48.5)	789 (51.7)	2593 (47.6)	
Yes	3591 (51.5)	738 (48.3)	2853 (52.4)	
Vigorous activity, n (%)				<.001
No	4470 (64.1)	1235 (80.8)	3235 (59.4)	
Yes	2507 (35.9)	294 (19.2)	2213 (40.6)	
BMI, n (%)				<.001
Normal (<30 kg/m ²)	4881 (72.3)	1115 (78.7)	3766 (70.7)	
Obesity (≥30 kg/m ²)	1865 (27.7)	301 (21.3)	1564 (29.3)	
Visual impairment, n (%)				<.001
No	6347 (91.2)	1281(83.9)	5066 (93.2)	
Yes	615 (8.8)	246 (16.1)	369 (6.8)	
Auditory impairment, n (%)				<.001
No	5381 (77.1)	1079 (70.5)	4302 (79.0)	
Yes	1597 (22.9)	451 (29.5)	1146 (21.0)	
Hypertension, n (%)				.905
No	2306 (33.1)	503 (33.0)	1803 (33.1)	
Yes	4663 (66.9)	1023 (67.0)	3640 (66.9)	

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Diabetes, n (%)				<.001
No	5218 (74.8)	1074 (70.3)	4144 (76.1)	
Yes	1757 (25.2)	453 (29.7)	1304 (23.9)	
Stroke, n (%)				<.001
No	6246 (89.6)	1289 (84.4)	4957 (91.1)	
Yes	726 (10.4)	239 (15.6)	487 (8.9)	
Number of ADL impairments, M ± SD	1.2 ± 0.7	1.5 ± 1.0	1.2 ± 0.6	<.001
Hospitalization, n (%)				<.001
No	5428 (77.9)	1071 (71.2)	4357 (80.0)	
Yes	1542 (22.1)	455 (29.8)	1087 (20.0)	
Depressive symptoms, n (%)				<.001
No	5974 (85.6)	1177 (76.9)	4797 (88.1)	
Yes	1004 (14.4)	353 (23.1)	651 (11.9)	
Homebound, n (%)				<.001
No	5509 (79.0)	937 (61.2)	4572 (83.9)	
Yes	1469 (21.0)	593 (38.8)	876 (16.1)	

Abbreviations: M, mean; SD, standard deviations; BMI, body mass index; ADL, activity of daily living.

Supplementary table 2. Results of logistic regression analysis of associations among depressive symptoms, homebound and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Independent variable(s)	Effect size for association, OR (95% CI) ^b			
	Dependent Variable			
	Model 1: Cognitive Impairment	Model 2: Homebound Status	Model 3: Cognitive Impairment	Model 4: Cognitive Impairment
Depressive symptoms	1.52 (1.27-1.81) ***	1.92 (1.59-2.33) ***	NA	1.47 (1.23-1.75) ***
Homebound status	NA	NA	1.51 (1.27-1.80) ***	1.46 (1.23-1.75) ***

Abbreviations: OR, odds ratio; NA, not applicable.

a * P < .05, ** P < .01, *** P < .001

b All models adjusted for demographics (age, sex, education, race/ethnicity, living arrangement) and health-related characteristics (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization).

Supplementary table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment excluding proxy respondents (N=6,746-6,978)

	Model 1 ^b	Model 2 ^c	Model 3 ^d
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Natural direct effect	1.71 (1.46-1.98) ***	1.63 (1.39-1.93) ***	1.47 (1.24-1.78) ***
Natural indirect effect	1.36 (1.29-1.43) ***	1.19 (1.14-1.24) ***	1.05 (1.02-1.08) ***
Marginal total effect	2.33 (2.00-2.71) ***	1.95 (1.66-2.30) ***	1.54 (1.30-1.86) ***
Proportion mediated ^a	57.3%	36.5%	12.7%

^a Proportion mediated by homebound status were calculated as the log of the indirect effect divided by the log of the total effect.

^b Model 1: independent variables of interest

^c Model 2: Model 1+ demographic covariates (age, sex, education, race/ethnicity, living arrangement)

^d Model 3: Model 2 + health-related covariates (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily life impairment, hospitalization)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6-7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-10
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	Page 11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10-11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 10-11
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	Page 7
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	Page 11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	In Page 7
		(b) Give reasons for non-participation at each stage	In Page 7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	Page 7

Outcome data	15*	Report numbers of outcome events or summary measures	Page 12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 12-13
		(b) Report category boundaries when continuous variables were categorized	Page 12
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mediating Role of Homebound Status between Depressive Symptoms and Cognitive Impairment among Community-Dwelling Older Adults in the U.S.: A Cross-Sectional Analysis of a Cohort Study

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Mediating Role of Homebound Status between Depressive Symptoms and Cognitive
Impairment among Community-Dwelling Older Adults in the U.S.: A Cross-Sectional
Analysis of a Cohort Study

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6 **Title:** Mediating Role of Homebound Status between Depressive Symptoms and Cognitive
7 Impairment among Community-Dwelling Older Adults in the U.S.: A Cross-Sectional
8 Analysis of a Cohort Study
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10
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Abstract

Objective: Depressive symptoms are known modifiable factors of cognitive impairment in older adults. However, the pathway through which depressive symptoms lead to cognitive impairment is not well understood. This study aimed to investigate whether homebound status (defined as usually unable to leave home unassisted) mediates the association between depressive symptoms and cognitive impairment in community-dwelling older adults in the United States.

Design: A secondary analysis of cross-sectional data.

Setting(s): Communities in the United States.

Participants: Community-dwelling older adults (N=7,537) from the 2011 National Health and Aging Trends Study (NHATS), a nationally representative survey of Medicare Beneficiaries in the United States.

Main outcome measures: Participants' cognitive impairment status was classified using a composite measure. Depressive symptoms were assessed using Patient Health Questionnaire-2. Homebound status was determined by the frequency, difficulty, and needing help in getting outdoors. We used logistic regression and the Paramed command in STATA to analyze whether homebound mediated the association between depressive symptoms and cognitive impairment.

Results: Participants were on average, 77.7 years old, female (58.3%), and non-Hispanic white (68.1%). About 26% of the participants were classified as having cognitive

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6 impairment, 16% reported depressive symptoms, and 25% were homebound. Depressive
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9 symptoms (adjusted OR, 1.60; 95% CI, 1.36-1.89) and homebound status (adjusted OR, 1.58;
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11 95% CI, 1.34-1.86) were independently associated with cognitive impairment. Homebound
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14 significantly mediated 12.5% of the total effect between depressive symptoms and cognitive
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17 impairment, with significant indirect effect (OR, 1.07; 95% CI, 1.04-1.10), direct effect (OR,
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19 1.61; 95% CI, 1.36-1.91) and total effect (OR, 1.72; 95% CI, 1.46-2.03).
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22 **Conclusions:** This study supports a mediating role of homebound status in the relationship
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24 between depressive symptoms and cognitive impairment. Interventions to promote outdoor
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26 mobility should be studied for their ability to delay cognitive impairment for older adults
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28 with depressive symptoms.
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36 **Keywords:** homebound; depressive symptoms; cognitive impairments; older adults;
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Strengths and limitations of this study

- The strengths of this study include the use of nationally large sample data and adjustment for potential confounders including demographics and health-related factors.
- The cross-sectional design does not examine causality.
- All indicators were self-reported retrospectively which may cause recall bias and report errors.
- The measurement of homebound did not collect reasons why individuals did not leave their homes.

Introduction

Cognitive impairment (including mild cognitive impairment and dementia [1]) causes disabilities in older adults' physical and psychological functions and is a major public health concern [2,3]. Approximately 25% of U.S. adults aged 50 and over suffer from cognitive impairment and this rate increases with age [1], bringing a huge economic burden to families and society [4]. Older adults with cognitive impairments have a high and growing demand for long-term care, which poses a significant challenge for healthcare systems, healthcare providers, and families. Thus, it is imperative to identify the modifiable factors and develop effective strategies to prevent and slow the progression of cognitive impairment in older adults.

Depressive symptoms are common in older adults and are associated with physical disability [5], social isolation [6], and cardiovascular diseases [7], all of which have been identified as contributors to declines in cognition [8,9]. A systematic review concluded that depressive symptoms are an independent risk factor for dementia [10]. In addition, multiple systematic reviews found that depressive symptoms are associated with the progression of mild cognitive impairment to dementia [11–13]. Despite these well-established associations between depressive symptoms and cognitive impairment, the mediating mechanisms of the association remain unclear.

In this paper, we examined homebound status as a potential mediator between depressive symptoms and cognitive impairment. Being homebound, defined as limited at

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6 home, is closely related to depression and cognitive impairment. Homebound older adults
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9 have consistently been found to experience depression in high numbers; in one population-
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11 based study, 59% of older adults who had not left their homes in the previous month had
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13 positive depressive symptoms [14–17]. Prior research has also found cognitive impairment
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15 more prevalent in the homebound population than the non-homebound population [18,19].
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17 The confluence of mental health, physical, and social impairments that result in homebound
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19 status [20], may lead to cognitive impairment and should be better understood as a potential
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21 target of intervention. For example, previous studies have shown that older adults with
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23 depressive symptoms were more likely to have physical impairments and loss of interest or
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25 energy in social participation [5,21], resulting in homebound status [19,20]. Rates of physical
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27 activity and social participation, well-known protective factors against cognitive impairment
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29 [22], are low in homebound older adults and may contribute to the higher rates of cognitive
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31 impairment in this population [20].
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42 Fortunately, homebound status is modifiable and can be improved using assistive
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44 devices, modifying the home environment, and accessing transportation [15]. It is therefore
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46 important to investigate the potential of homebound status as a target of interventions to
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48 improve cognitive function. However, to the best of our knowledge, no study has attempted
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50 to investigate whether homebound status mediates the association between depressive
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52 symptoms and cognitive impairment, suggesting the pathway through homebound status
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54 remains unclear. Given the reversibility of homebound status and depressive symptoms and
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6 the heavy burden of cognitive impairment, it is also important to understand the mediating
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8 role of homebound status between cognitive impairment and depressive symptoms. The study
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10 was to examine whether homebound status mediates the association between depressive
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12 symptoms and cognitive impairment in a nationally representative sample of community-
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14 dwelling older adults in the U.S. We hypothesized that homebound status is a significant
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16 mediator between depressive symptoms and cognitive impairment in community-dwelling
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Methods

Design and Sample

We used the first round (2011) of data from the National Health and Aging Trends Study (NHATS) [23], a nationally representative longitudinal cohort study of older adults in the U.S. who are Medicare beneficiaries aged 65 and older [24]. The NHATS study began in 2011 and aimed to understand the disability trends of older adults in late life. In the current study, data obtained from older adults who were aged 65 or above and lived in the community were included in data analyses. In the initial round, a total of 7,609 participants who lived in the community completed the sample person interview. We excluded 72 participants who had incomplete data on depressive symptoms, homebound or cognitive function, for a resulting analysis sample size of 7,537. Excluded participants were older, living alone, with less education, were less likely to perform vigorous activities, had a stroke, and tended to have more activities of daily living (ADL) impairments, visual impairment, and

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6 auditory impairment, compared to those who were not excluded. The NHATS used
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9 downloadable, nonidentifiable and publicly available data and was approved by the Johns
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11 Hopkins University Institutional Review Board (No.00002083). Prior to being interviewed,
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13 all NHATS participants completed a written informed consent form [25]. The current
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15 analyses were deemed exempt from review by the Xiangya School of Nursing Ethic
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19 Committee of Central South University.
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22 **Measurement**

23 *Dependent variables*

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28 Cognitive function was determined by a previously modified NHATS dementia
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30 definition including a diagnosis from physicians (self-reported), assessment of cognitive
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32 function in 3 domains (memory, orientation, and executive function) and AD8 Dementia
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34 Screening Interview provided by proxy respondents [26]. The AD8 contained 8 items and
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36 ranged 0 to 8. Cognitive impairments were determined by a cut-off of 2 and higher. The
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Cronbach's α coefficient of AD8 was 0.84 [27]. Participants were classified into three groups
as follows *probable dementia*, *possible dementia*, and *no dementia*. *Probable dementia* was
assessed by i) a diagnosis of dementia; ii) the AD8 scores ≥ 2 ; or iii) scores ≤ 1.5 Standard
Deviation (SDs) below the mean in at least 2 of 3 cognitive performance tests; *Possible*
dementia was determined by a score of ≤ 1.5 SDs below the mean in 1 cognitive performance
test. All other participants were classified as having *no dementia*. We considered participants
with a classification of probable dementia or possible dementia as having cognitive

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6 impairment; we considered participants with a classification of no dementia as without
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8 cognitive impairment. The NHATS dementia definition (defined as probable or possible
9 dementia) has shown high sensitivity (85.7%) and specificity (83.7%) compared to a
10 structured in-home clinical measurement in the landmark Aging, Demographics, and
11 Memory Study [26]. For terminology consistent with the cognitive impairment instrument,
12 the term “cognitive impairment” was used throughout this article to replace dementia.
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22 ***Independent variable***

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25 Depressive symptoms were measured using the Patient Health Questionnaire-2
26 (PHQ-2), a well-validated screening instrument for depression status [28]. Participants were
27 asked: “Over the last month, how often have you: 1) had little interest or pleasure in doing
28 things; 2) felt down, depressed, or hopeless.” Responses were recorded on a 4-point Likert
29 scale (scored 0-3) with total scores ranging from 0 to 6. A higher score suggested more
30 depressive symptoms. Following the recommendation from previous studies, we used a cut-
31 off of 3 and higher to determine depressive symptoms. The PHQ-2 had a good criterion
32 validity for major depression [29]. The cut-off of 3 has a sensitivity of 0.79, a specificity of
33 0.86, and the area under the curve of 0.90 for any type of depressive disorder [28].
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50 ***Mediator***

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52 Based on the measurement developed by Ornstein and colleagues, homebound status
53 was measured using four questions based on the reported frequency of outdoor mobility [15].
54 First, participants were asked about the frequency of going outside, and response options
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6 were on a 5-point Likert scale: never; rarely (≤ 1 day per week); some days (2-4 days per
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8 week); most days (5-6 days per week); and every day. Participants reporting going outside at
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10 least 2 days per week were asked whether they needed help from others to go outside. Those
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12 who reported needing help were also asked about the frequency of going outside
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14 independently. Those who reported ever going outside by themselves were asked whether
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16 they had any difficulties leaving home independently. Participants were classified as
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18 homebound if they never left home, or left home with any difficulties and assistance. All
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20 other participants were classified as non-homebound [15].
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28 *Covariates*

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30 Demographic and health-related characteristics that are common risk factors for
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32 depression, homebound status, and cognitive impairment were included as covariates in
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34 analyses.
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39 Demographic characteristics included age [1], sex (male/female) [30], race/ethnicity
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41 (non-Hispanic white, non-Hispanic Black, Hispanic, and other) [31], education (less than
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43 high school, high school, college or vocational school and bachelor or higher) [32], and living
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45 arrangement (alone, with spouse/partner only, with others only, with spouse/partner and with
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47 others) [33],
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52 Health-related characteristics included smoking status (never smoker and
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54 current/former smoker) [8]; whether they performed vigorous activities last month (yes/no)
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56 [34]; body mass index (BMI) (normal/obesity [≥ 30 kg/m²]) [8]; visual impairment (yes/no)
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6 [35]; auditory impairment (yes/no) [36]; diagnoses of hypertension (yes/no) [8], diabetes
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8 (yes/no) [8], and stroke (yes/no) [37]; number of activities of daily living impairments [38];
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10 whether the subjects were hospitalized in the last 12 months (yes/no) [39].
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13 14 **Statistical Analysis**

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17 Demographic and health-related characteristics were described using frequencies,
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19 proportions, means, and standard deviations (SDs). Chi-square test and two sample t-test
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21 were used to test the differences between groups with and without cognitive impairment for
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23 categorical and continuous variables, respectively. Using Baron and Kenny's method for
24
25 mediation [40], we assessed the associations among depressive symptoms, homebound status,
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27 and cognitive impairment in four logistic regression models. The first model assessed the
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29 direct relationship between the independent variable depressive symptoms and the dependent
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31 variable cognitive impairment. The second model examined whether depressive symptoms
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33 were associated with the hypothesized mediator homebound status. The third model
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35 evaluated the association between the hypothesized mediator homebound status and cognitive
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37 impairment. The fourth model estimated the association between the independent variable
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39 depressive symptoms and the dependent variable cognitive impairment upon inclusion of the
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41 hypothesized mediator homebound status to the model. All models were adjusted for
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43 demographics and health-related factors.
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55 Because all the associations in the above models were significant, we were able to
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57 further test homebound status as a mediator following Baron and Kenny's approach and
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6 using the Paramed command in Stata [40]. This procedure estimates the natural direct effects,
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8 natural indirect effects, and marginal total effects in the presence of exposure-mediator
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10 interaction. The product of direct and indirect effects was expressed as the total effect. We
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12 estimated direct and indirect effects using logistic regression models and performed a
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14 bootstrapping analysis with 1000 replications both with and without adjusting for covariates.
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17 The proportion of effect mediated by homebound status was calculated as the log of the
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19 indirect effect divided by the log of the total effect.
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25 Sensitivity analyses were performed to test the robustness of the findings. We
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27 excluded any data provided by proxy respondents (n=583) and reran the analysis (see
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29 supplementary table 1, 2 & 3). Odds ratio (ORs) and 95% confidence intervals (CI) were
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31 reported. Missing values on covariates ranged from 0.1% (stroke) to 3.5% (BMI). Given the
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33 large sample size, no particular technique was used to handle missing data. *P* values less than
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35 0.05 indicated statistical significance. All analyses were performed in Stata/SE 15.0 (Stata
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37 Corp., College Station, TX).
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44 **Patient and public involvement**

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46 No patients were involved in the development of the question, design, or data
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48 interpretation.
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52 **Results**

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54 Characteristics of all participants and their comparisons by cognitive status are
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56 presented in Table 1 (N = 7,537). The mean age of the participants was 77.7 years old. Fifty-
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eight percent were female and 68% were non-Hispanic white. About 26% of the participants had cognitive impairment, 16% reported depressive symptoms and 25% were homebound. Compared to participants with no cognitive impairment, those with cognitive impairment were more likely to be older and less educated, have ADL, visual and auditory impairments, have comorbidities of diabetes and stroke, and have been hospitalized ($P<.001$ for all comparisons). The prevalence of depressive symptoms and homebound status were significantly higher for those with cognitive impairment than those without (27.4% vs. 12.0% for depression status, and 48.1% vs. 16.7% for homebound).

Table 1. Characteristics of community-dwelling older adults, stratified by cognitive impairment status

Characteristics	Total (N=7,270- 7,537) ^a	Cognitive impairment (n=1,849- 1,988)	No cognitive impairment (n=5,421- 5,549)	<i>P</i> values
Age, M ± SD	77.7 ± 7.9	81.8 ± 7.8	76.2 ± 7.3	<.001
Sex, n (%)				.800
Female	4397 (58.3)	1155 (58.1)	3242 (58.4)	
Male	3140 (41.7)	833 (41.9)	2307 (41.6)	
Race/ethnicity, n (%)				<.001
White, non-Hispanic	5137 (68.1)	1119 (56.3)	4018 (72.4)	
Black, non-Hispanic	1648 (21.9)	563 (28.3)	1085 (19.5)	
Hispanic	449 (6.0)	191 (9.6)	258 (4.7)	
Other	303 (4.0)	115 (5.8)	188 (3.4)	
Education, n (%)				<.001
Less than high school	2020 (27.1)	906 (46.6)	1114 (20.3)	
High school	2056 (27.6)	492 (25.3)	1564 (28.4)	
Some college or vocational school	1801 (24.2)	307 (15.8)	1494 (27.1)	
College or higher	1570 (21.1)	240 (12.3)	1330 (24.2)	
Living arrangement, n (%)				<.001
Alone	2435 (32.4)	680 (34.3)	1755 (31.7)	
With spouse/partner only	3036 (40.5)	538 (27.2)	2498 (45.2)	
With others only	1351 (18.0)	568 (28.7)	783 (14.2)	
With spouse/partner and with others	684 (9.1)	195 (9.8)	489 (8.9)	

Smoking status, n (%)				<.001
No	3721 (49.4)	1064 (53.7)	2657 (47.9)	
Yes	3807 (50.6)	919 (46.3)	2888 (52.1)	
Vigorous activity, n (%)				<.001
No	4970 (66.0)	1652 (83.2)	3318 (59.8)	
Yes	2563 (34.0)	333 (16.8)	2230 (40.2)	
BMI, n (%)				<.001
Normal (<30 kg/m ²)	5316 (72.1)	1479 (80.0)	3837 (70.8)	
Obesity (≥30 kg/m ²)	1954 (28.9)	370 (20.0)	1584 (29.2)	
Visual impairment, n (%)				<.001
No	6684 (89.1)	1540 (78.2)	5144 (93.0)	
Yes	819 (10.9)	429 (21.8)	390 (7.0)	
Auditory impairment, n (%)				<.001
No	5716 (75.8)	1356 (67.7)	4371 (78.8)	
Yes	1821 (24.2)	643 (32.3)	1178 (21.2)	
Hypertension, n (%)				.367
No	2467 (32.8)	634 (32.0)	1833 (33.1)	
Yes	5061 (67.2)	1350 (68.0)	3711 (66.9)	
Diabetes, n (%)				<.001
No	5631 (74.7)	1407 (70.9)	4224 (76.1)	
Yes	1903 (25.3)	578 (29.1)	1325 (23.9)	
Stroke, n (%)				<.001
No	6655 (88.4)	1613 (81.2)	5042 (90.9)	
Yes	876 (11.5)	373 (18.8)	503 (9.1)	
Number of ADL impairments, M ± SD	1.3 ± 0.9	1.8 ± 1.1	1.2 ± 0.6	<.001
Hospitalization, n (%)				<.001
No	5770 (76.6)	1350 (68.0)	4420 (79.7)	
Yes	1759 (23.4)	634 (32.0)	1125 (20.3)	
Depressive symptoms, n (%)				<.001
No	6328 (83.0)	1444 (72.6)	4884 (88.0)	
Yes	1209 (16.0)	544 (27.4)	665 (12.0)	
Homebound, n (%)				<.001
No	5652 (75.0)	1032 (51.9)	4620 (83.3)	
Yes	1885 (25.0)	956 (48.1)	929 (16.7)	

Abbreviations: M, mean; SD, standard deviations; BMI, body mass index; ADL, activities of daily living.

^a Please note that the sample size has a range because missing values on covariates ranged from 0.1% (stroke) to 3.5% (BMI). Given the large sample size, no particular technique was used to handle missing data.

Table 2 presents the results of the associations among cognitive impairment,

depressive symptoms, and homebound status in accordance with the Baron and Kenny approach to study mediation. After adjusting for demographics and health-related factors, compared to participants without depressive symptoms or homebound status, those with depressive symptoms (adjusted OR, 1.67; 95% CI, 1.42-1.97) or homebound status (adjusted OR, 1.65; 95% CI, 1.40-1.94) had higher odds of cognitive impairment. Depressive symptoms were also a significant risk factor for homebound status (adjusted OR, 2.00; 95% CI, 1.67-2.40). Additionally, both homebound status (adjusted OR, 1.58; 95% CI, 1.34-1.86) and depressive symptoms (adjusted OR, 1.60; 95% CI, 1.36-1.89) were statistically significantly associated with cognitive impairment when they were both included as independent variables in the same model.

Table 2. Results of logistic regression analyses of associations among depressive symptoms, homebound status and cognitive impairment

Independent variable(s)	Effect size for association, OR (95% CI) ^b			
	Dependent Variable			
	Model 1: Cognitive Impairment	Model 2: Homebound Status	Model 3: Cognitive Impairment	Model 4: Cognitive Impairment
Depressive symptoms	1.67 (1.42-1.97) ***	2.00 (1.67-2.40) ***	NA	1.60 (1.32-1.89) ***
Homebound status	NA	NA	1.65 (1.40-1.94) ***	1.58 (1.34-1.86) ***

Abbreviations: OR, odds ratio; NA, not applicable.

^a * $P < .05$, ** $P < .01$, *** $P < .001$

^b All models adjusted for demographics (age, sex, education, race/ethnicity, living arrangement) and health-related characteristics (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization).

Table 3 and Figure 1 show the indirect contribution of being homebound in the relationship between depressive symptoms and cognitive impairment. Homebound status statistically significantly mediated this relationship. It partially explained the relationship; the

contribution of being homebound was 40.4% of the association between depressive symptoms and cognitive impairment in the unadjusted model (Model 1), and this proportion decreased to 12.5% after adjusting for all covariates (Model 3).

Table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment

	Model 1 ^b	Model 2 ^c	Model 3 ^d
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Natural direct effect	1.93 (1.68-2.22) ***	1.88 (1.61-2.18) ***	1.61 (1.36-1.91) ***
Natural indirect effect	1.56 (1.48-1.64) ***	1.33 (1.27-1.39) ***	1.07 (1.04-1.10) ***
Marginal total effect	3.01 (2.61-3.46) ***	2.49 (2.15-2.90) ***	1.72 (1.46-2.03) ***
Proportion mediated ^a	40.4%	31.3%	12.5%

^a Proportion mediated by homebound status was calculated as the log of the indirect effect divided by the log of the total effect.

^b Model 1: independent variables of interest

^c Model 2: Model 1+ demographic covariates (age, sex, education, race/ethnicity, living arrangement)

^d Model 3: Model 2 + health-related covariates (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization)

[Insert Figure 1 about here]

Results from a sensitivity analysis suggested that homebound status statistically significantly mediated the association between depressive symptoms and cognitive impairment (adjusted OR, 1.05; 95% CI, 1.02-1.08), even after excluding data from proxy respondents (supplementary table 3, additional information see supplementary table 1 and 2).

Discussion

We examined the mediating role of homebound status in the association of depressive symptoms and cognitive impairment using a nationally representative sample of community-dwelling older Americans. Our study found that depressive symptoms and

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6 homebound status were independently associated with cognitive impairment. Moreover, more
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8 than 10% of the effect of depressive symptoms on cognitive impairment was mediated by
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10 homebound status, suggesting that one of the ways the depression status influences cognitive
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12 impairment is through the decreased mobility outside the home that defines homebound
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14 status. Our findings shed light on homebound status as a target of intervention to prevent and
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16 slow cognitive impairment in later life.
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22 Our results showed that depressive symptoms and homebound status were each
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24 independently associated with a greater risk of cognitive impairment; findings are supported
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26 by previous studies [13,18]. Depression is a well-established predictor of cognitive
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28 impairment; however, we found a similar magnitude of association between homebound
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30 status and cognitive impairment as between depression symptoms and cognitive impairment,
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32 after accounting for demographic and health-related factors. This result was inconsistent with
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34 a cross-sectional study by Meng et al., which suggested that cognitive impairment was more
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36 strongly associated with homebound status compared with depressive symptoms [41].
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44 Possible explanations for different results are differences in the homebound status measures,
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46 covariates, and the U.S. and Chinese cultures. Meng et al.'s study included older adults from
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48 a rural province in China, with a smaller sample size (N = 720) and adjusted for
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50 sociodemographic variables only [41].
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54 The mediation findings of this study may be explained through several potential
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56 mechanisms. Depressed older adults often experience loss of interest and social connection
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6 [22], and have no energy to participate in outside activities, which for some leads to reduced
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8 mobility and becoming homebound [15,19,42]. There is robust evidence that physical activity
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10 and social participation are effective strategies to prevent cognitive impairment [22], and that
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12 homebound older adults are less likely to benefit from these strategies. Homebound status
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14 may also mediate the effects of depression on cognitive impairment via other mechanisms
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16 such as nutrition disorders, social isolation, and hospitalization [19,43], all of which have
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18 been associated with both depression and homebound status. The results of two previous
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20 studies (one cross-sectional [44] and one prospective [45]) found that functional disability
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22 mediated the relationship between depression status and cognitive impairment, and offer
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24 additional support to our mediation findings. Although homebound status is not equivalent to
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26 functional disability, there are overlapping characteristics between homebound older adults
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28 and those with a functional disability; older adults with functional disability frequently report
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30 difficulty going outside regularly and are at increased risk of being homebound [46].
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41 This study has important implications for public health practice and research. Our
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43 findings suggest the utility of efforts to improve cognitive function by reducing the effect of
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45 depressive symptoms and homebound status. For example, interventions that support
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47 depressed older adults to maintain ideal outdoor mobility through health education,
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49 psychosocial interventions, and creating a safe and convenient environment, may serve to
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51 decrease the risk of cognitive impairment. Some interventions have shown their potential to
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53 reduce depressive symptoms and improve cognitive impairments in depressed older adults,
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6 such as physical exercise [21,47,48]. Yet, existing interventions are geared toward improving
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8 other outcomes of home-dwelling older adults, instead of improving the status of the
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10 homebound. Some evidence-based physical activity intervention programs, such as
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12 Community Aging in Place-Advancing Better Living for Elders (CAPABLE) and Lifestyle
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14 Interventions and Independence for Elders (LIFE), have shown the effect to increase life-
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16 space mobility, falls efficacy, and reduce cognitive frailty among community-dwelling older
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18 adults [49,50]. Future research should further identify these programs' effects on changing
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20 homebound status. The Centers for Medicare & Medicaid Services have suggested improving
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22 health services for homebound older adults who receive health care at home.[51] We did not
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24 find studies of mobility interventions to reduce cognitive impairment among homebound
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26 older adults and suggest this as an area of future inquiry. By recognizing the associations of
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28 depressive symptoms and homebound with cognitive impairment, healthcare professionals
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30 can screen people who are at high risk of cognitive impairment or have cognitive impairment
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32 more easily by examining their depressive symptoms and homebound status profiles in their
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34 routine practice. Last but not least, for older adults with depressive symptoms or who are
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36 homebound, healthcare professionals can focus on whether these older adults have additional
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38 risk factors for cognitive impairment, such as physical inactivity, obesity, and social
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40 isolation, all of which are common in depressed or homebound older adults. Proactively
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42 managing these modifiable risk factors is beneficial to delay the onset of cognitive
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44 impairment and diagnosing it early.
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6 To the best of our knowledge, this study is the first to explore the mediation role of
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9 homebound status in the relationship between depressive symptoms and cognitive
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11 impairments in older adults. The strengths of this study include the use of nationally large
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13 sample data and adjustment for potential confounders including demographics and health-
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15 related factors. However, several limitations of the study should be noted. First, the cross-
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17 sectional design does not examine causality, suggesting future studies can further assess
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19 causal relationships among depressive symptoms, homebound status, and cognitive
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21 impairments using a prospective research design. Second, all indicators were self-reported
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23 retrospectively which may cause recall bias and report errors. Particularly, when we assessed
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25 homebound status, a month recall time may be too long for participants or their proxies to
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27 recall accurately. Third, Medicare defined a homebound individual as requiring “taxing
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29 effort” (i.e., physical, or personal assistance) to leave their home [52], which was consistent
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31 with the NHATS homebound definition. However, the measurement of homebound was
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33 limited by the items and skip patterns within the NHATS Mobility Questionnaire. For
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35 example, the mobility questions did not collect reasons why individuals did not leave their
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37 homes [15].
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49 **Conclusion**

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52 Based on a nationally representative sample of older adults in the U.S., we found
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54 that depressive symptoms and homebound status were associated with cognitive impairment,
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56 and homebound status partially mediated the relationship between depressive symptoms and
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6 cognitive impairment. Therefore, for future public health efforts on preventing cognitive
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9 impairment in depressed older adults, homebound status should be taken into account.
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For peer review only

Author contributions

Wenting Peng: Concept and design, analysis, drafting of the initial manuscript and revision.

Christina E. Miyawaki: Critical feedback and revision of the manuscript.

Safiyah M. Okoye: Critical feedback and revision of the manuscript.

Wenru Wang: Critical feedback and revision of the manuscript.

Yuqian Luo: Revision of the manuscript.

Cen Mo: Revision of the manuscript.

Minhui Liu: Supervision, validation, interpretation of data and critical revision of the manuscript.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval

NHATS was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB # 00002083). NHATS participants completed written informed consent prior to being interviewed. The current analyses were deemed exempt from review by the Xiangya School of Nursing Ethic Committee of Central South University. The study was conducted according to the guidelines of the Declaration of Helsinki.

Data availability statement

Data are available in a public, open access repository. The NHATS data analyzed in the current study are available for research purposes at www.nhats.org.

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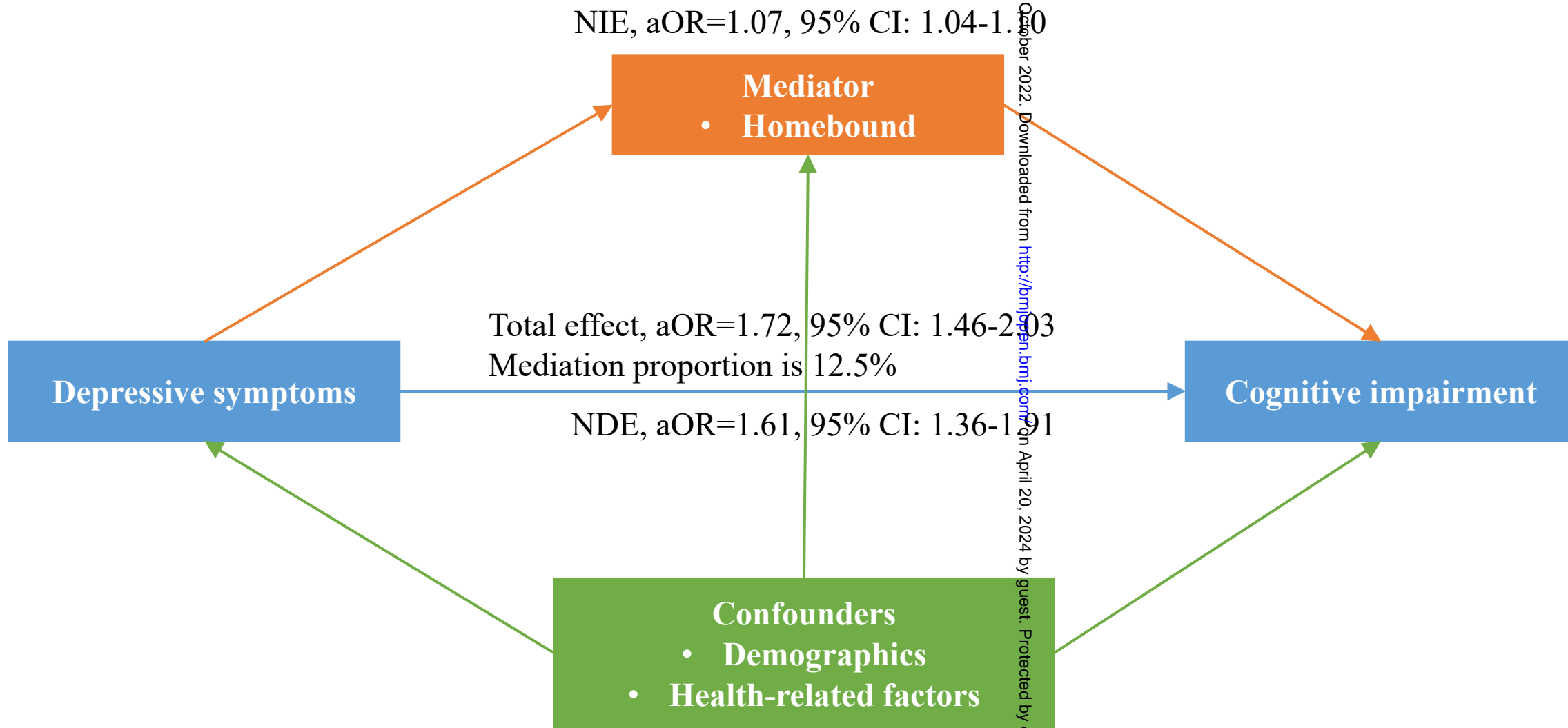
Figure Legend

Figure 1. Mediation model of homebound status between depressive symptoms and cognitive impairment.

Abbreviations: OR, odds ratio; NIE, natural indirect effect; NDE, natural direct effect.

The figure depicts that homebound status significantly mediated the relationship between depressive symptoms and cognitive impairment (NIE, aOR; 95% CI, 1.04, 1.10), with significant direct effect of depressive symptoms (NDE, aOR=1.61; 95% CI, 1.36, 1.91) and significant total effect (aOR,1.72; 95% CI, 1.46, 2.03) after adjusting for all covariates.

Figure 1. Mediation model of homebound status between depressive symptoms and cognitive impairment.



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Supplement

Supplementary table 1. Characteristics distribution stratified by self-reported cognitive status, M \pm SD, N (%)

Supplementary table 2. Results of logistic regression analysis of associations among depressive symptoms, homebound and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Supplementary table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Supplementary table 1. Characteristics distribution stratified by self-reported cognitive status

Characteristics	Total (N=6,746- 6,978)	Cognitive impairment (n=1,416-1,530)	Nocognitive impairment (n=5,330-5,448)	<i>P</i> values
Age, M ± SD	77.2 ± 7.7	81.2 ± 7.7	76.1 ± 7.3	<.001
Sex, n (%)				.800
Female	4051 (58.1)	858 (56.1)	3193 (58.6)	
Male	2927 (41.9)	672 (43.9)	2255 (41.4)	
Race/ethnicity, n (%)				<.001
White, non-Hispanic	4847 (69.5)	878 (57.4)	3969 (72.9)	
Black, non-Hispanic	1483 (21.2)	421 (27.5)	1062 (19.5)	
Hispanic	253 (3.6)	84 (5.5)	169 (3.1)	
Other	395 (5.7)	147 (9.6)	248 (4.5)	
Education, n (%)				<.001
Less than high school	1760 (25.5)	686 (45.6)	1074 (19.9)	
High school	1905 (27.6)	370 (24.6)	1535 (28.4)	
Some college or vocational school	1734 (25.1)	255 (17.0)	1479 (27.4)	
College or higher	1509 (21.8)	191 (12.7)	1318 (24.3)	
Living arrangement, n (%)				<.001
Alone	2315 (33.3)	575 (37.8)	1740 (32.1)	
With spouse/partner only	2913 (41.9)	447 (29.3)	2466 (45.5)	
With others only	1104 (15.9)	359 (23.6)	745 (13.7)	
With spouse/partner and with others	615 (8.9)	142 (9.3)	473 (8.7)	
Smoking status, n (%)				<.001
No	3382 (48.5)	789 (51.7)	2593 (47.6)	
Yes	3591 (51.5)	738 (48.3)	2853 (52.4)	
Vigorous activity, n (%)				<.001
No	4470 (64.1)	1235 (80.8)	3235 (59.4)	
Yes	2507 (35.9)	294 (19.2)	2213 (40.6)	
BMI, n (%)				<.001
Normal (<30 kg/m ²)	4881 (72.3)	1115 (78.7)	3766 (70.7)	
Obesity (≥30 kg/m ²)	1865 (27.7)	301 (21.3)	1564 (29.3)	
Visual impairment, n (%)				<.001
No	6347 (91.2)	1281(83.9)	5066 (93.2)	
Yes	615 (8.8)	246 (16.1)	369 (6.8)	
Auditory impairment, n (%)				<.001
No	5381 (77.1)	1079 (70.5)	4302 (79.0)	
Yes	1597 (22.9)	451 (29.5)	1146 (21.0)	
Hypertension, n (%)				.905
No	2306 (33.1)	503 (33.0)	1803 (33.1)	
Yes	4663 (66.9)	1023 (67.0)	3640 (66.9)	

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Diabetes, n (%)				<.001
No	5218 (74.8)	1074 (70.3)	4144 (76.1)	
Yes	1757 (25.2)	453 (29.7)	1304 (23.9)	
Stroke, n (%)				<.001
No	6246 (89.6)	1289 (84.4)	4957 (91.1)	
Yes	726 (10.4)	239 (15.6)	487 (8.9)	
Number of ADL impairments, M ± SD	1.2 ± 0.7	1.5 ± 1.0	1.2 ± 0.6	<.001
Hospitalization, n (%)				<.001
No	5428 (77.9)	1071 (71.2)	4357 (80.0)	
Yes	1542 (22.1)	455 (29.8)	1087 (20.0)	
Depressive symptoms, n (%)				<.001
No	5974 (85.6)	1177 (76.9)	4797 (88.1)	
Yes	1004 (14.4)	353 (23.1)	651 (11.9)	
Homebound, n (%)				<.001
No	5509 (79.0)	937 (61.2)	4572 (83.9)	
Yes	1469 (21.0)	593 (38.8)	876 (16.1)	

Abbreviations: M, mean; SD, standard deviations; BMI, body mass index; ADL, activity of daily living.

Supplementary table 2. Results of logistic regression analysis of associations among depressive symptoms, homebound and cognitive impairment excluding proxy respondents (N=6,746-6,978)

Independent variable(s)	Effect size for association, OR (95% CI) ^b			
	Dependent Variable			
	Model 1: Cognitive Impairment	Model 2: Homebound Status	Model 3: Cognitive Impairment	Model 4: Cognitive Impairment
Depressive symptoms	1.52 (1.27-1.81) ***	1.92 (1.59-2.33) ***	NA	1.47 (1.23-1.75) ***
Homebound status	NA	NA	1.51 (1.27-1.80) ***	1.46 (1.23-1.75) ***

Abbreviations: OR, odds ratio; NA, not applicable.

a * P < .05, ** P < .01, *** P < .001

b All models adjusted for demographics (age, sex, education, race/ethnicity, living arrangement) and health-related characteristics (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily living impairments, hospitalization).

Supplementary table 3. Mediation of homebound status in the association between depressive symptoms and cognitive impairment excluding proxy respondents (N=6,746-6,978)

	Model 1 ^b	Model 2 ^c	Model 3 ^d
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Natural direct effect	1.71 (1.46-1.98) ***	1.63 (1.39-1.93) ***	1.47 (1.24-1.78) ***
Natural indirect effect	1.36 (1.29-1.43) ***	1.19 (1.14-1.24) ***	1.05 (1.02-1.08) ***
Marginal total effect	2.33 (2.00-2.71) ***	1.95 (1.66-2.30) ***	1.54 (1.30-1.86) ***
Proportion mediated ^a	57.3%	36.5%	12.7%

^a Proportion mediated by homebound status were calculated as the log of the indirect effect divided by the log of the total effect.

^b Model 1: independent variables of interest

^c Model 2: Model 1+ demographic covariates (age, sex, education, race/ethnicity, living arrangement)

^d Model 3: Model 2 + health-related covariates (smoke, body mass index, vigorous activity, visual impairment, auditory impairment, hypertension, diabetes, stroke, number of activities of daily life impairment, hospitalization)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8-11
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8-11
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 11-12
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 11-12
		(b) Describe any methods used to examine subgroups and interactions	N/A
	(c) Explain how missing data were addressed	Page 12	
	(d) If applicable, describe analytical methods taking account of sampling strategy	N/A	
	(e) Describe any sensitivity analyses	Page 12	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	In Page 12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12-13
		(b) Indicate number of participants with missing data for each variable of interest	Page 7
Outcome data	15*	Report numbers of outcome events or summary measures	Page 12-13

1				
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 12-13
3			(b) Report category boundaries when continuous variables were categorized	Page 12-16
4			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
5				
6	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 16
7				
8	Discussion			
9	Key results	18	Summarise key results with reference to study objectives	Page 16-17
10				
11	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 20
12				
13	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-20
14				
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 20
16				
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.