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Changing predictors of statin initiation in US women over two decades

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Abstract

Purpose: To describe changing roles of predictors of statin initiation before and after incident coronary heart disease, and before and after publication of National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) guidelines in a cohort of US women.

Methods: We identified 34 382 women enrolled into the Women's Health Study from 1993 to 1995 and followed up until 2012. Proportions of previous nonusers initiating statins were described over time. We used multivariable linear regression models to estimate adjusted initiation proportion differences (IPDs) for initiation overall, separately before and after incident coronary heart disease, and separately for ATP-II and ATP-III time periods.

Results: Key predictors of initiation overall were self-reported total cholesterol, and previous incident coronary heart disease, cerebrovascular disease, and diabetes. Adjusted IPDs (percentage) for total cholesterol > 240 vs <200 mg/dL were 7.5 (95% confidence interval [CI], 7.0-8.0) and 9.3 (95% CI, 8.7-9.9) during ATP-II and ATP-III time periods, respectively. Adjusted IPDs in women with diabetes were 7.0 (95% CI, 6.3-7.8) and 11.9 (95% CI, 6.7-17.0) for primary and secondary prevention, respectively, and 3.1 (95% CI, 2.1-4.0) and 9.2 (95% CI 8.2-10.2) for before and after ATP-III, respectively.

Conclusions: Secular trends reflected evolution toward risk factor-based treatment indications for statin initiation with increased initiation among diabetics and women with normal and borderline cholesterol. The role of serum cholesterol changed over time, though the character was scale (multiplicative vs additive) dependent. In pharmacoepidemiologic studies of statins, strength of confounding by important variables sometimes unmeasured in claims data, such as cholesterol level, may be calendar time dependent.

KEYWORDS

drugs, hyperlipidemia, pharmacoepidemiology, prevention, utilization

1 | INTRODUCTION

In the early 1990s, the Scandinavian Simvastatin Survival Study demonstrated that statins reduced mortality by 30% in patients with

PRIOR PRESENTATIONS: Some material from this work was previously presented at the 30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management.

evidence of cardiovascular disease and high cholesterol.[1] Subsequent studies demonstrated benefits for patients with cardiovascular disease and normal cholesterol levels,[2,3] and for people at high risk of cardiovascular disease regardless of cholesterol level.[4,5] The National Cholesterol Education Program Adult Treatment Panel (ATP) has provided recommendations for treatment of hypercholesterolemia in the United States since 1988.[6] Updated first in 1993 (ATP-II),[7] the second update in 2001 (ATP-III) notably expanded use among people without prior cardiovascular disease, diabetics, and older individuals.[8,9] Male sex, ages 55 to 75 years, higher serum cholesterol, diabetes, cardiovascular disease, antihypertensive medication use, and increased health care encounters are known predictors of statin initiation.[10,11] However, whether predictors change with evolving guidelines or before versus after incident coronary heart disease has been incompletely described.[12-15] Understanding predictors sometimes not captured in claims data (eg, cholesterol level) is important in pharmacoepidemiologic studies of statins.

We therefore sought to describe the changing roles of predictors of statin initiation in a cohort of US women before and after incident coronary heart disease, and before and after the ATP-III guidelines in 2001.

KEY POINTS

- We aimed to describe changing roles of predictors of statin initiation before and after incident coronary heart disease and before and after the publication of the National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) guidelines in a cohort of US women initially free from cardiovascular disease.
- Key predictors of initiation overall were self-reported total serum cholesterol, previous incident coronary heart disease, cerebrovascular disease, and diabetes, and calendar time.
- Secular trends demonstrated increased initiation among diabetics and women with normal and borderline total cholesterol levels in later years.
- The changing role of serum cholesterol level was scale (multiplicative vs additive) dependent, with elevated total cholesterol predicting greater absolute increase of statin initiation after compared with before ATP-III but greater relative increase before ATP-III.
- In pharmacoepidemiologic studies of statins, the strength of confounding by important variables sometimes unmeasured in claims data, such as cholesterol level, may be calendar time dependent.

2 | METHODS

2.1 | Data source

The Women's Health Study (WHS) is a randomized controlled trial of low-dose aspirin, vitamin E, and beta-carotene for the primary prevention of cardiovascular disease and cancer in US women.[16-18] From 1993 to 1995, 39 876 female health professionals aged ≥ 45 years (Table 1) were randomly assigned to a regimen of aspirin (100 mg every other day) or placebo and vitamin E (600 IU every other day) or placebo in a 2 × 2 factorial design. The trial also initially included a beta-carotene component, which was discontinued after 2 years' median treatment duration.[19] Participants were followed up annually through the scheduled end of the trial (31 March 2004) and annually thereafter in a program of posttrial observational follow-up. Data were collected via written questionnaires that participants returned by mail. Details are described elsewhere.[20,21] Our study includes eligible questionnaires from all WHS participants from enrollment through 7 years posttrial.

2.2 | Statin use

Questions regarding current use of cholesterol-lowering medications were included in 13 of 20 questionnaires administered during the study period: before randomization (baseline); 12, 36, 48, 108, and 120 months following randomization; at trial conclusion in 2004; and 1, 2, 3, 4, 5, and 7 years after trial conclusion for participants (approximately 90%) of the observational follow-up phase (Table S1).

2.3 | Predictor variables

We examined statin initiation over time as a function of a set of core covariates available in the WHS. All covariates were measured before randomization and updated whenever possible. Race, education, and parental history of myocardial infarction before[22] age 60 years were collected once at baseline. Age was calculated at every questionnaire. Body mass index (BMI), smoking (current, previous but not current, or never), physical exercise, alcohol use, multivitamin use, menopausal status (premenopausal, postmenopausal, or uncertain), hormone replacement therapy use (current, previous, never), and self-reported total blood cholesterol were reassessed only on some questionnaires according to the study design. For these variables, the last recorded value was carried forward to later questionnaires where unmeasured or missing, unless described otherwise. Missing baseline values remained missing until updated by a recorded value on a later questionnaire, after which

TABLE 1 Eligibility criteria for enrollment into the Women's Health Study

Aged ≥ 45 y
Postmenopausal or had no intention of becoming pregnant
No previous history cardiovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness
No history of serious side effect to any study treatments
Not taking aspirin, aspirin-containing medications, nonsteroidal anti-inflammatories, vitamin A or E, or beta-carotene more than once per week
Willingness to forgo use of aspirin or anti-inflammatories during the trial
Not taking anticoagulants or corticosteroids
Successful completion of a 3-mo placebo run-in

the new value was carried forward until updated again. Missing values were not imputed with later values except for baseline height, which was imputed with values from later questionnaires if available. BMI was calculated from self-reported height and weight and was carried forward by linear interpolation when unreported. Self-reported weight was highly correlated with measured weight (r = 0.97) among similar women in the Nurses' Health Study.[23] Menopausal status was imputed to postmenopausal for all women at ages ≥ 60 years in the absence of self-report data indicating otherwise.[24] Physical exercise was classified as <7.5, 7.5 to 21, and >21 met-hours per week[25]; 7.5 met-hours represents the minimum physical activity for adults recommended by Federal guidelines.[26] Women reported their total serum cholesterol at baseline, if known within 5 years, and were asked for updated values if known 12 and 36 months postrandomization; at trial conclusion; and 1, 3, 5, and 7 years posttrial. At study entry, 6273 WHS participants (16%) had unknown or missing total cholesterol.[27] Total cholesterol was classified as <200 mg/dL (low risk), 200 to 239 mg/dL (moderate risk), and 240+ mg/dL (high risk).[7,8] Data were not consistently available for low-density lipoprotein (LDL) cholesterol. A validation study of the WHS cohort showed self-reported baseline total cholesterol values were 9.7 mg/dL (95% confidence interval [CI], 9.2-10.2) higher on average than values obtained from baseline blood samples but were strongly associated with incident cardiovascular disease during follow-up.[27]

Women were queried yearly regarding cardiovascular disease events and new diagnoses of diabetes and hypertension. Incident cardiovascular disease, a primary trial end point, underwent medical records verification by an end point committee of physician reviewers.[18] We only counted confirmed events. Confirmed myocardial infarction, angina, coronary artery bypass surgery, and percutaneous coronary angioplasty were combined into a single end point for coronary heart disease. Confirmed stroke, transient ischemic attack, and carotid endarterectomy surgery were combined into a single cerebrovascular disease end point. Self-reported diabetes diagnoses were followed up with a supplemental validated questionnaire.[28] Hypertension was defined as a self-reported diagnosis, self-reported antihypertensive medication use, or self-reported systolic blood pressure ≥ 140 or diastolic ≥ 90 mmHg. Dates of first lifetime incidence were identified for coronary heart disease, cerebrovascular disease, diabetes, and hypertension.

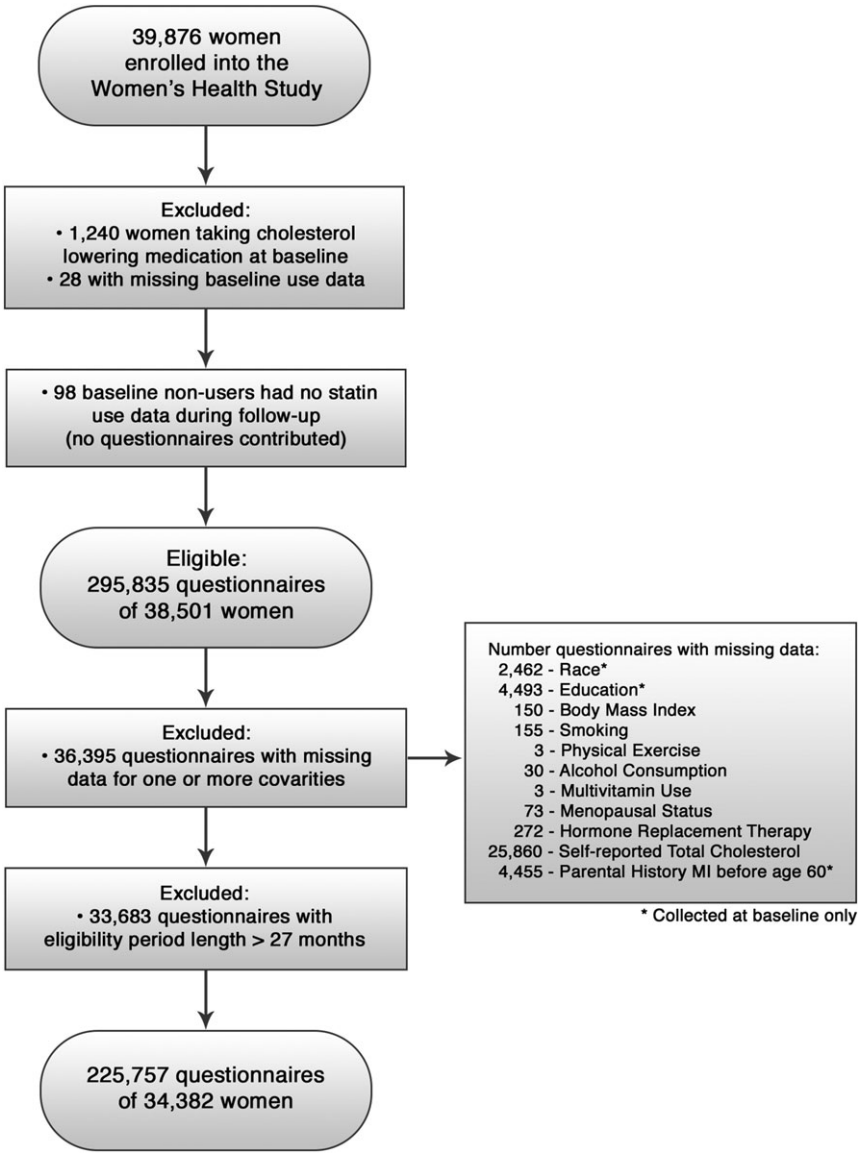

FIGURE 1 Flow diagram depicting the derivation of the study sample. A total of 34 382 women contributed 225 757 questionnaires to the analysis

TABLE 2 Covariate distributions among included women at selected survey times (number, %, of women)

		Questionnaire Year					
		1993-1995[a]		2004[b]		2011[c]	
All women	Number[d]	30 427		20 092		13 231	
Age (y)	<50	9843	(32)	—		—	
	50-54	8693	(29)	—		—	
	55-59	5482	(18)	6392	(32)	—	
	60-64	3417	(11)	5956	(30)	2697	(20)
	65-69	2051	(7)	3764	(19)	4688	(35)
	70-74	733	(2)	2148	(11)	2975	(22)
	75-79	171	(1)	1294	(6)	1609	(12)
	80+	37	(0)	538	(3)	1262	(10)
Race	Other	1523	(5)	862	(4)	524	(4)
	White non-Hispanic	28 904	(95)	19 230	(96)	12 707	(96)
Education	LVN/LPN	3910	(13)	2412	(12)	1290	(10)
	RN < 4 y	13 169	(43)	8913	(44)	5387	(41)
	Bachelors	7144	(23)	4816	(24)	3442	(26)
	Graduate	6204	(20)	3951	(20)	3112	(24)
Body mass index (kg/m^2)	<25	15 750	(52)	9328	(46)	6583	(50)
	25-30	9339	(31)	6533	(33)	4186	(32)
	>30	5338	(18)	4231	(21)	2462	(19)
Smoking	Never smoked	15 854	(52)	10 482	(52)	6692	(51)
	Past smoker	11 080	(36)	8089	(40)	5956	(45)
	Current smoker	3493	(11)	1521	(8)	583	(4)
Exercise (met-hours/wk)	<7.5	13 926	(46)	8143	(41)	4423	(33)
	7.5-21	9385	(31)	6194	(31)	3939	(30)
	>21	7116	(23)	5755	(29)	4869	(37)
Alcohol use	Rarely/never	13 397	(44)	8123	(40)	5157	(39)
	1-3 drinks/mo	4059	(13)	2400	(12)	1269	(10)
	1-6 drinks/wk	9895	(33)	7111	(35)	4629	(35)
	1+ drinks/d	3076	(10)	2458	(12)	2176	(16)
Multivitamin use	None	18 662	(61)	8716	(43)	4136	(31)
	1-20 d/mo	4067	(13)	1580	(8)	1290	(10)
	>20 d/mo	7698	(25)	9796	(49)	7805	(59)
Menopausal status	Premenopausal	8441	(28)	419	(2)	-	
	Uncertain/unclear	5617	(18)	1089	(5)	-	
	Postmenopausal	16 369	(54)	18 584	(92)	13 231	(100)
Hormone replacement therapy	Never	14 730	(48)	4069	(20)	2654	(20)
	Former	2624	(9)	9525	(47)	9010	(68)
	Current	13 073	(43)	6498	(32)	1567	(12)
Total cholesterol (mg/dL, self-reported)	<200	14 868	(49)	10 066	(50)	7276	(55)
	200-239	11 431	(38)	7675	(38)	4901	(37)
	240+	4128	(14)	2351	(12)	1054	(8)
Previous disease event or diagnosis							
Coronary heart disease[e,f]		122	(0)	440	(2)	294	(2)
Cerebrovascular disease[e,g]		13	(0)	310	(2)	228	(2)
Hypertension diagnosis[h]		7996	(26)	9831	(49)	7971	(60)
Diabetes diagnosis[h]		774	(3)	910	(5)	529	(4)
Parental history myocardial infarction at age < 60		4399	(14)	2642	(13)	1576	(12)

Abbreviations: LVN, Licensed Vocational Nurse; LPH, Licensed Practical Nurse; RN, Registered Nurse.

[a]Baseline covariate values among women contributing an observation from questionnaire administered 12 mo postrandomization.

[b]Updated covariate values among women contributing an observation from questionnaire administered at conclusion of randomized trial.

[c]Updated covariate values among women contributing an observation from seventh yearly posttrial observational follow-up questionnaire.

[d]Number of women who were eligible to initiate and provided statin use data on the specified questionnaire.

[e]Thirteen women who enrolled into the study having reported no history of cardiovascular disease were later discovered to have had myocardial infarction, coronary revascularization, or stroke prior to enrollment by medical records review. The remaining cases of heart or cerebrovascular disease prior to randomization were either incident cases that occurred during the run-in period or women discovered to have had angina or transient ischemic attack prior to enrollment.

[f]Confirmed myocardial infarction, coronary artery bypass graft, percutaneous angioplasty, or angina.

[g]Confirmed stroke, carotid endarterectomy, or transient ischemic attack.

[h]Self-reported physician diagnosis or use of antihypertensive or antidiabetic medications or insulin.

2.4 | Study design

We defined statin initiation as the first instance of reported use.[10,29] A woman reporting no use of statins on her first questionnaire was classified as a noninitiator for that questionnaire and became eligible to initiate on the next questionnaire, and so on; if she reported statin use, she was classified as an initiator and became ineligible to initiate thereafter. Each woman's follow-up time was thereby conceptualized as a sequence of discrete observations, each consisting of an inter-questionnaire period during which the woman was eligible to initiate ("eligibility period") culminating in the questionnaire where she indicated her current use or nonuse of statins. The up-to-date covariate values on first day of the eligibility period were used as the predictors for initiation on that questionnaire. Because statin use was asked at irregular intervals, the lengths of eligibility periods varied from 1 to 5 years. We restricted the analysis to questionnaires with eligibility period length < 27 months to limit variation of person-time between the discrete observations. This cut point would capture questionnaires scheduled 2 years apart allowing a 3 months' grace period for late returns. Sensitivity analyses were performed without this restriction. A total of 225 757 questionnaires of 34 382 women were included in the analyses (Figure 1).

2.5 | Analytic methods

Distributions of covariates were described cross-sectionally among women who contributed scheduled questionnaires at 12 months postrandomization, trial conclusion, and 7 years posttrial. Statin initiation was characterized as crude incidence rates (IRs) overall and by levels of covariates across 4-year time periods. Each day of person-time during the eligibility period was classified by calendar year period. When initiation occurred, dates of initiation were imputed as the midpoint of the eligibility period and person-days afterward omitted from calculations. We estimated initiation IRs per 100 person-years with 95% CIs for each time period and IR differences (IRDs) with 95% CIs comparing the latest time period with the earliest.

We used multivariable linear regression with empirical variance estimation to predict the nonrecurring binary outcome of statin initiation as a function of the covariates and to estimate initiation proportion differences (IPDs), expressed as percentages, with 95% CIs for the independent contribution of covariates on statin initiation.[30,31] The unit of analysis was the questionnaire. Women could contribute multiple questionnaires to the pooled analysis, but each woman could only initiate once.[32] Models were constructed overall, separately for questionnaires with and without a first lifetime incidence of coronary heart disease before the eligibility period, and separately for questionnaires with eligibility periods wholly contained before, and on or after 16 May 2001 (ATP-III guidelines publication date).[8] Models included terms for calendar year of questionnaire return. Logistic regression models were constructed using identical variables to estimate odds ratios (ORs) with 95% CIs for comparison with the additive models. Terms for interaction by incident coronary heart disease before the eligibility period and time period (ATP-II vs ATP-III) were tested using score tests for linear regression or likelihood ratio tests for logistic regression after fitting the respective full interaction models. Additive interactions of previous incident coronary heart disease and time period (ATP-II vs ATP-III) with selected ordinal and continuous covariates were described by estimating relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI) with 95% CIs after binary reclassification of the covariate.[33,34] We quantified residual confounding bias during ATP-II versus ATP-III time periods under a scenario of confounding of the association of statin initiation and cardiovascular disease outcomes by total cholesterol level using methods described elsewhere by Schneeweiss et al.[35] We used bivariate proportions of initiation and elevated total cholesterol from the WHS, and literature-based relative risks of elevated total cholesterol on incident cardiovascular disease among middle-aged women from the Framingham risk score prediction model.[36] SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

3 | RESULTS

3.1 | Trends and predictors of statin initiation

Prevalent use of statins among all 39 876 WHS participants was 3% at baseline and 43% in 2011; of 38 608 baseline nonusers, 17 451 (45%) initiated some time during follow-up. Covariate distributions of included women over the study period are shown in Table 2.

Crude incidence of initiation was characterized by a sharp peak during 2001-2004 (IR per 100 person-years 8.1 [95% CI, 7.8-8.4], up from 1.6 [95% CI, 1.5-1.7] during 1993-1996) followed by sequential decline to approximately half the peak rate in 2009-2012 (IR 3.8 [95% CI, 3.6-4.0]); this general pattern was mirrored within most covariate substrata, including age, suggesting that changes in statin initiation could not be attributed to aging in this fixed cohort (Figure 2; Table S2).

In the full multivariable model, the absolute initiation proportion (%) increased over calendar time until stabilizing during 2005-2008 and 2009-2012 at approximately 4.5 percentage points greater than that during 1993-1996 (adjusted IPDs 4.3 [95% CI, 4.0-4.6] and 4.6 [95% CI, 4.2-4.9], respectively) (Table S3). Key clinical predictors of increased initiation were total cholesterol > 240 vs <200 mg/dL (adjusted IPD 8.5 [95% CI, 8.1-8.9]), previous diabetes (7.2 [95% CI, 6.4-8.0]), previous coronary heart disease (5.1 [95% CI, 4.0-6.2]), and previous cerebrovascular disease (3.6 [95% CI, 2.3-4.9]). Decreased

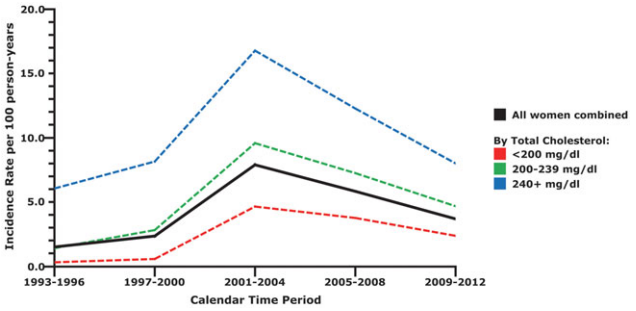

FIGURE 2 Line graph showing trends of crude incidence rates of statin initiation over five 4-y time periods overall (solid black line) and by level of most recently reported total cholesterol level (dashed colored lines) [Colour figure can be viewed at wileyonlinelibrary.com]

initiation was seen in the oldest age categories in this model that controlled for calendar time (comparing ages 75-79 yrs and 80+ yrs with 65-69 yrs, −1.5 [95% CI, −2.0 to −1.0] and −2.4 [95% CI, −3.1 to −1.8], respectively) (Table S3).

3.2 | Predictors before versus after incident coronary heart disease

In separate models representing primary and secondary prevention, respectively, there was increased initiation over calendar time for primary prevention but little change over time in initiation for secondary prevention; women with previous hypertension and diabetes, compared with those without disease, showed larger absolute increases in initiation in secondary prevention than in primary prevention (Table 3). Fewer multivitamin users and more current smokers initiated statins in settings of secondary prevention (nonuse vs 1+ d/mo multivitamin use: RERI 0.715 [95% CI, 0.255-1.174], AP 0.308 [95% CI, 0.150-0.467], and SI 2.185 [95% CI, 1.304-3.661]; current smoker vs current nonsmoker: RERI 1.490 [95% CI, 0.280-2.700], AP 0.430 [95% CI, 0.224-0.637], and SI 2.533 [95% CI, 1.475-4.349]) (Table 3). Decreased initiation was seen among younger (<55 y) age

TABLE 3 Selected adjusted initiation proportion (%) differences (95% confidence interval)[a] for statin initiation by prior incident coronary heart disease,[b] Women's Health Study, 1993-2012

		Prior Incident Coronary Heart Disease[c]	
		No (Primary Prevention)	Yes (Secondary Prevention)
	No. initiations	10 508	377
	No. questionnaires	222 567	3190
Age (y)	<50	0.2 (−0.2 to 0.6)	−6.6 (−14.5 to 1.2)
	50-54	0.1 (−0.2 to 0.5)	−4.5 (−10.6 to 1.6)
	55-59	0.0 (−0.3 to 0.4)	−1.1 (−5.3 to 3.0)
	60-64	0.0 (−0.3 to 0.3)	−0.1 (−3.5 to 3.3)
	65-69	0	0
	70-74	−0.4 (−0.8 to 0.0)	−0.5 (−4.4 to 3.4)
	75-79	−1.4 (−1.9 to −0.9)	−3.6 (−7.7 to 0.6)
	80+	−2.6 (−3.2 to −2.0)	2.7 (−3.0 to 8.4)
Body mass index (kg/m^2)	<25	0	0
	25-30	1.0 (0.8 to 1.2)	1.8 (−0.8 to 4.5)
	>30	0.7 (0.5 to 1.0)	1.2 (−1.8 to 4.1)
Smoking	Never smoked	0	0
	Past smoker	0.2 (0.0 to 0.4)	−0.5 (−2.8 to 1.8)
	Current smoker	0.5 (0.1 to 0.8)	6.0 (1.1 to 10.9)
Multivitamin use	None	0	0
	1-20 d/mo	−0.4 (−0.7 to −0.1)	−5.3 (−8.9 to −1.6)
	>20 d/mo	0.3 (0.1 to 0.5)	−1.8 (−4.3 to 0.6)
Total cholesterol (mg/dL, self-reported)	<200	0	0
	200-239	3.0 (2.9 to 3.2)	4.2 (1.8 to 6.7)
	240+	8.5 (8.1 to 8.9)	8.0 (4.2 to 11.8)
First incident cerebrovascular disease[d]	Never[e]	0	0
	Previously[f]	3.6 (2.2 to 5.0)	3.7 (−3.0 to 10.4)
	During eligibility period[g]	19.4 (15.7 to 23.0)	12.7 (−11.1 to 36.5)
First incident diabetes diagnosis	Never[e]	0	0
	Previously[f]	7.0 (6.3 to 7.8)	11.9 (6.7 to 17.0)
	During eligibility period[g]	14.7 (12.3 to 17.0)	28.7 (8.9 to 48.5)
First incident hypertension diagnosis	Never[e]	0	0
	Previously[f]	2.3 (2.1 to 2.5)	6.0 (3.6 to 8.4)
	During eligibility period[g]	3.4 (2.9 to 3.9)	8.9 (2.6 to 15.1)
Calendar year of questionnaire	1993-1996	0	0
	1997-2000	0.4 (0.2 to 0.6)	−3.4 (−8.4 to 1.7)
	2001-2004	3.2 (2.9 to 3.5)	0.7 (−4.8 to 6.2)
	2005-2008	4.4 (4.1 to 4.6)	1.0 (−4.2 to 6.3)
	2009-2012	4.6 (4.3 to 5.0)	−2.6 (−8.3 to 3.0)

[a]Initiation proportion, expressed as percentage, estimated using linear regression models (binary outcome) with empirical variance estimation. The model included all variables shown in Table 2. Variables exhibiting interaction by incident heart disease or calendar time are shown.

[b]Confirmed myocardial infarction, coronary artery bypass graft, percutaneous angioplasty, or angina.

[c]The key contributors to statistical interaction by prior incident coronary heart disease were incident hypertension, multivitamin use, calendar time, smoking, and incident diabetes (score tests for interaction term(s), P = 0.006, 0.03, 0.03, 0.05, and 0.09, respectively).

[d]Confirmed stroke, carotid endarterectomy, or transient ischemic attack.

[e]Statin initiation vs noninitiation without first lifetime incidence before the questionnaire date on which use or nonuse of statins was reported.

[f]Statin initiation vs noninitiation with first lifetime incidence before the start of the eligibility period.

[g]Statin initiation vs noninitiation without first lifetime incidence before the start of the eligibility period, but with first lifetime incidence during the eligibility period. For women who initiated in this category (n = 309 for coronary heart disease), the temporal order of disease incidence and statin initiation is unknown.

groups compared with midrange (60-74 y) groups in secondary prevention but not in primary prevention, though CIs for the youngest age groups in the secondary prevention model were wide (Table 3).

3.3 | Predictors during ATP-II versus ATP-III periods

In separate models representing ATP-II and ATP-III periods, higher total cholesterol predicted larger absolute increases in initiation in the ATP-III time period (total cholesterol 200+ vs <200: RERI 2.148 [95% CI, 1.505-2.792], AP 0.162 [95% CI, 0.120-0.204], and SI 1.213 [95% CI, 1.148-1.281]); in contrast, higher total cholesterol predicted larger relative increases of initiation in the ATP-II (earlier) period (adjusted ORs for ATP-II and ATP-III periods, respectively, 4.1 [95% CI, 3.5-4.7] and 2.2 [95% CI, 2.1-2.3] for total cholesterol 200-239 vs <200 mg/dL, and 14.2 [95% CI, 12.3-16.4] and 4.0 [95% CI, 3.7-4.3] for total cholesterol > 240 vs <200 mg/dL) (Table S4). Women with previous diabetes, compared with those without, demonstrated larger absolute increase in initiation during ATP-III than ATP-II (Table 4). First incident coronary heart disease, cerebrovascular

TABLE 4 Selected adjusted initiation proportion (%) differences (95% confidence interval)[a] for statin initiation by calendar time period, Women's Health Study, 1993-2012

		Calendar Time Period[b]	
		1993 to 05/15/2001 (ATP-II)	05/16/2001 to 2012 (ATP-III)
	No. initiations	2094	8791
	No. questionnaires	88 420	137 337
Age (y)	<50	−0.7 (−1.2 to −0.2)	—
	50-54	−0.6 (−1.1 to −0.1)	0.8 (−1.1 to 2.6)
	55-59	−0.5 (−1.0 to 0.0)	0.2 (−0.2 to 0.7)
	60-64	−0.6 (−1.1 to 0.0)	0.2 (−0.2 to 0.5)
	65-69	0	0
	70-74	−0.4 (−1.2 to 0.4)	−0.4 (−0.9 to 0.1)
	75-79	−1.5 (−2.7 to −0.4)	−1.5 (−2.1 to −1.0)
	80+	−3.1 (−4.7 to −1.5)	−2.4 (−3.1 to −1.7)
Body mass index (kg/m^2)	<25	0	0
	25-30	0.3 (0.1 to 0.6)	1.5 (1.3 to 1.8)
	>30	0.1 (−0.2 to 0.4)	1.2 (0.9 to 1.6)
Smoking	Never smoked	0	0
	Past smoker	0.1 (−0.1 to 0.3)	0.2 (−0.1 to 0.5)
	Current smoker	0.6 (0.2 to 1.0)	0.6 (0.0 to 1.1)
Multivitamin use	None	0	0
	1-20 d/mo	−0.1 (−0.4 to 0.2)	−0.8 (−1.2 to −0.3)
	>20 d/mo	0.0 (−0.2 to 0.3)	0.3 (0.1 to 0.6)
Total cholesterol (mg/dL, self-reported)	<200	0	0
	200-239	1.6 (1.5 to 1.8)	4.0 (3.8 to 4.3)
	240+	7.5 (7.0 to 8.0)	9.3 (8.7 to 9.9)
First incident coronary heart disease[c]	Never[d]	0	0
	Previously[e]	6.7 (4.4 to 9.0)	4.7 (3.5 to 6.0)
	During eligibility period[f]	16.4 (12.5 to 20.4)	50.2 (45.7 to 54.7)
First incident cerebrovascular disease[g]	Never[d]	0	0
	Previously[e]	4.3 (0.5 to 8.1)	3.3 (1.9 to 4.7)
	During eligibility period[f]	6.1 (2.1 to 10.2)	26.7 (21.7 to 31.8)
First incident diabetes diagnosis	Never[d]	0	0
	Previously[e]	3.1 (2.1 to 4.0)	9.2 (8.2 to 10.2)
	During eligibility period[f]	4.2 (1.7 to 6.8)	21.4 (18.0 to 24.8)
First incident hypertension diagnosis	Never[d]	0	0
	Previously[e]	1.6 (1.3 to 1.8)	2.8 (2.6 to 3.1)
	During eligibility period[f]	1.7 (1.2 to 2.3)	5.0 (4.2 to 5.8)

Abbreviation: ATP, Adult Treatment Panel.

[a]Initiation proportion, expressed as percentage, estimated using linear regression models (binary outcome) with empirical variance estimation. The model included all variables shown in Table 2. Variables exhibiting interaction by incident heart disease or calendar time are shown.

[b]05/15/2001 corresponds to the publication date of Adult Treatment Panel III Cholesterol Treatment Guidelines. There were no observations for which the eligibility period crossed over 15 May 2001 with restriction of eligibility period length to <27 mo because of the coincidence of a 5-y period without query of statin use in the survey design. The strongest contributors to statistical interaction by time period were total cholesterol, incident diabetes, coronary heart disease, and hypertension, and body mass index (score tests for interaction, all $P < .0001$).

[c]Confirmed myocardial infarction, coronary artery bypass graft, percutaneous angioplasty, or angina.

[d]Statin initiation vs noninitiation without first lifetime incidence before the questionnaire date on which use or nonuse of statins was reported.

[e]Statin initiation vs noninitiation with first lifetime incidence before the start of the eligibility period.

[f]Statin initiation vs noninitiation without first lifetime incidence before the start of the eligibility period, but with first lifetime incidence during the eligibility period. For women who initiated in this category, the temporal order of disease incidence and statin initiation is unknown.

[g]Confirmed stroke, carotid endarterectomy, or transient ischemic attack.

disease, diabetes, and hypertension occurring during the inter-questionnaire eligibility period were associated with markedly increased initiation overall with larger increases during ATP-III than ATP-II (Table 4), but the temporal order of disease incidence and initiation within the eligibility period was unknown. Stronger confounding was demonstrated on the multiplicative scale during ATP-II than ATP-III under a scenario of an observational study of statin initiation and cardiovascular disease outcomes confounded by total serum cholesterol (residual confounding bias, 15-20% and 8-11% for ATP-II and ATP-III, respectively) (Table 5).

Sensitivity analyses without eligibility period length restriction produced similar results overall, except that the peak in crude IR was later (2005-2008) and attenuated (IR per 100 person-years 5.9 [95% CI, 5.8-6.1]).

4 | DISCUSSION

4.1 | Previous studies

Lo-Ciganic et al[12] reported an increase in prevalent statin use from 13% to 39% from 1997 to 2008 in a US cohort of community-dwelling individuals aged > 70 years at inception. The authors could not identify a change in the trend of prevalent use in association with ATP-III guidelines, although the limited evidence on statin efficacy in older people during the time of their study may have influenced their results.[37,38] The National Health and Nutrition Examination Survey showed prevalent statin use among women aged ≥ 45 years increasing from 2.6% in 1988-1994 to 23.6% in 2005-2008.[39] Prevalent use approximately doubled from 1999-2002 to 2005-2008 among both men and women[39] aged ≥ 75 years and from 1999-2002 to 2007-2010 among type 2 diabetics.[14] Kildemoes et al[11] showed age-specific incidence of new use per 1000 person-years (shown graphically) increasing from approximately two to 10 in 1999 to 50 to 75 in 2008 among ages 55 to 84, with sharply lower incidence among ages < 55 and ≥85 and increasingly larger proportions of new users composed of asymptomatic individuals in the Danish Nationwide Cohort. Teng et al[13] reported a spike in incidence of statin initiation in 2004 followed by flat IRs in a population-based time series analysis using Canadian claims data from 2003 to 2010. The decline in crude incidence of initiation after 2001-2004 in the WHS cohort has not been evident in other studies or in our adjusted models. This absence could reflect a "depletion of susceptibles" effect in this closed cohort followed up over 20 years for a nonrecurring event (first-time initiation). Women remaining in the analysis near the end of follow-up were, on average, more highly educated with greater exercise levels, increased vitamin use, decreased smoking, and decreased hypercholesterolemia compared with earlier in follow-up (Table 2). Regarding predictors, Danaei et al[10] showed that male sex, ages 60 to 75 years, greater LDL cholesterol, diabetes, antihypertensive medication use, and more frequent medical encounters predicted new use of statins for primary prevention of coronary heart disease during 2000-2006 in the United Kingdom. We found that hypertension, multivitamin non-use, later calendar time, current smoking, and diabetes predicted statin initiation more strongly in the secondary than primary prevention setting (Table 3), while greater total cholesterol, previous hypertension, coronary heart disease, and diabetes and greater BMI predicted initiation more strongly during the ATP-III era than ATP-II (Table 4).

TABLE 5 Estimation of residual confounding bias for unmeasured total serum cholesterol during ATP-II and ATP-III periods

	Time Period	
	1993 to 05/15/2001 (ATP-II)	05/16/2001 to 2012 (ATP-III)
Observed odds ratio[a]	7.71	2.35
Relative risk of incident cardiovascular disease by total serum cholesterol (mg/dL)[b]		
200-239 vs <200	1.51	1.51
240+ vs <200	1.72	1.72
Residual confounding bias (%) by total serum cholesterol (mg/dL)[c]		
200-239 vs <200	15%	8%
240+ vs <200	20%	11%

Abbreviation: ATP, Adult Treatment Panel.

[a]Calculated from 2 × 2 bivariate proportions of statin initiation vs noninitiation and total cholesterol 200+ vs <200 from the Women's Health Study.

[b]Literature-based relative risk of elevated total cholesterol on incident cardiovascular disease from the Framingham risk prediction model, adjusted for age, high-density lipoprotein, blood pressure, smoking, and diabetes among middle-aged women.[36]

[c]Calculated using the method described by Schneeweiss et al.[35]

4.2 | Implications for future research

Our findings have implications for confounding control in pharmacoepidemiologic studies of statin initiation. For example, in settings where total cholesterol is a weaker predictor of statin initiation, the overall confounding potential from lack of cholesterol data (eg, an insurance claims analysis) may be reduced (Table 5). Furthermore, elevated total cholesterol predicted greater absolute increase of statin initiation after compared with before ATP-III (Table 4), but greater relative increase before ATP-III (Table S4), owing to the very low incidence of initiation among women with normal cholesterol during ATP-II (Figure 2). Therefore, temporal changes of confounding potential by unmeasured cholesterol may be model scale dependent.

4.3 | Limitations

It was unknown when during the eligibility period an initiator began use or whether a noninitiator may have started and stopped between questionnaires. Initiation without persistence to the next questionnaire was thus undetected and misclassified. Initiation occurring within the same eligibility period as first incidence of cardiovascular or other diseases was not classifiable with respect to predictor status. We parameterized these events separately to allow separate intercept estimations for those situations, thus improving sensitivity among those classified as exposed versus unexposed. Incident coronary heart

disease, cerebrovascular disease, and diabetes during the eligibility period were strongly associated with initiation. For coronary and cerebrovascular disease, it seems most likely that incident disease led to treatment; however, increased diabetes incidence has followed statin use in randomized trials.[40,41] Also, rates and predictors of statin initiation in this selected group of female health professionals who volunteered for a long-term prevention trial and knew their cholesterol level may not be generalizable to all US women. Finally, caution is warranted when interpreting parameter estimates from multivariable models as causal, as coefficients can represent different types of causal effects depending upon the covariate interrelationships.[42]

4.4 | Conclusions

The trends we observed in statin initiation over 20 years reflect an evolution from treatment largely targeted to those with hypercholesterolemia toward risk factor–associated treatment and increased initiation among women with diabetes and normal (<200 mg/dL) and borderline (200-239 mg/dL) total cholesterol.[7,8] The role of serum cholesterol has changed over time, though the character of change was scale (multiplicative vs additive) dependent. In pharmacoepidemiologic studies of statins, strength of confounding by important variables sometimes unmeasured in claims data, such as cholesterol level, may be calendar time dependent.

ETHICS STATEMENT

The study conforms with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, and US Federal Policy for the Protection of Human Subjects. Free and informed written consent of participants was obtained. The Partners Healthcare and University of North Carolina Institutional Review Boards approved the current study.

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CONFLICT OF INTEREST

The authors disclose the following financial relationships and potential conflicts of interest: Tracy Kinsey receives salary from Athens Orthopedic Clinic Foundation for work supported by grants from Stryker and Arthrex. Til Stürmer receives salary support from the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB, Merck) and research grants (Amgen, AstraZeneca) for the Department of Epidemiology, University of North Carolina; he also holds stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. Charles Poole has received salary support from the Center for Pharmacoepidemiology. Kenneth Rothman is an employee of the Research Triangle Institute, a nonprofit organization that does work for government agencies and private companies. Robert Glynn has received research grants (AstraZeneca, Kowa, Pfizer, and Novartis) for the Brigham & Women's Hospital.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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