2016

Surgical menopause and frailty risk in older community dwelling women: the study of osteoporotic fractures

BOSTON UNIVERSITY

SCHOOL OF PUBLIC HEALTH

Thesis

SURGICAL MENOPAUSE AND FRAILTY RISK IN COMMUNITY-DWELLING OLDER WOMEN: THE STUDY OF OSTEOPOROTIC FRACTURES

by

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B.A., Boston University, 2001

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2016

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SURGICAL MENOPAUSE AND FRAILTY RISK

IN COMMUNITY-DWELLING OLDER WOMEN:

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ABSTRACT

Background: Low testosterone levels in older women have been shown to be associated frailty. Whether older postmenopausal women with a history of bilateral oophorectomy before natural menopause resulting in lower testosterone levels (surgical menopause) have higher risk for frailty is not known. This prospective study investigated whether women who had surgically-induced menopause had a greater risk of frailty than naturally menopausal women. Furthermore, we also determined whether lower serum testosterone levels would be associated with frailty in our study population of older postmenopausal women.

Methods: The sample included 7699 community-dwelling white women aged ≥ 65 years from the Study of Osteoporotic Fractures (SOF). Participants were determined to have undergone surgical versus natural menopause based on whether or not they reported retrospectively having undergone a bilateral oophorectomy before or after menopause. Frailty status was classified as not frail, somewhat frail (hereafter referred to as Intermediate stage), frail or death at four interviews, conducted 6–18 years post-

baseline. Baseline serum total testosterone concentrations were available on a subset of 541 participants.

Results: Approximately 12.6% of the participants reported surgical menopause. A total of 39.7% were classified as somewhat frail (intermediate stage) and 10.1% as frail. Twenty-two (22.0%) of the participants died during the interview period when frailty was assessed. Mean age at baseline was 71.2 years. Total serum testosterone levels were significantly lower among surgically menopausal women compared to naturally menopausal women ($p<0.01$). Surgical menopause was not significantly associated with an increased risk of frailty (Odds Ratio=0.94; 95% CI=0.72–1.22), intermediate stage frailty (Odds Ratio=0.96; 95% CI=0.80–1.10) or death (Odds Ratio=1.17 ; 95% CI=0.97–1.42) after adjusting for age, BMI and number of IADL impairments. Stratified analyses showed that oral estrogen use did not modify these associations.

Conclusion: Among postmenopausal women, surgical menopause was not associated with a higher risk for frailty compared to naturally menopausal women, even in the absence of estrogen therapy. Future prospective studies are needed to investigate hormonal mechanisms involved in the development of frailty in older postmenopausal women.

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List of Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
IADL	Instrumental Activities of Daily Living
OR	Odds Ratio
SD	Standard Deviation
SOF	Study of Osteoporotic Fractures

BACKGROUND

Significance of Frailty in Older Postmenopausal Women

Frailty has become an increasingly important concept among clinicians as a complex biological syndrome in older individuals of increased vulnerability to stressors. Frailty results from age-related declines in physical function and physiologic reserves [1, 2]. As a result, frail individuals are at increased risk for disease and premature death [3]. Frailty has been consistently associated with higher rates of disability, morbidity and mortality [4]. Approximately 10.7% of community dwelling older individuals are frail and prevalence has been reported to be higher in women (9.2–10%) than in men (4.9–5.5%) [5]. The frailty phenotype was originally defined as having 3 or more of the following criteria: unintentional weight loss, self-reported exhaustion, weak grip strength, slow walking speed and low physical activity [2]; however, other modified definitions have been used [6]. The pathophysiology of frailty is not well understood but is thought to result from age-related dysregulation of multiple physiologic systems including inflammation, sarcopenia, nutrition and hormonal dysfunction [7–10]. Specifically, hormonal changes during menopause have been associated with decline in physical functioning and theorized to contribute to aging and frailty in older women [11]. Furthermore, approximately 1 in 9 women age 35–45 years has undergone hysterectomy, with 40% undergoing concurrent bilateral oophorectomy [12, 13], resulting in abrupt onset of menopause and decline in both serum testosterone and

estradiol levels. Although several studies have suggested an association of surgical menopause (premenopausal bilateral oophorectomy) with increased risk of cardiovascular disease, physical dysfunction, osteoporosis and mortality [14]; no prospective cohort study has assessed the impact of surgical menopause on long-term risk for frailty. Understanding how surgical menopause (a form of early menopause) contributes to the frailty syndrome is important in helping us target treatment and prevention strategies for better health outcomes as these women enter into older age.

Relationship of Menopause with Frailty

Age-related declines in sex steroids may be an important factor in the pathophysiology of frailty in older women. Lower serum testosterone levels in men have been shown in several studies to predict frailty in older men [15–17]. On the contrary, studies examining the association between sex hormones and frailty in women are scarce. Women experience age-related decline in hormones, particularly during the time of menopause. During natural menopause, the most significant change occurs with the sudden and permanent cessation of ovarian follicle formation and decline in estrogen production. In women, the menopausal transition has been associated with an accelerated loss of muscle mass and strength and subsequent decrease in physical function [18, 19], which in turn may increase risk for the development of frailty. Data from the Study of Women's Health Across the Nation (SWAN) study have also demonstrated association of the menopausal transition with decline in grip strength, an

important predictor of frailty status [19]. The decline in estrogen associated with menopause has long been suspected to be the cause of multiple aspects of poor health in women, including loss of muscle mass and strength, which are core features of the frailty syndrome. However, evidence is limited on whether this loss of estrogen significantly affects muscle mass and physical function as clinical trials of estrogen replacement in improving these measures in women have yielded conflicting results [20–22].

Relationship of Menopause and Testosterone Levels with Frailty

Because of the adverse sequelae related to sarcopenia, tremendous research has focused more recently on anabolic hormones (Testosterone, Insulin-like growth factor 1, dehydroepiandrosterone sulfate) and their relationship to physical health outcomes and frailty. Specifically, emerging evidence suggests that testosterone may play an important role in muscle performance and overall physical health in postmenopausal women. Serum testosterone levels are lower in older postmenopausal women than in young menstruating women; however, unlike estrogen, the decline does not change abruptly during natural menopause and becomes a major source of androgens contributing to approximately 50% of the total testosterone production [23]. In contrast to natural menopause, surgical menopause (premenopausal bilateral oophorectomy) does result in significant decline in testosterone levels [24]. Testosterone levels are known to decline progressively with age in women; and very low testosterone levels in older

women are associated with a higher prevalence of frailty [25]. Thus, women who have undergone surgical menopause may be at increased risk for frailty as bilateral oophorectomy is known to result in dramatic decline in testosterone levels [26].

Relationship Between Surgical Menopause and Physical Health Outcomes

In observational studies, surgically menopausal women report higher rates of physical limitation when compared to naturally menopausal women [11, 27]. In a large population-based longitudinal study of midlife women, women with surgical menopause (with or without estrogen) were found to have significantly reduced levels of several objective measures of physical function (2-pound lift, stair climb, timed walk, sit-to-stand) in addition to self-perceived decrease in physical functioning compared to naturally menopausal women [11]. Since lower testosterone levels are associated with frailty in older women [28], surgically menopausal women may be a population at risk. Evidence from these epidemiological studies raises the possibility that ovarian hormones may have a significant role in protection from physical disability and frailty. Hence, surgically menopausal women enter into a state of anabolic hormone deficiency (i.e. low testosterone) and may be at increased risk for physical limitations and frailty as they enter into older age. Thus, low testosterone levels may be a key regulator of the frailty process in these women. To our knowledge, no prospective study to date has compared the risk for developing frailty in surgically menopausal versus naturally menopausal women. Although previous studies have found that menopause is

associated with specific components of the frailty syndrome [19, 29], these studies did not differentiate between natural versus surgical menopause.

Aim of Current Study

Utilizing data from participants in the Study of Osteoporotic Fractures (SOF), we aimed to test the hypothesis that women who have undergone surgical menopause, which results in lower testosterone levels, would be at higher risk for developing frailty compared to women who went through menopause naturally; and that this risk would be attenuated with estrogen therapy. Furthermore, we hypothesized that lower serum testosterone levels would be associated with frailty.

METHODS

Study Sample

The sample for the current study was a subsample of participants enrolled in the Study of Osteoporotic Fractures (SOF). SOF is a multicenter, prospective cohort study of 9704 older community-dwelling white women ≥ 65 years of age recruited from 1986–1988 that was designed to study risk factors for osteoporosis, falls and fractures. Women who had previous history of fracture, undergone bilateral hip replacement or who were unable to walk without assistance were excluded. Participants were recruited from four U.S geographical areas: Baltimore, MD, Minneapolis, MN, the Monongahela Valley, PA and Portland, OR. Interviews and comprehensive clinical assessments were conducted approximately every two years since 1986 (Baseline visit through Visit 9, conducted between 1986 and 2008). A total of 9314 women at baseline, self-reported their age at menopause, whether they had one or both of their ovaries removed and if so, at what age. Of these 9314 women, 7699 had data on frailty status and death assessed at the 4th (conducted between 1992 and 1994), 5th (1995–1996), 6th (1997–1998) and 8th (2004–2005) SOF visits. A total of 1012 of the 9314 women died before the 1st frailty assessment. Thus, we used 18 years of prospectively collected incident frailty data from SOF. The present analysis was restricted to 7699 women with available data on menopause history, frailty status and death during these 18-years of follow-up. (**See Figure 1**)

Type of Menopause

At baseline, reproductive history by interviewer-administered questionnaire was obtained including history and age of hysterectomy and/or oophorectomy (unilateral or bilateral) and age at menopause (defined as "age of last menstrual period" + 1 year for naturally menopausal women or age when bilateral oophorectomy was performed for surgically menopausal women). A participant was considered to have had surgical menopause if she had both ovaries removed prior to menopause. Participants who had at least one ovary after her reported age at menopause were classified as having natural menopause, which was the reference group for our analyses. We also conducted secondary analyses defining natural menopause as women who underwent natural menopause without previous hysterectomy or oophorectomy in case there was misclassification bias with respect to their date and type of surgery.

Frailty

Frailty status was formally categorized at SOF visits 4, 5, and 6 which correspond to 6, 8 and 10 years of follow-up from baseline, respectively. We also used data from Visit 8 (18-years of follow-up) on the components specified to categorize frailty status as our measure of incident frailty. Frailty was defined based on the established SOF criteria, which is a variation on the Fried criteria [2]. The SOF criteria consisted of three components: (1) intentional or unintentional weight loss >5lbs in the past year, (2) inability to rise from a chair five consecutive times without using the arms, and (3)

perceived reduced energy level, based on an item from the Geriatric Depression Scale [6]. Participants who had at least two out of three criteria were categorized as “frail”; whereas 1 out of three was considered “intermediate” stage and participants who met no criteria were defined as “not frail”. A participant was considered an incident case of frailty at the first follow-up visit where she met criteria for frailty. For example, if a participant was classified at Visit 4 as “not frail” and reassessed as “frail” at Visit 5, she was classified as “frail” in the analysis. A participant who was “not frail” at Visit 4 and either terminated from the study before a subsequent visit, or was not re-assessed for frailty was classified as “not frail” in the analysis (similar for all other follow-up visits). A participant who was either “not frail” or “somewhat frail” at Visit 4 and died before a subsequent visit was classified as “died” in the analysis (similar for all other follow-up visits). The number of incident frail cases observed over the follow-up period was 149, 137, 152 and 339 at Visits 4, 5, 6, and 8, respectively. Thus, a total of 777 women became frail over the follow-up period; 3054 became Intermediate stage and 2176 who were assessed in at least one or more of these visits were not frail cases across all visits in our analytic sample. In addition, a total of 1692 women were classified as death cases between Visit 4 and Visit 8. The main analyses assessed the association of menopause status with all levels of the frailty outcome (not frail, Intermediate, or frail) and death.

Covariables

Data on age, years of education, smoking status, body mass index (BMI), number

of instrumental activities of daily living (IADL) the participant had difficulty performing, walking speed, oral corticosteroid use, oral estrogen use, total number of years on oral estrogen, chronic diseases and self-rated health were collected at baseline (Visit 1). Oral corticosteroid and oral estrogen use were categorized as never, past and current use. The number of chronic diseases was tabulated as a count of the following four diseases: coronary heart disease, diabetes mellitus, stroke and chronic obstructive pulmonary disease (COPD). Walking speed was measured as the time in seconds it took for a participant to walk at usual pace over a 6-meter course [30]

Blood Collection and Hormone measurements

Blood was collected at baseline examination from all participants from 1986 to 1988 after an overnight fast and was immediately frozen to -20°C. Within 2 weeks, all samples were shipped to a central repository and stored in liquid nitrogen at -190°C until hormones were assayed. Testosterone assays were available only on a small subset of women (n=541) included in the breast cancer and fracture substudies of SOF. Methodology of testosterone measurements was similar for total testosterone but not free testosterone between the two substudies. Therefore, only total testosterone was analyzed given consistency in assay measurement in this small subset of women. Serum concentrations of total testosterone (ng/dl) were measured by radioimmunoassay after extraction and aluminum oxide column chromatography with interassay coefficient of variation of 6.1–13.4% [31, 32].

Statistical analysis

Characteristics of women who underwent surgical versus natural menopause were compared using student t-test for continuous variables and Chi-square tests for categorical variables. Multinomial logistic regression was used to assess the association of menopause status with all levels of the frailty outcome (not frail, intermediate or frail) and death in a single model. Important known clinical correlates of frailty were determined a priori to be included in the multivariable model.

Covariates that were examined as potential confounders included the number of chronic diseases (count of the following diseases: coronary heart disease, diabetes mellitus, stroke, COPD), never/past/current oral estrogen use, never/past/current oral corticosteroid use, walking speed (m/s) and number of impairments in instrumental activities of daily living (IADL). Covariables that were significantly associated with both type of menopause and frailty were retained as covariates in the model ($p \leq 0.05$ for model entry). Age at baseline and Body Mass Index (BMI) were considered clinically important covariates that were forced into the multivariate model [5, 33]. We also performed stratification analysis investigating the association of type of menopause and frailty among never, past and current oral estrogen users. All statistical analyses were performed using SAS, version 9.1.

RESULTS

Sample Characteristics

Details of the SOF study participants included in our analysis are provided in **Figure 1**. Of the 9704 Caucasian participants in the original SOF cohort, 9314 had available data on menopause type. Of these 9314 women, 1012 died before Visit 4 (1st frailty assessment) and 603 had missing data on frailty status. A total of 1692 women died during the time period of frailty outcome assessments between Visit 4 and Visit 8 (18-years of follow-up from baseline visit). Therefore, a total of 7699 postmenopausal women with available data on menopause type, frailty status and death during the 18-years of follow-up were included in our analytic sample. Mean age and BMI were 71.2 ± 5.2 years and 26.4 ± 4.4 kg/m^2, respectively. 13.8% were current oral estrogen users while 27.6% used oral estrogen in the past. Surgically menopausal participants represented 12.6% of the analytic sample.

The baseline characteristics of our study sample are shown in **Table 1**. Compared to naturally menopausal women, surgically menopausal women went through menopause at a significantly younger age, had a longer time period since menopause, higher frequency of past and/or current oral estrogen use and longer time period of oral estrogen use (11.7 years vs. 7.7 years). Surgically menopausal women also had significantly lower serum total testosterone levels compared to naturally menopausal women (13.2 ± 8.2 vs. 21.7 ± 14.9 ng/dl; p<0.0001). However, surgically and naturally menopausal participants did not significantly differ in age, years of education, smoking

status, BMI, oral steroid use and walking speed. Nor were there differences in the percentage of women who reported poor health status or number of chronic medical conditions.

Association between Surgical Menopause and Risk of Frailty

Overall average age at frailty in our study was 79.6 years. In terms of frailty status, 3054 subjects (39.7%) were categorized as being intermediate stage and 777 subjects (10.1 %) as being frail in our sample. Using multinomial logistic regression, we found no significant association between type of menopause (surgical versus natural menopause) with all levels of the frailty outcome (not frail, intermediate stage or frail) including death. (Frailty: Odds Ratio=0.94; 95% CI=0.72–1.22; Intermediate Stage: Odds Ratio= Odds Ratio=0.96; 95% CI=0.80–1.10; Death: Odds Ratio=1.17; 95% CI=0.97–1.42) (**Table 2**) after adjusting for age, BMI and number of IADL impairments. The results were non-significant in setting of low prevalence of frail cases (10.1%).

Stratified Analyses by Oral Estrogen Use

To assess whether estrogen played a role in the association between surgical menopause and frailty status or death, stratified analyses between never, past or current oral estrogen users was performed using multinomial logistic regression and shown in **Tables 3a, 3b and 3c**. There was no significant effect modification by oral estrogen use across all levels of frailty including death.

Association of Serum Total Testosterone and Frailty

Using multinomial logistic regression in a subset of 541 participants, we found no significant association between baseline serum total testosterone levels with all levels of the frailty outcome including death in the overall study population. **(Table 4).** Due to small sample size, we did not have adequate power to assess for effect modification among surgically versus naturally menopausal women.

Sensitivity Analyses

When redefining natural menopause as women with both intact uterus and ovaries, women who had undergone surgical menopause did not have significantly higher risk for frailty or death compared to naturally menopausal women. **(Table 5)** Subsequent analyses excluding women older than 85 years also did not significantly alter the results. Adjustments for age at menopause also did affect the results. (data not shown)

DISCUSSION

In a large sample of older Caucasian women, we found that women with surgically-induced menopause were not at increased risk for developing frailty in comparison to naturally menopausal women. Contrary to our hypothesis, our findings suggest that low serum testosterone levels may not be a primary mechanism to explain higher rates of frailty in older postmenopausal women. Furthermore, estrogen use did not significantly alter this relationship. This is the first population-based cohort study investigating the association between surgically-induced menopause and frailty risk among postmenopausal women. These results advance the knowledge about age-related decline in testosterone concentrations and frailty in postmenopausal women, which has previously been confined to studies in men [15, 17].

In our study, women who had previously undergone bilateral oophorectomy had significantly lower serum testosterone levels and subsequently were hypothesized to be at increased risk for developing frailty. This is in contrast to natural menopause, where the ovary continues to secrete a substantial amount of androgens [34] so that circulating testosterone levels change very little during the perimenopausal period. However, the surgically menopausal women in our cohort did not have higher risk for frailty compared to naturally menopausal women over 18-years of follow-up. Androgens play an important role in the maintenance of muscle mass, bone health and physical function [35, 36]. Although frailty has not been previously assessed in surgically menopausal women, one clinical trial demonstrated that testosterone replacement

therapy in oophorectomized women resulted in significant increases in total lean body mass [37]. Although the ovaries are an important source of testosterone in women, our results do not support use of testosterone therapy to prevent sarcopenia and physical impairments associated with frailty in surgically menopausal women. Future prospective studies are needed to validate our findings.

In addition to low testosterone, other biological mechanisms possibly involved may include the mediating effects of estrogen on frailty. Estrogen decline during natural menopause has been associated with an accelerated loss of muscle mass and strength and subsequent decrease in physical function [18, 19], suggesting a beneficial role for estrogen replacement. In contrast to naturally menopause, surgically menopausal women in our study had higher rates of current and past estrogen use. However, frailty risk was not altered whether or not women used estrogen in our study. Our results contradict those of a recent study that found that higher endogenous estradiol levels were associated with frailty in older women who had undergone natural menopause [38]. Although the women in this study were not surgically menopausal, these results shed light into the uncertainty of whether estrogen has beneficial versus harmful effects in postmenopausal women. It also important to note that these women were enrolled in the late 1980s during a time when the safety concerns over hormone replacement therapy brought out by the Women's Health Initiative were not prominent, making our study population not representative of the estrogen prescribing practices today.

In the context of other physical health outcomes related to frailty, our results are

similar to findings in other studies evaluating association of surgical oophorectomy and osteoporotic fractures. Previous analyses of the SOF cohort showed that older postmenopausal women with history of bilateral oophorectomy before natural menopause were not at increased risk for nonvertebral fractures over 21 years of follow-up [12]. Similar findings on fracture risk were also found in women who had undergone postmenopausal bilateral oophorectomy [39]. The similar negative findings between these results and our study occurred despite the fact we had surgically menopausal women who were younger at oophorectomy (average age 44) versus the other study conducted in postmenopausal oophorectomized women (average age 49). In contrast to postmenopausal bilateral oophorectomy, surgical menopause is by definition bilateral oophorectomy prior to natural menopause; based on our data, it appears that experiencing more time in menopause (i.e. longer exposure time to low testosterone levels) does not confer higher risk for negative physical health outcomes associated with frailty which is reassuring.

Our study had notable strengths. This was a large sample size cohort representing older ambulatory women of diverse geographical areas in the U.S. No study to date has investigated the association between surgical menopause and frailty risk in older women. As many previous studies on frailty in women were of cross-sectional design, SOF was a prospective longitudinal study where the participants were followed through frequent biennial assessments over the course of 18 years. Additionally, we used a multinomial modeling to capture all levels of the frailty

syndrome as well as the competing risk of death in our study population. The SOF criteria for the frailty syndrome used in this study was a simpler and well-validated modification of the more complex Fried criteria, which may potentially be more practical for clinical settings [6].

Our study also had some limitations. The SOF sample was comprised of primarily white women, aged 65 and older without significant physical impairments at enrollment. Thus, our results are not representative of other races and high-risk populations for disability. While we can assume that menopause preceded frailty in our sample, we lacked medical records to confirm type of surgery and age at oophorectomy. Misclassification of surgical menopause, although possible, would have been very unlikely to occur because this group demonstrated the significantly lower serum testosterone concentrations that would be expected in comparison to natural menopause. Given that misclassification of natural menopause could have also occurred, sensitivity analyses restricting the natural menopause group to women with both intact ovaries and uterus was conducted and did not alter the results. The sample size of our frailty cases represented only 10% of our population and was possibly too small of a proportion to detect significant differences. Because the age at menopause occurred over a very wide range (18–59 years) and frailty was only assessed at 4 time points over 18-years of follow-up, there may not have been sufficient time for many subjects to develop frailty, which is a more slowly progressive chronic condition. In addition, frailty was not assessed in a large number of participants given that they had

died during the frailty outcome assessment period. Thus, the relatively low percentage of prevalent frailty cases and competing risk of death may explain the null findings observed in our study. Although the frailty syndrome is on a continuum, it is unclear whether surgically menopausal women in our study could have progressed to frailty with time. As this is a retrospective cohort study design, the covariates used in our multivariate analysis such as BMI and IADL impairments were all measured at enrollment into the study (age>65), long after the time of baseline exposure (i.e. surgical vs. natural menopause), making it possible for these variables to be on the causal pathway rather than confounders. In addition, hormone measurements (total testosterone) were only measured at a single time point and in small subset of participants, which may not be representative of individual and diurnal variations that are commonly seen. Additionally, total testosterone was measured by a less sensitive radioimmunoassay and not by gold standard technique of tandem mass spectrometry (LC-MS/MS) [40].

In conclusion, our study demonstrates that surgically-induced menopause is not associated with increased risk for frailty. Furthermore, serum total testosterone concentrations were also not significantly associated with frailty in both surgically and naturally menopausal women. These findings provide some reassurance that long-term risk of frailty is not significantly increased in women who experienced surgical menopause, regardless if they were taking estrogen therapy. Our results were limited in the setting of small sample size, low prevalence of frailty cases and competing risk of

death. Despite our negative findings, questions still remain regarding the benefits versus harms of prophylactic oophorectomy in women undergoing hysterectomy to prevent ovarian cancer [41]. Thus, the risk to benefit ratio for bilateral oophorectomy should be considered carefully in these women as the surgery may predispose them to future disability or other adverse health outcomes later in life. More research is needed to further investigate this relationship to better understand the hormonal mechanisms involved in the development of frailty in older women.

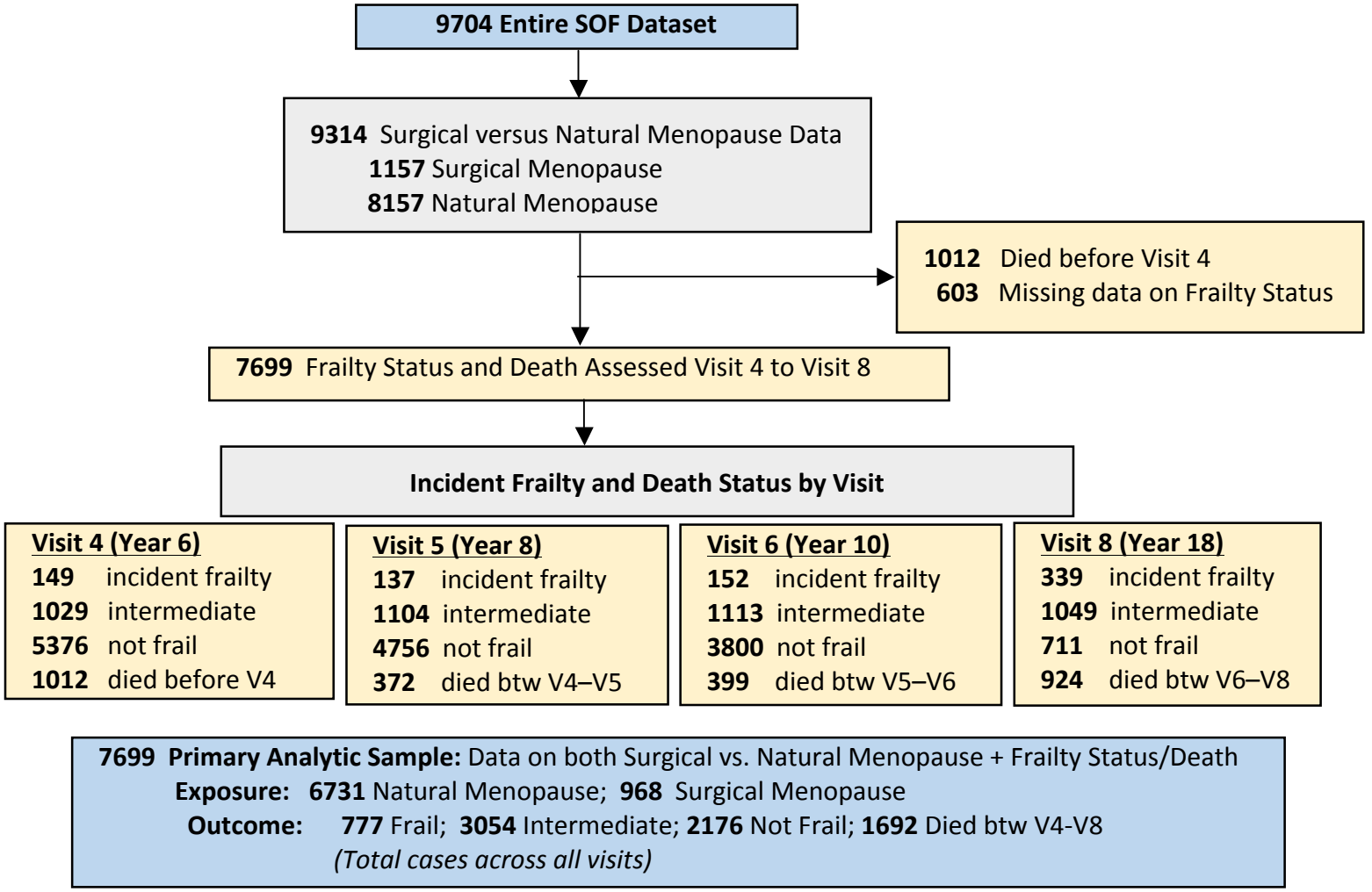

Figure 1. Study Participants in the Study of Osteoporotic Fractures (SOF). 7699 women with both data on exposure (surgical/natural menopause) and outcome (frailty status or death) constituted the analytical sample

Table 1. Baseline Characteristics of 7699 SOF Participants

Characteristics	Natural Menopause (n=6731)	Surgical Menopause (n=968)	P-value
Age (yr)	71.3 (5.0)	70.6 (4.7)	<0.01
Smoking Status (n/%)			0.34
Nonsmoker	4131 (61.6)	575 (59.5)	
Former smoker	1962 (29.3)	292 (30.2)	
Current smoker	614 (9.2)	100 (10.3)	
Education (yrs)	12.8 (2.8)	12.3 (2.7)	<0.01
BMI (kg/m^2)	26.4 (4.4)	26.6 (4.7)	0.24
Age at Menopause (yr)	48.7 (5.0)	44.4 (7.4)	<0.01
Hysterectomy (n/%)	1946 (29.0)	967 (99.9)	<0.01
Number of chronic conditions (n/%)	0.2 (0.5)	0.3 (0.5)	0.01
Number of IADL impairments	1.0 (2.1)	1.3 (2.3)	<0.01
Walking speed (m/s)	1.0 (0.2)	1.0 (0.2)	0.51
Oral Corticosteroid use (n/%)			
Never	5847 (88.3)	841 (89.7)	0.91
Past	658 (9.9)	91 (9.6)	
Current	120 (1.8)	16 (1.7)	
Oral Estrogen use (n/%)			
Never	4012 (60.4)	350 (36.6)	<0.01
Past	1840 (27.7)	311 (32.5)	
Current	792 (11.9)	295 (30.9)	
Total Number of Years on Oral Estrogen (yrs)	7.7 (8.6)	11.7 (10.6)	<0.01
Self-rated health (n/%)			<0.01
Excellent	2256 (33.5)	272 (28.1)	
Good	3497 (52.0)	512 (52.9)	
Fair/Poor/Very Poor	978 (14.5)	183 (18.9)	
Total Testosterone (n=541)	21.7 (14.8)	13.2 (7.8)	<0.01

*Values are expressed as mean ± sd and/or percentages (%) by type of menopause. P-values represent T-tests or chi-square tests for comparison of characteristics by menopause type. Number of chronic conditions (heart disease, stroke, COPD, diabetes)

Table 2. Association Between Type of Menopause and Incidence of Frailty among 7699 SOF Participants

Exposure		**Odds Ratios (95% CIs)**					
Type of Menopause	**n/% Frail**	**Frail**		**Intermediate**		**Died**	
		Crude	**Adjusted***	**Crude**	**Adjusted***	**Crude**	**Adjusted***
Natural	687 (10.21)	1.00	1.00	1.00	1.00	1.00	1.00
Surgical	90 (9.30)	0.90 (0.70–1.16)	0.94 (0.72–1.22)	0.99 (0.84–1.18)	0.96 (0.8–1.1)	1.07 (0.89–1.30)	1.17 (0.97–1.42)

*adjusted for age, BMI and number IADL impairments. Naturally menopausal women is the reference group

STRATIFICATION ANALYSES BY ORAL ESTROGEN USE

Table 3a. Association Between Type of Menopause and Incidence of Frailty among 4461 SOF Participants (Never Estrogen Users)

Exposure	Odds Ratios (95% CIs)					
	Frail		Intermediate		Died	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Natural	1.00	1.00	1.00	1.00	1.00	1.00
Surgical	1.02 (0.69–1.51)	0.98 (0.65–1.47)	0.97 (0.74–1.28)	0.97 (0.73–1.29)	1.26 (0.94–1.70)	1.26 (0.93–1.72)

*adjusted for age, BMI and number IADL impairments

Table 3b. Association Between Type of Menopause and Incidence of Frailty among 2250 SOF Participants (Past Estrogen Users)

Exposure	Odds Ratios (95% CIs)					
	Frail		Intermediate		Died	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Natural	1.00	1.00	1.00	1.00	1.00	1.00
Surgical	0.94 (0.60–1.47)	0.95 (0.60–1.50)	0.99 (0.75–1.31)	1.01 (0.75–1.34)	1.01 (0.72–1.42)	1.06 (0.75–1.50)

*adjusted for age, BMI and number IADL impairments

Table 3c. Association Between Type of Menopause and Incidence of Frailty among 1186 SOF Participants (Current Estrogen Users)

Exposure	Odds Ratios (95% CIs)					
	Frail		Intermediate		Died	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Natural	1.00	1.00	1.00	1.00	1.00	1.00
Surgical	1.05 (0.64–1.73)	1.10 (0.66–1.85)	1.01 (0.74–1.39)	1.04 (0.76–1.44)	1.18 (0.82–1.70)	1.29 (0.89–1.88)

*adjusted for age, BMI and number IADL impairments

Table 4. Association of Serum Total Testosterone Concentrations and Incidence of Frailty among 541 SOF participants

Exposure	Odds Ratios (95% CIs)					
	Frail		Intermediate		Died	
	Crude	*Adjusted	Crude	*Adjusted	Crude	*Adjusted
Total Testosterone	1.00 (0.99–1.02)	1.00 (0.98–1.01)	0.99 (0.98–1.01)	0.99 (0.98–1.01)	0.99 (0.97–1.00)	0.99 (0.97–1.00)

*adjusted for age, BMI and number IADL impairments

Table 5. Association of Serum Total Testosterone Concentrations and Incidence of Frailty among 5480 SOF Participants (Natural menopause defined as intact bilateral ovaries & uterus)

Exposure	Odds Ratios (95% CIs)					
	Frail		Intermediate		Died	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Natural	1.00	1.00	1.00	1.00	1.00	1.00
Surgical	0.89 (0.68–1.15)	0.97 (0.82–1.16)	0.93 (0.79–1.11)	0.92 (0.70–1.12)	1.08 (0.89–1.31)	1.16 (0.95–1.42)

*adjusted for age, BMI and number IADL impairments

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Peer reviewed publications in print or other media

Research investigations

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