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Social isolation and loneliness associate with early menopause and mortality in women: a UK Biobank cohort study

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Abstract

Background: Reproductive aging is an emerging public health priority amid demographic shifts. Early menopause (EM), indicative of accelerated reproductive aging, is associated with an elevated risk of premature mortality. While social isolation (SI) and loneliness (LO) are established psychosocial determinants of health, their associations with EM and their combined effects with menopausal status on mortality risk remain unquantified. This study investigated the associations of SI and LO with EM and all-cause mortality.

Methods: This study included 79,578 Caucasian women from the UK Biobank cohort, of whom 6,778 experienced EM (menopause at age 40-45) and 72,800 experienced normal menopause (NM, age 46-55). SI (score: 0-≥2) was derived from three indicators: living arrangement, frequency of social contact, and participation in social activities; LO (score 0–2) was assessed based on self-reported loneliness and frequency of confiding in someone close. Multivariable-adjusted models were used to evaluate the odds of EM. All-cause mortality risk was assessed using Cox proportional hazards models, stratified by menopause status.

Results: Higher levels of SI and LO were independently associated with an increased prevalence of EM (e.g. SI ≥2: OR=1.09, 95% CI 1.00-1.20; LO=2: OR=1.13, 95% CI 1.02-1.25). Critically, the detrimental impact of social adversity on survival was significantly greater in women with EM compared to those with NM. After full adjustment, women with EM and SI index ≥2 had a 55% increased mortality risk (HR=1.55, 95% CI 1.21–1.99), whereas the risk increase for women with NM was 17% (HR=1.17, 95% CI 1.07–1.28). A similar pattern was observed for LO (e.g. LO=2, EM: HR=1.42, 95% CI 1.07–1.88 vs. NM: HR=1.14, 95% CI 1.02–1.27). Moreover, Kaplan-Meier curves showed a progressively wider survival gap between EM and NM as SI/LO levels increased. Lower SI and LO were associated with lower EM-related excess mortality.

Conclusions: SI and LO were associated with EM and premature mortality. Women with EM are especially vulnerable to the negative effects of social adversity. Integrating psychological and social support into menopause care is essential, and reducing SI and LO may promote healthier aging.

Trial registration: NA

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Keywords: Social isolation; Loneliness; Early menopause; Mortality; Reproductive health; UK Biobank

Background

Promoting health and well-being across the female lifetime is a central part of the global public health agenda, particularly in the context of worldwide population aging. Menopause marks the end of reproductive capacity and ushers in a period of increased vulnerability to chronic diseases.[1] While a natural process, its timing carries significant long-term health implications. Early menopause (EM), occurring between the age of 40 to 45, affects approximately 10% of women globally and presents a significant public health challenge. This condition is associated with a constellation of adverse health outcomes, including elevated risks of cardiovascular disease, osteoporosis, cognitive decline, and premature mortality.[2, 3] Therefore, identifying modifiable risk factors for EM is a public health priority, essential for developing preventive strategies that promote healthy aging and longevity in women.[4]

While genetic predisposition, adverse lifestyle factors (e.g., smoking, obesity), and metabolic factors have been implicated in the timing of menopause, the role of psychosocial factors remains incompletely understood.[5, 6] Emerging evidence suggests that psychosocial well-being, particularly social connectedness, influences menopause transition.[7] Social isolation (SI), the objective state of having few social relationships, and loneliness (LO), the subjective feeling of social disconnection, are distinct yet overlapping constructs with profound health consequences, especially in aging populations.[8] They have been recognized as important determinants of mortality, with a risk magnitude comparable to that of established factors such as smoking and alcohol consumption.[9]

There is biological plausibility for a link between these psychosocial stressors and reproductive health. SI and LO are thought to accelerate biological aging through pathways including chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis[10], systemic inflammation[11], and the adoption of unhealthy behaviors[12]—mechanisms that also have been implicated in the regulation of ovarian function and reproductive senescence.[13–15] However, the temporal relationship between SI/LO and reproductive aging remains unclear, and existing evidence suggests a potentially bidirectional association. EM and its associated health and psychosocial sequelae, including menopausal symptoms, chronic disease burden, psychological distress, and disruptions in social roles, may also contribute to increased SI/LO.[16, 17] Despite this biological rationale, there is still lack of large-scale epidemiological evidence investigating the association between SI/LO and the risk of EM. Furthermore, it remains unknown whether these psychosocial factors interact with EM to synergistically increase the risk of premature mortality. This knowledge gap limits our understanding of how social determinants, such as SI and LO, interact with reproductive aging to influence subsequent health outcomes,

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including mortality.

To address these gaps, we conducted a large-scale, ambispective cohort study using data from the UK Biobank (UKB). Our primary objective was to examine the independent associations of SI and LO with the incidence of EM. The secondary objective was to investigate the joint effects of SI/LO and EM on the risk for all-cause mortality. By elucidating these relationships, this study aims to deepen the understanding of the social determinants of female reproductive health and inform the development of integrated public health strategies to enhance long-term health and longevity across the female life course.

Methods

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. We used data from UKB, which was approved by the North West Multicenter Research Ethics Committee and the National Health Service Health and Social Care Information Centre.[18] All participants provided informed consent. The overall study design, including participant selection and analytical framework, is illustrated in Additional file 1: Fig. S1.

Study population

The UKB is a large-scale prospective cohort study that recruited approximately 500,000 participants (both men and women aged 37–73 years) from 22 assessment centers across United Kingdom[18]. For the present analysis, we restricted the sample to women of Caucasian ethnicity and applied exclusion criteria to minimize potential bias: (1) missing data on SI/LO; (2) premenopausal status or iatrogenic menopause, including women who reported hysterectomy or bilateral oophorectomy before natural menopause; (3) extreme age at menopause (<40 or >55 years); and (4) missing data on covariates (age, body mass index [BMI], education level, Townsend deprivation index, household income, smoking status, alcohol consumption, age at menarche, and parity). After applying these criteria, a total of 79,578 participants remained for the final analysis. The detailed flowchart of participant selection and analytical procedures is presented in Additional file 1: Fig. S1.

Definition of Social Isolation and Loneliness

SI reflects the objective structural dimension of social relationships, whereas LO represents the subjective perception of social disconnection. Both indices were derived from self-reported questionnaires. The SI index was constructed from three questions, while the LO index was derived from two questions. Given the relatively small number of participants with an SI index of 3, those with a score of 3 were combined into SI≥2 group, yielding a total range of 0 to 2 or greater. For LO, scores ranged from 0 to 2. Each index was calculated by summing the responses to its corresponding items, with higher values indicating greater levels of SI/LO. Detailed

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scoring criteria are provided in Additional file 1: Table S1.

These measures are comparable to those used in previous population-based studies[19-22].

Definition of menopause status

Age at menopause is defined as the self-reported age at the final menstrual period, confirmed after 12 consecutive months of amenorrhea. Using self-reported age at menopause, participants were categorized as EM group for those experiencing menopause between 40-45 years, and normal menopause (NM) group for those with menopause onset between 46-55 years.

Covariates and Sensitivity analyses

Baseline covariates included age, BMI, education level, Townsend deprivation index, household income, smoking status, drinking status, age at menarche, and parity. Covariates were selected a priori based on prior literature and their potential roles as confounders in the associations between social factors, reproductive aging, and mortality.[20, 22, 23] To examine robustness of the models, we conducted sensitivity analyses, including: (1) excluding participants with psychiatric disorders, especially depression or anxiety (Additional file 1: Table S2); (2) excluding ever users of hormone replacement therapy (HRT); (3) modeling age at menopause as a continuous outcome in a linear framework; and (4) mutually adjusting SI and LO in the same model.

Modeling age at menopause as a continuous outcome was intended to evaluate whether the associations were robust to outcome specification and not dependent on the categorical definition of early menopause, thereby capturing variation across the full distribution of menopause timing. As SI and LO are related but distinct psychosocial constructs that may co-occur, mutually adjusted models including both SI and LO were used to assess whether their associations with EM were independent of each other. As HRT may act as a mediator or be influenced by menopausal status and related symptoms[24], it was not included as a covariate in the primary models. Instead, we conducted sensitivity analyses excluding participants who had ever used HRT to assess the robustness of the findings.

Definition of mortality outcomes

The primary outcome was all-cause mortality. Mortality status and dates were obtained through linkage to national death registries, including the National Health Service (NHS) Digital for England and Wales and the NHS Central Register for Scotland. Follow-up time was defined from the date of recruitment until the date of death or censoring, whichever occurred first. For this analysis, the censoring date was set as December 31, 2021.

Statistical Analysis

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Descriptive statistics were summarized as medians with interquartile ranges (IQRs) for continuous variables (Shapiro–Wilk test for normality) and as counts with percentages for categorical variables. Non-normally distributed continuous variables were compared using Wilcoxon rank-sum tests; categorical variables used chi-square tests.

In Step 1 (Additional file 1: Fig. S1), we investigated the association between SI/LO and EM using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Three sequential models were specified: Model 1 adjusted for age and BMI; Model 2 extended Model 1 by adding education level, Townsend deprivation index, household income, smoking status, and drinking status; and Model 3 further adjusted for age at menarche and parity in addition to all Model 2 covariates.

In Step 2 (Additional file 1: Fig. S1), survival analyses were conducted to assess the association between menopausal status and all-cause mortality. Kaplan–Meier curves were generated to visualize survival probabilities across different menopausal categories, and the log-rank test was used to evaluate differences between groups. In Step 3 (Additional file 1: Fig. S1), Cox proportional hazards regression models were employed to estimate hazard ratios (HRs) and 95% CIs. The same three adjustment models (Model 1, Model 2, and Model 3) were applied.

To formally assess effect modification, multiplicative interaction terms between SI/LO and menopause status were included in Cox proportional hazards models, and P for interaction values were calculated using likelihood ratio tests.

In all models, SI and LO were analyzed as ordinal categorical variables (0, 1, ≥2 for SI; 0, 1, 2 for LO) to estimate P for trend values. All analyses were performed using R software (version 4.4.2), with two-sided $P<0.05$ considered statistically significant.

Results

Baseline Characteristics of Participants

A total of 79,578 women were included in the analysis, comprising 6,778 women with EM and 72,800 with NM. Baseline characteristics are summarized in Table 1. Compared to the women with NM, those with EM had higher BMI, relatively greater socioeconomic deprivation, lower income, and lower educational attainment. Current smoking was more prevalent among EM women. Notably, the EM group exhibited a higher prevalence of elevated SI and LO scores (Additional file 1: Fig. S2).

Baseline characteristics stratified by SI and LO levels were also examined. Higher SI was associated with lower education and income, greater deprivation, higher BMI, smoking, and earlier menopause (Additional file 1: Table S3). Similar patterns were observed across LO categories (Additional file 1: Table S4).

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Associations between SI/LO and EM

In Step 1 (Additional file 1: Fig. S1), both SI and LO showed significant associations with EM risk in logistic regression analyses, with a dose-response trend (P for trend <0.05) (Table 2). Compared with women without SI, those with an SI index of 1 or ≥2 had higher odds of experiencing EM (OR = 1.17 [95% CI: 1.11–1.24] and OR = 1.35 [95% CI: 1.24–1.47], respectively) in Model 1. After adjustment for common covariates (Model 2), the associations remained significant, although attenuated (OR=1.08 [95% CI: 1.02–1.14] for index 1; OR=1.13 [95% CI: 1.03–1.23] for index≥2). A similar pattern was observed in the fully adjusted model (Model 3): SI=1 was significantly associated with increased risk (OR=1.06, 95% CI: 1.00–1.12), whereas SI≥2 showed a borderline significant association (OR=1.09, 95% CI: 1.00–1.20).

Similarly, higher LO scores significantly predicted increased EM risk. In the unadjusted model, the ORs were 1.12 (95% CI: 1.05-1.18) for index 1 and 1.28 (95% CI: 1.16-1.42) for index 2. These associations remained robust in Model 1, with identical ORs of 1.12 (95% CI: 1.05-1.18) for index 1 and 1.26 (95% CI: 1.14-1.40) for index 2. Further adjustment in Model 2 and Model 3 maintained the statistical significance for index 2 (OR=1.13, 95% CI: 1.02-1.25 in both models).

Sensitivity analyses

To confirm the robustness of the findings, we performed sensitivity analyses. After excluding individuals with depression or anxiety disorders, 67,643 women remained in the analysis (11,935 excluded). The associations were attenuated: the effect of SI was no longer statistically significant in Model 2 and 3, while the association for LO became nonsignificant at index 1 but remained evident at higher levels (Additional file 1: Table S5). Conversely, after excluding women with a history of HRT, 45,216 women remained, and both SI and LO continued to show robust associations with EM (Additional file 1: Table S6). When age at menopause was analyzed as a continuous outcome, higher levels of SI and LO were consistently associated with an earlier age at menopause, supporting the main findings (Additional file 1: Table S7). Finally, in mutually adjusted models, both SI and LO retained independent EM associations (Additional file 1: Table S8). Taken together, these results indicate that the associations are generally robust, although partially attenuated in certain subgroups.

Association of SI and LO with Mortality Stratified by Menopause Status

In Step 2 (Additional file 1: Fig. S1), we performed survival analysis. During a median follow-up of 12.87 years, a total of 5,915 deaths were recorded (Additional file 1: Fig. S3). Kaplan-Meier curves stratified by menopausal status and SI/LO levels showed higher all-cause mortality risks in women with EM and those with elevated SI/LO (Additional file 1: Fig. S4), in line with prior reports[8, 25]. In the Cox proportional hazards models (Additional file 1: Tables S9 and S10, Figure 1), both

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SI and LO were associated with increased all-cause mortality with dose-response trends. Moreover, stronger associations were found among EM women. Specifically, compared with women without SI, those with SI index ≥2 had an elevated hazard of death in the total population (HR = 1.25, 95% CI: 1.15–1.36) and particularly in the EM group (HR = 1.55, 95% CI: 1.21–1.99), while the association was weaker in women with NM (HR = 1.17, 95% CI: 1.07–1.28). A similar pattern was observed for LO, with women reporting LO index 2 having increased mortality risk in the total population (HR = 1.19, 95% CI: 1.08–1.32), more pronounced in the EM group (HR = 1.42, 95% CI: 1.07–1.88) than in the NM group (HR = 1.14, 95% CI: 1.02–1.27). The trends remained robust across all adjustment models, indicating that both SI and LO exert stronger deleterious effects on survival among women with EM compared to those with NM. Moreover, Cox models comparing EM with NM within each SI/LO stratum showed that the mortality difference between EM and NM became more pronounced at higher SI/LO levels (Additional file 1: Table S11).

To further evaluate whether menopause status modifies the association between SI/LO and mortality, multiplicative interaction terms were included in Cox models. As shown in Additional file 1: Table S12, significant interactions were observed between SI and menopause status across all models (P for interaction <0.05). For LO, the interaction was weaker and became marginally non-significant after full adjustment.

Reducing Social Isolation and Loneliness Attenuates the Excess Mortality Risk in Women with Early Menopause

In Step 3 (Additional file 1: Fig. S1), to directly represent the joint effects of menopausal status and social factors on survival, we stratified women into EM and NM groups and further categorized each by SI/LO levels (0, 1, ≥2). Kaplan-Meier curves showed comparable survival probabilities between EM and NM groups when SI/LO was absent (index=0) (Figure 2). This pattern was further quantified by the corresponding 5-year and 10-year survival probabilities (Additional file 1: Table S13), which showed minimal differences between EM and NM at low SI/LO levels but progressively larger absolute survival differences at higher SI/LO levels.

However, as SI/LO levels increased, a progressively wider survival gap emerged, with women in the EM group exhibiting disproportionately higher mortality risk compared with those in the NM group at the same level of SI/LO. These findings suggest that reducing SI and LO may be associated with lower mortality risk.

Discussion

Through this cohort study, we found significant associations of both SI and LO with an increased risk of EM and all-cause mortality. Importantly, the mortality associations were stronger among women with EM than those with NM, which may indicate that adverse social environments could potentially exacerbate the long-term risks associated with early reproductive aging. However, the temporal sequence of

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these associations remains unclear. Moreover, our analyses indicate that reducing SI/LO levels could attenuate EM-related excess mortality, highlighting the potential value of social and behavioral interventions.

Prior studies have documented the detrimental effects of SI and LO on health, particularly their strong associations with psychiatric conditions such as depression and dementia[26]. Notably, a UKB study found that SI associated with reduced gray matter volume, contributing to cognitive decline[27], suggesting potential neurobiological pathways through which psychosocial stress may impact brain health. Given that EM has also been linked to increased risks of cognitive impairment and neurodegenerative conditions [28], these findings highlight a possible shared vulnerability between psychosocial adversity and reproductive aging. Beyond neurological outcomes, SI and LO have also been consistently linked to adverse physical health, including elevated risks of cardiovascular disease, metabolic disease, and mortality[9, 29]. Importantly, accumulating evidence suggests that the influence of SI and LO also extends to reproductive health. Studies on animal models showed that socially housed female mice display greater levels of receptive sexual behavior compared with those in isolated housing[30]. In human populations, a cross-sectional study of 570 women in western Turkey reported that LO was associated with infertility, highlighting the potential role of social adversity in shaping female reproductive trajectories[31].

Our study extends existing knowledge by demonstrating that SI and LO detrimentally interact with reproductive aging. Specifically, we show for the first time that women with EM are disproportionately vulnerable to the mortality risks conferred by SI and LO. This finding underscores a previously underrecognized intersection between social adversity and reproductive health, suggesting that menopause timing may constitute a critical biological window during which social environments exert long-term influences on women’s health trajectories.

Several biological mechanisms may underlie the observed associations. Social adversity, including SI and LO, represents a chronic psychosocial stressor that activates the HPA axis and sympathetic nervous system, leading to sustained elevations in cortisol and catecholamines[10, 32]. Dysregulation of these neuroendocrine pathways has been linked to accelerated ovarian aging and impaired hypothalamic–pituitary–gonadal axis function[14]. In addition, SI and LO are associated with systemic low-grade inflammation and altered immune responses, characterized by elevated levels of pro-inflammatory cytokines and impaired cellular immunity[11, 33]. These changes may contribute to ovarian dysfunction by impairing ovarian immune microenvironment. Those combined effect of systemic and local alterations also could explain the heightened mortality risk among women with EM[14, 15, 34, 35]. Furthermore, metabolic disturbances such as insulin resistance and dyslipidemia, which have been previously reported in individuals with SI/LO, may serve as additional mediators linking social adversity, EM, and long-term health outcomes[36, 37]. Notably, after excluding individuals with depression or

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anxiety disorders, the associations were attenuated, suggesting that the observed relationships are not entirely explained by comorbid psychiatric conditions. The loss of significance for SI, but persistence at higher levels of LO, further indicates that severe loneliness may exert a more robust or independent effect.

Our findings highlight the potential value of social and behavioral interventions in mitigating the adverse health consequences associated with reproductive aging. Unlike genetic or immutable biological factors, SI and LO are modifiable and may be targeted through structured community engagement programs, counseling services, and social support initiatives[38–40]. Such interventions may not only improve mental well-being but also delay reproductive aging and reduce long-term mortality risk. From a clinical perspective, routine assessment of social connectedness during midlife could help identify women at higher risk of EM or premature mortality, enabling timely preventive strategies. On a broader public health scale, policies that promote social participation and reduce isolation among women may yield substantial benefits for healthy aging and longevity.

This study has several notable strengths. The UKB database allows us to investigate the associations of SI and LO with both EM and mortality using a large sample size and long-term follow-up. Comprehensive data on sociodemographic, lifestyle, and reproductive factors allowed thorough adjustment for potential confounders, strengthening the validity of the findings. Moreover, the simultaneous evaluation of both social and reproductive domains provides novel insights into the interplay between psychosocial exposures and women's health across the life course.

Nevertheless, limitations should be acknowledged. SI and LO were assessed using brief self-reported questionnaires, which may not fully capture the complexity or stability of social relationships. Notably, the temporal relationship between SI/LO and EM cannot be definitively established in this study. Reverse causation is plausible, as EM and its associated symptoms, such as vasomotor disturbances, psychological distress, and increased chronic disease burden, may lead to reduced social participation and increased feelings of SI/LO. Therefore, the observed associations may reflect, at least in part, bidirectional relationships rather than a unidirectional effect of SI/LO on reproductive aging. Future longitudinal studies with repeated measurements of social and reproductive factors are needed to clarify the directionality of these associations. In addition, the study population comprised individuals of European ancestry, limiting generalizability to other populations. As an observational study, causal inference cannot be established despite careful adjustment for multiple confounders.

Conclusions

In summary, the present study demonstrated that both SI and LO were significant risk factors for EM and all-cause mortality, and their association with mortality was stronger in women with EM. Lower SI and LO were associated with lower EM-related excess mortality. Therefore, interventions aimed at alleviating SI and LO

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may be valuable components of strategies to promote healthy reproductive aging and reduce premature mortality.

Abbreviations

EM: early menopause

NM: normal menopause

SI: social isolation

LO: loneliness

HPA: hypothalamic–pituitary–adrenal

UKB: UK Biobank

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

BMI: body mass index

NHS: National Health Service

IQR: interquartile range

OR: odds ratio

CI: confidence interval

HR: hazard ratio

HRT: hormone replacement therapy

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Declarations

Ethics approval and consent to participate

This research used data from UK Biobank (Application Number: 77336), which received ethical approval from the North West Multi-center Research Ethics Committee. All participants provided written informed consent for data use in health-related research. As this study involved secondary analysis of anonymized UK Biobank data, no additional ethics approval was required.

Consent for publication

Not applicable.

Data Availability

The data analyzed in this study were obtained from the UK Biobank Resource under Application Number 77336. UK Biobank data are available to approved researchers through application to UK Biobank at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. No additional publicly available datasets requiring

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separate dataset citation were used in this study. The UK Biobank resource article has been cited in the reference list.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.W. and Y.Qi contributed equally to this work. T.G., S.T., and Y.Qin supervised the study, provided overall academic guidance, and acquired funding. Y.W. led the social isolation/loneliness exposure-related analytical work, conducted the main statistical analyses, prepared the figures and tables, and drafted the original manuscript. Y.Qi led the reproductive-health analytical module of the original study, and contributed to reproductive-health-related sensitivity analyses. Z.C. curated the UK Biobank data, performed data validation, and contributed to statistical implementation. K.X. contributed to methodological implementation, model checking, and analytical quality control. R.X. contributed to data interpretation and critical revision of the manuscript. S.Z. contributed to interpretation of the findings and manuscript revision for important intellectual content. L.C. contributed to clinical and reproductive-health interpretation and critical revision of the manuscript. D.W. contributed to interpretation of the results and revision of the manuscript. H.Z. contributed to data interpretation and manuscript review. S.T., Y.Qin, and T.G. critically revised the manuscript for important intellectual content and supervised the final version.

All authors read and approved the final manuscript.

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Table 1. Characteristics of participants by age at menopause.

□	EM(n=6,778)	NM(n = 72,800)	*P*
Age (year)	60.0 [54.0;64.0]	60.0 [56.0;64.0]	<0.001
BMI (kg/m2)	26.2 [23.5;29.7]	25.9 [23.4;29.3]	<0.001
Education level			<0.001
Low	3386 (50.0%)	32864 (45.1%)	
Medium	1501 (22.1%)	16499 (22.7%)	
High	1891 (27.9%)	23437 (32.2%)	
Townsend deprivation index	-2.19 [-3.60;0.36]	-2.42 [-3.77;-0.18]	<0.001
Income level (USD/year)			<0.001
Less than 18,000	2123 (31.3%)	19510 (26.8%)	
18,000 to 30,999	1970 (29.1%)	21648 (29.7%)	
31,000 to 51,999	1497 (22.1%)	17753 (24.4%)	
52,000 to 100,000	953 (14.1%)	11176 (15.4%)	
Greater than 100,000	235 (3.47%)	2713 (3.73%)	
Drinker status			0.001
Never	317 (4.68%)	2997 (4.12%)	
Previous	268 (3.95%)	2392 (3.29%)	
Current	6193 (91.4%)	67411 (92.6%)	
Smoker status			<0.001
Never	3466 (51.1%)	42281 (58.1%)	
Previous	2495 (36.8%)	24936 (34.3%)	
Current	817 (12.1%)	5583 (7.67%)	
Parity	2.00 [1.00;2.00]	2.00 [1.00;2.00]	<0.001
Age at menarche (year)	13.0 [12.0;14.0]	13.0 [12.0;14.0]	0.036
Age at menopause (year)	42.0 [41.0;43.0]	51.0 [49.0;53.0]	<0.001
Social isolation index			<0.001
0	3278 (48.4%)	38530 (52.9%)	
1	2782 (41.0%)	28011 (38.5%)	
≥2	718 (10.6%)	6259 (8.60%)	
Loneliness index			<0.001
0	4546 (67.1%)	50981 (70.0%)	
1	1777 (26.2%)	17840 (24.5%)	
2	455 (6.71%)	3979 (5.47%)	

EM: early menopause; NM: normal menopause.

Continuous variables are presented as median [interquartile range] and categorical

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variables as number (percentage). *P* values were calculated using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables, as appropriate.

Table 2. Association of social isolation and loneliness index with risk of early menopause.

Exposure	Index = 0 OR (95%CI)	Index = 1 OR (95%CI)	*P*	Index ≥2 OR (95%CI)	*P*
Social isolation					
Unadjusted model		1.17 (1.11 - 1.23)	9.27E-09	1.35 (1.24 - 1.47)	5.70E-12
Model 1	1 [Reference]	1.17 (1.11 - 1.24)	3.87E-09	1.35 (1.24 - 1.47)	4.71E-12
Model 2		1.08 (1.02 - 1.14)	0.007	1.13 (1.03 - 1.23)	0.007
Model 3		1.06 (1.00 - 1.12)	0.038	1.09 (1.00 - 1.20)	0.052
Loneliness					
Unadjusted model		1.12 (1.05 - 1.18)	1.58E-04	1.28 (1.16 - 1.42)	1.61E-06
Model 1	1 [Reference]	1.12 (1.05 - 1.18)	1.71E-04	1.26 (1.14 - 1.4)	6.427E-06
Model 2		1.03 (0.98 - 1.1)	0.257	1.13 (1.02 - 1.25)	0.022
Model 3		1.03 (0.97 - 1.09)	0.309	1.13 (1.02 - 1.25)	0.023

OR: odds ratio; CI: confidence interval.

Model 1 was adjusted for age and body mass index;

Model 2 was adjusted for Model 1 plus education level, Townsend deprivation index, household income, smoking status, and drinking status;

Model 3 was adjusted for Model 2 plus age at menarche and parity.

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Figure legends

Figure 1. Associations of social isolation (SI) and loneliness (LO) with all-cause mortality, stratified by menopause status. Adjusted hazard ratios (HRs) and 95% CIs derived from Cox proportional hazards models. (a) SI index categories (0, 1, ≥2) compared with SI = 0 (reference). (b) LO index categories (0, 1, 2) compared with LO = 0 (reference). Analyses were stratified by menopause status: normal menopause (NM) and early menopause (EM).

NM: normal menopause; EM: early menopause.

Figure 2. All-cause mortality by social isolation (SI) or loneliness (LO) and menopause status. Kaplan–Meier survival curves for all-cause mortality stratified by menopause status (normal menopause [NM] and early menopause [EM]) and levels of (a) SI and (b) LO (index categories 0, 1, and ≥2).

NM: normal menopause; EM: early menopause.

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Additional files

Additional file 1: Supplementary figures and tables.

Fig. S1. Flowchart of study design and analytical procedures.

Fig. S2. Distribution of (a) social isolation and (b) loneliness by menopause status.

Fig. S3. Distribution (a) and boxplot (b) of follow-up time.

Fig. S4. All-cause mortality by menopause status, social isolation (SI), or loneliness (LO). Kaplan–Meier survival curves for all-cause mortality stratified by (a) menopause status (normal menopause [NM] and early menopause [EM]), (b) levels of SI (index categories 0, 1, and ≥ 2), and (c) levels of LO (index categories 0, 1, and ≥ 2). NM = normal menopause; EM = early menopause.

Table S1. Definition and scoring of social isolation and loneliness.

Table S2. Self-reported and ICD-10 codes for depression and anxiety.

Table S3. Characteristics of participants by social isolation index.

Table S4. Characteristics of participants by loneliness index.

Table S5. Association of social isolation and loneliness index with risk of early menopause after excluding individuals with depression or anxiety.

Table S6. Association of social isolation and loneliness index with risk of early menopause after excluding individuals with a history of hormone replacement therapy.

Table S7. Association of social isolation and loneliness index with age at menopause treated as a continuous variable.

Table S8. Mutual adjustment of social isolation and loneliness index in association with early menopause.

Table S9. Associations of social isolation (SI) with all-cause mortality, stratified by menopause status.

Table S10. Associations of loneliness (LO) with all-cause mortality, stratified by menopause status.

Table S11. Association of social isolation (SI) and loneliness (LO) levels with mortality risk: stratified case-control comparison within each SI/LO group based on cox proportional hazards models.

Table S12. Interaction between social isolation/loneliness and menopause status in relation to all-cause mortality.

Table S13. Five-year and ten-year survival probabilities according to social isolation and loneliness categories.

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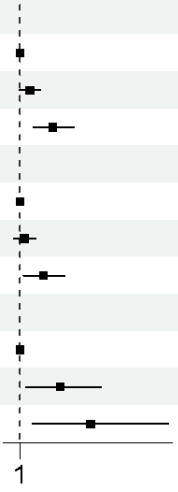
a

Population	HR (95%CI)	*P*
Total population		
SI = 0	Reference	Reference
SI = 1	1.04 (0.98–1.10)	0.153
SI ≥ 2	1.25 (1.15–1.36)	1.95e−07
NM		
SI = 0	Reference	Reference
SI = 1	1.02 (0.96–1.08)	0.613
SI ≥ 2	1.17 (1.07–1.28)	9.27e−04
EM		
SI = 0	Reference	Reference
SI = 1	1.15 (0.96–1.39)	0.130
SI ≥ 2	1.55 (1.21–1.99)	4.99e−04

b

Population	HR (95%CI)	*P*
Total population		
LO = 0	Reference	Reference
LO = 1	1.06 (1.00–1.12)	0.061
LO = 2	1.19 (1.08–1.32)	4.69e−04
NM		
LO = 0	Reference	Reference
LO = 1	1.03 (0.96–1.09)	0.426
LO = 2	1.14 (1.02–1.27)	0.018
EM		
LO = 0	Reference	Reference
LO = 1	1.24 (1.04–1.48)	0.019
LO = 2	1.42 (1.07–1.88)	0.014



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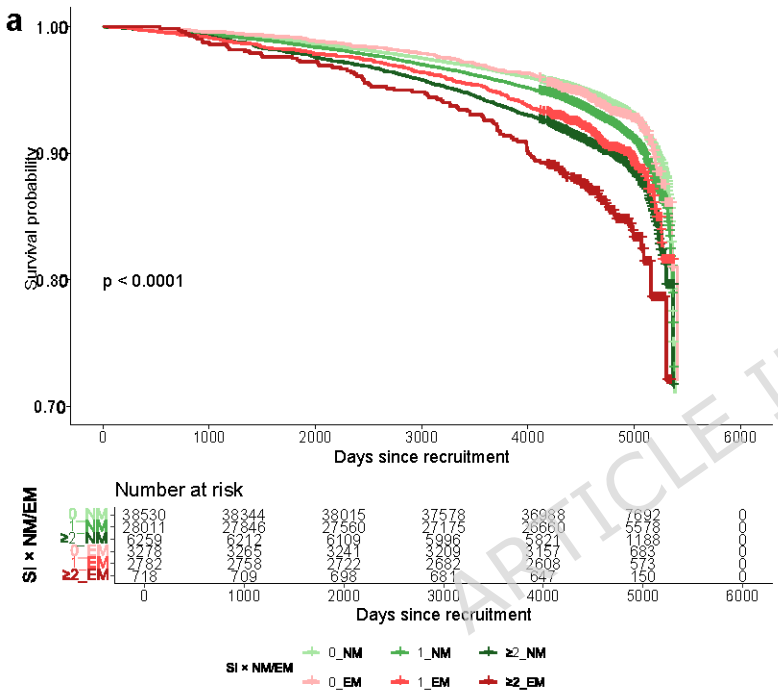

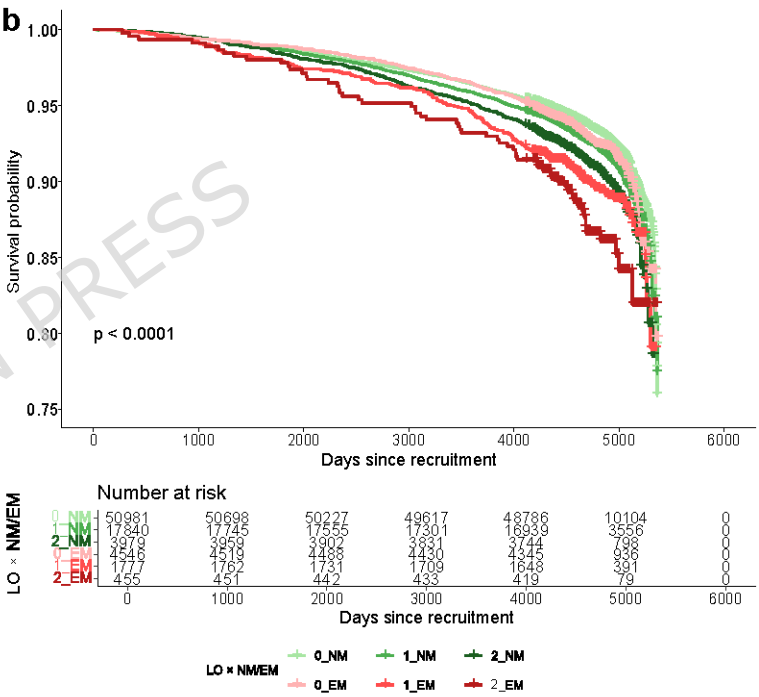

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