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Research Article

Frailty Is Inversely Related to Age at Menopause and Elevated in Women Who Have Had a Hysterectomy: An Analysis of the Canadian Longitudinal Study on Aging

Chris P. Verschoor, MSc, PhD[1,2] and Hala Tamim, PhD, MPH[3]

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada. [2]McMaster Institute for Research on Aging, Ontario, Canada. [3]School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada.

Address correspondence to: Chris P. Verschoor, MSc, PhD, Department of Health Research Methods, Evidence and Impact, McMaster University, 1280 Main Street West, MIP 207A, Hamilton, Ontario L8S 4K1, Canada. E-mail: cversch@mcmaster.ca

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Abstract

Background: Frailty is a complex pathophysiological phenomenon that will impact a significant proportion of adults over the age of 65 and contributes to the risk of several adverse health outcomes. Although women have a disproportionately higher risk of frailty, the sex-specific factors related to this syndrome are not well described. Hence, we sought to examine the relationship of age at menopause, hysterectomy status, and hormone replacement therapy use with prevalent frailty in older women.

Methods: We performed a cross-sectional analysis of the Canadian Longitudinal Study on Aging (CLSA) Baseline Comprehensive Cohort (n = 30,097, 45–85 years old). Frailty was operationalized using both the deficit accumulation (frailty index) and frailty phenotype (Fried) models. Postmenopausal women were categorized as follows: premature (30–39 years), early (40–45 years), normal (46–54 years), and late (55+ years) menopause, or hysterectomy. Associations were determined using multivariate analysis, adjusting for sociodemographics, lifestyle factors, social support, and hormone replacement therapy use.

Results: Age at menopause was inversely related to frailty in older Canadian women. The frailty index decreased 1.2% of the mean (p < .001) with every year of menopause onset and was significantly higher for women in the premature (24%; p < .001) and early (8%; p < .01) menopause and hysterectomy (21%; p < .001) groups, compared to the normal menopause group. The odds for being classified as frail using Fried's criteria was higher for the premature menopause (OR = 1.45, 95% CI = 0.75–2.81) and hysterectomy (OR = 1.48, 95% CI = 1.11–1.99) groups.

Conclusions: Our study supports a role for age at menopause and hysterectomy in the risk of frailty in older women and warrants further investigation.

Keywords: Frailty, Menopause, Aging, Hormone replacement therapy, CLSA.

The geriatric syndrome known as frailty represents a decline in physical strength, endurance, and physiological function, resulting in an increased vulnerability to disease, loss of independence, and, ultimately, likelihood of death (1). Not surprisingly, it also represents a significant economic burden, increasing health care costs related to acute, ambulatory, and end-of-life care (2,3). While frailty naturally occurs with age, research over the past 15 years has shed much light on its determinants, which include adverse events, both acute and chronic, lifestyle choices, and factors related to social vulnerability and socioeconomic status (4). Interestingly, results have consistently shown that women have higher rates of frailty, which cannot be simply explained by their commonly longer life span (5). A recent meta-analysis of five studies totaling nearly 40,000 participants found that regardless of age, women have higher rates of frailty as well as lower rates of mortality; hence, compared to men, women are better at accumulating deficits that contribute to the frailty syndrome without dying (6).

Menopause is one of the most significant biological events in a woman's life, featuring a sharp decline in female sex hormone levels over an average of 5 years to levels below that of the prepubertal

years (7). This is in stark contrast to men, who experience only a gradual decline in testosterone as they age and can exhibit substantial levels well into their 90s (8). The age at natural menopause is around 50 years but can occur in women as early as their late 30s, and for reasons that have yet to be elucidated, women who reach menopause prematurely are at a much greater risk of negative health outcomes, including cardiovascular disease (9) and mortality (10); this has been similarly shown for women who received an ovariectomy prior to the natural age at menopause (11). Establishing that frailty is related to the time at which female sex hormone exposure declines (ie, menopause) would provide an important clue regarding the underlying biological mechanisms that drive the risk of frailty in women. To our knowledge, this relationship has yet to be examined in the literature.

In the following study, we sought to examine the relationship between frailty and age at menopause in community-dwelling adults. As a secondary objective, we also considered other factors related to women's health, such as the characteristics of hormone replacement therapy (HRT) usage. For this, we performed a cross-sectional analysis of the Canadian Longitudinal Study on Aging (CLSA), operationalizing frailty using both the deficit accumulation (Rockwood's frailty index (12)) and frailty phenotype (Fried's frailty (13)) models.

Methods

Cohort Description

The following study was a cross-sectional analysis of data from the CLSA baseline collection (2012–2015). The CLSA is a 20-year longitudinal study, including 50,000 community-dwelling participants between the ages of 45 and 85 who are able to read and speak in English or French, and excludes those who reside in nursing homes, on First Nations reserves or the Canadian territories, full-time members of the armed forces, or those with significant cognitive impairment (14). Our study was based on the comprehensive cohort (Comprehensive Baseline Dataset, version 3.0), which includes 30,097 community-dwelling adults aged 45–85 (15,320 women, 14,777 men) who provide data in-person at one of ten data collection sites nationwide. The remainder of CLSA participants, known as the tracking cohort (n = 20,000), provide data by telephone interview and have been previously employed for studies of women's health (15) and frailty (16). The CLSA study design and methods have been previously described by Raina and colleagues (14).

Menopause-Related Classifications and Other Women's Health-Related Variables of Interest

For all variables considered, questions answered as "refused" or "do not know" were treated as missing data. For analyses involving age at menopause or related variables, we excluded women who were diagnosed with breast, ovarian, or other genital cancer, as these cancers are known risk factors for early menopause (17); who refused, did not know, or had missing data with regards to menopause classification; whose reported age at menopause was less than 30 or greater than 62 (similar to previous work (18)); and whose age at menopause was 5 years or less from their chronological age (considered the perimenopause period, which is physiologically distinct from the postmenopausal period and may, therefore, skew health-related measures (19)). After exclusion, 9,561 women remained in the sample. Our final menopause-related classifications were as follows: premature (30–39 years; n = 298), early (40–45 years; n = 1,213), normal (46–54 years; n = 4,747), and late (55–62 years; n = 1,121); women who reported having a hysterectomy represent 2,182 of the final sample (Figure 1). Classifying premature menopause earlier than 40 has been previously suggested (20), and the range for normal menopause represents the upper and lower quintile range for age at menopause. Age and type (eg, including removal of ovaries) of hysterectomy was not available.

In addition to menopause-related classification, we also investigated variables associated with HRT use. This includes HRT use ever, age at first use, length of use, and types of HRT used. Summary statistics for menopause classification and HRT-related variables can be found in Supplementary Table 1.

Operationalization of Frailty and Construct Validity

We operationalized frailty in our study using the two most commonly used approaches in the literature: the deficit accumulation model (frailty index) (12) and the frailty phenotype model (Fried's frailty) (13). The frailty index represents a non-weighted sum of accumulated health-related deficits, and for our study was based on 93 deficits including variables related to chronic diseases, functional status, activities of daily living, depression, satisfaction with life, nutritional risk, physical activity, and perceived health. Specific details regarding the CLSA variables employed, deficit classification, and relevant summary statistics can be found in Supplementary Table 2. We considered a frailty index measurement as missing if 15% or more deficits (14 in total) were missing for any given participant (n = 345). Fried's frailty assesses five dimensions of adverse functioning and disability at the core of the frailty syndrome (weakness, exhaustion, weight loss, slowness, and low physical activity) and is scored between 0 and 5, based on the presence of each component. Specific details regarding the classification of each dimension/component including the CLSA variables employed and relevant summary statistics can be found in Supplementary Table 3. We considered the Fried's frailty measurement as missing if any of the five components were missing for any given participant (n = 4,055). For this study, the frailty index was considered only as a continuous variable, while Fried's frailty only as a categorical variable using the following commonly used scoring cut-points (13): healthy/robust = 0, pre-frail = 1–2, and frail = 3 or more dimensions present.

As a means to validate our frailty constructs, we assessed their relationship with health-related variables that would be expected to occur with frailty, but are not specifically included in either construct. They include: needing professional or family care, able to stand or walk without assistance, and number of falls or injuries over the past 12 months. Summary statistics for these variables and our frailty constructs can be found in Supplementary Table 1.

Covariates

We assessed the following variables as potential confounders in the relationship between menopause-related classifications and frailty: age, ethnicity, smoking, alcohol consumption, marital/partner status, coresidence (not living alone), income, education, and social vulnerability/support. Sex was also considered as a covariate in models in which women's health-related variables were not included. For ethnicity, participants were asked the ethnic background of their parents. Smoking and alcohol consumption were based on the reported frequency over the last 12 months, and excessive (binge) drinking was classified by the CLSA as having four or more drinks in a single sitting if female, and five or more if male. Social support/vulnerability was measured using the Medical Outcomes Study Social Support Survey (MOS-SSS); it is scored between 0 and 5, where lower scores indicate lower social support and greater social

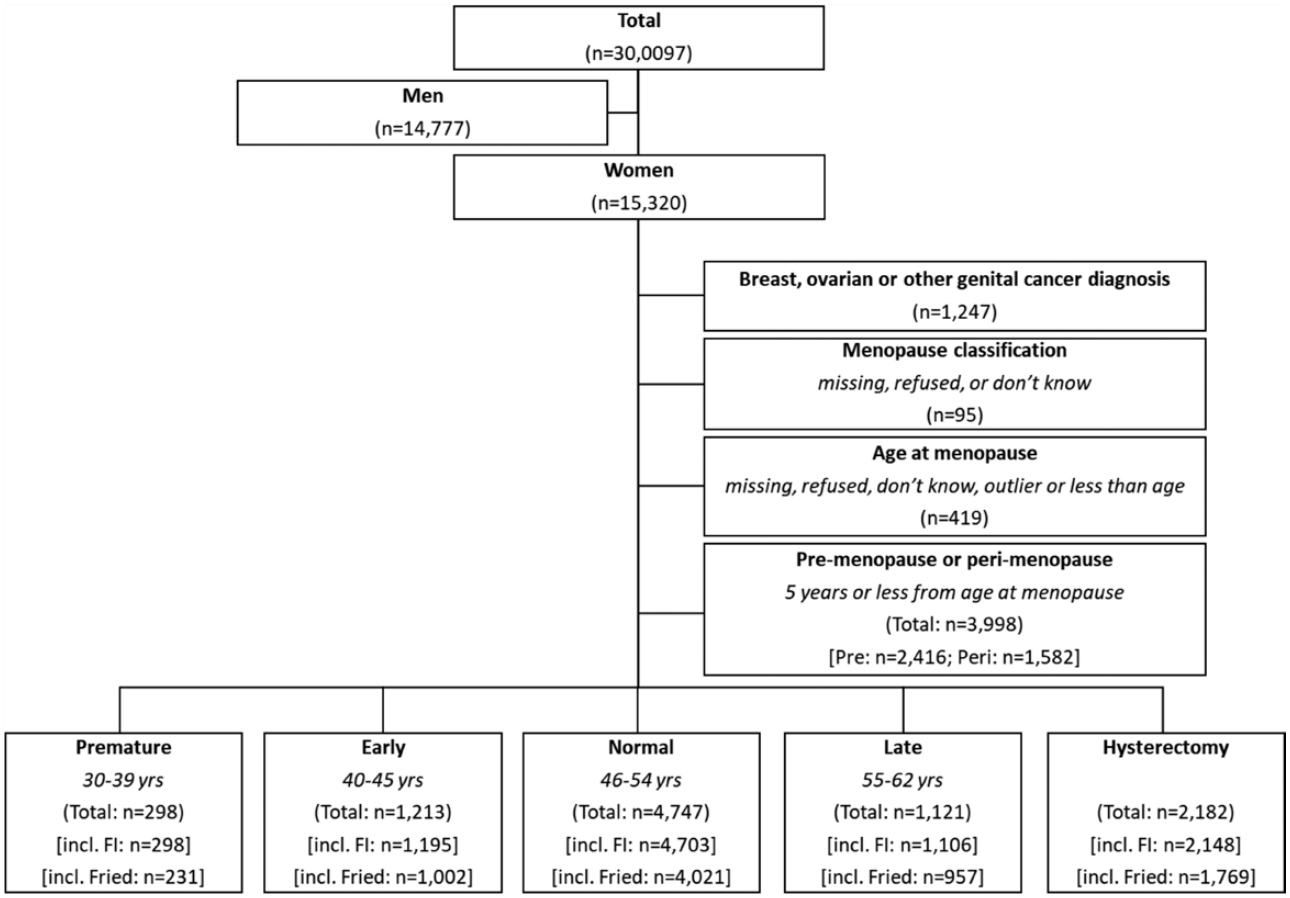

Figure 1. Flowchart describing the inclusion and exclusion of participants for analyses involving age at menopause and related factors. Age at menopause was classified as normal (46–54 years), premature (30–39 years), early (40–45 years), or late (55–62 years). After exclusion, 9,561 women remained in the sample. "Incl. FI" and "incl. Fried" indicate the number of participants in that group that also have a frailty measurement for the frailty index (FI) and Fried's frailty, respectively.

vulnerability. Summary statistics for these variables can be found in Supplementary Table 1.

Statistics

All statistics and analyses were performed in R version 3.3.2. Descriptive statistics are presented as the mean ± *SD*, unless specified otherwise. Multiple linear and logistic regressions were used to determine associations with the frailty index and Fried's frailty, respectively. Associations with the frailty index are presented as the regression coefficient (β) with the 95% confidence interval, whereas associations with Fried's frailty are presented as the odds ratio (OR) for being classified as frail (three or more components) with the 95% confidence interval. A p value <.05 was considered statistically significant. Regression models for frailty against covariates and adverse outcomes were adjusted for age and sex, whereas models investigating age at menopause and related variables were adjusted for age, marital status, ethnicity, coresidence, smoking, alcohol consumption, annual income, education, social support score, and HRT use. The adjusted effect of age at menopause on the frailty index was plotted using the R package "effects."

Results

The Prevalence of Frailty in Older Canadian Adults

In our total sample, including all men and women in the CLSA Baseline Comprehensive Cohort, the average (±*SD*) frailty index was 0.101 ± 0.069 (min/max = 0/0.53); women exhibited higher frailty, 0.109 ± 0.073, as compared to men, 0.093 ± 0.063. Frailty increased linearly with age, 0.0023 (2.3% of the mean) per year, with the 99th percentile plateauing around 60 years of age (Figure 2A). In women, this yearly increase was 0.0026 (2.6% of the mean), whereas in men, the increase was 0.0021 (2.1% of the mean). Using Fried's frailty, the prevalence of frailty in our total sample was 5.9%, or 2.5% in participants 45–65 years old, and 11.6% in those older than 65 (Figure 2B). In the total sample, 6.1% of women were classified as frail, whereas 5.7% of men were frail; in those older than 65, 12.5% of women and 10.8% of men were frail. We also directly compared our estimates of frailty using the frailty index and Fried's frailty (Figure 2C). As expected, the frailty index increases in a linear fashion with each component level of Fried's frailty, and the average frailty index corresponding to a frail classification using Fried's criteria is 0.20 (median = 0.19).

The Association Between Frailty and Factors Related to Sociodemographics, Lifestyle, Social Vulnerability, and Health

To further examine our frailty constructs, we used regression analysis to assess their relationship with factors that have been previously associated with frailty. Both the frailty index and the odds of being classified as frail by Fried's criteria are higher in women, lower for participants whose parents were born in the United Kingdom or

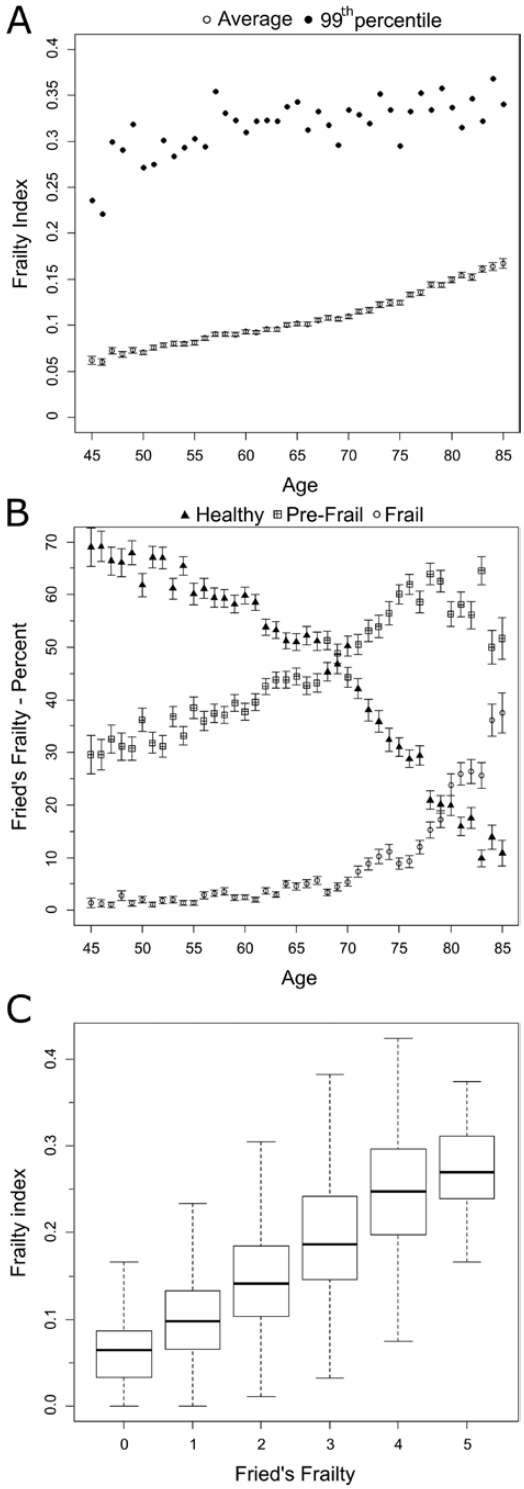

Figure 2. Patterns of frailty with age in the Canadian Longitudinal Study on Aging (CLSA), including both men and women. (A) The average frailty index increases with age in a linear fashion, while the 99th percentile plateaus around 60 years of age. (B) The percentage of individuals classified as healthy/robust (0 components) using Fried's frailty decreases with age, while the percentage of individuals classified as pre-frail (one or two components) or frail (three or more components) increases. For (A) and (B), error bars represent the *SE*. (C) The distribution of the frailty index for each level of Fried's frailty indicates that both indices are highly correlated.

Ireland (as compared to Canada), and increase with age and smoking (current status and daily frequency) (Supplementary Table 4). Interestingly, frailty is reduced with alcohol consumption, where those who never drink have a higher frailty index and an odds of being classified as frail as compared to those that drink at various intervals monthly, weekly and daily; however, the opposite is observed when considering excessive alcohol consumption (binge drinking) (Supplementary Table 4).

We also considered variables related to social vulnerability and socioeconomic status, need for assistance, falls, and injuries. Both the frailty index and odds for being classified as frail were significantly lower for participants that are married or widowed (as compared to being single) and live with at least one other person (Supplementary Table 5). Similarly, frailty was lower for those with a greater reported income, higher level of education obtained, and better overall social support (estimated using the MOS-SSS social support scale; higher scores indicate greater social support) (Supplementary Table 5). As expected, both frailty measures were associated with the need for family or professional care, an inability to stand or walk without assistance, and increased with the frequency of falls or injuries over the past 12 months (Supplementary Table 5).

Early Menopause and Having Had a Hysterectomy Is Associated With Greater Frailty Later in Life

Our primary objective was to assess whether the age a woman reaches menopause or if having had a hysterectomy is associated with frailty later in life. After removing pre- and perimenopausal women as well as women with potentially confounding medical histories, we categorized age at menopause accordingly: premature (30–39 years), early (40–45 years), normal (46–54 years), and late (55–62 years). For the frailty index, although there appears to be little difference between women that reached menopause normally and late, it is markedly higher for women who reached menopause early or prematurely, or had a hysterectomy (Figure 3A). After adjusting for age, marital status, ethnicity, coresidence, smoking, alcohol consumption, annual income, education, social support, and HRT use ever (adjusted $r^2 = 0.283$), frailty was 0.008 higher (8% of the mean; $p < .01$) for early menopause, 0.024 higher (24% of the mean; $p < .001$) in premature menopause, and 0.021 higher (21% of the mean; $p < .001$) with hysterectomy, compared to normal menopause (Table 1). The frailty index was also significantly associated with age at menopause as a continuous measure, declining 0.0012 (1.2% of the mean; $p < .001$) per year (Figure 3C; Table 1). The odds of being classified as frail by Fried's criteria was only significantly associated with having had a hysterectomy (OR = 1.48; $p < .01$), although the effect of premature menopause is notable (OR = 1.45, 95% CI = 0.75–2.81) (Figure 3B; Table 1). Of note, we repeated the above analyses with body mass index included as a covariate and did not see any appreciable difference in the subsequent results (data not shown).

Relationship Between Frailty and HRT Use

Given that HRT use is known to be associated with health outcomes (21), we also examined the relationship between frailty and HRT-related variables that are collected by the CLSA; namely, HRT use ever, age of onset and length of use, and type of HRT used. Only HRT use ever, adjusted for the aforementioned covariates, was found to be significantly associated with frailty. The frailty index was 0.005 higher (5% of mean; $p < .01$) in women who had taken HRT, while the odds for being classified as frail using Fried's criteria was

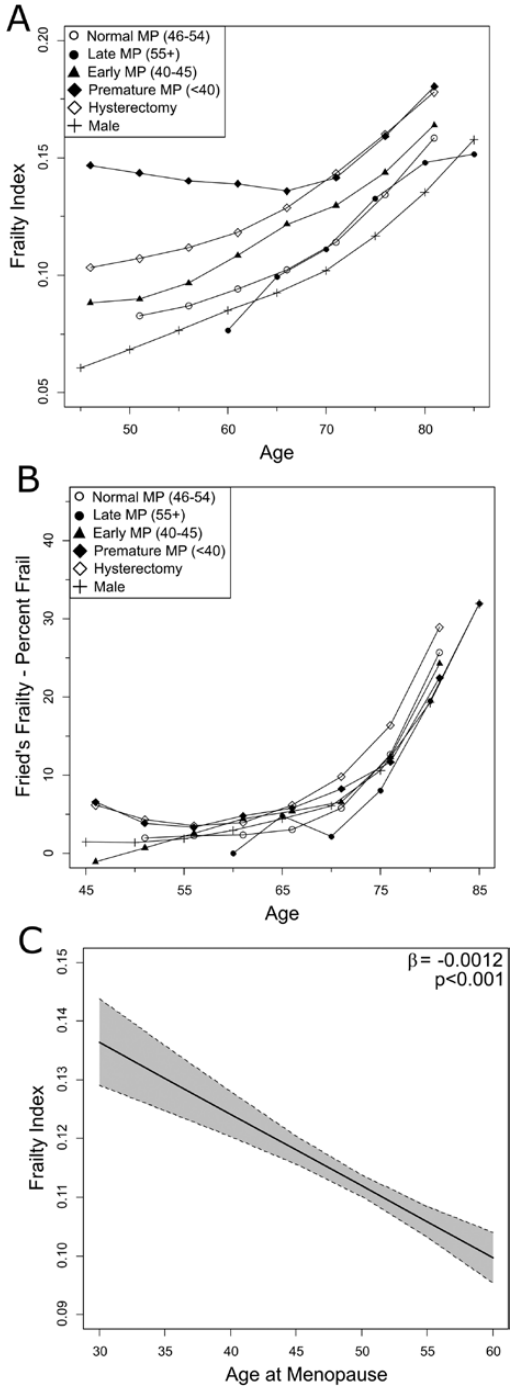

Figure 3. Frailty is higher for woman who reached menopause (MP) earlier or who had a hysterectomy. Age was plotted against (A) the frailty index, and (B) the percentage of individuals considered frail (three or more components) by Fried's frailty, for women classified as reaching MP normally (46–54 years), premature (30–39 years), early (40–45 years), or late (55–60 years), or as reporting having had a hysterectomy; males are also shown as a benchmark. Each curve was generated using a LOESS smoothing procedure. (C) Age at MP is also significantly inversely related to the frailty index when considered as a continuous measure, adjusting for age, marital status, ethnicity, coresidence, smoking, alcohol consumption, annual income, education, social support score (Medical Outcomes Study Social Support Survey [MOS-SSS]), and hormone replacement therapy use ever; β= regression coefficient, and the shaded area represents the 95% confidence interval.

1.17, but not significant (95% CI = 0.91–1.50) (Table 2). None of the other variables were found to be associated with frailty (Table 2).

Discussion

The primary objective of this study was to examine the relationship between the age at which a woman reaches menopause (naturally or surgically) and frailty, measured using a deficit accumulation (Rockwood's frailty index) and phenotype (Fried's) model. To our knowledge, this was the first study to do so. For our investigation of age at menopause, we considered it both as a continuous variable and categorically. We divided postmenopausal women into five categories: premature (30–39 years), early (40–45 years), normal (46–54 years), and late (55+ years) menopause, and having had a hysterectomy. The premature and early group made up 1.9% and 7.9% of our total female sample, respectively, which is similar to that reported for other developed nations (22). Using multivariate regression, we found that premature and early menopause and hysterectomy status was associated with a significantly increased frailty index, while classification as frail using Fried's criteria was significantly associated with hysterectomy status and trended towards significance for premature menopause; we also found that the frailty index significantly correlated with age at menopause as a continuous variable, declining 1.2% per year. When placed in the context of other factors examined in this study, the effect of age at menopause/hysterectomy on frailty is substantial. The effect of early menopause is similar to that of occasional smoking or excessive drinking once a week, while premature menopause or hysterectomy status is similar to that of excessive drinking two to three times per week, living alone, or being married/widowed.

Age at menopause and having had a hysterectomy being associated with frailty later in life is in line with our hypothesis and consistent with others studies investigating health outcomes. For example, early or premature menopause has been related to the risk of stroke (23) and osteoporosis (24), as well as mortality (10); similar observations have been shown regarding hysterectomy status (11). Although a specific mechanism has yet to be established, recent work has suggested that it is likely biologically driven. For example, accelerated cellular aging, which is strongly associated with frailty (25), can be observed with early age at menopause in humans (26) and artificially induced menopause (ovariectomy) in mice (27). Chronic inflammation, a phenomenon that occurs with age and age acceleration (28), and increases the risk of adverse health outcomes may also play a role. While the data are sparse in humans, rodent studies have shown that artificially induced menopause increases the levels of proinflammatory cytokines (29). It is tempting to surmise that the loss of female sex hormones acts harbinger of adverse health-related outcome later in life; however, further examination is required in order to substantiate such a conclusion. That being said, free testosterone, which declines gradually with age in both men and women, has been previously reported to predict frailty decline in men (30) and sarcopenia (muscle wasting) in women (31).

We also found that frailty was significantly higher in women that had previously used HRT, but not for other HRT-related variables, such as age of onset, length of use, or type of HRT used. This finding is perplexing given the state of the literature on the effects of HRT on different health outcomes. Most recent systematic reviews indicate that HRT use is beneficial or has no effect on the risk of or survival following breast, lung, or other cancers (32,33), while the effects on cognitive decline (34) and cardiovascular disease (35) is debatable. Many authors agree that conclusions drawn from observational data regarding the relationship between HRT use and health outcomes need to be approached with caution given the potential effect of

Table 1. Relationship Between Frailty and Age at Menopause/Hysterectomy Status

	Frailty Index, β (95% CI)		Fried–Healthy/Pre-frail vs. Frail, OR (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Age at menopause (years)	−0.0014 (−0.0017 to −0.0011)***	−0.0012 (−0.0016 to −0.0009)***	0.99 (0.97–1.01)	0.98 (0.95–1.01)
Menopause classification				
Normal (46–54 y)	Ref.	Ref.	Ref.	Ref.
Premature (30–40 y)	0.038 (0.029–0.046)***	0.024 (0.015–0.034)***	1.17 (0.7–1.95)	1.45 (0.75–2.81)
Early (41–45 y)	0.012 (0.008–0.017)***	0.008 (0.002–0.013)**	1.22 (0.94–1.6)	1.04 (0.71–1.53)
Late (55+ y)	0.003 (−0.002 to 0.008)	−0.004 (−0.01 to 0.001)	1.04 (0.78–1.38)	0.78 (0.51–1.19)
Hysterectomy	0.029 (0.025–0.032)***	0.021 (0.017–0.025)***	1.76 (1.44–2.14)***	1.48 (1.11–1.99)**

Note: CI = confidence interval; OR = odds ratio; Ref. = reference category. Age at menopause and menopause groups were analyzed in separate models. Adjusted models include age, marital status, ethnicity, coresidence, smoking, alcohol consumption, annual income, education, social support score (Medical Outcomes Study Social Support Survey [MOS-SSS]), and hormone replacement therapy use ever. Models analyzing age at menopause (years) does not include women that reported having had a hysterectomy.

$^{**}p < .01$. $^{***}p < .001$.

Table 2. Relationship Between Frailty and Patterns of HRT Use

	Frailty Index, β (95% CI)		Fried–Healthy/Pre-frail vs. Frail, OR (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HRT use[a], yes (ref. = no)	0.011 (0.008–0.014)***	0.005 (0.002–0.009)**	1.17 (0.99–1.38)	1.17 (0.91–1.5)
Length of HRT use (years)[b]	0.0012 (0.0009–0.0014)***	0.0002 (−0.0002 to 0.0005)	1.03 (1.02–1.04)***	0.99 (0.97–1.01)
Age at HRT onset (years)[b]	−0.0013 (−0.0016 to −0.00099)***	−0.0004 (−0.0008 to 0.00005)	0.98 (0.97–1)*	1.01 (0.98–1.04)
Type of HRT used[b]				
Combined (estrogen + progesterone)	Ref.	Ref.	Ref.	Ref.
Estrogen alone	0.016 (0.011–0.021)***	0.003 (−0.003 to 0.009)	1.29 (0.98–1.71)	1.04 (0.68–1.58)
Progesterone alone	−0.001 (−0.011 to 0.01)	−0.002 (−0.015 to 0.01)	0.78 (0.39–1.58)	0.6 (0.2–1.81)
Estrogen gel	−0.01 (−0.018 to −0.001)*	−0.007 (−0.017 to 0.003)	0.67 (0.38–1.2)	1 (0.44–2.27)
IUD with progesterone	−0.015 (−0.043 to 0.012)	−0.006 (−0.04 to 0.028)	na	na

Note: CI = confidence interval; HRT = hormone replacement therapy; IUD = intrauterine device; na = unable to calculate the OR due to lack of events ($n = 0$); OR = odds ratio; Ref. = reference category.

[a]Adjusted model includes age, menopause classification, marital status, ethnicity, coresidence, smoking, alcohol consumption, annual income, education, and social support score. [b]Adjusted model includes length of HRT use, age of HRT onset, type of HRT used, and covariates employed in the above model.

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

latent confounders, discrepancies in self-reported data, and appropriate consideration for the exact HRT regimens used (21).

Major strengths of our study are the relatively large sample size and balanced design of the CLSA cohort as well as the completeness of its data, which is important given the low prevalence of women reaching menopause in their 30s and early 40s. Our study was inherently limited due to its cross-sectional nature, and the fact that many of the variables included were obtained via self-reported questionnaire. This raises the possibility of misclassification bias, although self-reported age at menopause has been previously shown to be nearly 90% accurate within 1–2 years (36), while self-reported HRT use is greater than 60% accurate (37). Also, while we were thorough in our inclusion of potential confounding variables in our analytical models evaluating the relationship between frailty and women's health-related variables, these models accounted for approximately 30% of the variation in frailty, and therefore a role for latent confounders is reasonable.

In summary, we show that age at menopause and having had a hysterectomy are significantly related to frailty later in life. Although our findings do not necessarily offer solid evidence regarding the disparity in frailty risk between women and men, they do suggest that the time at which sex hormones decline in women is certainly an important factor. Hence, the role of age at menopause and female sex hormones in the risk of frailty in older women warrants further investigation.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None reported.

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