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Statin Use and Incident Frailty in Women Aged 65 Years or Older: Prospective Findings From the Women's Health Initiative Observational Study

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Background. Inflammatory biomarkers have shown consistent associations with disability and frailty in older adults. Statin medications may reduce the incidence the frailty because of their anti-inflammatory effects. This study examines associations between current use, duration, and potency of statin medications and incident frailty in initially nonfrail women 65 years old or older.

Methods. The authors conducted a prospective analysis of data from the Women's Health Initiative Observational Study (WHI-OS) conducted at 40 clinical centers in the United States. Eligible women were nonfrail and 65–79 years old at baseline ($n = 25,378$). Current statin use at baseline was ascertained through direct inspection of medicine containers during clinic visits. Frailty was ascertained through self-reported indicators and physical measurements at baseline and 3-year clinic contacts. Components of frailty included self-reported low physical function, exhaustion, low physical activity, and unintended weight loss. Multinomial logistic regression models were used to adjust for covariates predicting incident frailty.

Results. Among the 25,378 eligible women, 3453 (13.6%) developed frailty by the 3-year follow-up contact. Current statin use had no association with incident frailty (multivariate-adjusted odds ratio [OR] = 1.00; 95% confidence interval [CI], 0.85–1.16). Duration and potency of statin use were also not significantly associated with incident frailty. Among low potency statin users, longer duration of use was associated with reduced risk of frailty (p for trend = .02). A similar pattern of results was observed when frailty was studied in the absence of intervening, incident cardiovascular events.

Conclusions. Overall, incidence of frailty was similar in current statin users and nonusers.

***Key Words*:** Statin use—Frailty—Disability—Women's Health Initiative.

In geriatric medicine, the term ''frailty'' has been used to describe older adults who are physically vulnerable, weak, and lack physiological reserve. The past several years have witnessed progress in moving toward a standard and measurable conceptualization of the frailty syndrome (1,2). A growing body of evidence suggests a relationship between inflammation and risk of disability, frailty, walking speed, and strength (3–5). Statin medications have anti-inflammatory effects and therefore may be candidates for preventing frailty (6–10). Statin use has been associated with improved walking speed in patients with peripheral arterial or vascular disease (11–13). To the best of our knowledge, studies have not examined the relationship between statin use and the frailty phenotype. The objective of this article is to examine whether use of statins at baseline was associated with less incident frailty over 3 years in nonfrail women 65 years old or older in the Women's Health Initiative Observational Study (WHI-OS) of postmenopausal women.

Method

Study Sample

The data for this study are from the WHI-OS, a prospective study of 93,676 women ages 50–79 recruited from 1993 through 1998 from 40 clinical centers in the United States. Details of the design, recruitment, and data collection methods have been published (14,15). Women were eligible if they were postmenopausal, unlikely to relocate or die within 3 years, and not enrolled in any of the WHI clinical trials. The study was reviewed and approved by human subjects review committees at each participating institution.

This report focuses on women ages 65–79 years who did not have frailty at baseline. Women were excluded if they reported at baseline a diagnosis or disease that manifests as frailty (Parkinson disease, congestive heart failure, stroke, coronary heart disease [CHD], use of antidepressant medications). Women without health insurance were also

excluded because they were presumed to have relatively limited access to statin prescriptions. The frailty outcome could not be classified among 956 women who died prior to their 3-year follow-up visit and 4046 women who did not provide information on the frailty components, as described below, leaving a sample of 25,378.

Measurement of Frailty

Definition of the frailty phenotype in WHI was guided by the criteria used in the Cardiovascular Health Study (1) and was strongly associated with future mortality, disability, hospitalization, and hip fracture among older women in the WHI-OS (2). Briefly, the Rand-36 physical function scale was used as a self-report indicator of muscle weakness and slow walking speed. A score in the lowest quartile of this scale was associated with observed slow walking speed and low grip strength in the WHI Clinical Trial (WHI-CT). The Rand-36 Vitality Scale (range 0–100) was used to measure exhaustion using four items pertaining to the past 4 weeks: ''Did you feel . . . . worn out?; tired?; full of pep?; have a lot of energy?''. Low physical activity was classified using a questionnaire that assessed the frequency and duration of four speeds of walking and activities in the prior week (16,17). Kilocalories of energy expended in a week on leisure time activity was calculated (MET score = kcal/wk * kg) (18). A dichotomous variable was created indicating unintentional weight loss of >5% of body weight in the past 2 years, based on measured weight at the baseline and 3-year clinic visits in combination with a self-reported item on whether recent weight loss was intentional at the 3-year follow-up.

For each measure described above, a frailty component was classified as present if the participant had a score in the lowest quartile of the distribution for that component or unintentional weight loss. To align the scoring with Fried's frailty measure, poor physical function was scored as two points because both the muscle strength and walking ability components were measured by this scale. The number of frailty components that were present was summed, yielding a range of 0–5. A frailty cut point of $\geq$3 was used, as in previous studies (1,19).

Statin Exposure

WHI participants were asked to bring all current regularly taken medications (prescription and over-the-counter) to their first screening interview. Clinic interviewers entered each medication name and strength directly from the containers into a database that assigned drug codes using Medi-Span software (First DataBank, Inc., San Bruno, CA). Women reported duration of use for each current medication. Information on tablet strength, but not prescribed dose, was available. Information on starting or stopping medications during the 3-year follow-up interval is not available.

Little information is available regarding the relative effect of statins on inflammatory markers. Some studies suggest that effects on C-reactive protein (CRP), an acute phase protein, may be independent of degree of lipid lowering (6,20), but comparative metrics are not available for anti-inflammatory effects. To compare across statins, we categorized the medications into three groups based on units of equivalent dose indicating potency for lipid-lowering effect from comparative clinical trials (21,22). One unit of equivalent dose was based on lipid-lowering effect of 10 mg of atorvastatin (fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, rosuvastatin 5 mg). Low potency was defined as <0.25 standardized unit, medium potency as 0.5 standardized unit, and high potency as $\geq$1 standardized unit. This categorization was based in part on distribution of equivalent doses, and it should be recognized that ''high potency'' includes usual doses of some agents. We repeated the analysis ignoring lipid-lowering equivalence by simply creating a binary variable indicating ''high'' or ''low'' strength for each type of statin medication based on dichotomizing at the median pill strength of statin prescriptions in the data set.

Potential Confounders

Data on demographic (race or ethnicity, age, family income, education), medical history, and health behavior characteristics were obtained by self-report at baseline. Alcohol consumption was estimated from a food-frequency questionnaire. Smoking status was classified as current, past, or never. Medical conditions at baseline included self-reported physician diagnosis of arthritis, treated diabetes, hypertension (on medication and/or blood pressure >140/90 mmHg), and cancer. Incident cardiovascular outcomes included clinical myocardial infarction, definite or possible CHD death, angina, revascularization, carotid artery disease, congestive heart failure, and stroke. These events were ascertained initially by annual self-report and confirmed through medical record review and adjudication by local clinic physicians and then a panel of central adjudicators (23). Level of physical activity above the range indicating frailty was measured in kilocalories of energy expenditure as described above. Body mass index (BMI) was defined using measured height and weight at baseline as weight (kg) divided by height (m^2). Depressive symptoms were assessed by an eight-item short form (24,25) of the Center for Epidemiologic Studies Depression Scale (26). Postmenopausal hormone therapy was ascertained by interview and categorized as current, past, or never use of any estrogen with or without progestin.

Statistical Analysis

Baseline demographic, medical history, and health behavior characteristics were compared for women according to duration of statin use. Corresponding p values are based on chi-square tests for heterogeneity.

Multinomial logistic regression models were used to examine associations between statin use (current use, duration, potency, and strength) and incident frailty adjusting for important confounding factors. The response variable was coded as not frail (referent category), intermediate frailty (frailty score of 1–2), or frail (score $\geq$3). The models adjusted for independent predictors of incident frailty identified in our previous report (2) including age, income, education, ethnicity, BMI, smoking status, alcohol consumption, physical activity, hormone therapy use, self-reported health, whether the participant lived alone, and comorbid conditions. Interactions between current statin use

and age, BMI, diabetes, smoking status, and baseline frailty score (0, 1, or 2) were explored by testing the significance of cross-product terms. At the design stage, we estimated that this analysis had 80% power to detect odds ratios (OR) in the range of 0.80–0.85.

Statin use is associated with elevated cardiovascular risk, and users in an epidemiologic study could experience higher rates of CHD than nonusers. Because incident CHD events could lead to frailty, an association of statin use with frailty could be masked. To examine this issue, additional multinomial logistic models were constructed to examine statin use in relation to non-cardiovascular disease (CVD) frailty by separating out women who experienced an intervening CVD event.

Results

At baseline, 8.4% of women ($n = 2122$) were current users of statin medications, and 3.6% of women were current users of $\geq$3 years duration ($n = 800$) (Table 1). When examining potency of the statins, 404 women (1.6%) were using low potency, 1088 women (4.3%) medium potency, and 620 (2.4%) high potency.

Statin use at baseline was associated with lower education, minority race/ethnicity, higher BMI, lower alcohol consumption, less current hormone replacement therapy use, having a current health care provider, not living alone, lower self-rated health status, treated diabetes, hypertension, and higher levels of comorbidity (Table 1). Some associations with statin use are very small in magnitude, but reach statistical significance because of large numbers.

Among the 25,378 women who were free of frailty at baseline, 3453 had developed frailty (13.6%) by the 3-year follow-up contact. Current statin use had no association with incident frailty (OR = 1.00; 95% CI, 0.85–1.16; Table 2). Overall, duration and potency of statin use were also not significantly associated with incident frailty. Although the trend was not statistically significant, statin users with the longest duration of use had the lowest risk of frailty (OR 0.88; 95% CI, 0.68–1.14), p for trend = .10). Likewise, the OR was reduced in the low potency category (0.81), whereas there was no indication of any reduced risk with medium or high potency use (differences not significant).

When analyses were restricted to users of a low potency statin (composed of 11.9% simvastatin, 25.6% lovastatin, 15.5% pravastatin, and 47.1% fluvastatin users), there was a stronger association between duration of statin use and reduced risk of frailty (Table 3). OR values were reduced for women who had used statin medication for at least 1 year, and the OR for women with $\geq$3 years of use was 0.55 (95% CI, 0.28–1.09; p for trend = .02).

A similar pattern of results was observed when incident frailty was studied in the absence of intervening cardiovascular events. OR values stratified by duration and potency of statin use were similar to those described above. A trend toward reduced risk of frailty among longer term users of low potency statin medications was also observed (OR = 0.62; 95% CI, 0.31–1.24, p for trend = .03).

Other Analyses

OR values were not affected by additional adjustment for propensity scores. There were no significant interactions between current statin use and age, BMI, diabetes, smoking status, and baseline frailty score. Interactions between statin use and use of several medications (angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, glucocorticosteroids, and/or warfarin) were also not statistically significant, although for some combinations the data were sparse. Strength of statin medications based on the median split of pill strengths in the data set (ignoring lipid-lowering equivalence) was also unrelated to incident frailty, with OR values of 1.0 for both ''high'' and ''low'' categories of strength. When analyses were repeated including older women with a history of CHD or use of antidepressants at baseline, the results were not appreciably different from those presented here, except that the trend toward less risk of frailty among older women using low potency statins was obscured.

Discussion

In this prospective study of more than 25,000 women 65 years old or older who were initially free of frailty, current use of statin medications was not significantly related to the development of frailty at 3-year follow-up. Although OR values for frailty were in the direction of benefit for long-term statin users and those using low potency statin doses, interaction terms for duration and potency failed to reach statistical significance. Results were similar when frailty outcomes in the absence of intervening cardiovascular events were studied and also when the exclusion criteria were relaxed to include women with CHD or concurrent use of antidepressants at baseline.

To our knowledge, this is the first large prospective study to examine statin use in relation to the future development of frailty. A large randomized trial testing pravastatin (27) showed no effect on disability, despite impressive reductions in cardiovascular events in older adults. This trial enrolled older adults with substantial disease burdens and cardiovascular risk including current smoking, diabetes, hypertension, and history of coronary disease and other vascular morbidity. A high prevalence of these disabling conditions at entry could obscure any beneficial effects of statin use on components of frailty. Smaller trials and nonrandomized clinical studies of patients with vascular disease have shown associations between statin use and improved walking speed, improved walking distance, better physical performance, and improved physical activity (11–13,28).

Older women in the WHI-OS were likely healthier at entry than older people with vascular disease or high cardiovascular risk enrolled in the large statin trials. About 96% of the women in this study described their health status as ''good'' to ''excellent'' at baseline. Nonetheless, statin users were more likely to have diabetes, hypertension, comorbidity, and/or high BMI. Both obesity and comorbidity increased risk of frailty in this cohort (2). Observational studies of statin use must necessarily address the potential for confounding by indication (29), which in this case could

Table 1. Baseline Characteristics of WHI Observational Study Participants by Duration of Statin Use

	Nonuser		<1 Year		(1 – <3) Years		≥3 Years		
Baseline Characteristic	*N*	%	*N*	%	*N*	%	*N*	%	*p* Value
Age group at screening, y									.10
65–69	11991	51.6	335	54.7	373	52.5	386	48.3	
70–79	11265	48.4	277	45.3	337	47.5	414	51.8	
Education									<.0001
High school/GED or less	4750	20.5	138	22.7	196	27.6	179	22.5	
School after high school	8482	36.7	221	36.3	259	36.5	308	38.7	
College degree or higher	9910	42.8	249	41.0	254	35.8	309	38.8	
Ethnicity									.0002
White	20732	89.1	541	88.4	608	85.6	696	87.0	
Black	974	4.2	28	4.6	33	4.6	35	4.4	
Hispanic	444	1.9	14	2.3	23	3.2	8	1.0	
American Indian	43	0.2	2	0.3	3	0.4	3	0.4	
Asian/Pacific Islander	744	3.2	20	3.3	36	5.1	48	6.0	
Unknown	319	1.4	7	1.1	7	1.0	10	1.3	
Body mass index (kg/m^2)									<.0001
Underweight (<18.5)	351	1.5	3	0.5	2	0.3	2	0.3	
Normal (18.5–24.9)	10700	46.4	185	30.4	235	33.3	311	39.1	
Overweight (25.0–29.9)	8063	35.0	265	43.6	323	45.8	320	40.2	
Obese (≥30)	3934	17.1	155	25.5	145	20.6	163	20.5	
Smoking									.82
Never smoked	12555	54.8	323	53.2	387	55.5	418	53.0	
Past smoker	9449	41.2	260	42.8	288	41.3	337	42.7	
Current smoker	912	4.0	24	4.0	22	3.2	34	4.3	
Alcohol intake									.001
Non/past drinker	6132	26.5	191	31.3	203	29.0	242	30.3	
<1 drink/wk	7045	30.5	173	28.4	225	32.1	256	32.0	
1–14 drinks/wk	8777	38.0	228	37.4	250	35.7	266	33.3	
>14 drinks/wk	1158	5.0	18	3.0	23	3.3	35	4.4	
Hormone therapy use									.0007
Never used	10734	46.2	298	48.7	364	51.3	368	46.1	
Past user	3839	16.5	121	19.8	129	18.2	141	17.6	
Current user	8658	37.3	193	31.5	217	30.6	290	36.3	
Nonstatin lipid-lowering medication	359	1.5	6	1.0	17	2.4	17	2.1	.10
Living alone at baseline	7389	32.0	177	29.2	197	27.9	217	27.3	.002
In general, your health is:									<.0001
Excellent	4708	20.4	82	13.5	80	11.4	95	12.0	
Very good	11137	48.2	252	41.6	319	45.5	362	45.6	
Good	6528	28.3	250	41.3	275	39.2	303	38.2	
Fair/Poor	718	3.1	22	3.6	27	3.9	34	4.3	
ADL disability (≥1 limitation)	235	1.0	2	0.3	8	1.2	7	0.9	.38
Treated diabetes (pills or shots)	526	2.3	26	4.2	37	5.2	51	6.4	<.0001
Hypertensive (treated or measured)	9612	41.8	321	52.8	401	56.9	454	57.1	<.0001
Depression score									.12
0	6960	30.4	175	29.2	191	27.2	214	27.5	
1–2	9116	39.8	227	37.9	301	42.9	336	43.2	
3–4	4474	19.5	119	19.9	131	18.7	147	18.9	
5+	2343	10.2	78	13.0	78	11.1	81	10.4	
History of arthritis	11766	51.0	339	55.7	354	50.1	422	53.0	.09
History of cancer	3282	14.2	91	14.9	107	15.2	111	14.0	.86
Comorbid condition(baseline)	10819	46.5	331	54.1	369	52.0	432	54.0	<.0001
Number of chronic diseases									<.0001
0	4237	18.2	77	12.6	88	12.4	99	12.4	
1	380	1.6	12	2.0	18	2.5	15	1.9	
2	8200	35.3	204	33.3	253	35.6	269	33.6	
3	6476	27.8	216	35.3	224	31.5	259	32.4	
4	2935	12.6	69	11.3	93	13.1	118	14.8	
5+	1028	4.4	34	5.6	34	4.8	40	5.0	

Note: WHI = Women's Health Initiative; GED = general educational development; ADL = activities of daily living.

Table 2. Adjusted* Odds Ratios (OR) Relating Current Statin Use and Duration and Potency of Statin Use to Risk of Frailty at 3 Years of Follow-Up: Women's Health Initiative Observational Study

	OR (95% CI)						
	Not Frail	Intermediate Frailty		Frail			
Classification of Statin Use	*N*	*N*	OR (95% CI)	*N*	OR (95% CI)	Overall *p* Value†	Trend *p* Value‡
Current statin use							
Nonusers	13,217	6927	1.00	3112	1.00	.97	
Users	1117	664	0.99 (0.88–1.11)	341	1.00 (0.85–1.16)		
Years of statin medication use							
Nonusers	13,217	6927	1.00	3112	1.00	.45	.10, .10
<1	308	188	0.98 (0.80–1.21)	116	1.19 (0.92–1.54)		
1–3	384	216	0.90 (0.75–1.10)	110	0.94 (0.73–1.22)		
>3	425	260	1.07 (0.89–1.28)	115	0.88 (0.68–1.14)		
Potency of statin medication							
Nonusers	13,217	6927	1.00	3112	1.00	.16	.24, .23
Low	229	114	0.71 (0.54–0.92)	61	0.81 (0.58–1.14)		
Medium	572	353	1.11 (0.95–1.30)	163	1.03 (0.83–1.27)		
High	310	195	0.99 (0.80–1.21)	115	1.07 (0.83–1.39)		

Notes: *OR values were derived from multivariate multiple logistic regression analysis adjusting age, income, education, ethnicity, body mass index, smoking status, alcohol use, physical activity, hormone replacement therapy use, whether a participant lives alone, self-reported health, diabetes, hypertension (treated or high blood pressure), depression, arthritis, and history of cancer.

†*p* value from a multivariate logistic regression model to test whether statin exposure has an effect on intermediate frailty and/or frailty.

‡*p* values from a multivariate logistic regression model to test whether statin duration has a linear effect on frailty. The first *p* value tests whether this effect is linear for intermediate frailty and/or frailty. The second *p* value tests whether effect the effect is linear for frailty only.

CI = confidence interval.

obscure or mask completely any protective association between statin use and development of frailty. In the present study, we used restriction (exclusion of women with diseases that manifest as frailty), multivariate adjustment, multinomial logistic regression, interaction testing, and various sensitivity analyses to deal with the problem that statins are disproportionately prescribed to older women with a greater risk of CVD events and frailty. The results presented here were robust to these analytic approaches. However, only the randomized trial design can completely eliminate confounding that may arise from the initially poorer health status of statin users compared to nonusers.

Statin medications are associated clinically with muscle complaints including myalgia, weakness, and cramps. A recent expert panel that reviewed the evidence on this topic concluded that myopathies were a class effect of statins that was related to dose and blood level, but not to the lipid-lowering potency of the various statins (30). In the present study, doses producing lower lipid-lowering effects, the low potency group, appeared to be associated with a reduced risk of frailty that was related to duration (stronger in longer term users). The low potency group was taking very low statin doses, usually the starting doses of these agents, thus this grouping could have identified individuals with less need for

Table 3. Adjusted* Odds Ratios (OR) Relating Current Statin Use and Duration of Statin Use Among Low Potency Statin Users to Risk of Frailty at 3 Years of Follow-up: The Women's Health Initiative Observational Study

	OR (95% CI)						
	Not Frail	Intermediate Frailty		Frail			
Classification of Statin Use	*N*	*N*	OR (95% CI)	*N*	OR (95% CI)	Overall *p* Value†	Trend *p* Value‡
Current statin use							
Nonusers	13,217	6927	1.00	3112	1.00	.04	
Users	229	114	0.71 (0.54–0.92)	61	0.82 (0.58–1.15)		
Years of statin medication use							
Nonusers	13,217	6927		3112		.03	.05, .02
<1	62	37	0.79 (0.48–1.29)	29	1.46 (0.85–2.51)		
1–3	98	40	0.63 (0.41–0.96)	19	0.62 (0.34–1.11)		
>3	69	37	0.75 (0.47–1.19)	13	0.55 (0.28–1.09)		

Notes: *ORs were derived from multivariate multiple logistic regression analysis adjusting age, income, education, ethnicity, body mass index, smoking status, alcohol use, physical activity, hormone replacement therapy use, whether a participant lives alone, self-reported health, diabetes, hypertension (treated or high blood pressure), depression, arthritis, and history of cancer.

†*p* value from a multivariate logistic regression model to test whether statin exposure has an effect on intermediate frailty and/or frailty.

‡*p* values from a multivariate logistic regression model to test whether statin duration has a linear effect on frailty. The first *p* value tests whether this effect is linear for intermediate frailty and/or frailty. The second *p* value tests whether the effect is linear for frailty only.

CI = confidence interval.

cholesterol reduction and less subclinical CVD perhaps reducing risk of frailty. We found no association between the strength of the tablets and incident frailty. Explanations that are compatible with these findings include differences among the statin medications in their effects on frailty, unmeasured confounding associated with type of statin, or the role of chance. The finding suggests the possibility that all statin medications and users of statin medications should not be assumed to be equal in future studies of effects on frailty or physical performance measures. In addition, the overall null association between current and long-term statin use and development of frailty is reassuring in the context of concerns about statin-induced myopathies.

Statins decrease systemic inflammation and may influence development of frailty via this mechanism. Recent studies of older adults consistently support associations between markers of inflammation (e.g., interleukin 6 [IL-6], CRP, tumor necrosis factor-α) and measures of disability, frailty, or physical performance (3–5,31,32). Large trials have shown that statins reduce CRP by 14%–17%, and this effect does not appear to be related to degree of lipid lowering (6,33). Statins have been shown to decrease IL-6–induced CRP expression in human hepatocytes (7). In addition to these direct effects, statins may reduce risk of frailty by reducing the severity of clinical and subclinical CVD, which contributes to frailty (19). Measurements of inflammatory markers and disease severity were not available in the present study, which precludes empiric evaluation of these mechanisms in this report.

Strengths of this study include its prospective design, objective assessment of statin use, inclusion of more than 2000 current statin users, the diversity of the women enrolled, consideration of a large number of covariates related to the development of frailty, and the ability to separate out adjudicated, intervening CVD events. Information on prescription strength but not prescribed dose of statin medication was captured, and medication adherence was unknown. The timing of initiation and discontinuation of statin use in relation to the onset of disability during follow-up was not measured. Other weaknesses include the relatively short follow-up duration and lack of physical performance and inflammatory biomarker measures. Finally, all observational studies of pharmacologic exposures are subject to issues related to confounding by indication.

Conclusion

This large prospective study of generally healthy older women showed no association between current statin use and the development of frailty over 3-years of follow-up. Trends toward benefit in longer term users of statin medications and those taking low potency formulations, though not statistically significant, leave open the possibility that longer term statin use or low potency formulations could reduce the risk of frailty. Future randomized trials of statins in older adults should include investigation of noncardiovascular outcomes including effects on physical performance, other components of frailty, and a broad spectrum of physical abilities used in everyday life.

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