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Combined social determinants of health, mortality, and adverse health outcomes in early natural menopause

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Abstract

Objective: Early natural menopause (ENM) is associated with a higher long-term health burden, yet whether social determinants of health (SDH) modulate this risk is understudied. This study aimed to estimate the association of combined SDH with mortality and adverse health outcomes among women with ENM.

Methods: We analyzed data from 19,912 women with ENM in the UK Biobank. Based on 14-item combined SDH scores, participants were categorized into tertiles representing favorable, medium, and unfavorable SDH groups. Multivariable Cox proportional hazards models were used to evaluate the associations of combined SDH with mortality, as well as incident cardiovascular disease (CVD), cancer, and dementia. In addition, we externally validated the mortality findings in the US National Health and Nutrition Examination Survey.

Results: In the UK Biobank cohort, higher combined SDH scores showed a progressive association with all-cause mortality and the incidence of CVD and dementia (all P for trend < 0.001). Compared with the favorable SDH group, the unfavorable SDH group was linked to higher risks of all-cause mortality (hazard ratio [HR] = 1.75; 95% CI: 1.51-2.03), CVD (HR = 1.48; 95% CI: 1.29-1.70), and dementia (HR = 1.83; 95% CI: 1.30-2.57). Consistently, these all-cause mortality associations were further validated in the US National Health and Nutrition Examination Survey cohort. Notably, among all SDH variables, unemployment exhibited the strongest associations with both all-cause mortality and incident dementia.

Conclusion: Cumulative social disadvantage significantly amplifies the risks of mortality and multimorbidity in women with ENM. These findings warrant the integration of multidimensional SDH assessments into clinical management to tailor preventive strategies and mitigate disease burden in this vulnerable population.

Key Words: Cancer, Cardiovascular disease, Dementia, Mortality, Early natural menopause, Social determinants of health.

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In developed regions, natural menopause typically occurs between ages 50 and 51.[1] However, early natural menopause (ENM) constitutes a distinct reproductive phenotype affecting ~8% of women in these nations and 12% globally.[2] Beyond marking the cessation of fertility, ENM serves as a critical sentinel for long-term health. Prospective data from the UK and Korea indicated that ENM significantly potentiated risks for all-cause mortality.[3,4] Complementing these findings, multinational studies reported a higher incidence of cardiovascular disease (CVD) and a marked predisposition to dementia in women with ENM.[5,6] Current clinical management of ENM prioritizes hormone therapy (HT) and lifestyle modifications, yet frequently overlooks the critical role of socioeconomic disadvantage.[7-9]

Social determinants of health (SDH) encompass the environmental conditions in which individuals are born, reside, receive education, work, engage in leisure activities, worship, and age.[10,11] These upstream factors are increasingly recognized as primary drivers of health inequities, often exerting a stronger influence on outcomes than clinical care or

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personal lifestyle choices.[12,13] Prior studies have established that adverse SDH could contribute to earlier menopausal onset and exacerbate symptom burden.[14,15] However, it remains unclear how these factors shape long-term health outcomes specifically in women who have already experienced ENM. Incorporating SDH assessment into ENM management enables the identification of vulnerable subgroups, guiding targeted and effective interventions.[16] Given that social disadvantages tend to co-occur, assessing the impact of combined SDH is crucial to quantify their aggregate risk.

To bridge these gaps, utilizing a large prospective cohort from the UK Biobank (UKB), this study aimed to comprehensively investigate the associations of combined SDH with mortality and the incidence of CVD, cancer, and dementia among women with ENM. To ensure the robustness of our results, we externally validated the mortality associations using data from the US National Health and Nutrition Examination Survey (US NHANES). Furthermore, to identify the primary SDH contributors to these adverse outcomes, we evaluated the independent impact of each SDH variable.

METHODS

Study design and participants

We employed the UKB as the discovery cohort. Briefly, the UKB is a population-based prospective cohort study comprising over 500,000 individuals aged 37-73 years, recruited from 22 national centers across England, Scotland, and Wales between March 13, 2006 and October 1, 2010.[17] The mortality analysis included women identified with ENM at baseline who had complete data on SDH (Fig. 1A). For the analysis of incident outcomes, we excluded participants with outcomes of interest at baseline (Fig. 1A).

For external validation, we extracted data from the 1999-2018 cycles of the US NHANES. The US NHANES is a continuous cross-sectional program conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. The survey has operated annually since 1999, with detailed protocols available on the NHANES website (Accessed September 4, 2024: www.cdc.gov/nchs/nhanes). In this validation cohort, we excluded women with missing data on SDH or mortality follow-up (Fig. 1B).

Assessment of early natural menopause

In both cohorts, participants retrospectively reported their age at natural menopause using baseline questionnaires. Given that the median age of menopause is approximately 50-51 years,[1] we defined ENM as reaching natural menopause before age 48 to capture women who experience menopause earlier than the population average. This definition is consistent with other large-scale cohort studies.[14,18] Accordingly, we excluded women with a history of surgery, such as a hysterectomy or oophorectomy.

Assessment of social determinants of health

We selected SDH variables based on the Healthy People 2030 framework and previous studies.[11,16] Due to differences in study design, the specific SDH variables differed between the two cohorts (Supplemental Table S1, Supplemental Digital Content 1, https://links.lww.com/GME/A12). In the UKB, we integrated 14 SDH variables across five domains: (1) financial circumstances included household income, employment status, and area-level income deprivation; (2) education access and quality included educational attainment and area-level education deprivation; (3) health care access and quality included area-level health care deprivation; (4) neighborhood and built environment included accommodation stability, area-level crime scores, and the natural environment; and (5) social and community context included living alone, social support, social activity, social isolation, and emotional distress. Similarly, in US NHANES, we analyzed 9 SDH variables: (1) financial circumstances included household income, employment status, and food security; (2) education access and quality included educational attainment; (3) health care access and quality included health insurance coverage and health care access; (4) neighborhood and built environment included accommodation stability; and (5) social and community context included race and marital status. Area-level SDH variables were based on the index of multiple deprivation corresponding to the Lower-layer Super Output Area in the UKB. All individual-level SDH variables were obtained through baseline questionnaires (Supplementary Table S1, Supplemental Digital Content 1, https://links.lww.com/GME/A12).

In our analysis, we divided each SDH variable into "advantaged" and "disadvantaged" levels, scored as 0 and 1, respectively (Supplemental Table S1, Supplemental Digital Content 1, https://links.lww.com/GME/A12).[11,16] Then, we calculated the combined SDH scores as the sum of scores for each SDH variable, ranging from 0 to 14 in the UKB and 0 to 9 in the US NHANES, where higher scores reflect worse social conditions. Finally, participants were categorized into favorable (bottom third), medium (middle third), and unfavorable (top third) groups based on tertiles of the combined SDH scores. These tertiles represent approximately equal participant numbers rather than equal score intervals. Sample sizes differ across groups due to tied scores at the cutoffs.

Definitions of outcomes

Primary outcomes included the incidence of cancer, CVD, dementia, and all-cause mortality, while secondary outcomes consisted of cause-specific mortality from CVD and cancer. We ascertained these outcomes using International Classification of Diseases-10 (ICD-10) codes, consistent with established protocols in previous UKB studies (Supplemental Tables S2 and S3, Supplemental Digital Content 1, https://links.lww.com/GME/A12).[11,16] Mortality data were derived from linkage to the National Death Index and the NHS Information Centre, with follow-up extending through December 31, 2019, in both the US NHANES and UKB cohorts.

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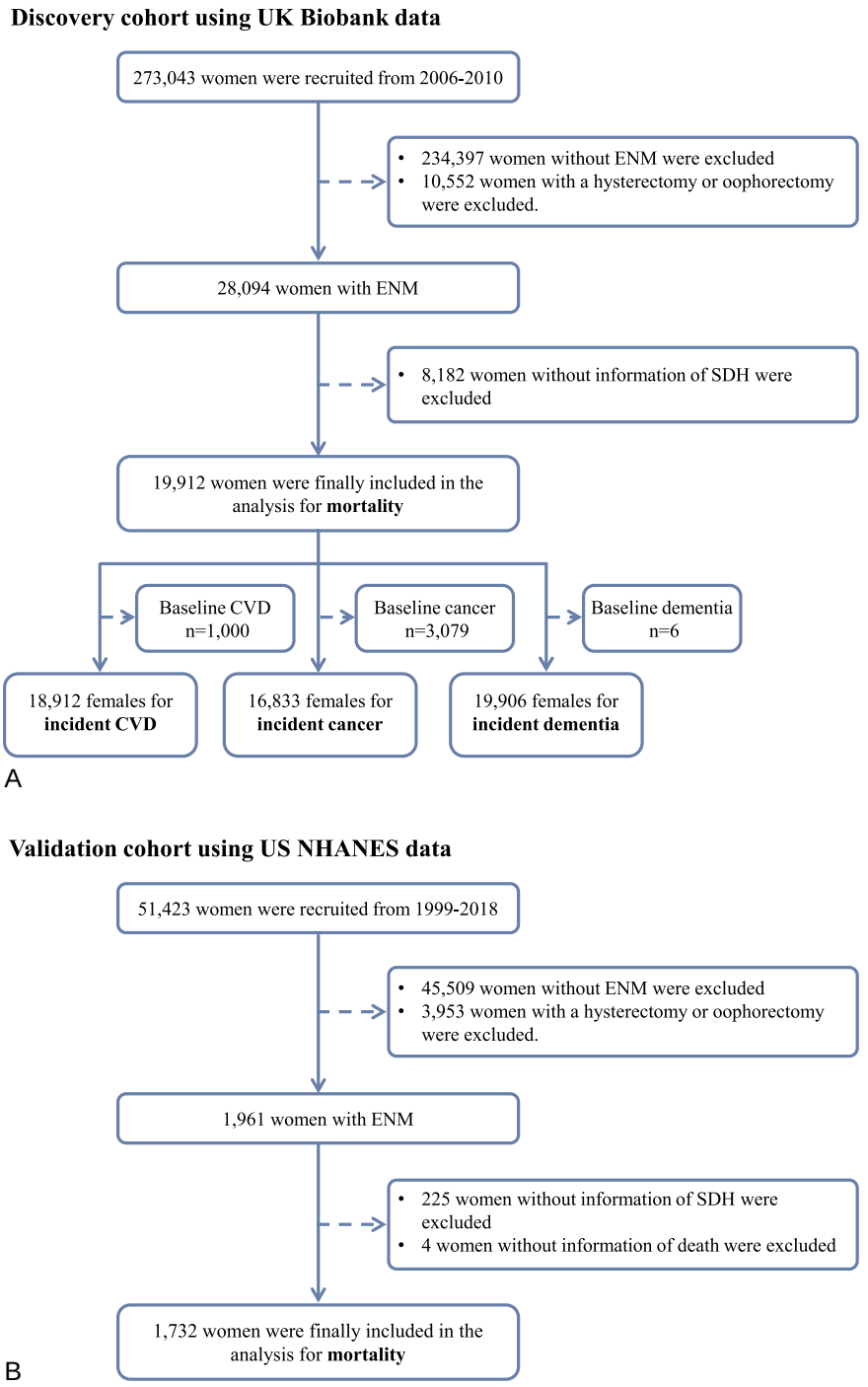

FIG. 1. Flowchart of the participants' selection. (**A**) The UK Biobank cohort. (**B**) The US NHANES cohort. CVD, cardiovascular disease; ENM, early natural menopause; NHANES, National Health and Nutrition Examination Survey; SDH, social determinants of health.

Data on specific incident non-fatal outcomes were available only in the UKB, as detailed in Supplemental Table S3 (Supplemental Digital Content 1, https://links.lww.com/GME/A12). To ensure a baseline population free of prevalent conditions, we excluded participants based on a combination of self-reported medical history and hospital inpatient records. For the ascertainment of incident non-fatal events, we relied on hospital admission data linked to ICD-10 codes, supplemented by death registries and information on loss to follow-up. We determined the time-to-event by calculating the interval between the date of recruitment and the first occurrence

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of censoring events: diagnosis of the outcome, death, loss to follow-up, or the administrative end of the study (December 31, 2019).

Measurements of covariates

Covariates were selected based on previous literature and directed acyclic graph analysis (Supplemental Fig. S1, Supplemental Digital Content 1, https://links.lww.com/GME/A12).[14,19] These included age, body mass index (BMI), lifestyle behaviors (smoking status and drinking status), history of hypertension and diabetes, and reproductive factors (number of live births, age at menarche, and ever use of HT). Specifically, smoking status and drinking status were classified as never and ever. Height and weight were measured by trained technicians to calculate BMI, which was categorized as <25, 25-29.9, and ≥ 30 kg/m^2. In the UKB, hypertension and diabetes were identified using ICD-10 codes (I10-I50 and E10-E14, respectively). In the US NHANES, these conditions were defined based on clinical examinations (blood pressure $\geq 140/90$ mm Hg or HbA1c $\geq 6.5\%$), medication history (current use of antihypertensive or diabetes treatments), or a doctor's diagnosis (self-reported medical history). Reproductive factors were classified as follows: number of live births (0, 1-3, and ≥ 4), age at menarche (<12, 12-14, and ≥ 15 y), and ever use of HT (yes and no).[19,20] The detailed information of covariates was documented in Supplementary methods and Supplemental Table S4 (Supplemental Digital Content 1, https://links.lww.com/GME/A12).

To handle missing covariates, we performed multiple imputation by chained equations using the "mice" package in R to generate five imputed data sets.[11] Specifically, continuous variables were imputed using linear regression models, while categorical variables were handled using logistic regression models.

Statistical analysis

Baseline characteristics were summarized according to the combined SDH groups (favorable, medium, and unfavorable). Continuous variables were expressed as means ± SDs for normally distributed data, or medians with interquartile ranges (IQRs) for skewed distributions. To compare differences across groups, we used one-way analysis of variance for data meeting assumptions of normality and homogeneity, whereas the Kruskal-Wallis test served as the nonparametric alternative. Categorical variables were reported as frequencies (percentages), with between-group differences assessed using χ^2 tests.

We used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for the associations of combined SDH scores with mortality (all-cause, CVD, and cancer) and non-fatal incidents (CVD, cancer, and dementia) among women with ENM. The proportional hazards assumption was verified for the combined SDH scores and covariates, with no violations detected. We constructed three sequential models to progressively control for potential confounders. Model 1 adjusted for age to account for basic demographics. Model 2, in addition, adjusted for lifestyle factors (BMI, smoking, and drinking status) and comorbidities (hypertension and diabetes) to ensure the observed associations were independent of baseline health status. Model 3 further adjusted for reproductive factors (age at menarche, number of live births, and ever use of HT), given their close links to menopause timing and health trajectories in women with ENM. In addition, we plotted Kaplan-Meier curves to visualize survival patterns, comparing the three SDH groups using the log-rank test. Furthermore, to identify the primary SDH contributors to adverse health outcomes, we included all SDH variables simultaneously in a single Cox model adjusted for model 3 covariates. Potential multicollinearity was assessed through Spearman correlation coefficients and variance inflation factors.

Stratified analyses were performed to evaluate potential effect modification by demographics, lifestyle, and health conditions. These included age (<60 and ≥ 60 y), BMI (<25, 25-29.9, and ≥ 30 kg/m^2), smoking and drinking status (never and ever), hypertension (yes and no), and diabetes (yes and no). Furthermore, acknowledging the prognostic implications of reproductive history highlighted in prior studies,[19,21] we extended the stratification to include age at menarche (<12, 12-14, and ≥ 15 y), number of live births (0, 1-3, and ≥ 4), and ever use of HT (yes and no). Tests for interaction were conducted by simultaneously including the combined SDH scores, the subgroup variable, and their interaction term (the product of the two) into the models. In these analyses, we adjusted for the full set of model 3 covariates, excluding the specific variable used for stratification.

We conducted a series of sensitivity analyses to validate the robustness of our findings. First, we excluded participants with prevalent CVD or cancer at baseline to minimize potential reverse causality. Second, we performed a complete-case analysis by excluding participants with any missing covariate data to address potential bias introduced by data imputation. Third, we redefined ENM as occurring before age 45 to align with established definitions used in prior studies.[22,23] Fourth, given that the median time since menopause was 15.0 years (IQR: 9.0-20.0) at the baseline survey, we stratified the analyses by this median value to account for potential healthy survivor effects and variations in health risks.

Data analyses were performed using R software version 4.4.1 (R Foundation for Statistical Computing). Statistical significance was defined as a two-sided P-value <0.05. To account for multiple comparisons in subgroup analyses, we applied a Bonferroni-corrected threshold of $P < 2.38\times10^{-3}$ (0.05/21).

Use of artificial intelligence

During the preparation of this work, we used Google Gemini to assist with language polishing and refinement of the manuscript text, as well as debugging and optimization of R statistical code. Following the use of this tool, we thoroughly reviewed and edited the content as needed and take full responsibility for the accuracy and integrity of the final manuscript.

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TABLE 1. Baseline characteristics of the study population grouped by combined SDH in the UK Biobank and US NHANES cohort[a]

	UK Biobank[b]					US NHANES[b]				
	Total (n = 19,912)	**Favorable (n = 8,391)**	**Medium (n = 5,408)**	**Unfavorable (n = 6,113)**	***P***	**Total (n = 1,732)**	**Favorable (n = 765)**	**Medium (n = 581)**	**Unfavorable (n = 386)**	***P***
Combined SDH score range	0, 14	0, 4	5, 6	7, 14		0, 9	0, 3	4, 5	6, 9	
Age (y), median (Q1,Q3)	59 (53, 64)	59 (53, 63)	59 (53, 64)	59 (53, 64)	0.007	63 (55, 73)	63 (54, 73)	65 (56, 75)	60 (53, 66)	< 0.001
BMI (kg/m^2), n (%)					< 0.001					< 0.001
< 25	7,938 (39.9)	3,839 (45.8)	2,104 (38.9)	1,995 (32.6)		488 (28.2)	248 (32.4)	156 (26.9)	84 (21.8)	
25-29.9	7,455 (37.4)	3,179 (37.9)	2,038 (37.7)	2,238 (36.6)		537 (31.0)	244 (31.9)	182 (31.3)	111 (28.8)	
≥ 30	4,519 (22.7)	1,373 (16.4)	1,266 (23.4)	1,880 (30.8)		707 (40.8)	273 (35.7)	243 (41.8)	191 (49.5)	
Smoking status, n (%)					< 0.001					0.012
Never	10,480 (52.6)	4,995 (59.5)	2,806 (51.9)	2,679 (43.8)		975 (56.3)	448 (58.6)	335 (57.7)	192 (49.7)	
Ever	9,432 (47.4)	3,396 (40.5)	2,602 (48.1)	3,434 (56.2)		757 (43.7)	317 (41.4)	246 (42.3)	194 (50.3)	
Drinking status, n (%)					< 0.001					< 0.001
Never	1,943 (9.8)	536 (6.4)	509 (9.4)	898 (14.7)		783 (45.2)	308 (40.3)	301 (51.8)	174 (45.1)	
Ever	17,969 (90.2)	7,855 (93.6)	4,899 (90.6)	5,215 (85.3)		949 (54.8)	457 (59.7)	280 (48.2)	212 (54.9)	
Hypertension, n (%)					< 0.001					< 0.001
No	14,956 (75.1)	6,609 (78.8)	4,092 (75.7)	4,255 (69.6)		618 (35.7)	319 (41.7)	169 (29.1)	130 (33.7)	
Yes	4,956 (24.9)	1,782 (21.2)	1,316 (24.3)	1,858 (30.4)		1,114 (64.3)	446 (58.3)	412 (70.9)	256 (66.3)	
Diabetes, n (%)					< 0.001					< 0.001
No	19,062 (95.7)	8,180 (97.5)	5,183 (95.8)	5,699 (93.2)		1,302 (75.2)	629 (82.2)	416 (71.6)	257 (66.6)	
Yes	850 (4.3)	211 (2.5)	225 (4.2)	414 (6.8)		430 (24.8)	136 (17.8)	165 (28.4)	129 (33.4)	
No. live births, n (%)					< 0.001					< 0.001
0	4,287 (21.5)	1,598 (19.0)	1,249 (23.1)	1,440 (23.6)		201 (11.6)	105 (13.7)	60 (10.3)	36 (9.3)	
1-3	14,407 (72.4)	6,423 (76.5)	3,852 (71.2)	4,132 (67.6)		1,015 (58.6)	533 (69.7)	292 (50.3)	190 (49.2)	
4 or more	1,218 (6.1)	370 (4.4)	307 (5.7)	541 (8.8)		516 (29.8)	127 (16.6)	229 (39.4)	160 (41.5)	
Age at menarche (y), n (%)					< 0.001					0.025
< 12	4,310 (21.6)	1,779 (21.2)	1,145 (21.2)	1,386 (22.7)		315 (18.2)	134 (17.5)	100 (17.2)	81 (21.0)	
12-14	12,127 (60.9)	5,305 (63.2)	3,314 (61.3)	3,508 (57.4)		1,077 (62.2)	499 (65.2)	350 (60.2)	228 (59.1)	
≥ 15	3,475 (17.5)	1,307 (15.6)	949 (17.5)	1,219 (19.9)		340 (19.6)	132 (17.3)	131 (22.5)	77 (19.9)	
Ever use of HT, n (%)					< 0.001					< 0.001
No	9,927 (49.9)	4,036 (48.1)	2,767 (51.2)	3,124 (51.1)		1,315 (75.9)	498 (65.1)	475 (81.8)	342 (88.6)	
Yes	9,985 (50.1)	4,355 (51.9)	2,641 (48.8)	2,989 (48.9)		417 (24.1)	267 (34.9)	106 (18.2)	44 (11.4)	

BMI, body mass index; NHANES, National Health and Nutrition Examination Survey; SDH, social determinants of health; HT, hormone therapy.

[a]For continuous variables, differences across three groups were tested through Kruskal-Wallis tests when the data were not normally distributed or homogeneity of variance. For categorical variables, differences across groups were tested by the χ^2 test.

[b]The study population was divided into three groups based on the tertiles of the combined SDH score. Sample sizes differ across tertiles due to tied values at the cutoff points of the discrete combined SDH.

RESULTS

Baseline characteristics

Table 1 summarized the baseline characteristics of the study population stratified by combined SDH categories. In the UKB, a total of 28,094 women were identified with ENM. Following the exclusion of 8,182 participants due to missing data on SDH, 19,912 women (median age: 59 y) were retained for the mortality analysis. In the US NHANES, out of 1,961 eligible women, we excluded 229 individuals lacking complete SDH or mortality data, resulting in a final sample of 1,732 women (median age: 63 y).

Across both cohorts, women in the unfavorable SDH group exhibited a poorer health profile compared with those in the favorable group. Specifically, they were more likely to be ever smokers, have a higher BMI, and report more live births. Furthermore, this group demonstrated a greater burden of comorbidities, including hypertension and diabetes, as well as a history of early menarche. The detailed distribution of disadvantaged levels for individual SDH variables is provided in Supplemental (Table S5, Supplemental Digital Content 1, https://links.lww.com/GME/A12).

Association of combined social determinants of health with mortality among women with early natural menopause

During a median follow-up of 10.82 years in the UKB, 1,057 deaths were recorded, including 160 from CVD and 614 from cancer (Table 2). In the fully adjusted model (model 3), higher combined SDH scores were significantly associated with increased risks of all-cause, CVD, and cancer mortality (all P for trend < 0.05). Compared with the favorable SDH group, the HRs in the unfavorable SDH group were 1.75 (95% CI: 1.51-2.03) for all-cause mortality, 1.69 (95% CI: 1.15-2.47) for CVD mortality, and 1.35 (95% CI: 1.11-1.63) for cancer mortality. Supplemental Figure S2A (Supplemental Digital Content 1, https://links.lww.com/GME/A12) showed the survival curves for the three combined SDH groups. In addition, the associations between SDH and all-cause mortality remained consistent across subgroups (most P for interaction > 0.05; Supplemental Fig. S3A, Supplemental Digital Content 1, https://links.lww.com/GME/A12). Furthermore, findings from all sensitivity analyses largely supported the main results (Supplemental Tables S6-S9, Supplemental Digital Content 1, https://links.lww.com/GME/A12).

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TABLE 2. Associations between the combined SDH and mortality among women with early natural menopause[a]

	UK Biobank cohort[b]				US NHANES cohort[b]			
	Favorable	Medium	Unfavorable	*P*-trend	Favorable	Medium	Unfavorable	*P*-trend
Combined SDH Score Range	0, 4	5, 6	7, 14		0, 3	4, 5	6, 9	
All-cause mortality								
No. participants	8,391	5,408	6,113	—	765	581	386	—
No. cases; person-years	321; 89,737	247; 57,855	489; 64,605	—	158; 6,945	176; 4,692	88; 3,129	—
HR (95% CI) in model 1	1.00 (Ref.)	1.17 (0.99-1.38)	2.07 (1.80-2.38)	2.1×10^{-24}	1.00 (Ref.)	1.62 (1.23-2.13)	1.89 (1.37-2.61)	8.9×10^{-8}
HR (95% CI) in model 2	1.00 (Ref.)	1.10 (0.93-1.30)	1.79 (1.54-2.07)	9.0×10^{-15}	1.00 (Ref.)	1.58 (1.21-2.06)	1.62 (1.14-2.32)	2.2×10^{-5}
HR (95% CI) in model 3	1.00 (Ref.)	1.09 (0.92-1.28)	1.75 (1.51-2.03)	1.0×10^{-13}	1.00 (Ref.)	1.50 (1.15-1.96)	1.53 (1.06-2.20)	4.4×10^{-4}
Cardiovascular disease mortality								
No. cases	45	37	78	—	57	60	23	—
HR (95% CI) in model 1	1.00 (Ref.)	1.20 (0.78-1.86)	2.23 (1.54-3.21)	1.0×10^{-4}	1.00 (Ref.)	1.59 (1.00-2.53)	1.55 (0.84-2.86)	2.2×10^{-3}
HR (95% CI) in model 2	1.00 (Ref.)	1.09 (0.71-1.69)	1.76 (1.20-2.57)	1.6×10^{-2}	1.00 (Ref.)	1.40 (0.85-2.31)	1.14 (0.57-2.28)	8.6×10^{-2}
HR (95% CI) in model 3	1.00 (Ref.)	1.06 (0.69-1.65)	1.69 (1.15-2.47)	3.0×10^{-2}	1.00 (Ref.)	1.36 (0.82-2.26)	1.11 (0.55-2.25)	1.7×10^{-1}
Cancer mortality								
No. cases	217	153	244	—	32	29	22	—
HR (95% CI) in model 1	1.00 (Ref.)	1.08 (0.87-1.32)	1.54 (1.28-1.85)	5.1×10^{-6}	1.00 (Ref.)	1.64 (0.84-3.18)	2.63 (1.40-4.94)	2.7×10^{-3}
HR (95% CI) in model 2	1.00 (Ref.)	1.03 (0.83-1.26)	1.37 (1.13-1.65)	1.7×10^{-3}	1.00 (Ref.)	1.75 (0.92-3.32)	2.74 (1.41-5.32)	2.5×10^{-3}
HR (95% CI) in model 3	1.00 (Ref.)	1.01 (0.82-1.25)	1.35 (1.11-1.63)	3.4×10^{-3}	1.00 (Ref.)	1.68 (0.89-3.18)	2.61 (1.29-5.29)	5.1×10^{-3}

HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; SDH, social determinants of health.

[a]Model 1 was adjusted for age (continuous, years); model 2 was, in addition, adjusted for BMI (<25, 25-29.9, and ≥30 kg/m^2), smoking status (never and ever), drinking status (never and ever), hypertension (yes and no), and diabetes (yes and no). Model 3 was further adjusted for age at menarche (<12, 12-14, and ≥15 y), number of live births (0, 1-3, and ≥4), and ever use of hormone therapy (yes and no).

[b]The study population was divided into three groups based on the tertiles of the combined SDH scores. Sample sizes differ across tertiles due to tied values at the cutoff points of the discrete combined SDH.

For external validation, the US NHANES cohort documented 422 deaths (including 140 from CVD and 83 from cancer) over a median follow-up of 7.7 years. After multivariable adjustment (model 3), we observed associations that were highly consistent with those in the UKB cohort (Table 2). Higher combined SDH scores remained significantly associated with increased risks of all-cause and cancer mortality (both *P* for trend <0.05). Specifically, compared with the favorable SDH group, the HRs in the unfavorable SDH group were 1.53 (95% CI: 1.06-2.20) for all-cause mortality and 2.61 (95% CI: 1.29-5.29) for cancer mortality (Table 2).

Association of combined social determinants of health with incident diseases among women with early natural menopause

In the UKB cohort, 2,373 participants had incident cancer during a median follow-up of 10.66 years; 1,172 had incident CVD during 10.77 years; and 205 had incident dementia during 10.81 years. After multivariable adjustment (model 3), the unfavorable SDH group was associated with a significantly increased risk of both CVD and dementia compared with the favorable SDH group. Specifically, the HR for incident CVD was 1.48 (95% CI: 1.29-1.70), while the HR for incident dementia was 1.83 (95% CI: 1.30-2.57). Conversely, no significant association was observed for incident cancer (HR 0.99, 95% CI: 0.89-1.09; Table 3). These associations were visually supported by KM survival curves (Supplemental Figs. S2B-D, Supplemental Digital Content 1, https://links.lww.com/GME/A12) and remained robust across all subgroup and sensitivity analyses (Supplemental Figs. S3B-D; Supplemental Tables S6-S9, Supplemental Digital Content 1, https://links.lww.com/GME/A12).

Unemployment as the primary driver for all-cause mortality and incident dementia among women with early natural menopause

To evaluate the independent contribution of individual SDH variables to adverse outcomes, we included all factors simultaneously in the fully adjusted model. Multicollinearity assessments revealed mild to moderate correlations among the variables, and all variance inflation factor values remained below 5, confirming no substantial multicollinearity (Supplemental Figs. S4, S5, Supplemental Digital Content 1, https://links.lww.com/GME/A12).

After multivariable adjustment (model 3 + all SDH variables), unemployment was identified as the strongest risk factor for all-cause mortality in both cohorts. Compared with the employed or retired group, the HRs for unemployment were 1.91 (95% CI: 1.55-2.36) in the UKB and 1.43 (95% CI: 1.09-1.88) in the US NHANES (Fig. 2A, B). Furthermore, unemployment exhibited the strongest association with incident dementia (HR = 1.98, 95% CI: 1.38-2.86; Fig. 2D). In contrast, for incident CVD, household income $<$£31,000 showed the highest risk (HR = 1.36, 95% CI: 1.17-1.58; Fig. 2C).

DISCUSSION

This prospective cohort study finds that compared with the favorable SDH group, the unfavorable SDH group is associated with increased risks of mortality, incident CVD, and dementia among women with ENM. These associations remain robust across subgroup and sensitivity analyses, and are externally validated using the US NHANES cohort. Notably, unemployment emerges as the strongest individual risk factor for both all-cause mortality and incident dementia.

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TABLE 3. Associations between the combined SDH and incident diseases among women with early natural menopause[a]

	UK Biobank cohort[b]			
	Favorable	**Medium**	**Unfavorable**	***P*-trend**
Combined SDH score range	0, 4	5, 6	7, 14	
Incident cardiovascular disease				
No. participants	8,134	5,164	5,614	—
No. cases; person-years	401; 85,327	296; 54,090	475; 57,517	—
HR (95% CI) in model 1	1.00 (Ref.)	1.14 (0.98-1.33)	1.73 (1.51-1.98)	7.2×10^{-20}
HR (95% CI) in model 2	1.00 (Ref.)	1.07 (0.92-1.24)	1.48 (1.29-1.70)	4.0×10^{-11}
HR (95% CI) in model 3	1.00 (Ref.)	1.07 (0.92-1.25)	1.48 (1.29-1.70)	4.9×10^{-11}
Incident cancer				
No. participants	7,097	4,591	5,145	—
No. cases; person-years	1,003; 71,710	611; 46,567	759; 51,443	—
HR (95% CI) in model 1	1.00 (Ref.)	0.92 (0.83-1.01)	1.03 (0.94-1.14)	8.4×10^{-1}
HR (95% CI) in model 2	1.00 (Ref.)	0.90 (0.81-0.99)	0.98 (0.89-1.09)	4.0×10^{-1}
HR (95% CI) in model 3	1.00 (Ref.)	0.90 (0.81-1.00)	0.99 (0.89-1.09)	4.2×10^{-1}
Incident dementia				
No. participants	8,389	5,407	6,110	—
No. cases; person-years	56; 89,587	50; 57,747	99; 64,341	—
HR (95% CI) in model 1	1.00 (Ref.)	1.25 (0.86-1.84)	2.23 (1.60-3.09)	3.7×10^{-7}
HR (95% CI) in model 2	1.00 (Ref.)	1.17 (0.80-1.72)	1.90 (1.36-2.67)	8.7×10^{-5}
HR (95% CI) in model 3	1.00 (Ref.)	1.16 (0.79-1.70)	1.83 (1.30-2.57)	3.0×10^{-4}

HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; SDH, social determinants of health; UKB, UK Biobank.

[a]Model 1 was adjusted for age (continuous, years); model 2 was, in addition, adjusted for BMI (<25, 25-29.9, and ≥30 kg/m^2), smoking status (never and ever), drinking status (never and ever), hypertension (yes and no), and diabetes (yes and no). Model 3 was further adjusted for age at menarche (<12, 12-14, and ≥15 years), number of live births (0, 1-3, and ≥4), and ever use of hormone therapy (yes and no).

[b]The study population was divided into three groups based on the tertiles of the combined SDH scores. Sample sizes differ across tertiles due to tied values at the cutoff points of the discrete combined SDH.

Socioeconomic inequities in women with ENM are well documented, including lower income, limited educational attainment, adverse marital status, and poor social support.[14,24,25] Such disadvantaged SDH lead to chronic physiological dysregulation, including increased stress hormone levels, inflammation, immune dysfunction, and cellular aging, thereby contributing to long-term adverse health outcomes.[26-28] In addition, adult social disadvantages are often linked to adverse childhood experiences,[29-31] and existing evidence shows that these early experiences are associated with earlier menopause, multimorbidity, and mortality.[32-34] Despite this, clinical protocols for ENM predominantly focus on biomedical interventions like HT and weight management,[7-9] while the critical impact of social factors is frequently neglected. Our results suggest that disadvantaged SDH significantly increase mortality risks in women with ENM. Consequently, we conclude that the comprehensive evaluation of SDH, coupled with targeted support for socially vulnerable patients, should be integrated as a fundamental principle of ENM care.

With respect to cardiovascular outcomes, large-scale prospective cohort studies indicate that disadvantaged SDH contribute significantly to the global burden of CVD.[35,36] In addition, the link between ENM and CVD morbidity and mortality has been established.[23,37] Building on these dual risks, our study identifies a specific association between unfavorable SDH and increased CVD risk within the ENM population. Regarding the underlying mechanism, the prevailing theory attributes the elevated cardiovascular risk in ENM to the loss of protective endogenous estrogens.[6] Our results support this hypothesis: women with unfavorable SDH who never use HT face a higher risk of CVD (HR = 1.29, 95% CI: 1.17-1.41) than those who use it (HR = 1.18, 95% CI: 1.09-1.28). Beyond estrogen pathways, other mechanisms likely contribute to this risk, including altered circulating androgen and sex hormone-binding globulin levels,[38,39] along with shared genetic and environmental factors.[40]

Regarding cognitive health, evidence from a systematic review and meta-analysis of 19 longitudinal cohort studies identifies social isolation as a key predictor of incident dementia.[41] Significant associations are documented for low social participation (relative risk [RR] = 1.41, 95% CI: 1.13-1.75), infrequent social contact (RR = 1.57, 95% CI: 1.32-1.85), and increased loneliness (RR = 1.58, 95% CI: 1.19-2.09).[41] Similarly, disadvantaged SDH—specifically low socioeconomic status, education level, food security, and neighborhood factors—correlate with a higher incidence of Alzheimer disease-related dementia,[42] whereas active social engagement exerts a protective effect.[42] Furthermore, multinational data from five prospective cohort studies demonstrate that women with ENM face a higher dementia burden compared with those with menopause onset at 50-52 years (HR = 1.13-1.49).[43] Such patterns are mirrored in our own data. We explicitly assess combined SDH among women with ENM, indicating that modifying these social risk factors is essential for the comprehensive management of this population.

In our study, unemployment shows the strongest association with both all-cause mortality and incident dementia. These results are consistent with existing literature. For instance, a comprehensive review notes that

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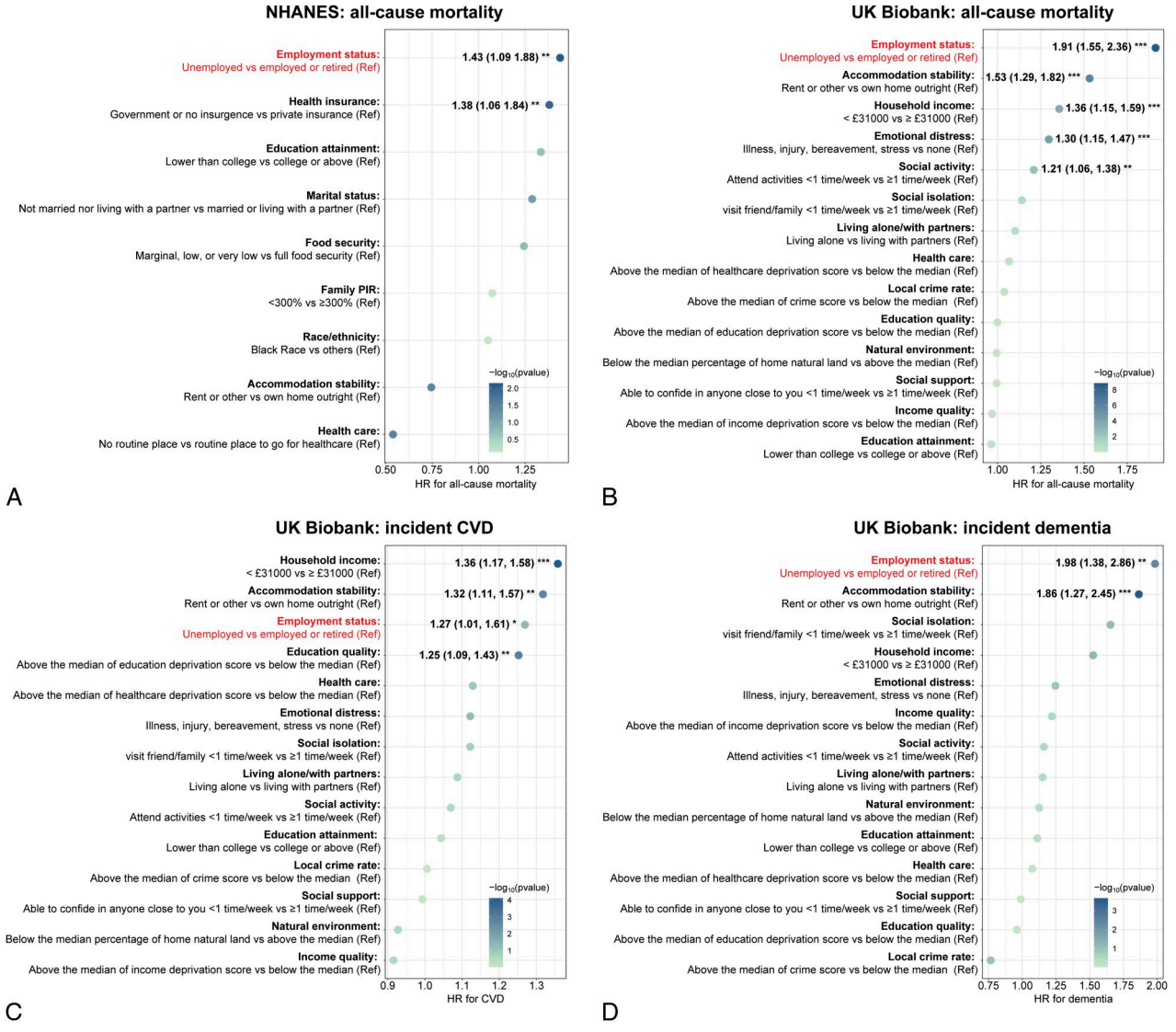

FIG. 2. Associations of individual SDH variable with all-cause mortality and incident diseases among women with early natural menopause. (**A**) Unemployment showing the strongest independent association with all-cause mortality in the US NHANES cohort. (**B**) Unemployment acting as the major independent risk factor for all-cause mortality in the UKB cohort. (**C**) Low household income is emerging as the leading independent contributor to incident CVD in the UKB cohort. (**D**) Unemployment identified as the most significant independent risk factor for incident dementia in the UKB cohort. Models were adjusted for age (continuous, years), BMI (<25, 25-29.9, and ≥30 kg/m^2), smoking status (never and ever), drinking status (never and ever), hypertension (yes and no), diabetes (yes and no), age at menarche (<12, 12-14, and ≥15 y), number of live births (0, 1-3, and ≥4), and ever use of hormone therapy (yes and no). *P<0.05, **P<0.01, ***P<0.001. BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; SDH, social determinants of health; UKB, UK Biobank.

national unemployment rates correlate positively with overall mortality.[44] Similarly, a meta-analysis of 20 million people finds that unemployment raises the risk of all-cause mortality by 67%.[45] Regarding dementia, a large prospective cohort links unemployment to a higher risk of early-onset dementia in women (HR = 1.51, 95% CI: 1.27-1.78).[46] Three mechanisms likely explain these associations. First, unemployed individuals often experience depression, which subsequently influences a broad spectrum of health outcomes.[47,48] Second, psychosocial stress from unemployment could trigger systemic inflammatory dysregulation, a well-established risk factor for mortality, CVD, and dementia.[26] Third, unemployment frequently leads to adverse lifestyle changes, such as increased smoking and alcohol consumption, which further elevate the long-term burden of chronic disease.[49]

As far as we know, this study is the first to explore the relationship between combined SDH and multiple health

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outcomes in women with ENM. The reliability of our findings is supported by the large sample size, long duration of follow-up, and consistent results from sensitivity and subgroup analyses. Furthermore, the similar patterns observed in two independent, nationally representative cohorts validate the generalizability of our results, supporting the potential applicability of assessing combined SDH in diverse clinical and public health settings.

However, several limitations should be acknowledged. First, the retrospective self-reporting of ENM introduces potential recall bias, though this method is consistent with established literature.[14,18] Second, although this study utilizes a longitudinal design to track health outcomes, the SDH and covariates are assessed only once at baseline. This reliance on baseline data limits our ability to capture temporal changes in participants' social conditions, potentially introducing measurement error. Future studies utilizing repeated measurements of SDH variables are recommended to evaluate dynamic social trajectories. Third, although we adjust for various SDH, the scoring system does not adequately reflect interactions among them, highlighting the need for refined evaluation methods. Fourth, our observational design cannot fully rule out reverse causation. As observed at the study baseline, the unfavorable SDH group already exhibits more poor health variables. Consequently, the strong association with unemployment might partially reflect underlying health issues predating this unemployed status. Although our long follow-up and baseline adjustments help mitigate this concern, further research is needed to clarify these associations. Finally, the 'healthy survivor effect' is an inherent limitation of this study. Given that the survey was conducted a median of 15.0 years (IQR: 9.0-20.0) after menopause onset, individuals who died or became severely ill shortly after menopause were not captured, potentially biasing our sample toward healthier participants. Although sensitivity analysis stratified by this interval showed consistent results, future studies recruiting participants closer to the onset of menopause are warranted to minimize this bias and further validate our findings.

CONCLUSIONS

Longitudinal data from the UKB and US NHANES cohorts reveal that socioeconomic disadvantages significantly amplify adverse health trajectories in women with ENM. Notably, unemployment exhibits the strongest association with both all-cause mortality and incident dementia. Women with ENM frequently encounter more adverse SDH, and ENM itself can further exacerbate these disadvantages. To disrupt this reciprocal deterioration, a comprehensive SDH assessment should be established as a fundamental principle in the clinical and public health management of ENM.

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