Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative

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Background: This study investigates whether the incidence of new-onset diabetes mellitus (DM) is associated with statin use among postmenopausal women participating in the Women's Health Initiative (WHI).

Methods: The WHI recruited 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 with ongoing follow-up. The current analysis includes data through 2005. Statin use was captured at enrollment and year 3. Incident DM status was determined annually from enrollment. Cox proportional hazards models were used to estimate the risk of DM by statin use, with adjustments for propensity score and other potential confounding factors. Subgroup analyses by race/ethnicity, obesity status, and age group were conducted to uncover effect modification.

Results: This investigation included 153 840 women without DM and no missing data at baseline. At baseline, 7.04% reported taking statin medication. There were 10 242 incident cases of self-reported DM over 1 004 466 person-years of follow-up. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38-1.59) and was observed for all types of statin medications. Subset analyses evaluating the association of self-reported DM with longitudinal measures of statin use in 125 575 women confirmed these findings.

Conclusions: Statin medication use in postmenopausal women is associated with an increased risk for DM. This may be a medication class effect. Further study by statin type and dose may reveal varying risk levels for new-onset DM in this population.

GIVEN THE SUCCESS OF statins in both primary and secondary prevention of cardiovascular morbidity and mortality,[1-6] their use is progressively increasing, especially among older Americans.[7] With such widespread use, even small risks are apparent alongside benefits. One emerging risk is an increased incidence of diabetes mellitus (DM). There is evidence that incident DM associated with statin use may be more common in the elderly, in women, and in Asians.[8-12] A recent analysis suggests that preexisting metabolic risk factors control incident DM rate with statin medication.[13] It is unclear if this risk varies with individual statins or if this is a dose-driven class effect.[9,14] Although experimental and clinical studies find that individual statins act differently on glucose homeostasis as a function of relative lipophilicity and/or potency of action,[15] other findings differ. A recent meta-analysis of 17 randomized controlled trials by Mills et al[16] found a class effect increase of new-onset DM with

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statins (odds ratio [OR], 1.09; 95% CI, 1.02-1.16) similar to that reported by Sattar et al.[9] Possibly, the grouping of statins masks the effect variation of individual statins. Still, at some given dose threshold, differences may be overcome, as implied by a meta-analysis of 5 trials comparing intensive to moderate dosing regimens using

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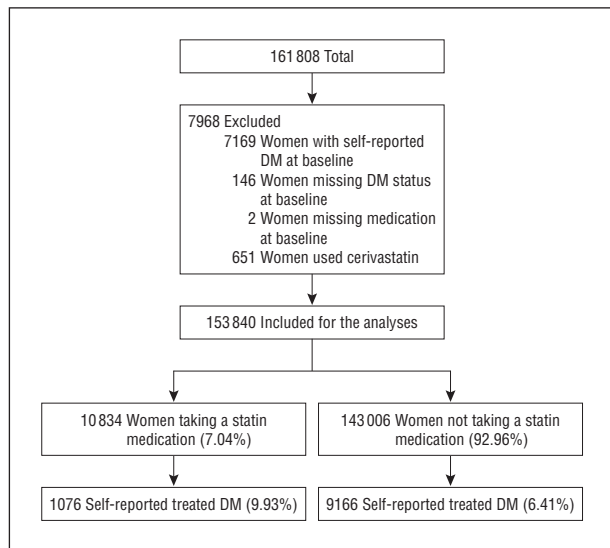
Figure. Flowchart for statin users and diabetes mellitus (DM) analyses using data sets from the Women's Health Initiative.

mainly atorvastatin and simvastatin.[13,17] Notably, meta-analysis results display intertrial and intratrial variability in diagnostic and statistical methods and do not consistently consider confounding factors. Moreover, contributing sample sizes do not permit balanced comparison by statin type, sex, race/ethnicity, and age. Similarly, single studies may uncover only part of a greater topography.

As a large part of the aging population, postmenopausal women have not been fully represented in past clinical trials.[16] Sex differences in DM pathogenesis are well recognized.[18,19] Using the Women's Health Initiative (WHI) data, we evaluated the overall effect of statin medication use on incident DM risk and examined these associations by specific statin agent. We stratified analyses by race/ethnicity, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) category, and age group to determine if any associations were modified by these factors. In addition, we conducted subgroup analysis in women with and without self-reported cardiovascular disease (CVD) at baseline to address potential confounding and selection bias.

METHODS

PARTICIPANTS

The WHI recruited 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 and followed consenting participants. Of these women, 68 132 were enrolled in 1, 2, or all 3 of the clinical trial (CT) arms: the Dietary Modification Trial, the Hormone Trial, and the Calcium and Vitamin D Trial. Another 93 676 women were enrolled into a prospective observational study (OS).[20-23] The WHI eligibility criteria included the ability to complete study visits with expected survival and local residency for at least 3 years. Original exclusion criteria addressed conditions that would limit full participation in the study. This analysis used WHI data through 2005. After exclusion for prevalent DM, missing data, and use of cerivastatin (this medication was withdrawn from the market in 2001 for safety reasons), a total of 153 840 women were included (**Figure**).

MEASUREMENT AND CLASSIFICATION OF STATIN MEDICATIONS

The current medication regimens of all CT participants were inventoried at baseline and at years 1, 3, 6, and 9. In the OS, medication data were inventoried at baseline and year 3. At each inventory, the brand or generic name on the medication label was matched to the corresponding item in the Master Drug Data Base (Medi-Span, Indianapolis, Indiana). We sorted for statin use as users or nonusers at baseline and year 3. Given that Sattar et al[9] found a null effect of lipophilicity among statins, and in the absence of dose information, we determined statin categories by relative potency of action to decrease low-density lipoprotein cholesterol. Accordingly, statins were designated as low (fluvastatin, lovastatin, pravastatin) or high (simvastatin, atorvastatin) potency.[24,25]

IDENTIFICATION OF DM

At baseline and at each semiannual (CT) or annual (OS) contact, incident treated DM was identified by questionnaire and was defined as a self-report of a new physician diagnosis of treated DM. This method of identification of prevalent and incident DM has been used in prior publications by the WHI investigators.[18,26-28] The accuracy of self-reported DM in the WHI trials has been assessed using medication and laboratory data, and self-reported DM was found to be reliable.[29]

COVARIATES

Baseline questionnaires ascertained demographic and health history information, including race/ethnicity, age, educational attainment, family history of DM, family history of depression, self-report of CVD, hormone therapy use, and smoking status. Baseline self-report for CVD has been previously validated in the WHI[30,31] and found to have reasonable agreement with hospital discharge *International Classification of Diseases, Ninth Revision (ICD-9)* codes.

The metabolic equivalents of physical activities and average daily nutrient intake were computed, using detailed methods described elsewhere.[32,33] Trained and certified clinic staff measured height using a fixed stadiometer and weight by a calibrated balance-beam scale. Relative weight as BMI was calculated from these values. Blood was analyzed for glucose and insulin for the random 6% WHI-CT blood subsample at baseline, year 1, year 3, year 6, and year 9. Fasting glucose was analyzed using the hexokinase method with interassay coefficients of variation less than 2%.[26] Insulin was measured by enzyme-linked immunosorbent assay. The WHI used the homeostasis model assessment of insulin resistance (HOMA-IR), which was developed for application in large epidemiologic investigations as an alternative to the glucose clamp. HOMA-IR = fasting plasma insulin (μIU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5.[34]

STATISTICAL ANALYSIS

Cox proportional hazards (PH) models were used to estimate hazard ratios (HRs) of DM by statin medication use. The dependent variable was time to occurrence of DM determined by self-report (ie, time to event). The time to event was calculated as the interval between enrollment date and the earliest of the following: (1) date of annual medical history update when new DM was ascertained (observed outcome) and (2) date of the last annual medical update during which DM status was ascertained (censored outcome). The primary independent variable in these analyses was statin use at baseline, coded as a bi-

nary variable. We present 3 Cox PH models to examine the association between baseline statin use and DM: model 1 estimates the unadjusted HRs (and associated 95% CIs) of the effects of statin use on incident DM; model 2 presents age- and race/ethnicity–adjusted HRs; and model 3 presents HRs adjusted for all potential confounding variables at baseline (age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arm, and self-report of CVD). Similar analyses were conducted for specific type of statin medication use at baseline, categorized as low vs high potency.

Since individuals using statins may have different underlying conditions that could put them at elevated risk for DM, we conducted several subgroup analyses to control confounding by indication. First, we conducted subgroup analyses by age, race/ethnicity, and BMI categories to examine whether the associations of statin use and onset of DM differed by categories of these variables. Age was categorized into 3 groups (50-59 years, 60-69 years, and ≥70 years). Race/ethnicity was assessed according to 4 major groups (white, African American, Hispanic, Asian). Body mass index was categorized into 3 groups (<25.0, 25.0-29.9, ≥30.0). Second, we conducted similar analyses in 2 subgroups of women either with or without self-reported CVD at baseline. Finally, propensity score analysis[35] was performed to reduce the confounding effects of other factors in the evaluation of the association between statin use and DM risk within an observational study setting. Participant-specific propensity scores were estimated from a logistic regression model to predict the probability of statin prescription. Covariates considered for inclusion into the logistic regression model included age, BMI, self-report of hypertension, self-report of CVD, family history of DM, smoking status, and physical activity. The final propensity score model retained all covariates noted herein with the exception of physical activity, which was an insignificant predictor of statin use. The association between statin use and DM risk was evaluated in Cox PH models after adjusting for the estimated propensity score.

After exclusion for cases of DM before year 3 (146 women), use of cerivastatin (651 women), and missing medication data at year 3 (2 women), our longitudinal analyses were conducted in a subset of 125 575 women from the OS and the CT arm at baseline and year 3 visits. Statin use was sorted into 4 categories: (1) never took statin; (2) use at both baseline and at the year 3 visit, (3) use only at baseline; and (4) use only at the year 3 visit. The HRs for DM by statin use were estimated similarly based on Cox PH models.

<div style="text-align:center">

RESULTS

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PARTICIPANTS' CHARACTERISTICS

Participant characteristics are listed in **Table 1**. At baseline, the mean (SD) age of women included in our sample was 63.2 (7.3) years. Approximately 16.30% of the women were from racial/ethnic groups other than white, of which the largest representation was African American (8.32%). Only 2.56% (3922 women) were Asian. At baseline, 7.04% of participants took statin medication. Of these, 30.29% took simvastatin; 27.29%, lovastatin; 22.52%, pravastatin; 12.15%, fluvastatin; and 7.74%, atorvastatin. Comparison between statin users and nonusers showed significant differences in baseline characteristics.

STATIN USE AT BASELINE AND DM INCIDENCE

A total of 10 242 incident cases of DM were reported over 1 004 466 person-years of follow-up. **Table 2** presents results regarding the association between statin use at baseline and risk of incident DM. In unadjusted models, statin use at baseline was significantly associated with an increased DM risk (HR, 1.71; 95% CI, 1.61-1.83) when compared with nonuse. This association was decreased but remained significant after adjusting for potential confounders (HR, 1.48; 95% CI, 1.38-1.59). This association was observed for all types of statin. Similar risk associations were found in use of either high- or low-potency statins, with multivariate-adjusted HRs of 1.45 (95% CI, 1.36-1.61) and 1.48 (95% CI, 1.36-1.61) compared with nonusers, respectively. **Table 3** shows subgroup analyses by race/ethnicity, BMI category, and age group. In both unadjusted and adjusted models, statin use was consistently associated with increased risk of DM across subgroups by age. We observed significantly increased risk of DM by statin use within subgroups of white, Hispanic, and Asian women in both unadjusted and adjusted models. In adjusted models, we observed HRs of 1.49 (95% CI, 1.38-1.62), 1.18 (95% CI, 0.96-1.45), 1.57 (95% CI, 1.14-2.17), and 1.78 (95% CI, 1.32-2.40) among whites, African Americans, Hispanics, and Asians, respectively. Statin use was also associated with a significantly increased risk of DM within 3 subgroups according to BMI (<25.0, 25.0-29.9, ≥30.0). Moreover, a significantly increased risk of DM associated with statin use was observed among women with BMI lower than 25.0 when compared with women with BMI of 30.0 or higher after adjusting for all potential confounders. In adjusted models, the HRs were 1.89 (95% CI, 1.57-2.29), 1.66 (95% CI, 1.48-1.87), and 1.20 (95% CI, 1.09-1.33) within the groups of women with BMI of less than 25.0, 25.0 to 29.9, and 30.0 or higher, respectively.

STATIN USE AT BASELINE AND RISK OF DM AMONG POSTMENOPAUSAL WOMEN WITH AND WITHOUT HISTORY OF CVD

To address potential confounding and selection bias, we conducted subgroup analyses among postmenopausal women with and without a history of CVD (**Table 4**). Among a subset of 24 842 women who self-reported CVD at baseline, we found that statin use was associated with an increased risk of DM (HR, 1.52; 95% CI, 1.36-1.71). These associations remained significant after adjusting for potential confounders (HR, 1.46; 95% CI, 1.29-1.65). Similar findings were observed among women without CVD at baseline.

PROPENSITY SCORE ANALYSES

In unadjusted models, statin use was significantly related to DM risk (HR, 1.71; 95% CI, 1.61-1.83). When the propensity score was included, the estimated HR attenuated to 1.38 (95% CI, 1.29-1.47). On inclusion of other confounders in the model, the HR was essentially unaltered (HR, 1.40; 95% CI, 1.31-1.51). Propensity score

Table 1. Characteristics of 153 840 Study Participants, Women's Health Initiative[a]

Variable	Total (N = 153 840)	Statin Users (n = 10 834)	Non–Statin Users (n = 143 006)	P Value
Age, y	63.17 (7.25)	65.66 (6.48)	62.98 (7.27)	<.001
BMI	27.77 (5.81)	28.56 (5.32)	27.70 (5.84)	<.001
Dietary variable				
Energy intake, kcal/d	1625.24 (711.56)	1541.81 (690.42)	1631.56 (712.75)	<.001
Carbohydrate, % of energy	50.34 (9.37)	52.12 (9.34)	50.21 (9.36)	<.001
Protein, % of energy	16.71 (3.21)	17.06 (3.31)	16.68 (3.20)	<.001
Fat, % of energy	32.53 (8.39)	30.79 (8.37)	32.66 (8.38)	.81
Saturated fat, % of energy	10.84 (3.33)	9.94 (3.15)	10.91 (3.34)	<.001
Trans fat, g/d	4.29 (3.22)	4.02 (3.08)	4.31 (3.23)	<.001
Fiber, g/d	15.88 (7.14)	15.63 (7.07)	15.90 (7.14)	.18
Alcohol intake, g/d	5.32 (10.58)	4.47 (9.44)	5.38 (10.65)	<.001
Physical activity				
Minutes of recreational physical activity per week[b]	183.40 (180.53)	177.50 (167.28)	183.86 (181.52)	<.001
Categorical variable, No. (%)				
Race/ethnicity				
Asian or Pacific Islander	3922 (2.56)	401 (3.71)	3521 (2.47)	<.001
African American	12 772 (8.32)	862 (7.97)	11 910 (8.35)	
Hispanic/Latino	5978 (3.90)	322 (2.98)	5656 (3.96)	
European American, not of Hispanic origin	12 8458 (83.71)	9065 (83.87)	119 393 (83.69)	
Education				
<High school	7711 (5.05)	651 (6.05)	7060 (4.97)	<.001
High school/GED	25 955 (17.0)	2241 (20.83)	23 714 (16.71)	
>High school, <4 y college	57 740 (37.81)	4205 (39.08)	53 535 (37.72)	
≥4 y college	61 285 (40.14)	3663 (34.04)	57 622 (40.60)	
Smoking status				
Never	77 364 (50.94)	5178 (48.48)	72 186 (51.13)	<.001
Former	63 893 (42.07)	4858 (45.49)	59 035 (41.81)	
Current	10 605 (6.98)	644 (6.03)	9961 (7.06)	
Hormone therapy use				
Never	49 198 (32.94)	3654 (34.42)	45 544 (32.83)	<.001
Former	34 430 (23.05)	2633 (24.80)	31 797 (22.92)	
Current	65 720 (44.0)	4330 (40.78)	61 390 (44.25)	
Family history of DM				
Yes	47 329 (30.93)	3653 (33.91)	43 676 (30.70)	<.001
No	98 686 (64.48)	6599 (61.26)	92 087 (64.73)	
Type of statin medication use at baseline				
Lovastatin	2957 (27.29)	2957 (27.29)	NA	NA
Simvastatin	3282 (30.29)	3282 (30.29)	NA	NA
Fluvastatin	1316 (12.15)	1316 (12.15)	NA	NA
Atorvastatin	839 (7.74)	839 (7.74)	NA	NA
Pravastatin	2440 (22.52)	2440 (22.52)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; HR, hazard ratio; NA, not applicable.

[a] Data are continuous variables given as means (SDs) except where noted. Numbers and percentages may not add up to 153 840 and 100% owing to missing data.
[b] Geometric means (SDs) were presented.

adjusted models yielded HRs of 1.38 (95% CI, 1.23-1.54) and 1.40 (95% CI, 1.29-1.53) for respective increased risk with either high- or low-potency statin use at baseline compared with nonuse.

LONGITUDINAL MEASURES OF STATIN USE AND RISK OF DM

When compared with those who never received statin therapy, unadjusted HRs of 1.82 (95% CI, 1.65-2.00), 1.75 (95% CI, 1.43-2.14), and 1.81 (95% CI, 1.67-1.97) were observed for the groups of women who reported statin use at both baseline and at the year 3 visit, reported statin use only at baseline, and reported statin use only at the year 3 visit, respectively (**Table 5**). The risk associations remained significant after adjusting for age, race/ethnicity, other potential confounders, and propensity score. The multivariate adjusted HRs were 1.47 (95% CI, 1.32-1.64), 1.44 (95% CI, 1.15-1.80), and 1.60 (95% CI, 1.47-1.75), respectively.

SENSITIVITY ANALYSIS

A sensitivity analysis was conducted on a subset of 3706 women without DM at baseline and enrolled in the WHI CT for whom fasting glucose measurements were available at baseline and at least 1 additional follow-up visit. Diabetes mellitus was identified based on fasting glucose levels of 126 mg/dL (6.99 mmol/L) or higher. In unadjusted models, statin use at baseline was not significantly related to DM risk (HR, 1.06; 95% CI, 0.61-1.86). However, using baseline through year 6 data in the CT arm,

Table 2. Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline in 153 840 Participants

Variable	Patients, No.	Cases of New-Onset DM	Unadjusted HR	Age- and Race/Ethnicity-Adjusted HR [a]	Multivariate-Adjusted HR [b]
Taking statin medications at baseline					
Yes	10 834	1076 (9.93)	1.71 (1.61-1.83)	1.69 (1.58-1.80)	1.48 (1.38-1.59)
No	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Years of statin medication use					
<1.0	3614	360 (9.96)	1.74 (1.57-1.94)	1.71 (1.54-1.90)	1.46 (1.30-1.64)
1.0-2.9	3650	365 (10.00)	1.72 (1.55-1.91)	1.67 (1.51-1.86)	1.42 (1.26-1.59)
≥3.0	3570	351 (9.83)	1.68 (1.51-1.87)	1.68 (1.51-1.87)	1.57 (1.40-1.77)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Type of statin medications at baseline					
Lovastatin					
Yes	2949	281 (9.53)	1.52 (1.35-1.71)	1.51 (1.33-1.70)	1.35 (1.19-1.55)
Other statins	7885	795 (10.08)	1.85 (1.72-1.99)	1.82 (1.69-1.97)	1.56 (1.43-1.69)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Simvastatin					
Yes	3247	310 (9.55)	1.71 (1.52-1.92)	1.72 (1.53-1.93)	1.41 (1.25-1.61)
Other statins	7587	766 (10.10)	1.77 (1.64-1.91)	1.73 (1.61-1.87)	1.54 (1.41-1.67)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Fluvastatin					
Yes	1313	145 (11.04)	1.99 (1.69-2.35)	1.90 (1.61-2.24)	1.61 (1.35-1.92)
Other statins	9521	931 (9.78)	1.72 (1.60-1.84)	1.71 (1.59-1.83)	1.48 (1.37-1.60)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Atorvastatin					
Yes	839	79 (9.42)	1.99 (1.58-2.49)	1.99 (1.58-2.49)	1.61 (1.26-2.06)
Other statins	9995	997 (9.97)	1.74 (1.63-1.86)	1.72 (1.61-1.84)	1.49 (1.39-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Pravastatin					
Yes	2423	256 (10.57)	1.87 (1.65-2.13)	1.83 (1.61-2.07)	1.63 (1.43-1.87)
Other statins	8411	820 (9.75)	1.71 (1.59-1.84)	1.70 (1.58-1.83)	1.46 (1.34-1.58)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Potency of statin at baseline					
Low potency: lovastatin, fluvastatin and pravastatin	6701	682 (10.18)	1.68 (1.56-1.82)	1.64 (1.52-1.78)	1.48 (1.36-1.61)
High-potency: simvastatin and atorvastatin	4133	394 (9.53)	1.74 (1.58-1.93)	1.75 (1.58-1.93)	1.45 (1.36-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: HR, hazard ratio; PH, proportional hazards.

[a] The HRs were estimated from Cox PH models adjusting for age and race/ethnicity.

[b] The HRs were estimated from Cox PH models, adjusting for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline.

we found that the statin users had higher fasting glucose levels and HOMA-IR compared with non–statin users, with increasing values from baseline to year 6 follow-up.

COMMENT

The results of this study imply that statin use conveys an increased risk of new-onset DM in postmenopausal women. In keeping with the findings of other studies,[9,13,36] our results suggest that statin-induced DM is a medication class effect and not related to potency or to individual statin. However, the data set contains unequal representation of statins that may have influenced the outcomes. In addition, women who took statins may have changed statin type prior to incident DM. Results may actually reflect a changing market and demand and include those statins that were not available at baseline. For example, rosuvastatin was not available until 2003, after the baseline and year 3 capture points, and may affect follow-up results. Rosuvastatin was associated with increased risk for DM in the postmenopausal women in the JUPITER trial (HR, 1.49; 95% CI, 1.11-2.01).[10] In the absence of dose information, we could not explore further comparisons.

Women with a BMI lower than 25.0 were at greater risk for new-onset DM than those with BMI of 30.0 or higher, who seem to be at lowest relative risk among BMI categories. Given no other reports of this incidence pattern in other studies, we can only speculate that differences in phenotype, such as weight distribution, may contribute to this finding. Native hormonal changes in menopause permit a redistribution of weight in favor of visceral fat that may be independent of BMI as a risk factor for DM.[37] Weight gain within a BMI category may also increase risk for DM.[38] Alternatively, there may be some paradoxical protection against DM among postmenopausal women, akin to that reported for recurrent coronary artery events. This may in fact be a sign of index event bias.[15] This is an area to explore further.

Overlaps in 95% CIs erase significant ethnic differences, although the trend for greater risk among Asian women compared with others agrees with evidence for increased sensitivity to statin effects in this group.[8,12,34,35] Our sample size urges cautious interpretation.

Table 3. Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline, Within Age, Race/Ethnicity, and BMI Subgroups in 153 840 Participants

Variable	Patients, No.	Cases of New-Onset DM, No. (%)	Unadjusted HR[a]	Multivariate-Adjusted HR[b]
Age, y				
50-59				
Statin users	1936	205 (10.59)	1.82 (1.58-2.09)	1.50 (1.29-1.76)
Nonusers	49 685	3169 (6.38)	1 [Reference]	1 [Reference]
60-69				
Statin users	5641	566 (10.03)	1.66 (1.52-1.81)	1.47 (1.34-1.62)
Nonusers	63 035	4145 (6.58)	1 [Reference]	1 [Reference]
≥70				
Statin users	3257	305 (9.36)	1.65 (1.46-1.86)	1.47 (1.29-1.68)
Nonusers	30 286	1852 (6.12)	1 [Reference]	1 [Reference]
Race/ethnicity				
White				
Statin users	9065	814 (8.98)	1.82 (1.69-1.96)	1.49 (1.38-1.62)
Nonusers	119 393	6534 (5.47)	1 [Reference]	1 [Reference]
African American				
Statin users	862	128 (14.85)	1.26 (1.05-1.50)	1.18 (0.96-1.45)
Nonusers	11 910	1546 (12.98)	1 [Reference]	1 [Reference]
Hispanic				
Statin users	322	51 (15.84)	1.64 (1.23-2.18)	1.57 (1.14-2.17)
Nonusers	5656	617 (10.91)	1 [Reference]	1 [Reference]
Asian or Pacific Islander				
Statin users	401	59 (14.71)	2.12 (1.59-2.81)	1.78 (1.32-2.40)
Nonusers	3521	264 (7.50)	1 [Reference]	1 [Reference]
BMI				
<25.0				
Statin users	2824	144 (5.10)	2.50 (2.11-2.98)	1.89 (1.57-2.29)
Nonusers	52 446	1208 (2.30)	1 [Reference]	1 [Reference]
25.0-29.9				
Statin users	4367	391 (8.95)	1.91 (1.71-2.12)	1.66 (1.48-1.87)
Nonusers	49 048	2561 (5.22)	1 [Reference]	1 [Reference]
≥30.0				
Statin users	3549	532 (14.99)	1.23 (1.13-1.35)	1.20 (1.09-1.33)
Nonusers	40 239	5306 (13.19)	1 [Reference]	1 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline. Age was excluded in models within age subgroups. Similarly, race and BMI were individually excluded in models fitted within race/ethnicity and BMI subgroups.

Table 4. Risk of Diabetes Mellitus (DM) by Statin Use Among Women With and Without Medical History of Cardiovascular Disease (CVD) at Baseline

Description	Women With CVD (n = 24 842)		Women Without CVD (n = 120 173)	
	Statin Users	Nonusers	Statin Users	Nonusers
Participants, No.	3338	21 504	7089	113 084
Incident DM cases, No.	369	1695	645	6786
Cumulative incidence rate, %	11.05	7.88	9.10	6.0
Unadjusted HR (95% CI)[a]	1.52 (1.36-1.71)	1 [Reference]	1.65 (1.52-1.79)	1 [Reference]
Age- and race/ethnicity–adjusted HR (95% CI)[b]	1.52 (1.36-1.70)	1 [Reference]	1.61 (1.49-1.75)	1 [Reference]
Multivariate adjusted HR (95% CI)[c]	1.46 (1.29-1.65)	1 [Reference]	1.48 (1.36-1.62)	1 [Reference]

Abbreviations: HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age and race/ethnicity.
[c] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, body mass index, physical activity, alcohol intake, energy intake, family history of DM, and hormone therapy use.

Overlapping 95% CIs indicate similar risk for incident DM with statin use for women with CVD (adjusted HR, 1.46; 95% CI, 1.29-1.65) and without CVD (adjusted HR, 1.48; 95% CI, 1.36-1.62). Given that specific indications for statin use was not available among all women, and that our analysis did not include cardiovascular outcomes, we could not compare risk and benefit for statins in primary or secondary prevention in

Table 5. Risk of Diabetes Mellitus (DM) by Statin Use at Baseline and 3-Year Follow-up in 125 575 Participants

Description	Statin Use Only at Baseline	Statin Use Only at 3-y Follow-up	Statin Use at Baseline and 3-y Follow-up	Never Use
Participants, No.	1531	9571	7076	107 397
Incident DM cases, No.	98	644	442	4294
Cumulative incidence rate, %	6.40	6.73	6.25	4.00
Unadjusted HR (95% CI)[a]	1.75 (1.43-2.14)	1.81 (1.67-1.97)	1.82 (1.65-2.00)	1 [Reference]
Adjusted HR (95% CI)				
Age and race/ethnicity[b]	1.65 (1.35-2.01)	1.79 (1.65-1.95)	1.81 (1.64-2.00)	1 [Reference]
Multivariate[c]	1.49 (1.19-1.86)	1.65 (1.51-1.81)	1.56 (1.41-1.74)	1 [Reference]
Propensity score[d]	1.49 (1.20-1.85)	1.63 (1.49-1.78)	1.43 (1.28-1.58)	1 [Reference]
Multivariate, including propensity score[e]	1.44 (1.15-1.80)	1.60 (1.47-1.75)	1.47 (1.32-1.64)	1 [Reference]

Abbreviations: BMI, body mass index; HR, hazard ratio; PH, proportional hazards.

[a] The HRs were estimated from Cox PH models.

[b] The HRs were estimated Cox PH models, adjusted for age and race/ethnicity.

[c] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of CVD at baseline.

[d] The HRs were estimated from Cox PH models, adjusted for propensity score.

[e] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, self-report of CVD at baseline, and propensity score.

this population. Current and impending guidelines for cardiometabolic risk assessment and statin therapy include monitoring for DM and DM risk,[39,40] which seems prudent.

Several strengths are worth noting: the WHI includes a large, racially diverse cohort of postmenopausal women, and its prospective design enables an examination of temporal associations. When the WHI began, statin use in women with CHD risk factors was not prevalent, allowing comparative study of statin use and nonuse in women with similar risk factors. Our study was also uniform in terms of ascertainment of DM and consistent with data collection for confounders and risk factors over several years.

There are several limitations. First, as this was a observation study, we could not control all confounding factors. While our subgroup analyses in women either with or without CVD found that statin use remains a significant risk for DM, we cannot rule out variations in health care. The sensitivity analyses also attempt to discover and resolve detection and/or selection bias, but it is possible that such biases remain. Second, we did not have data on blood lipid, C-reactive protein, or hemoglobin A_{1c} levels to distinguish if those using statins were at higher risk than those not using statins. Third, although incident DM in older women is likely of the type 2 variety, the WHI question did not specify for type.[26,27,29] Despite a lower sensitivity in self-reports for newly incident DM, statin users and nonusers should have a similar bias of underreporting.[41,42] Fourth, the inability to track intermittent or inconsistent medication use limits analysis.[43] We cannot reliably say that women who reported statin use at 1 or both collection points continued therapy in a way that was likely to provide the intended effect. Moreover, the WHI data up to 2005 reveal that only 7.4% of women used statins, and this proportion may not reflect attributable risk patterns of greater use. Finally, we could not measure drug-drug or drug-disease interactions.

Clearly, statins address the cardiovascular consequences of DM, and current American Diabetes Association guidelines for primary and secondary prevention should not change.[44] The Cholesterol Treatment Trialists' Collaboration found that statins significantly benefit vascular mortality and morbidity and all-cause mortality in diabetic populations with rates comparable with those without DM.[45] Likewise, guidelines for statin use in nondiabetic populations should not change.[39,40] However, the consequences of statin-induced DM have not been specifically defined and deserve more attention. Given the wide use of statins in the aging population, further studies among women, men, and diverse ethnicities will clarify DM risk and risk management to optimize therapy.

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REFERENCES

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.
2. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239.
3. Pedersen TR, Kjekshus J, Berg K, et al; Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Atheroscler Suppl*. 2004;5(3):81-87.
4. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339(19):1349-1357.
5. Sacks FM, Pfeffer MA, Moye LA, et al; Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335 (14):1001-1009.
6. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361(9374):2005-2016.
7. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. *Ann Pharmacother*. 2008;42(9):1208-1215.
8. Crestor prescription information. http://www1.astrazeneca-us.com/pi/crestor .pdf. Accessed November 18, 2011.
9. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716): 735-742.
10. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010;121(9):1069-1077.
11. Yokote K, Saito Y; CHIBA. Influence of statins on glucose tolerance in patients with type 2 diabetes mellitus: subanalysis of the collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). *J Atheroscler Thromb*. 2009;16(3):297-298.
12. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301(20):2129-2140.
13. Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol*. 2011;57(14):1535-1545.
14. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2010;87(1):98-107.
15. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA*. 2011;305(8):822-823.
16. Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM*. 2011;104(2):109-124.
17. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011; 305(24):2556-2564.
18. Liu S, Tinker L, Song Y, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. *Arch Intern Med*. 2007;167(15):1676-1685.
19. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2006; 295(11):1288-1299.
20. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61-109.
21. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S87-S97.
22. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S78-S86.
23. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9)(suppl):S107-S121.
24. Vaughan CJ, Gotto AM Jr. Update on statins: 2003. *Circulation*. 2004;110(7):886-892.
25. Igel M, Sudhop T, von Bergmann K. Pharmacology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), including rosuvastatin and pitavastatin. *J Clin Pharmacol*. 2002;42(8):835-845.
26. de Boer IH, Tinker LF, Connelly S, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care*. 2008;31(4):701-707.

27. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia.* 2006;49(3):459-468.

28. Margolis KL, Bonds DE, Rodabough RJ, et al; Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia.* 2004;47(7):1175-1187.

29. Margolis KL, Lihong Qi, Brzyski R, et al; Women Health Initiative Investigators. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials.* 2008; 5(3):240-247.

30. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol.* 2004;160(12):1152-1158.

31. Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *Eur Heart J.* 2007; 28(23):2937-2943.

32. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol.* 1999;9(3):178-187.

33. McTiernan A, Kooperberg C, White E, et al; Women's Health Initiative Cohort Study. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA.* 2003;290(10): 1331-1336.

34. Song Y, Manson JE, Tinker L, et al. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. *Diabetes Care.* 2007;30(7):1747-1752.

35. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med.* 1997;127(8, pt 2):757-763.

36. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care.* 2009;32(10):1924-1929.

37. Janssen I, Powell LH, Kazlauskaite R, Dugan SA. Testosterone and visceral fat in midlife women: the Study of Women's Health Across the Nation (SWAN) fat patterning study. *Obesity (Silver Spring).* 2010;18(3):604-610.

38. Biggs ML, Mukamal KJ, Luchsinger JA, et al. Association between adiposity in midlife and older age and risk of diabetes in older adults. *JAMA.* 2010;303 (24):2504-2512.

39. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001; 285(19):2486-2497.

40. Brunzell JD, Davidson M, Furberg CD, et al; American Diabetes Association; American College of Cardiology Foundation. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 2008; 31(4):811-822.

41. Oksanen T, Kivimäki M, Pentti J, Virtanen M, Klaukka T, Vahtera J. Self-report as an indicator of incident disease. *Ann Epidemiol.* 2010;20(7):547-554.

42. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol.* 2004;57(10):1096-1103.

43. Simpson RJ Jr, Mendys P. The effects of adherence and persistence on clinical outcomes in patients treated with statins: a systematic review. *J Clin Lipidol.* 2010; 4(6):462-471.

44. American Diabetes Association. Standards of medical care in diabetes: 2011. *Diabetes Care.* 2011;34(suppl 1):S11-S61.

45. Cholesterol Treatment Trialists' Collaboration (CTT). Accessed September 30, 2011. http://www.ctsu.ox.ac.uk/projects/ctt.

EDITOR'S NOTE

ONLINE FIRST

Increased Diabetes Mellitus Risk With Statin Use

Tipping the Balance

In this issue of the *Archives*, Culver et al report an association between use of statins and increased risk of developing diabetes mellitus in a large cohort of women enrolled in the Women's Health Initiative. These data confirm and extend associations previously demonstrated among participants in randomized trials. Although observational data are potentially susceptible to bias by indication, we thought it was noteworthy that the increased risk of diabetes mellitus with statin use was similar among women with and without a history of cardiovascular disease, a finding that may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality.

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