Independent and joint associations of loneliness and social isolation with subjective cognitive decline in perimenopausal women

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Abstract

Objective: This study aimed to clarify the independent and joint associations of loneliness and social isolation with subjective cognitive decline (SCD) among perimenopausal women.

Methods: This cross-sectional study was conducted between March and September 2024 and comprised 903 perimenopausal women. Subjective perceived loneliness, objective social isolation, and severity of SCD were measured using a set of self-reported online questionnaires. Latent class analysis was employed to determine the high-risk SCD groups among perimenopausal women, and restricted cubic spline model and logistic regression models were further utilized to investigate the independent and joint associations of loneliness and social isolation with SCD.

Results: The mean SCD score across all participants was 3.77 (SD = 2.99). Latent class analysis categorized the participants into a "mild SCD group" (47.8%) and "severe SCD group" (52.2%). Logistic regression analysis revealed that both loneliness and social isolation were independently associated with SCD. Notably, joint analysis revealed that compared with participants without loneliness and social isolation, those with moderate to severe loneliness and social isolation exhibited the highest odds of severe SCD. Furthermore, significant additive and multiplicative interactions were observed between moderate to severe loneliness and social isolation.

Conclusion: In perimenopausal populations, loneliness and social isolation were not only independently associated with SCD but also exhibited a joint relationship. These findings offer deeper insights into understanding the relationship between social connections and SCD, and provide empirical evidence for developing psychosocial interventions aimed at preserving cognitive health in perimenopausal women.

Key Words: Loneliness, Perimenopausal women, Social isolation, Subjective cognitive decline.

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Perimenopause is a critical stage wherein women transition from the reproductive period to menopause. Typically occurring between the ages of 45 and 55 years, it is characterized by a gradual ovarian decline and fluctuating estrogen levels.[1] This physiological transition may not only lead to physical symptoms such as hot flashes and sleep disturbances but also frequently accompany significant emotional and cognitive changes.[2,3] Among these, subjective cognitive decline (SCD), defined as an individual's self-perceived cognitive decline—such as in memory, attention, or processing speed—while objective neuropsychological assessments remain within normal limits, has been recognized as a preclinical manifestation of Alzheimer disease and serves as a stronger marker for future cognitive decline in women than in men.[4-6] In recent years, a growing body of research has reported an increased prevalence of SCD among perimenopausal women.[7-9] Therefore, identifying perimenopausal women at high risk of SCD and related factors is of great public health significance for the early implementation of interventions to mitigate cognitive deterioration.

The mechanisms underlying SCD during perimenopause are complex, and in addition to neuroendocrine changes, increasing attention has been paid to the role of psychosocial factors.[10-14] Loneliness is a subjective social experience reflecting an individual's dissatisfaction with existing social relationships and the perceived lack of

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emotional connection,[15] whereas social isolation is an objective state characterized by a limited social network, infrequent social interactions, and reduced social participation.[16] Previous studies have demonstrated that both loneliness and social isolation are significant risk factors for a range of adverse health outcomes, including cognitive decline, cardiovascular disease, and all-cause mortality.[17-19] Loneliness and social isolation are interrelated but distinct concepts: an individual may have an extensive number of social connections, while still experiencing feelings of loneliness, or conversely, be socially isolated without experiencing a sense of loneliness.[20] Loneliness and social isolation are reported to be associated with an increased risk of cognitive deterioration in middle-aged and older adults; however, their roles among perimenopausal women remain unclear.[21] Perimenopausal women often face multiple psychosocial stressors, including increased family caregiving responsibilities, occupational role transitions, children leaving home, and physical changes, which may heighten their vulnerability to loneliness and social isolation.[22] Moreover, estrogen level fluctuations may influence brain regions involved in emotional regulation, increasing women's sensitivity to stress and negative emotional information, thereby intensifying the psychological impact of loneliness and social isolation.[23]

Although loneliness and social isolation are often discussed together, their independent associations and interrelationships are frequently overlooked. Recently, a large longitudinal study involving 7299 older adults revealed that incident, transient, and persistent social isolation or loneliness accelerated cognitive decline, and that persistent loneliness and any form of social isolation were associated with a higher risk of cognitive impairment.[24] These findings underscore the distinct yet interrelated impacts of loneliness and social isolation on cognitive health. However, empirical research is lacking on how loneliness and social isolation are independently associated with SCD and whether they exhibit joint associations that correlate with the subjective experience of cognitive deterioration among perimenopausal women.

Hence, this study aims to identify high-risk groups of SCD among perimenopausal women based on the latent class analysis (LCA), and further investigate the independent and joint associations of loneliness and social isolation with SCD, thereby providing insights for the early identification and intervention of cognitive deterioration, laying a foundation for enhancing psychosocial adaptation, and promoting healthy aging in this population.

METHODS

Participants

This cross-sectional study was conducted in Shandong Province between March and September 2024. Participants were recruited via online announcements that explicitly detailed the study's objectives, methodology, and eligibility criteria. Eligible perimenopausal women indicated their consent to engage in the study by completing and submitting the online survey. The inclusion criteria were as follows: (1) aged 45-55 years, (2) in perimenopause, and (3) able to comprehend the questionnaire. According to the Stages of Reproductive Aging Workshop +10 (STRAW+10) criteria, perimenopause encompasses three stages: early menopause transition, characterized by a persistent difference of 7 days or longer in consecutive cycle length; late menopause transition, marked by the occurrence of amenorrhea lasting 60 days or longer; and early postmenopause, defined as the initial 1-year period following the final menstrual period.[1] Exclusion criteria included the following: (1) oral contraceptives in the past 3 months, (2) history of severe medical conditions, and (3) underwent hysterectomy or oophorectomy.

Sample size

Sample size was determined using the formula $N = z^2p(1-p)/d^2$. In the present study, the parameters in the formula and their assigned values were as follows: a two-sided 95% CI was adopted, yielding a z value of 1.96; p denotes the prevalence of SCD, previously estimated at ~18.8% in Chinese populations;[25] d denotes the margin of error and was set at 0.03. According to the standard formula, a minimum sample size of 652 was required. A target sample size of 815 was set after considering a 20% invalid rate. Finally, a total of 978 questionnaires were collected in this study. After excluding invalid questionnaires, such as those with patterned responses, 903 questionnaires remained in the final data analysis, yielding a validity rate of 92.3%.

Measures

Subjective cognitive decline

The self-reported SCD-Q9 was utilized to assess the severity of SCD among perimenopausal women. It is a nine-item instrument comprising four items evaluating overall functional memory and time comparison, and five items assessing the activities of daily living.[26] Items are scored on either a binary (0 = no, 1 = yes) or a three-point scale (0 = never, 0.5 = sometimes, 1 = always). Higher total scores indicate greater severity of SCD. The validity and reliability of SCD-Q have been demonstrated in the Chinese population,[27] and the Cronbach α in this study was 0.893.

Loneliness

The six-item revised UCLA Loneliness Scale (ULS-6) was used to quantify subjective loneliness.[28] The total score, calculated by summing all the items (range: 6-24), served as an index of loneliness, with elevated scores indicating greater severity. In this study, participants were further categorized into three groups: no loneliness (score: 6-9), mild loneliness (score: 10-13), and moderate to severe loneliness (score: 14 and higher). The Cronbach α of the ULS-6 in this study was 0.954.

Social isolation

Objective social isolation was assessed using the six-item Lubben Social Network Scale (LSNS-6), which measures the size of social networks through interaction frequency and relationship closeness with family and friends.[29] Each item was rated on a six-point scale, with total scores ranging from 0 to 30. A cutoff score of 12 was set for LSNS-6, with lower scores indicating the risk of social isolation. However, in this study, all items were reverse-scored for analysis as continuous variables to remain consistent with the binary classification of social isolation, with higher scores indicating smaller social networks and greater social isolation. The Cronbach α of the LSNS-6 in this study was 0.908.

Covariates

Based on existing literature, several potential confounding factors that may affect cognitive function were collected through the online questionnaire, including sociodemographic, lifestyle, health-related, and menstruation-related factors.[8,14,30]

Sociodemographics included age, body mass index (BMI), educational level, economic conditions, place of residence, type of work, and socioeconomic status. Socioeconomic status was assessed using the MacArthur Scale of Subjective Social Status, a single-item instrument that measures self-perceived standing relative to others in the social group.

Lifestyle and health-related factors included major life events, drinking status, exercise frequency, and presence of chronic diseases.

Menstruation-related factors included age at menarche, menopausal symptoms, use of hormone therapy, and presence of gynecological diseases. The Menopause Rating Scale (MRS) was used to measure the severity of menopausal symptoms, including the somato-vegetative, psychological, and urogenital domains. Each item is scored on a five-point scale, from 0 (absent) to 4 (very severe). In this study, the Cronbach α of MRS was 0.943.

Statistical analysis

LCA is a person-centered statistical approach that aims to identify subpopulations within a sample based on the response patterns to observed categorical variables.[31] In this study, the LCA was employed to identify distinct subgroups of SCD among perimenopausal women.[31] To ensure consistent measurement levels, 9 items of SCD-Q9 were dichotomized, with the absence of a symptom (a score of 0) coded as "0" and the presence of a symptom at any severity level (a score of 0.5 or 1) coded as "1." Models ranging from 1 to k classes were fitted and the following indices compared with determine the best-fitting model: the Akaike information criterion (AIC), Bayesian information criterion (BIC), and sample size adjusted BIC, where lower values indicate better model fit; entropy, where a value closer to 1 indicates greater classification accuracy; and the Lo-Mendell-Rubin Likelihood Ratio Test (LMRT) and Bootstrap Likelihood Ratio Test (BLRT), where a significant *P* value suggests the superior fit of the k-class model over the k-1-class model. Following the identification of latent classes, descriptive statistics for the total sample and for each class were conducted using the "tableone" package in R software, with continuous variables summarized as mean (M) and standard deviation (SD), and categorical variables as frequency (n) and percentage (%). Basic characteristics across the latent classes of SCD were compared using univariate analyses.

A restricted cubic spline (RCS) model was used to visualize potential linear or nonlinear associations of loneliness and social isolation with SCD. The analyses were performed using the lrm function of the "rms" package in R software, with the optimal number of knots for the RCS curves guided by the minimization of AIC. Subsequently, logistic regression was performed to assess the independent associations of loneliness and social isolation with SCD. Two models were fitted sequentially, and loneliness and social isolation were analyzed as both continuous and categorical variables. Model 1 was unadjusted, and Model 2 was adjusted for age, BMI, educational level, economic conditions, place of residence, type of work, socioeconomic status, major life events, drinking status, exercise frequency, age at menarche, and menopausal symptoms. Results are presented as odds ratios (ORs) with 95% CIs.

To explore the joint associations of loneliness and social isolation with SCD, we combined the 3-category loneliness (no/mild/moderate to severe) with the two-category social isolation (no/yes), forming six mutually exclusive groups. An adjusted logistic regression model was constructed with the "no loneliness and no social isolation" group as the reference. In addition, the additive and multiplicative interactions were assessed. The total sample was partitioned into two subsets to facilitate separate interaction analyses: the first subset included participants with "no" and "mild" loneliness, while the second comprised participants with "no" and "moderate to severe" loneliness. Within each subset, we evaluated the interactions between the specific loneliness level and social isolation on SCD, with the "no loneliness and no social isolation" group as the common reference. Additive interaction was evaluated using the relative excess risk of interaction (RERI), attributable proportion of interaction (AP), and synergy index (SI), where a significant additive interaction was defined as the 95% CIs of RERI and AP not including 0, and the 95% CI of SI not including 1. Multiplicative interaction was assessed by adding a product term to the adjusted logistic model.

Finally, to substantiate the primary findings, sensitivity analyses were performed by excluding participants with chronic diseases, gynecological diseases, or those undergoing hormone therapy. In addition, multiple linear regression was conducted to evaluate the associations of loneliness and social isolation with the severity of SCD (Supplementary Tables S1 and S2, Supplemental Digital Content 1, http://links.lww.com/MENO/B494).

All analyses were performed using Mplus version 8.3 (Muthén & Muthén, Los Angeles, CA) and R

software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance set at a two-tailed $P < 0.05$.

RESULTS

Sample characteristics

A total of 903 perimenopausal women were included in the final data analysis, with a mean age of 48.90 years (SD = 3.28). Table 1 presents further details on the sample characteristics. The mean SCD score of all participants was 3.77 ± 2.99, with 41.6% of participants experiencing mild to severe loneliness and 27.2% reporting a risk of social isolation.

LCA was used to determine the latent categories of SCD based on participants' dichotomous responses to the SCD-Q9. The AIC, BIC, and adjusted BIC values were generally consistent across models with increasing class numbers, and LMRT and BLRT indicated statistical significance in all models (all $P < 0.001$; Table 2). The two-category model demonstrated the highest entropy (0.914), indicating superior classification accuracy. Considering

TABLE 1. Characteristics of participants in the mild and severe SCD groups

	Total sample ($N = 903$)	Mild SCD ($n = 432$)	Severe SCD ($n = 471$)	P
Age (y) (M ± SD)	48.90 (3.28)	48.87 (3.26)	48.94 (3.31)	0.747
BMI (kg/m^2) (M ± SD)	24.05 (3.26)	23.90 (3.21)	24.19 (3.29)	0.182
Educational level, n (%)				0.011
College or higher vocational college or above	164 (18.2)	61 (14.1)	103 (21.9)	—
High school or technical secondary school	199 (22.0)	100 (23.1)	99 (21.0)	—
Junior high school or below	540 (59.8)	271 (62.7)	269 (57.1)	—
Economic conditions, n (%)	—	—	—	< 0.001
More than sufficient	125 (13.8)	61 (14.1)	64 (13.6)	—
Sufficient for essentials	585 (64.8)	306 (70.8)	279 (59.2)	—
Insufficient	193 (21.4)	65 (15.0)	128 (27.2)	—
Place of residence, n (%)	—	-	—	0.309
Urban	412 (45.6)	189 (43.8)	223 (47.3)	—
Rural	491 (54.4)	243 (56.2)	248 (52.7)	—
Type of work, n (%)	—	—	—	0.062
Mainly mental work	209 (23.1)	89 (20.6)	120 (25.5)	—
Mainly physical labor	562 (62.2)	286 (66.2)	276 (58.6)	—
Without a job	132 (14.6)	57 (13.2)	75 (15.9)	—
Socioeconomic status (M ± SD)	4.34 (2.07)	4.55 (2.05)	4.14 (2.07)	0.003
Major life events, n (%)	—	—	—	< 0.001
No	710 (78.6)	377 (87.3)	333 (70.7)	—
Yes	193 (21.4)	55 (12.7)	138 (29.3)	—
Drinking status, n (%)	—	-	—	0.517
No	763 (84.5)	361 (83.6)	402 (85.4)	—
Yes	140 (15.5)	71 (16.4)	69 (14.6)	—
Exercise frequency, n (%)	—	—	—	0.073
Often	334 (37.0)	156 (36.1)	178 (37.8)	—
Sometimes	286 (31.7)	152 (35.2)	134 (28.5)	—
Never	283 (31.3)	124 (28.7)	159 (33.8)	—
Presence of chronic diseases, n (%)	—	—	—	< 0.001
No	735 (81.4)	375 (86.8)	360 (76.4)	—
Yes	168 (18.6)	57 (13.2)	111 (23.6)	—
Age at menarche (y), n (%)	—	—	—	0.167
≤ 12	102 (11.3)	50 (11.6)	52 (11.0)	—
13-16	698 (77.3)	324 (75.0)	374 (79.4)	—
≥ 17	103 (11.4)	58 (13.4)	45 (9.6)	—
MRS (M ± SD)	7.97 (7.91)	5.03 (6.87)	10.66 (7.84)	< 0.001
Use of hormone therapy, n (%)	—	—	—	0.354
No	867 (96.0)	418 (96.8)	449 (95.3)	
Yes	36 (4.0)	14 (3.2)	22 (4.7)	
Presence of gynecological diseases, n (%)	—	—	-	< 0.001
No	752 (83.3)	383 (88.7)	369 (78.3)	—
Yes	151 (16.7)	49 (11.3)	102 (21.7)	—
Total score of loneliness (M ± SD)	9.50 (4.22)	8.00 (3.34)	10.89 (4.46)	< 0.001
Loneliness, n (%)	—	—	—	< 0.001
No	527 (58.4)	326 (75.5)	201 (42.7)	—
Mild	235 (26.0)	75 (17.4)	160 (34.0)	—
Moderate to severe	141 (15.6)	31 (7.2)	110 (23.4)	—
Total score of social isolation (M ± SD)	15.38 (6.52)	14.44 (6.93)	16.25 (6.00)	< 0.001
Social isolation, n (%)	—	—	—	0.002
No	657 (72.8)	336 (77.8)	321 (68.2)	—
Yes	246 (27.2)	96 (22.2)	150 (31.8)	—

BMI, body mass index; M, mean; MRS, Menopause Rating Scale; SCD, subjective cognitive decline; SD, standard deviation.

TABLE 2. Potential category model fit indices for SCD

Model	AIC	BIC	aBIC	Entropy	LMRT (*P*)	BLRT (*P*)	Class probability
1	10,980.003	11,023.255	10,994.672	—	—	—	1
2	8,075.378	8,166.686	8,106.345	0.914	<0.001	<0.001	0.522/0.478
3	7,705.605	7,844.971	7,752.872	0.867	<0.001	<0.001	0.421/0.293/0.286
4	7,449.436	7,636.86	7,513.002	0.863	<0.001	<0.001	0.321/0.275/0.230/0.174

aBIC, sample size adjusted BIC; AIC, akaike information criterion; BIC, Bayesian information criterion; BLRT, Bootstrap Likelihood Ratio Test; LMRT, Lo-Mendell-Rubin Likelihood Ratio Test; SCD, subjective cognitive decline.

the accuracy and interpretability of the latent classes, the 2-category model was ultimately selected as the optimal solution in this study.

The conditional probabilities of the two latent classes are visualized in Figure 1, with the specific values provided in Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/MENO/B494. Class 1 (47.8% of the total) was named "mild SCD group," wherein the scoring probabilities for all items were below 0.3. Conversely, class 2 (52.2% of the total) was designated "severe SCD group," wherein the scoring probabilities for most items were above 0.75. Univariate analyses revealed that there were significant differences in educational level, economic status, socioeconomic status, major life events, chronic disease prevalence, MRS scores, gynecological disease prevalence, loneliness, and social isolation between the mild SCD group and severe SCD group (Table 1).

Independent associations of loneliness and social isolation with SCD

We assessed the potential linear or nonlinear associations of loneliness and social isolation with SCD using the RCS model. A nonlinear trend in the association of loneliness with SCD was observed (*P* for overall < 0.0001, *P* for nonlinear = 0.0001; Fig. 2), appearing as a tilted N-shaped curve. Differently, a significant linear trend was identified in the association between social isolation and SCD (*P* for overall = 0.0037, *P* for nonlinear = 0.3622). The odds of severe SCD increased in a dose-dependent manner with increasing score of social isolation.

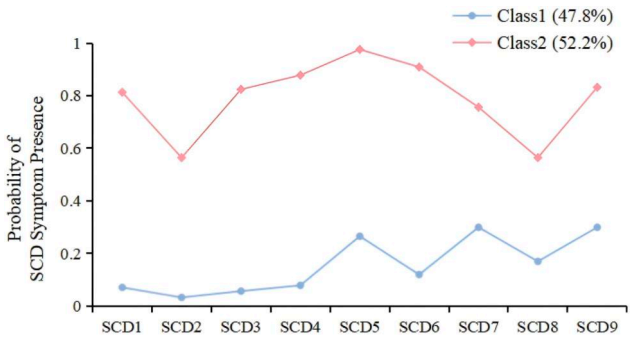

FIG. 1. Conditional probabilities of two latent classes of SCD. SCD, subjective cognitive decline.

Table 3 displays the independent associations of loneliness and social isolation with SCD in perimenopausal women. After adjusting for confounders, when loneliness and social isolation were analyzed as continuous variables, each one-point increase in loneliness and social isolation scores was associated with 12% (OR = 1.12, 95% CI: 1.07-1.17) and 4% (OR = 1.04, 95% CI: 1.02-1.06) increased odds of severe SCD, respectively. When analyzed as categorical variables, compared with participants without loneliness, the adjusted ORs were 2.24 (95% CI: 1.55-3.25) and 2.39 (95% CI: 1.43-4.00) for those with mild and moderate to severe loneliness. Similarly, compared with those without social isolation, the adjusted OR for severe SCD was 1.56 (95% CI: 1.11-2.20) in those experiencing social isolation. The results of model 2, including coefficients of all covariates, are presented in Supplementary Tables S4 and S5, Supplemental Digital Content 1, http://links.lww.com/MENO/B494.

Joint associations of loneliness and social isolation with SCD

The results of joint analysis of loneliness and social isolation with SCD are presented in Figure 3 and Supplementary Table S6, Supplemental Digital Content 1, http://links.lww.com/MENO/B494. Compared with participants reporting neither loneliness nor social isolation, among participants with mild loneliness, those without social isolation exhibited an adjusted OR of 2.25 (95% CI: 1.46-3.47), while those with concurrent social isolation exhibited a higher adjusted OR of 2.82 (95% CI: 1.54-5.18). Among participants with moderate to severe loneliness, those without social isolation reported an adjusted OR of 1.77 (95% CI: 1.00-3.15), while those with concurrent social isolation exhibited the highest adjusted OR of 8.25 (95% CI: 2.71-25.15). In addition, the interaction analysis revealed a significant positive additive interaction between moderate to severe loneliness and social isolation on SCD (Table 4), with a RERI of 5.69 (95% CI: 0.62-21.57), an AP of 0.76 (95% CI: 0.02-0.86), and an SI of 7.88 (95% CI: 1.39-44.69). A significant multiplicative interaction was also observed between moderate to severe loneliness and social isolation (*P* = 0.041). However, no significant interactions were observed between mild loneliness and social isolation on SCD.

Sensitivity analyses

We additionally controlled for disease state in the sensitivity analyses. After excluding participants with chronic diseases, gynecological diseases, and those receiv-

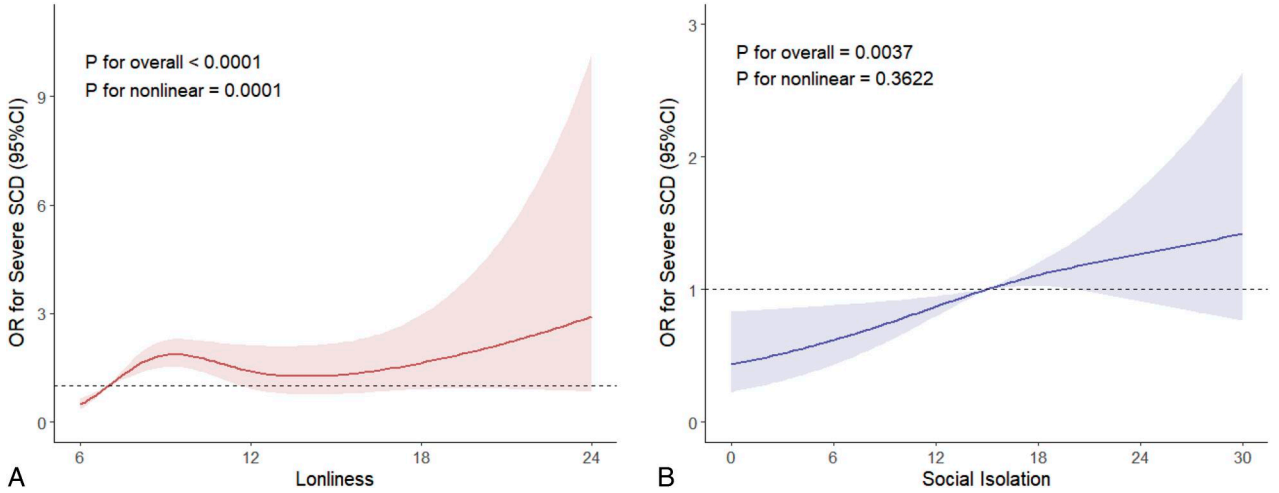

FIG. 2. Restricted cubic spline curves for loneliness (**A**) and social isolation (**B**) associated with SCD. Loneliness was quantified by the total score of the ULS-6, while social isolation was calculated using the reverse-coded total score of the LSNS-6. Solid lines indicate OR, and shadow shape indicate 95% CI. Potential confounding factors were controlled, including age, BMI, educational level, economic conditions, place of residence, type of work, socioeconomic status, major life events, drinking status, exercise frequency, age at menarche, and menopausal symptoms. LSNS-6, Lubben Social Network Scale; OR, odds ratio; SCD, subjective cognitive decline; ULS-6, UCLA Loneliness Scale.

ing hormone therapy, the independent and joint associations of loneliness and social isolation with SCD remained similar to the primary results, demonstrating their reliability and stability (Supplementary Tables S7, S8, and S9, Supplemental Digital Content 1, http://links.lww.com/MENO/B494).

DISCUSSION

This study examined the independent and joint associations of loneliness and social isolation with SCD in a sample of 903 perimenopausal women, providing new evidence for understanding the different psychosocial mechanisms underlying cognitive health in this population. Our analysis identified distinct subgroups of SCD, with a substantial portion of participants being "severe SCD group." Consistent with previous studies,[32,33] we found that both loneliness and social isolation were independently associated with SCD, even after adjusting for potential confounders. Interestingly, while both factors were linked to poorer outcomes, loneliness exhibited a stronger association with severe SCD than social isolation. This suggests that for perimenopausal women, the subjective experience of social disconnection may be more closely related to cognitive function than the objective lack of social contact, which parallels previous findings on female older adults.[34] Furthermore, Zhang et al[35] reported that individuals with SCD experiencing loneliness showed decreased regional gray matter volume in the bilateral thalamus—a critical region for memory

TABLE 3. Independent associations of loneliness and social isolation with SCD

	Model 1[a]		Model 2[b]	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Total score of loneliness	1.21 (1.17-1.26)	< 0.001	1.12 (1.07-1.17)	< 0.001
Loneliness				
No	Reference		Reference	
Mild	3.46 (2.50-4.79)	< 0.001	2.24 (1.55-3.25)	< 0.001
Moderate to severe	5.75 (3.72-8.90)	< 0.001	2.39 (1.43-4.00)	< 0.001
Total score of social isolation	1.04 (1.02-1.07)	< 0.001	1.04 (1.02-1.06)	0.001
Social isolation				
No	Reference		Reference	
Yes	1.64 (1.21-2.20)	< 0.001	1.56 (1.11-2.20)	0.011

OR, odds ratio; SCD, subjective cognitive decline.
[a]Model 1 was unadjusted.
[b]Model 2 was adjusted for age, BMI, educational level, economic conditions, place of residence, type of work, socioeconomic status, major life events, drinking status, exercise frequency, age at menarche, and menopausal symptoms.

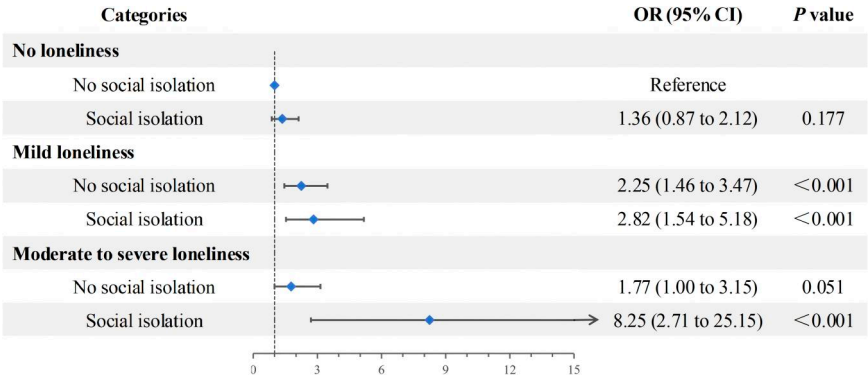

FIG. 3. Joint associations of loneliness and social isolation with SCD. Points indicate OR, and solid lines indicate 95% CI. The model was adjusted for age, BMI, educational level, economic conditions, place of residence, type of work, socioeconomic status, major life events, drinking status, exercise frequency, age at menarche, and menopausal symptoms. OR, odds ratio; SCD, subjective cognitive decline.

and cognitive processing—providing neuroimaging evidence for the relationship between loneliness and SCD. One possible explanation for the association of loneliness with SCD lies in its close relationship with emotional dysregulation and negative cognitive bias, as described in a review by Cacioppo and Hawkley.[36] Loneliness often co-occurs with depression, anxiety, and sleep disturbances, all of which are well-established predictors of cognitive decline.[37] A review on the interactions of estrogen changes and psychosocial stress indicated that perimenopausal women are particularly vulnerable to emotional instability and alterations in the processing of negative emotional information.[23] Functional magnetic resonance imaging studies show that during the low-estrogen phase of the menstrual cycle, women exhibit greater negative emotional responses and reduced hippocampal activity under acute psychosocial stress compared with the high-estrogen phase.[38] Consequently, we propose that women experiencing loneliness during this period may exhibit greater emotional distress and hypothalamic-pituitary-adrenal (HPA) axis dysregulation,[23] potentially explaining why loneliness appeared more strongly associated with SCD than social isolation in this demographic.

Notably, this study confirmed the joint associations of loneliness and social isolation with SCD in perimenopausal women. Compared with participants reporting neither loneliness nor social isolation, those experiencing loneliness exhibited significantly higher odds of severe SCD regardless of whether they were socially isolated. In addition, participants experiencing both moderate to severe loneliness and social isolation demonstrated the highest odds. This finding was further supported by our interaction analyses, which identified a significant interaction between moderate to severe loneliness and social isolation. This suggests a synergistic relationship, where the emotional deprivation associated with loneliness and the lack of social resources caused by social isolation may jointly constitute a compound burden on cognitive health through different but mutually reinforcing pathways. On the one hand, loneliness may trigger neuroinflammation and hippocampal structural changes by activating the HPA axis and increasing proinflammatory cytokine release.[39] On the other hand, social isolation has been linked to reduced cognitive stimulation and opportunities for social interaction, which may impair the structure and function of the hippocampus and default mode network.[17,40] Their combination may involve sustained

TABLE 4. Additive and multiplicative interactions between loneliness and social isolation on SCD

	Social isolation			Additive interaction		
	No OR (95% CI)	Yes OR (95% CI)	Multiplicative interaction OR (95% CI); *P*	RERI (95% CI)	AP (95% CI)	SI (95% CI)
Loneliness	—	—	0.90 (0.40-2.01); 0.799	0.14 (−1.58 to 2.34)	0.05 (−0.99 to 0.43)	1.09 (0.36-3.27)
No	Reference	1.37 (0.88-2.15)	—	—	—	—
Mild	2.15 (1.39-3.34)	2.66 (1.44-4.91)	—	—	—	—
Loneliness	—	—	3.76 (1.05-13.46); 0.041	5.69 (0.62-21.57)	0.76 (0.02-0.86)	7.88 (1.39-44.69)
No	Reference	1.38 (0.87-2.17)	—	—	—	—
Moderate to severe	1.45 (0.79-2.66)	7.52 (2.40-23.53)	—	—	—	—

AP, attributable proportion of interaction; OR, odds ratio; RERI, relative excess risk of interaction; SI, synergy index.
All models were adjusted for age, BMI, educational level, economic conditions, place of residence, type of work, socioeconomic status, major life events, drinking status, exercise frequency, age at menarche, and menopausal symptoms.

psychological stress activation and decreased neural plasticity, potentially explaining the significantly higher odds of severe SCD observed in this study. Interestingly, previous studies have reported inconsistent findings regarding the relative strengths of loneliness and social isolation in predicting cognitive decline. For example, Holwerda et al found that loneliness, rather than social isolation, predicted the onset of dementia,[41] whereas Huang et al[24] observed that both factors increased the risk of cognitive decline. These discrepancies may be attributed to differences in population characteristics, measurement tools, and cultural contexts.

Sensitivity analyses confirmed the robustness of our findings. After excluding participants with chronic diseases, gynecological conditions, and those receiving hormone therapy, the independent and joint associations of loneliness and social isolation with SCD remained consistent, indicating that these associations are not merely attributable to disease status or treatment, but underscore the potential relevance of loneliness and social isolation with cognitive health. These results highlight the critical role of social and emotional health in the context of cognitive function, particularly during hormonal and physiological transitions.

Strengths and limitations

To our knowledge, this is the first study to demonstrate the independent and joint associations of loneliness and social isolation with SCD in perimenopausal women, underscoring the critical need for targeted psychosocial interventions during this period. Future interventions could prioritize evidence-based strategies aimed at reducing loneliness and social isolation, combining increased social interactions, emotional and instrumental support, and mental and physical well-being promotion.[42] Approaches such as group activities, educational support groups and recreational programs can enhance social connectedness and cognitive engagement in perimenopausal women. Furthermore, future research should explore the neurobiological mechanisms underlying the interaction between loneliness and social isolation, such as HPA axis reactivity, inflammatory markers, and functional brain network connectivity, to elucidate the neuropsychological pathways through which these factors jointly influence cognitive health.

This study also has several limitations. First, its cross-sectional nature limits the inference of causal relationships. Second, data on loneliness, social isolation, and cognitive function were collected through self-reported questionnaires, which may have been influenced by recall bias or social desirability, potentially reducing measurement accuracy. Third, we employed an online convenience sampling strategy. Since the sample consisted solely of perimenopausal women from a specific geographic area, potential selection bias exists (eg, residents with limited digital literacy may be underrepresented). Coupled with the relatively small sample size, these may limit the generalizability of the results. Therefore, caution should be exercised when extrapolating these findings to the broader population. Moreover, several potential confounders—such as lifestyle factors (eg, dietary patterns), living arrangements (eg, living alone or with parents), and participation in social activities (eg, community support groups)—were not comprehensively controlled, which could have affected the observed associations. Finally, menopausal status was determined based on participants' self-screening against the STRAW +10 criteria listed in the recruitment announcements. Specific menstrual history data and objective biological markers were not collected, which may result in a potential bias.

CONCLUSION

In conclusion, our study revealed that loneliness and social isolation were not only independently associated with SCD but also exhibited a joint relationship in perimenopausal women. These findings highlight the importance of psychosocial factors in cognitive health during the menopause transition, providing evidence for the early identification of high-risk individuals and offering guidance for the development of multidimensional, comprehensive psychosocial interventions, with important implications for promoting healthy aging in women.

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