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Earlier menopause is associated with higher risk of incident frailty in community-dwelling older women in England

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Abstract

Background: Although it is well known that women have higher risk of frailty, mechanisms are not clear. Reproductive history may be related to the sex difference in frailty.

Methods: A total of 1249 community-dwelling women aged ≥60 in England were examined for associations between age at menopause and risk of developing frailty. Frailty defined by the frailty phenotype was measured at baseline and 4 years later. Age at menopause was used as a continuous variable and categorical groups: premature/early (10–45 years), normal (46–55 years), and late (56 years or older). Men with comparable conditions from the same cohort were also used as a comparison.

Results: Earlier age at menopause was significantly associated with higher risk of incident frailty. One year later menopause age was associated with a 3% decrease in incident frailty risk (Odds ratio [OR] = 0.97, 95% CI = 0.95–1.00, $p = 0.02$). Women with premature or early menopause had a significantly higher risk of developing frailty compared with those with normal menopause (OR = 1.90, 95%CI = 1.28–2.81, $p = 0.001$), while those with late menopause did not. In a supplementary analysis with older men, older women with premature or early menopause were more likely to develop frailty compared with older men (OR = 2.29, 95% CI = 151–3.48, $p < 0.001$), however, there was no significant difference between women with normal or late menopause.

Conclusions: Earlier menopause was significantly associated with higher risk of developing frailty. Our findings suggest that menopause or its related factors, such as decline in estrogen after menopause, potentially play an important role in the sex difference in frailty.

KEYWORDS
epidemiology, frailty, menopause

INTRODUCTION

Frailty is a medical condition of vulnerability to poor resolution of homeostasis after a stressor event and age-related decline in many physiological systems.[1,2] Frail older adults are predisposed to adverse health outcomes, including falls,[3] fractures,[4] disabilities,[5] hospitalization,[6] and nursing home placement,[7,8] and have substantially high mortality risk.[9] Previous studies have consistently shown that women are frailer than men in all age groups and in different populations.[10]

Although the mechanism of the sex gaps in frailty risk has not been completely clarified, several biological, behavioral, and social factors are considered to potentially explain the sex differences in frailty.[11] For example, inflammation seems to play an important role in the pathophysiology of frailty,[12,13] more in women than in men due to more accumulated abdominal fat in women.[14] Other frailty risk-related behaviors, such as smoking or drinking,[15–17] may put greater risks of related morbidity and mortality as well as frailty on women than men.[18,19] In addition, women may be more vulnerable than men because of social factors, such as living situation[20] or marital status.[21] Among the potential contributors, reproductive history is unique to women and may be related to the sex difference in frailty.[22] Menopause is associated with a drastic decline in sex hormones, which could negatively affect women's health and possibly increase their risk of frailty.[23] In fact, women who experienced menopause earlier in life (before age 45) have been shown to have increased risks of overall mortality, cardiovascular diseases, and neurological diseases.[24] However, there is limited evidence of associations between menopause and frailty; only two cross-sectional studies were found in the literature, providing inconsistent findings.[25,26] Further attempts to explore associations between menopause and frailty would shed light on underlying mechanisms of sex disparity in frailty. Therefore, the objective of this study was to examine the associations between age at menopause and subsequent risk of developing frailty over 4 years in community-dwelling postmenopausal older women.

Key points

- Earlier menopause (10–45 years old) was significantly associated with a higher risk of developing frailty compared with normal menopause (46–55 years old).
- Women with earlier menopause had a significantly higher incident frailty risk compared with older men.

Why does this paper matter?

Decline in estrogen after menopause may potentially play an important role in the sex difference in frailty.

METHODS

Study setting and population

The English Longitudinal Study of Aging (ELSA) is a multi-center longitudinal panel study of a nationally representative sample of community-dwelling men and women aged 50 years and older in England, and was launched in 2002.[27] The study covers a wide range of topics related to human aging processes, including physical and mental health, cognitive function, social and economic circumstances, social relationships and relationships between these factors.[27] The initial wave 1 cohort was recruited from households participating in the Health Survey for England (HSE), which is an annual cross-sectional survey to examine the health of the general population in England, in 1998, 1999, and 2001.[28] The ELSA participants have been followed at waves every 2 years and were asked to complete the main interview. In addition, they were invited to have a nurse visit for measurement of physical functions, anthropometry data, and blood sampling at every other wave, starting with wave 2 (waves 2, 4, 6...). Ethical approval for all ELSA waves was obtained from the National Research and Ethics Committee and informed consent was obtained from all participants.

Information on age at menopause was not available from wave 2 but only from wave 3. Therefore, the present study used data of female participants who were aged 60 years or older at wave 2 (2004, baseline), answered questions regarding menopause at wave 3 (2006), and participated at wave 4 (2008, follow-up).

Of 3432 women participating at wave 2, those who missed data regarding frailty status ($n = 946$) or those who were already frail at wave 2 ($n = 358$), those who had missing data of age at menopause ($n = 529$) or those who were still having period ($n = 4$), and those who had missing data of frailty status at wave 4 ($n = 346$) were excluded, leaving the final analytic sample of 1249 women (Figure S1).

As a comparison with women, male participants with comparable conditions were selected. Of the 2751 males who participated at wave 2, 745 men who had missing data of frailty and 225 men who were frail at wave 2 were

TABLE 1 Baseline characteristics of community-dwelling older women ($n = 1249$) and men ($n = 1060$) in England[a]

Variable	All women $N = 1249$	Premature/early menopause (10–45 years old) $n = 354$	Normal menopause (46–55 years old) $n = 793$	Late menopause (56–75 years old) $n = 102$	p value[b]	Men $N = 1060$	p value[c]
Frailty status							
Robust	676 (54.1%)	174 (49.1%)	441 (55.6%)	61 (59.8%)	0.06	625 (59.0%)	0.02
Prefrail	573 (45.9%)	135 (50.9%)	352 (44.4%)	41 (40.2%)		435 (41.0%)	
Age group							
60–64	374 (29.8%)	109 (30.8%)	225 (28.4%)	38 (37.3%)	0.69	313 (27.9%)	0.81
65–69	345 (27.6%)	90 (25.4%)	229 (28.9%)	26 (25.5%)		304 (27.1%)	
70–74	256 (20.5%)	70 (19.8%)	166 (20.9%)	20 (19.6%)		243 (21.7%)	
75–79	178 (14.3%)	55 (15.5%)	112 (14.1%)	11 (10.8%)		160 (14.3%)	
80+	98 (7.9%)	30 (8.5%)	61 (7.7%)	7 (6.9%)		102 (9.1%)	
Smoking							
Never smoker	607 (48.7%)	153 (43.2%)	398 (50.4%)	56 (54.9%)	0.01	316 (28.2%)	<0.001
Past smoker	518 (41.6%)	152 (42.9%)	326 (41.3%)	40 (39.2%)		686 (61.1%)	
Current smoker	121 (9.7%)	49 (13.8%)	66 (8.4%)	6 (5.9%)		120 (10.7%)	
Alcohol							
None	127 (10.8%)	33 (10.0%)	85 (11.3%)	9 (9.1%)	0.18	79 (7.0%)	<0.001
1/y-2/m	433 (36.7%)	136 (41.3%)	267 (35.5%)	30 (30.3%)		202 (18.0%)	
1/w-4/w	376 (31.9%)	95 (28.9%)	239 (31.8%)	42 (42.4%)		439 (39.1%)	
5/w-daily	244 (20.7%)	65 (19.8%)	161 (21.4%)	18 (18.2%)		320 (28.5%)	
Wealth quintile							
Richest	304 (24.6%)	75 (21.2%)	198 (25.3%)	31 (30.4%)	0.16	316 (28.2%)	0.01
2nd	277 (22.4%)	85 (24.0%)	169 (21.6%)	23 (22.6%)		251 (22.4%)	
3rd	257 (20.8%)	63 (17.8%)	174 (22.3%)	20 (19.6%)		221 (19.7%)	
4th	234 (18.9%)	77 (21.8%)	137 (17.5%)	20 (19.6%)		191 (17.0%)	
Poorest	166 (13.4%)	54 (15.3%)	104 (13.3%)	8 (7.8%)		125 (11.1%)	
Education							
Higher education	105 (8.4%)	32 (9.0%)	63 (7.9%)	10 (9.8%)	0.47	189 (16.8%)	<0.001
Intermediate	639 (51.2%)	167 (47.2%)	420 (53.0%)	52 (51.0%)		605 (53.9%)	
No qualification	505 (40.4%)	155 (43.8%)	310 (39.1%)	40 (39.2%)		328 (29.2%)	
Marital status							
Married	733 (58.7%)	189 (53.4%)	477 (60.2%)	67 (65.7%)	0.03	870 (77.5%)	<0.001
Never married	50 (4.0%)	10 (2.8%)	34 (4.3%)	6 (5.9%)		43 (3.8%)	
Separated/divorced	121 (9.7%)	38 (10.7%)	72 (9.1%)	11 (10.8%)		73 (6.5%)	
Widowed	345 (27.6%)	117 (33.1%)	210 (26.5%)	18 (17.7%)		136 (12.1%)	
Age at menarche	13.1 ± 1.68	13.1 ± 1.78	13.1 ± 1.62	13.2 ± 1.76	0.69	—	—
Number of children	2.28 ± 1.37	2.29 ± 1.40	2.25 ± 1.36	2.47 ± 1.36	0.30	2.40 + 1.49	0.05
Cardiovascular diseases	630 (50.4%)	182 (51.4%)	396 (49.9%)	52 (51.0%)	0.89	576 (51.3%)	0.80
Cause of menopause							
Natural/No reason	943 (75.5%)	175 (49.4%)	685 (86.4%)	83 (81.4%)	<0.001	—	—
Surgery	278 (22.3%)	173 (48.9%)	95 (12.0%)	10 (9.8%)		—	—
Others	28 (2.2%)	6 (1.7%)	13 (1.6%)	9 (8.8%)		—	—

[a]Data are mean ± deviation or n (%).
[b]p value across age at menopause groups, using a one-way ANOVA for continuous variables and a chi square test for categorical variables.
[c]p value for comparison between women and men, using t-test for continuous variables and a chi square test for categorical variables.

excluded. Further excluding 438 men who did not participate in wave 3 and 283 men who had missing data of frailty at wave 4 left 1060 men for analysis.

Predictor variables, outcome variable, covariates, and statistical analyses are summarized in Text S1.

RESULTS

To assess incident frailty risk according to age at menopause, those who were already frail at baseline (wave 2) and those with missing information of frailty status at follow-up (wave 4) were excluded, leaving 1249 non-frail older women for analysis. Table 1 presents the baseline characteristics of 1249 older women according to age at menopause groups. The range of age at menopause was from 10 to 75 years old, with a mean of 47.9 years and a median of 50 years. Women with earlier age at menopause tended to be prefrail rather than robust, current smokers, not married, and widowed. No significant associations over age at menopause groups were observed regarding age, alcohol, wealth, education, age at menarche, number of children, and cardiovascular diseases. Women with premature or early menopause were more likely to have surgical menopause (48.9%) compared with women with normal (12.0%) or late menopause (9.8%). Women ($n = 23$) who had participated at waves 2 and 3 but had not survived until wave 4 were significantly more likely to be older ($p = 0.02$) and more prefrail rather than robust ($p = 0.01$). There were no significant associations between these two groups in smoking, alcohol, wealth, and education.

Table 2 shows the results of binomial logistic regression models. First, age at menopause was used as a continuous variable. Model 1 adjusting for age showed that one-year later menopause age was associated with a 3% decrease in incident frailty risk (Odds ratio [OR] = 0.97, 95%CI = 0.95–0.99, $p < 0.01$). Further adjusting for smoking, alcohol, wealth, education (Model 2: OR = 0.97, 95%CI = 0.95–1.00, $p = 0.001$) and additionally for marital status, age at menarche, and number of children (Model 3: OR = 0.97, 95%CI = 0.95–1.00, $p = 0.02$) showed similar results. Proportions of participants who developed frailty over 4 years are depicted in Figure 1. Restricted cubic splines with Model 3 showed no evidence of nonlinearity in association between age at menopause (as a continuous variable) and incident frailty risk ($p = 0.11$, Figure S2).

Second, age at menopause was categorized into premature/early, normal, and late menopause groups and entered into the models with the normal menopause age group as a reference group. In Model 1 adjusting for age, women with premature or early menopause were significantly more likely to develop frailty (OR = 1.93, 95% CI = 1.34–2.77, $p < 0.001$) than women with normal menopause. The findings did not essentially change in Model 2 adjusting further for smoking, alcohol, wealth, and education and in Model 3 adjusting further for marital status, age at menarche, and number of children (Model 2: OR = 1.90, 95%CI = 1.28–2.81, $p = 0.001$, Model 3: OR = 2.00, 95%CI = 1.35–2.97, $p = 0.001$).

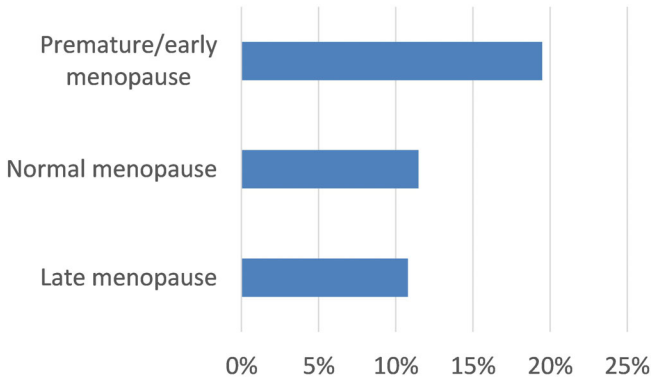

FIGURE 1 Proportions of participants who developed frailty over 4 years across age at menopause groups

TABLE 2 Age at menopause and risk of incident frailty over 4 years among 1249 non-frail (robust or prefrail) community-dwelling older women in England

Variable (incident case/total)	Model 1 Odds ratio (95%CI)	*p* value	Model 2 Odds ratio (95%CI)	*p* value	Model 3 Odds ratio (95%CI)	*p* value
Age at menopause (171/1249)	0.97 (0.95–0.99)	<0.01	0.97 (0.95–1.00)	0.02	0.97 (0.95–1.00)	0.02
Age at menopause groups						
Premature/early menopause (69/354)	1.93 (1.34–2.77)	<0.001	1.90 (1.28–2.81)	0.001	2.00 (1.35–2.97)	0.001
Normal menopause (91/793)	1.0	ref	1.0	ref	1.0	ref
Late menopause (11/102)	1.02 (0.51–2.05)	0.95	1.08 (0.52–2.22)	0.84	1.08 (0.52–2.24)	0.83

Note: Model 1: Adjusted for age. Model 2: Adjusted for age, smoking, alcohol, wealth, and education. Model 3: Adjusted for age, smoking, alcohol, wealth, education, marital status, age at menarche, and number of children.

Abbreviations: CI, confidence interval; ref, reference.

TABLE 3 Supplementary analyses on age at menopause and risk of incident frailty

Variable (incident case/total)	Model 4[a] Odds ratio (95%CI)	*p* value	Model 5 Odds ratio (95%CI)	*p* value	Model 6 Odds ratio (95%CI)	*p* value	Model 7[a] Odds ratio (95%CI)	*p* value
Age at menopause (171/1249)	0.97 (0.94–1.00)	0.03	—	—	—	—	0.97 (0.95–0.99)	0.02
Age at menopause groups								
Premature/early menopause (69/354)	2.22 (1.37–3.61)	0.001	—	—	2.29 (1.51–3.48)	<0.001	2.05 (1.38–3.05)	<0.001
Normal menopause (91/793)	1.0	ref	—	—	1.19 (0.82–1.73)	0.36	1.0	ref
Late menopause (11/102)	1.20 (0.55–2.60)	0.65	—	—	1.29 (0.62–2.70)	0.50	1.05 (0.51–2.19)	0.89
Surgical menopause	—	—	1.27 (0.82–1.97)	0.28	—	—	—	—
Men (94/1060)	—	—	—	—	1.00	ref	—	—

Note: Model 4: Adjusted for age, smoking, alcohol, wealth, education, marital status, age at menarche, and number of children, without those who had surgical menopause. Model 5: Adjusted as Model 4, with surgical menopause as a predictor variable. Model 6: Adjusted for age, smoking, alcohol, wealth, education, marital status, and number of children, with 1,060 non-frail men as reference. Model 7: Adjusted as Model 4 and further for cardiovascular diseases.
Abbreviations: CI, confidence interval; ref, reference.
[a]Includes two sets of results with age at menopause as a continuous variable and categorical variable.

There were no significant differences in incident frailty risk between women with late menopause and women with normal menopause in all models.

Four additional models, Models 4 to 7 were conducted as supplementary analyses (Table 3). Results of Model 4, which excluded those who reported surgical menopause, was similar to that of Model 3. In Model 5, surgical menopause was used as a predictor variable and found to be not significantly associated with incident frailty risk (OR = 1.27, 95%CI = 0.82–1.97, $p = 0.28$). In Model 6, 1060 non-frail male participants aged 60 or older who also participated in the Life History Interview were included and used as a reference group. Women with premature or early menopause had more than twice greater risk of indent frailty compared with men (OR = 2.29, 95%CI = 1.51–3.48, $p < 0.001$). The incident frailty risk of women with normal and late menopause was not statistically different from that of men (OR = 1.19, 95%CI = 0.82–1.73, $p = 0.36$ and OR = 1.29, 95%CI = 0.62–2.70, $p = 0.50$, respectively). In Model 7, further adjusting for cardiovascular diseases did not produce significant changes (1 year increase in age at menopause: OR = 0.97, 95%CI = 0.95–0.99, $p = 0.02$, premature or early menopause: OR = 2.05, 95%CI = 1.38–3.05, $p < 0.001$, late menopause: OR = 1.05, 95%CI = 0.51–2.19, $p = 0.89$).

The results of two sets of sensitivity analyses including 23 women who died during follow-up assigned as either developing frailty or not developing frailty were essentially unchanged (data not shown).

DISCUSSION

The current study analyzed the data of community-dwelling women aged 60 or older from ELSA and showed the existence of a significant inverse association between age at menopause and incident frailty risk and that women with premature or early menopause had a significantly higher risk of incident frailty than women with normal menopause. Surgical menopause does not appear to be associated with incident frailty. Incident frailty risk of women with normal and late menopause was similar to that of men.

Evidence on the associations between age at menopause and frailty risk is scarce. Only two cross-sectional studies[25,26] were found focusing on associations between age at menopause and frailty. The first cross-sectional study from South Korea examined the association between age at menopause and frailty defined by the modified Cardiovascular Health Study frailty criteria, i.e. the same as those used in our study, in 1264 older women aged 70–84.[25] The study found that 1 year increase in age at menopause was significantly associated with 5% decrease in risk of being frail (OR = 0.95, 95%CI = 0.91–0.98) controlling for multiple covariates.[25] It also used age at menopause as a categorical variable and found a decreasing tendency of frailty risk as age at menopause increased: adjusted ORs were 0.83, 0.58, and 0.38 for early (age 40–45), normal (age 46–54), and late (age 55–64), with premature (age 30–39) as a reference group, although all OR were statistically insignificant.[25] Another cross-sectional study including more than 9000 middle-aged and older

women from the Canadian Longitudinal Study of Aging used two frailty criteria, the Cardiovascular Health Study criteria and the Frailty Index, and analyzed associations with age at menopause in separate models.[26] Age at menopause was used as a continuous variable as well as a categorical variable (premature: 30–39 years old, early: 40–44 years old, normal: 46–54 years old, and late: 55–62 years old). Although no significant association was found between both continuous and categorical age at menopause variables and prevalent frailty defined by the Cardiovascular Health Study criteria, there was a similar decreasing trend: adjusted ORs were 1.33, 1.11, and 0.89 for premature, early, and late menopause, with normal menopause as a reference group. Linear regression models using the Frailty Index showed that a 1 year increase in age at menopause was associated with decreased degree of frailty ($\beta = -0.0012$, $p < 0.001$) and that premature and early menopause were significantly associated with increased degree of frailty compared with normal menopause ($\beta = 0.024$, $p < 0.001$; $\beta = 0.012$, $p < 0.01$, respectively) while late menopause was not ($\beta = 0.003$).[26] Although a precise comparison is not possible due to study design (cross-sectional vs. prospective), all previous and current studies showed an overall, either significant or nonsignificant, tendency of decreasing risk of frailty as age at menopause increased.

Only one study was found that examined surgical menopause as a predictor of frailty in 7699 community-dwelling women aged 65 and older from the Study of Osteoporotic Fracture.[29] Surgical menopause was defined as self-report of undergoing bilateral oophorectomy before menopause. This is a more detailed definition than self-report of "surgery" as a cause of surgical menopause used in our study.[29] Frailty was defined using the Study of Osteoporotic Fracture index, which has been validated as being comparable with the Cardiovascular Health Study criteria.[29] Surgical menopause was not associated with risk of incident frailty (OR = 0.94, 95%CI = 0.72–1.22), which is similar to the findings of our study.

Although the present study has found that earlier menopause was associated with higher risk of incident frailty, exact mechanisms underlying this association are not fully understood. Menopause is a normal physiological event in women and is characterized by drastic hormonal changes as a result of loss of ovarian function. Estrogen, which decreases with menopause, is one of the sex hormones that have various impacts on multiple physiological systems. It is considered that estrogen is beneficial to musculoskeletal systems and its decreased levels impair muscle mass, strength, and function.[30] Women with earlier menopause may experience shorter duration of estrogen exposure or earlier onset of estrogen deficiency, and eventually have higher risk of frailty, as shown in this study. In fact, menopause was shown to be an independent predictor of decreased muscle strength and balance,[31] and a meta-analysis has found that estrogen-based hormone therapy in postmenopausal women improves muscle strength.[32] In addition, a recent systematic review and meta-analysis including four cross-sectional studies showed that premature and early menopause were associated with weaker grip strength and lower gait speed, both of which are components of the frailty phenotype criteria.[33]

Another possibility accounting for the link between earlier menopause and higher frailty incidence may be related to certain conditions that cause menopause at earlier age and increase risk of frailty. Etiology of premature menopause (menopause at age 40 or younger) is frequently idiopathic, but some of the causes include genetic, autoimmune, or infectious diseases.[34] Iatrogenic causes are surgery, such as oophorectomy or hysterectomy, radiation, and chemotherapy.[34] These diseases and medical conditions requiring such treatments (cancer etc.) may well cause physiological decline and increase risk of frailty in women.

The major strengths of this study are a large sample size, a prospective study design, and the use of a wide range of potential confounders for adjustment. Moreover, several supplementary analyses were conducted to explore incident frailty risk according to surgical menopause or stratified by age at menopause in women compared with that in men. However, this study is not without limitations. First, information about menopause was collected via self-reported questionnaire therefore may potentially be subject to recall bias. Nonetheless, being a major event in women's lives, menopause onset may be less affected by recall bias, and self-reported age at menopause was shown to be reasonably accurate within 1–2 years.[35] Second, frailty phenotype components were slightly modified according to the availability of ELSA data, as in other frailty studies, which may have affected the findings.[36] While the original low physical activity criterion was defined as being in the lowest quintile of expended kilocalories based on the Minnesota Leisure Time Activities Questionnaire,[37] the criterion used in this study was defined as being sedentary or low activity based on the responses to interview questions on intensity and frequency of physical activities. This methodology was derived from a validated physical activity interview employed in the HSE[38] and has been validated against muscle strength, inflammatory markers, and depressive symptoms in older adults.[39,40] Third, although various covariates were used for adjustment, possibility of unknown or unmeasurable residual confounding factors cannot be eliminated. Fourth, information regarding the type or date of surgery that had caused menopause was not available. Fifth, given that frailty is associated with

mortality, death might have introduced bias by competing the risk. Twenty-three women who died during follow-up were significantly older and more prefrail rather than robust compared with those who survived, therefore, the risk of incident frailty might have been underestimated. In addition, sensitivity analyses assigning those who died during follow-up as either developing frailty or not developing frailty did not essentially change the results. Last, the ELSA cohort includes only the population of England and may not be generalizable to populations in other countries.

In conclusion, this study showed that earlier menopause was significantly associated with higher risk of developing frailty in community-dwelling older women. Our findings suggest that menopause or its related factors, such as, possibly, a decline in estrogen at menopause, potentially play an important role in the sex difference in frailty. Further research is warranted to better understand the pathophysiology of frailty in order to develop effective preventive strategies and therapeutic approaches for a better management of patients' quality of life.

AUTHOR CONTRIBUTIONS

Study concept and design: Gotaro Kojima, Yu Taniguchi, Reijiro Aoyama, and Tomohiko Urano. Analysis and interpretation of data: Gotaro Kojima, Yu Taniguchi, Reijiro Aoyama, and Tomohiko Urano. Drafting the article: Gotaro Kojima. Revising the article critically for important intellectual content: Yu Taniguchi, Reijiro Aoyama, and Tomohiko Urano. Final approval of the version to be published: Gotaro Kojima, Yu Taniguchi, Reijiro Aoyama, and Tomohiko Urano.

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CONFLICT OF INTEREST

None.

SPONSOR'S ROLE

None.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Figure S1. Flow chart of ELSA participants.

Figure S2. Restricted cubic spline curve describing association between age at menopause and incident frailty risk.

Text S1. Methods.

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