SUPPLEMENTARY MATERIALS

Lipid-lowering drug use and cancer incidence and mortality in the ARIC Study

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Supplementary Methods

Study population

Men and women were recruited from four US communities – Jackson, Mississippi; Washington County, Maryland; suburban Minneapolis, Minnesota; and Forsyth County, North Carolina – with the goal of better understanding risk factors of atherosclerosis and cardiovascular disease, including among Black participants and women. A total of 15,792 participants, aged 45 to 66 years, were enrolled between 1987 and 1989. 27.0% of participants were Black and 55.2% were women. All participants attended a visit 1 examination and were re-invited for 3 follow-up visits during a ten-year period, each approximately 3 years apart. Participants provided informed consent; 99.7% gave approval for follow-up and research for non-cardiovascular diseases. Institutional review boards at each field center approved the ARIC protocol.

Cancer ascertainment

Participants who self-reported a diagnosis of cancer on an annual or semi follow-up telephone call were contacted separately for more information on cancer diagnoses, and medical records pertaining to cancer diagnoses and treatment were collected. For bladder, breast, colorectal, liver, lung, pancreas, and prostate cancers not previously identified by the registries, medical records were abstracted to confirm the diagnosis of cancer. Cancer-related hospitalizations not previously identified by registry linkage were included as cases after medical records were obtained and abstracted to confirm the diagnosis of cancer. Smoking-associated cancers, consisting of lung/bronchus, bladder, kidney, head and neck, stomach, pancreatic, liver and other urinary cancers, were grouped together. Obesity-associated cancers consisted of oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-
menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer, were grouped together.

**Lipid-lowering drug use, duration of use, and age of first use**

Lipid-lowering drug use was ascertained by trained study personnel in five in-person study visits through visit 5 (2011-2013). Prevalent users at visit 1 were excluded from all analyses. Participants were asked to bring in all medications taken in the previous two weeks. During annual/semi-annual follow-up telephone calls beginning in 2006, participants were asked to read the labels of any prescription medications taken in the previous two weeks. Lipid-lowering drug use in ARIC was found to be highly accurate.¹ Participants taking a lipid-lowering drug at visit 2 were categorized as a current user, or as a never user until the first report of lipid-lowering drug use at a study visit or follow-up call. Missing information on lipid-lowering drug use was imputed with the prior assessment carried forward. Participants classified as current lipid-lowering drug users were assumed to be (ever) users until date of censor. Duration of use was calculated as the time of first reported use from visit 2 until date of censor or cancer event. For participants reporting first use of a lipid-lowering drug during visits 2-4, 1.5 years was added to their duration of use to account for the 3-year interval between study visits 2-4. Participants reporting lipid-lowering drug use during an annual/semi-annual phone call or at visit 5 did not have additional time added to their duration of use. Because the most recent follow-up call preceded visit 5 by ≤6 months, we did not add 1.5 years to duration of use. Age of first use was based on the decade of life in which the participants first reported use of a lipid-lowering drug (<50, 50-59, 60-69, >70 years of age). Because of small numbers in the category of <50 years of age and similar associations among participants 60-69 years of age and >70 years of age, we combined categories to include...
participants <60 years of age and ≥60 years of age. Lipid-lowering drug use, duration of use, and age of first use were modeled as time-dependent variables.

**Covariate assessment**

We used data collected during the visits including age (years, visit 2), sex (women/men, visit 2), race (Black/White, visit 1), field center (visit 1), attained education (visit 1), healthcare utilization (physical examination in last 5 years, visit 2), and health insurance status (self-reported, visit 2), body mass index (BMI, kg/m²; visit 2-5), cigarette smoking status (visits 2-5), packyears (visits 2-5), aspirin use (self-reported use in past two weeks, visits 2-5), hormone replacement therapy (female, self-reported use in past two weeks, visits 2-5), alcohol consumption (visit 2-5), and red meat and processed meat consumption (visits 2 and 3). We categorized participants (visits 2-5) as having diagnosed diabetes if they self-reported a physician diagnosis or used diabetes medications. Participants without diagnosed diabetes were classified as undiagnosed diabetes (fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL), at risk for diabetes (fasting glucose of 100 to <126 mg/dL or non-fasting glucose of 140 to <200 mg/dL), or as not diabetic and not at risk for diabetes. We used total cholesterol previously measured in blood collected during visits 2 to 5 to classify participants as having borderline high or high cholesterol (≥5.2 nmol/L) or normal (<5.2 nmol/L). We used as cancer family history a report of mother/father had cancer (visit 1 and 3) and a report of a first degree relative with a site-specific cancer (visit 3). Missing covariate information was imputed with the prior assessment carried forward. At visit 3, participants were asked if they had received a sigmoidoscopy or colonoscopy to detect an abnormality in their colon, large intestine, or rectum.
Statistical analysis

We calculated means and proportions of demographic, lifestyle, and health-related characteristics by current lipid-lowering drug use for participants attending visit 4. To estimate the association of time-updated ever lipid-lowering drug use (yes/no), duration of use (never use, <10, ≥10 years), and age of first use (never use, <60, ≥60 years) with cancer incidence and mortality, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of total, smoking-associated, and obesity-associated, and site-specific (first primary bladder, breast, colorectal, lung, prostate) cancer incidence and mortality. Participants contributed person-time at risk from visit 2 until cancer diagnosis (incidence analyses) or cancer death (mortality analyses), death, or end of follow-up in 2015, whichever came first. For the analysis of age of first use, we used age as the time scale, adjusted for visit 2 age, and stratified by birth cohort in 5-calendar year intervals that allowed for separate baseline hazards by birth cohort. To test for trend across categories of duration of use we included a single ordinal variable with values equal to the median duration of use (years) (never use: 0 years; <10 years: 4.4 years; and ≥10 years: 18.5 years), we used an ordinal variable with values of 0, 1, 2, for each category of age of first use (never user, <60, ≥60 years) the coefficients for which we evaluated using the Wald test. All models were adjusted for visit 2 age (continuous), education level (less than high school, high-school graduate/vocational school/some college, college graduate or graduate school, missing), and joint terms for race and field center (Minneapolis White; Jackson Black; combined Forsyth County and Washington County White; and combined Minneapolis, Forsyth County, and Washington County Black). Models were further adjusted for BMI (time dependent, continuous), cigarette smoking status (time dependent; current, former, never), packyears (time dependent; continuous), cigarette smoking status and time since quitting smoking was used in prostate cancer analyses (time dependent; current/former quit <10 years, former that quit ≥10
years, never), and diagnosed diabetes, undiagnosed diabetes, at-risk for diabetes and normal glycemia (i.e., not diabetic/not at risk for glycemia, time dependent), aspirin use (time dependent; yes, no), family history of cancer, and family history of site-specific cancer. We conducted these analyses separately in men and women and in Black and White participants. We used the likelihood ratio test to test for interaction between lipid-lowering drug use and sex and race. For race, models did not include joint-terms for race and field center which were adjusted for in the race-specific analyses.

We conducted several sensitivity analyses. First, we evaluated ever use of statin drugs separately from ever use of other lipid-lowering drugs. Second, because statin drugs are sometimes prescribed to patients for indications other than an elevated serum cholesterol level, and one mechanism by which statin drugs may influence cancer is via cholesterol lowering, we restricted to participants with normal total cholesterol (<5.2 nmol/L) prior to the report on use of a lipid-lowering drug. Third, to address the possibility of biases related to uptake of screening for elevated cholesterol and screening for cancer, we restricted the analysis to participants who had routine physical examinations (at least every 5 years), and to participants who had health insurance at visit 2. For colorectal cancer, we restricted to participants who reported having had an endoscopy at visit 3, and participants contributed person-time at risk from visit 3 in this analysis. We did not report associations for analyses in which <6 events were observed in any one stratum.

We confirmed the proportional hazards assumption in the multivariable-adjusted models with a global test based on Schoenfeld’s residuals. Statistical analyses were conducted using Stata 15. All statistical tests were two sided and P<0.05 was considered to be statistically significant.
References

1. Bhaskara S, Whitsel EA, Ballantyne CM, Folsom AR. Validity of self-report of lipid medication use: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 2015;242(2):625-629.

2. Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. *Curr Opin Pharmacol*. 2012;12(6):751-759.
## Supplementary Table 1. Association of statins with total, obesity-associated, smoking-associated, and site-specific cancer mortality and incidence in ARIC (1990-2015)

### Total cancer mortality

| Modela | Overall | Women | Men |
|--------|---------|-------|-----|
| | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) |
| **Use** | | | | | | | | | |
| Never user | 1243 | 213873 | 1 (Ref) | 546 | 122397 | 1 (Ref) | 697 | 91476 | 1 (Ref) |
| Ever user | 418 | 53599 | 0.79 (0.69-0.89) | 191 | 29486 | 0.83 (0.69-1.00) | 227 | 24113 | 0.74 (0.62-0.88) |
| **Duration of use** | | | | | | | | | |
| Never user | 1243 | 213873 | 1 (Ref) | 546 | 122397 | 1 (Ref) | 697 | 91476 | 1 (Ref) |
| <10 years | 317 | 36735 | 0.84 (0.73-0.97) | 140 | 20322 | 0.86 (0.69-1.06) | 177 | 16412 | 0.81 (0.67-0.99) |
| ≥10 years | 101 | 16864 | 0.67 (0.55-0.83) | 51 | 9164 | 0.74 (0.62-0.88) | 50 | 7701 | 0.59 (0.44-0.79) |
| **Age of first use** | | | | | | | | | |
| Never user | 1243 | 213874 | 1 (Ref) | 546 | 122398 | 1 (Ref) | 697 | 91476 | 1 (Ref) |
| <60 years of age | 56 | 9093 | 1.12 (0.85-1.48) | 30 | 4565 | 1.42 (0.97-2.07) | 20 | 4528 | 0.92 (0.61-1.37) |
| ≥60 years of age | 358 | 43299 | 0.76 (0.66-0.87) | 158 | 24244 | 0.75 (0.62-0.90) | 200 | 19055 | 0.75 (0.62-0.90) |
| **Total cancer incidence** | | | | | | | | | |
| Use | | | | | | | | | |
| Never user | 2992 | 193408 | 1 (Ref) | 1349 | 112385 | 1 (Ref) | 1643 | 81023 | 1 (Ref) |
| Ever user | 877 | 44591 | 1.00 (0.92-1.09) | 414 | 25474 | 1.01 (0.89-1.15) | 463 | 19117 | 0.99 (0.88-1.12) |
| **Duration of use** | | | | | | | | | |
| Never user | 2992 | 193408 | 1 (Ref) | 1349 | 112385 | 1 (Ref) | 1643 | 81023 | 1 (Ref) |
| <10 years | 613 | 30266 | 1.06 (0.95-1.17) | 288 | 17505 | 1.05 (0.90-1.21) | 325 | 12761 | 1.06 (0.92-1.23) |
| ≥10 years | 264 | 14325 | 0.92 (0.80-1.04) | 126 | 7970 | 0.96 (0.80-1.16) | 138 | 6356 | 0.89 (0.74-1.06) |
| **Age of first use** | | | | | | | | | |
| Never user | 2992 | 200132 | 1 (Ref) | 1349 | 115488 | 1 (Ref) | 1644 | 87217 | 1 (Ref) |
| <60 years of age | 146 | 8281 | 1.05 (0.88-1.24) | 67 | 4159 | 1.18 (0.92-1.51) | 2027 | 100303 | 0.98 (0.78-1.24) |
| ≥60 years of age | 719 | 36392 | 0.71 (0.65-0.78) | 340 | 21198 | 0.71 (0.63-0.82) | 1727 | 89232 | 0.70 (0.62-0.80) |
| **Obesity-associated cancer mortality**c | | | | | | | | | |
| Use | | | | | | | | | |
| Never user | 743 | 213873 | 1 (Ref) | 299 | 122397 | 1 (Ref) | 444 | 91476 | 1 (Ref) |
| Ever user | 246 | 53599 | 0.79 (0.67-0.93) | 101 | 29486 | 0.79 (0.61-1.01) | 145 | 24113 | 0.78 (0.62-0.97) |
| Age of first use | Observed cases | Adjusted incidence rate | 95% CI | \( P_{\text{trend}} \) |
|-----------------|----------------|-------------------------|-------|-----------------|
| <10 years       | 185            | 36735                   | 0.84 (0.69-1.01) | 0.004 |
| \( \geq 10 \) years | 61           | 16864                   | 0.69 (0.53-0.90) | 0.004 |
| \( P_{\text{trend}} \) | 0.27           | 0.01 |

**Obesity-associated cancer incidence**

| Use | Observed cases | Adjusted incidence rate | 95% CI | \( P_{\text{trend}} \) |
|-----|----------------|-------------------------|-------|-----------------|
| Never user | 743          | 213874                  | 1 (Ref) | 0.87 (0.68-1.12) |
| <60 years of age | 30       | 9093                    | 1.01 (0.69-1.47) | 0.76 (0.44-1.32) |
| \( \geq 60 \) years of age | 212       | 43299                   | 0.76 (0.63-0.90) | 0.78 (0.62-0.99) |
| \( P_{\text{trend}} \) | 0.002         | 0.03 |

**Smoking-associated cancer mortality**

| Use | Observed cases | Adjusted incidence rate | 95% CI | \( P_{\text{trend}} \) |
|-----|----------------|-------------------------|-------|-----------------|
| Never user | 1754          | 201569                  | 1 (Ref) | 1 (Ref) |
| <10 years | 375           | 33295                   | 1.05 (0.92-1.20) | 0.97 (0.78-1.19) |
| \( \geq 10 \) years | 155       | 15406                   | 0.89 (0.75-1.05) | 0.77 (0.58-1.02) |
| \( P_{\text{trend}} \) | 0.22           | 0.07 |

**Smoking-associated cancers incidence**

| Use | Observed cases | Adjusted incidence rate | 95% CI | \( P_{\text{trend}} \) |
|-----|----------------|-------------------------|-------|-----------------|
| Never user | 722           | 213873                  | 1 (Ref) | 1 (Ref) |
| <10 years | 180           | 36735                   | 0.83 (0.69-1.00) | 0.86 (0.68-1.12) |
| \( \geq 10 \) years | 61       | 16864                   | 0.71 (0.54-0.92) | 0.58 (0.39-0.84) |
| \( P_{\text{trend}} \) | 0.007         | 0.04 |

**Obesity-associated cancer incidence**

| Use | Observed cases | Adjusted incidence rate | 95% CI | \( P_{\text{trend}} \) |
|-----|----------------|-------------------------|-------|-----------------|
| Never user | 1179          | 206507                  | 1 (Ref) | 1 (Ref) |
| <10 years | 371           | 50672                   | 0.95 (0.83-1.09) | 0.89 (0.74-1.07) |
| Duration of use | Never user | <10 years | ≥10 years | \( P_{\text{trend}} \) |
|-----------------|------------|-----------|-----------|-----------------|
| 1179 | 206507 | 1 (Ref) | 489 | 118736 | 1 (Ref) | 690 | 87771 | 1 (Ref) |
| 258 | 34762 | 0.97 (0.82-1.13) | 110 | 19422 | 0.94 (0.74-1.20) | 148 | 15341 | 0.97 (0.78-1.20) |
| 113 | 15909 | 0.92 (0.75-1.12) | 58 | 8676 | 1.14 (0.86-1.51) | 55 | 7233 | 0.76 (0.57-1.01) |

| Age of first use | Never user | <60 years of age | ≥60 years of age | \( P_{\text{trend}} \) |
|------------------|------------|-----------------|-----------------|-----------------|
| 1179 | 208457 | 1 (Ref) | 489 | 119570 | 1 (Ref) | 690 | 88887 | 1 (Ref) |
| 58 | 8792 | 1.05 (0.80-1.37) | 26 | 4394 | 1.26 (0.84-1.88) | 32 | 4398 | 0.94 (0.65-1.36) |
| 305 | 41160 | 0.72 (0.62-0.83) | 135 | 23250 | 0.72 (0.58-0.89) | 170 | 17910 | 0.70 (0.58-0.85) |

| Bladder cancer mortality | Use | Duration of use | Age of first use | \( P_{\text{trend}} \) |
|---------------------------|-----|----------------|-----------------|-----------------|
| Never user | 25 | 213873 | 1 (Ref) | ─ | ─ | ─ | 18 | 91476 | 1 (Ref) |
| Ever user | 12 | 53599 | 0.84 (0.38-1.85) | ─ | ─ | ─ | 9 | 24113 | 1.03 (0.40-2.65) |

| Bladder cancer incidence | Use | Duration of use | Age of first use | \( P_{\text{trend}} \) |
|--------------------------|-----|----------------|-----------------|-----------------|
| Never user | 121 | 210563 | 1 (Ref) | 33 | 120676 | 1 (Ref) | 88 | 89887 | 1 (Ref) |
| Ever user | 60 | 52377 | 1.38 (0.96-2.00) | 13 | 29008 | 0.91 (0.44-1.87) | 47 | 23369 | 1.67 (1.09-2.56) |

| Breast cancer mortality | Use | Duration of use | Age of first use | \( P_{\text{trend}} \) |
|-------------------------|-----|----------------|-----------------|-----------------|
| Never user | 121 | 210837 | 1 (Ref) | ─ | ─ | ─ | 88 | 90091 | 1 (Ref) |
| <60 years of age | 10 | 8926 | 1.34 (0.68-2.64) | ─ | ─ | ─ | 8 | 4450 | 1.47 (0.68-3.17) |
| ≥60 years of age | 49 | 42394 | 0.92 (0.63-1.34) | ─ | ─ | ─ | 39 | 18499 | 1.07 (0.69-1.66) |
|                          | Use          | Ever user | Duration of use | Never user | <10 years | ≥10 years | Ref | (0.56-1.48) | 0.91 | 1.00 (0.59-1.71) | 0.71 (0.30-1.66) | 0.45 | 0.52 | 0.42 | 1.14 (0.74-1.76) | 0.67 (0.52-0.86) | 0.49 (0.25-0.97) |
|--------------------------|--------------|-----------|----------------|------------|-----------|-----------|-----|-------------|------|----------------|------------------|------|------|------|----------------|------------------|----------------|
| Never user               |              |           |                |            | 84        | 122420    | 1 (Ref) |             | 0.45 |                |                  |      |      |      |                |                  |                |
| Ever user                |              |           |                |            | 29        | 29426     | 0.91     | (0.56-1.48) |      |                |                  |      |      |      |                |                  |                |
| Duration of use          |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 84        | 122420    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| <10 years                |              |           |                |            | 84        | 122420    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| ≥10 years                |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Age of first use         |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 84        | 122420    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| <60 years of age         |              |           |                |            | 23        | 20298     | 1.00     | (0.59-1.71) |      |                |                  |      |      |      |                |                  |                |
| ≥60 years of age         |              |           |                |            | 6         | 9128      | 0.71     | (0.30-1.66) |      |                |                  |      |      |      |                |                  |                |
| Breast cancer incidence  |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Use                      |              |           |                |            |          |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 444       | 117189    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| Ever user                |              |           |                |            | 112       | 27546     | 1.06     | (0.84-1.35) |      |                |                  |      |      |      |                |                  |                |
| Duration of use          |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 444       | 117189    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| <10 years                |              |           |                |            | 82        | 18953     | 1.25     | (0.94-1.65) |      |                |                  |      |      |      |                |                  |                |
| ≥10 years                |              |           |                |            | 30        | 8593      | 0.81     | (0.56-1.19) |      |                |                  |      |      |      |                |                  |                |
| Age of first use         |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 444       | 118579    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| <60 years of age         |              |           |                |            | 22        | 4323      | 1.14     | (0.74-1.76) |      |                |                  |      |      |      |                |                  |                |
| ≥60 years of age         |              |           |                |            | 90        | 22760     | 0.67     | (0.52-0.86) |      |                |                  |      |      |      |                |                  |                |
| Colorectal cancer mortality |            |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Uses                     |              |           |                |            |          |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            | 107       | 214362    | 1 (Ref) |             |      |                |                  |      |      |      |                |                  |                |
| Ever user                |              |           |                |            | 21        | 53705     | 0.45     | (0.27-0.74) |      |                |                  |      |      |      |                |                  |                |
| Duration of use          |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| <10 years                |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| ≥10 years                |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Age of first use         |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| Never user               |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| <60 years of age         |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
| ≥60 years of age         |              |           |                |            |           |           |       |             |      |                |                  |      |      |      |                |                  |                |
|                          | Colorectal cancer incidence | Lung cancer mortality | Lung cancer incidence |
|--------------------------|------------------------------|-----------------------|-----------------------|
| **Use**                  |                              |                       |                        |
| Never user               | 295                          | 118                   | 417                   |
| Ever user                | 61                           | 367                   | 135                   |
| **Duration of use**      |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <10 years                | 35                           | 83                    | 98                    |
| ≥10 years                | 26                           | 35                    | 37                    |
| **Age of first use**     |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |
| **Age of first use**     |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |

**Duration of use**

| Never user               | 295                          | 367                   | 417                   |
| <10 years                | 35                           | 83                    | 98                    |
| ≥10 years                | 26                           | 35                    | 37                    |
| **Age of first use**     |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |

| **Age of first use**     |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |

**Duration of use**

| Never user               | 295                          | 367                   | 417                   |
| <10 years                | 35                           | 83                    | 98                    |
| ≥10 years                | 26                           | 35                    | 37                    |
| **Age of first use**     |                              |                        |                        |
| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |

**Age of first use**

| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |

**Age of first use**

| Never user               | 295                          | 367                   | 417                   |
| <60 years of age         | 10                           | 17                    | 23                    |
| ≥60 years of age         | 49                           | 100                   | 111                   |
|                     | $P_{\text{trend}}^b$ | 0.21 | 0.72 | 0.02 |
|---------------------|-----------------------|------|------|------|
| Prostate cancer mortality |                       |      |      |      |
| **Use**             |                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| Ever user           | –                     | –    | –    | –    |
|                      | 70 91476              | 1 (Ref) |
| **Duration of use** |                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| <10 years           | –                     | –    | –    | –    |
| ≥10 years           | –                     | –    | –    | –    |
|                      | 70 91476              | 1 (Ref) |
| **Age of first use**|                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| <60 years of age    | –                     | –    | –    | –    |
| ≥60 years of age    | –                     | –    | –    | –    |
|                      | 7 7701                | 0.87 (0.39-1.95) |
|                      | 0.60                  |      |      |      |
| Prostate cancer incidence |                     |      |      |      |
| **Use**             |                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| Ever user           | –                     | –    | –    | –    |
|                      | 645 85102             | 1 (Ref) |
| **Duration of use** |                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| <10 years           | –                     | –    | –    | –    |
| ≥10 years           | –                     | –    | –    | –    |
|                      | 645 85102             | 1 (Ref) |
| **Age of first use**|                       |      |      |      |
| Never user          | –                     | –    | –    | –    |
| <60 years of age    | –                     | –    | –    | –    |
| ≥60 years of age    | –                     | –    | –    | –    |
|                      | 645 87068             | 1 (Ref) |

$^a$All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packy years, drinking status, and family history of any cancer. Models for bladder cancer, breast cancer, colorectal cancer, lung cancer and prostate cancer additionally adjusted for family history of site-specific cancer (not including total cancer, smoking-associated cancers, and obesity-associated cancer). Breast cancer models did not include a term for sex and are additionally adjusted for hormone replacement therapy use. Models for colorectal cancer, and lung cancer are additionally adjusted for joint terms for sex and HRT use (female nonuser, female user [reference is men]). Models for colorectal cancer are additionally adjusted for processed meat and red meat consumption. Models for prostate cancer did not include a term for sex and are adjusted for smoking status and time since quitting smoking (current/former that quit <10 years, former that quit ≥10 years, [reference is never]). CI = confidence interval; HR = hazard ratio; Ref = reference.
The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

Obesity-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

Smoking-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, kidney and other urinary cancer.
Supplementary Table 2. Association of lipid-lowering medications with total, obesity-associated, and smoking-associated cancer mortality and incidence among participants with health insurance at visit 1 in ARIC (1990-2015)

| Model<sup>a</sup> | Overall | Women | Men |
|-------------------|---------|-------|-----|
|                   | Cases   | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) |
| Total cancer mortality |        |       |     |        |       |     |        |       |     |
| Use                |         |       |     |         |       |     |         |       |     |
| Never user         | 1021    | 182417 | 1 (Ref) | 452  | 104377 | 1 (Ref) | 569  | 78040 | 1 (Ref) |
| Ever user          | 464     | 62290  | 0.80 (0.71-0.91) | 204  | 33312  | 0.82 (0.68-0.99) | 260  | 28978 | 0.77 (0.65-0.92) |
| Duration of use    |         |       |     |         |       |     |         |       |     |
| Never user         | 1021    | 182417 | 1 (Ref) | 452  | 104377 | 1 (Ref) | 569  | 78040 | 1 (Ref) |
| <10 years          | 307     | 37936  | 0.85 (0.73-0.99) | 135  | 20783  | 0.85 (0.68-1.06) | 172  | 17153 | 0.82 (0.67-1.01) |
| ≥10 years          | 157     | 24354  | 0.74 (0.62-0.88) | 69   | 12529  | 0.78 (0.60-1.01) | 88   | 11825 | 0.71 (0.56-0.89) |
| P<sub>trend</sub>  | <0.001  | 0.06   | 0.004 |
| Age of first use   |         |       |     |         |       |     |         |       |     |
| Never user         | 1021    | 182418 | 1 (Ref) | 452  | 104378 | 1 (Ref) | 569  | 78040 | 1 (Ref) |
| <60 years of age   | 77      | 15649  | 0.88 (0.69-1.12) | 41   | 7457   | 1.20 (0.86-1.66) | 36   | 8192  | 0.68 (0.48-0.97) |
| ≥60 years of age   | 378     | 44926  | 0.79 (0.69-0.91) | 159  | 24808  | 0.76 (0.62-0.92) | 219  | 20118 | 0.81 (0.67-0.97) |
| P<sub>trend</sub>  | <0.001  | 0.01   | 0.01 |
| Total cancer incidence |      |       |     |         |       |     |         |       |     |
| Use                |         |       |     |         |       |     |         |       |     |
| Never user         | 2508    | 165039 | 1.02 (0.94-1.11) | 452  | 29053  | 0.99 (0.88-1.12) | 1372 | 69327 | 1 (Ref) |
| Ever user          | 1020    | 52354  | 1.02 (0.94-1.11) | 452  | 29053  | 0.99 (0.88-1.12) | 568  | 23291 | 1.05 (0.94-1.18) |
| Duration of use    |         |       |     |         |       |     |         |       |     |
| Never user         | 2508    | 165039 | 1 (Ref) | 1136 | 95712  | 1 (Ref) | 1372 | 69327 | 1 (Ref) |
| <10 years          | 644     | 31551  | 1.13 (1.02-1.25) | 288  | 17978  | 1.06 (0.91-1.23) | 356  | 13574 | 1.19 (1.03-1.37) |
| ≥10 years          | 376     | 20793  | 0.91 (0.81-1.02) | 164  | 11076  | 0.92 (0.77-1.08) | 212  | 9718  | 0.92 (0.79-1.07) |
| P<sub>trend</sub>  | 0.11    | 0.32   | 0.27 |
| Age of first use   |         |       |     |         |       |     |         |       |     |
| Never user         | 2508    | 170731 | 1 (Ref) | 1136 | 98336  | 1 (Ref) | 1372 | 72394 | 1 (Ref) |
| <60 years of age   | 224     | 14262  | 0.92 (0.80-1.07) | 95   | 6911   | 0.99 (0.80-1.22) | 129  | 7351  | 0.89 (0.74-1.08) |
| ≥60 years of age   | 772     | 37977  | 0.74 (0.67-0.81) | 345  | 21724  | 0.72 (0.63-0.82) | 427  | 16253 | 0.76 (0.67-0.86) |
| P<sub>trend</sub>  | <0.001  | <0.001 | <0.001 |
| Obesity-associated cancer mortality<sup>c</sup> | | | |
| Use                |         |       |     |         |       |     |         |       |     |
| Never user         | 610     | 182417 | 1 (Ref) | 252  | 104377 | 1 (Ref) | 358  | 78040 | 1 (Ref) |
| Ever user          | 275     | 62290  | 0.81 (0.69-0.96) | 108  | 33312  | 0.76 (0.59-0.97) | 167  | 28978 | 0.82 (0.66-1.02) |
| Duration of use    |         |       |     |         |       |     |         |       |     |
| Never user         | 610     | 182417 | 1 (Ref) | 252  | 104377 | 1 (Ref) | 358  | 78040 | 1 (Ref) |
| Age of first use | Ever user | Never user | \(P_{\text{trend}}\) |
|-----------------|-----------|------------|-----------------|
| <10 years       | 181       | 37936      | 0.01            |
| \(\geq 10\) years | 94        | 24354      | 0.08            |
| \(P_{\text{trend}}\) |           |            | 0.050           |

### Obesity-associated cancer incidence of age

#### Use

| Age of first use | Ever user | Never user | \(P_{\text{trend}}\) |
|-----------------|-----------|------------|-----------------|
| <10 years       | 1466      | 171887     | 0.13            |
| \(\geq 10\) years | 601       | 56920      | 0.046           |
| \(P_{\text{trend}}\) |           |            | 0.22            |

### Smoking-associated cancer mortality of age

#### Use

| Age of first use | Ever user | Never user | \(P_{\text{trend}}\) |
|-----------------|-----------|------------|-----------------|
| <10 years       | 591       | 182417     | 0.001           |
| \(\geq 10\) years | 269       | 62290      | 0.004           |
| \(P_{\text{trend}}\) |           |            | 0.004           |

### Smoking-associated cancer incidence of age

#### Use

| Age of first use | Ever user | Never user | \(P_{\text{trend}}\) |
|-----------------|-----------|------------|-----------------|
| <10 years       | 978       | 176141     | 0.02            |
| \(\geq 10\) years | 429       | 58980      | 0.01            |
| \(P_{\text{trend}}\) |           |            | 0.16            |
### Duration of use

|                | Never user | <10 years | ≥10 years | \( P_{\text{trend}} \) |
|----------------|------------|-----------|-----------|-------------------------|
| Never user     | 978        | 265       | 164       | 0.50                    |
| <10 years      | 176141     | 35944     | 23035     | 0.94 (0.79-1.12)        |
| ≥10 years      | 1 (Ref)    | 1 (Ref)   | 1 (Ref)   |                         |
| \( P_{\text{trend}} \) | 0.76       | 0.75      | 0.86      |                         |

### Age of first use

|                | Never user | <60 years of age | ≥60 years of age | \( P_{\text{trend}} \) |
|----------------|------------|------------------|------------------|-------------------------|
| Never user     | 978        | 177781           | 1 (Ref)          | 0.50                    |
| <60 years of age | 15127     | 0.91 (0.73-1.14) | 0.75 (0.65-0.87) | 0.76                    |
| ≥60 years of age | 42729     | 1.11 (0.79-1.56) | 1.04 (0.80-1.35) | 0.63-0.92               |
| \( P_{\text{trend}} \) | <0.001     | 0.004            | 0.003            |                         |

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a All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. CI = confidence interval; HR = hazard ratio; Ref = reference.

b The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

c Obesity-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

d Smoking-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, kidney and other urinary cancer.
Supplementary Table 3. Association of lipid-lowering medications with total, obesity-associated, and smoking-associated cancer mortality and incidence among participants with physical exam at least every 5 years in ARIC (1990-2015)

| Modela | Overall | Women | Men |
|--------|---------|-------|-----|
|        | Cases   | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) |
| Total cancer mortality |  |  |  |  |  |  |  |  |  |
| Use    |         |       |       |       |       |       |       |       |       |
| Never user | 759   | 141863 | 1 (Ref) | 386   | 88695 | 1 (Ref) | 373   | 53168 | 1 (Ref) |
| Ever user | 355   | 50802  | 0.79 (0.68-0.91) | 169   | 29046 | 0.76 (0.62-0.93) | 186   | 21756 | 0.80 (0.65-0.98) |
| Duration of use |  |  |  |  |  |  |  |  |  |
| Never user | 759   | 141863 | 1 (Ref) | 386   | 88695 | 1 (Ref) | 373   | 53168 | 1 (Ref) |
| <10 years | 229   | 30338  | 0.83 (0.70-0.99) | 114   | 18147 | 0.80 (0.63-1.02) | 115   | 12191 | 0.84 (0.66-1.08) |
| ≥10 years | 126   | 20464  | 0.73 (0.60-0.88) | 55    | 10899 | 0.70 (0.52-0.94) | 71    | 9565  | 0.75 (0.57-0.98) |
| \(P_{\text{trend}}\) |  |  |  |  |  |  |  |  |  |
| Age of first use |  |  |  |  |  |  |  |  |  |
| Never user | 759   | 141864 | 1 (Ref) | 386   | 88696 | 1 (Ref) | 373   | 53168 | 1 (Ref) |
| <60 years of age | 62    | 13242  | 0.84 (0.64-1.10) | 34    | 6614  | 1.08 (0.75-1.55) | 28    | 6628  | 0.68 (0.45-1.01) |
| ≥60 years of age | 287   | 36125  | 0.78 (0.66-0.91) | 133   | 21570 | 0.71 (0.57-0.89) | 154   | 14555 | 0.81 (0.65-1.02) |
| \(P_{\text{trend}}\) |  |  |  |  |  |  |  |  |  |
| Total cancer incidence |  |  |  |  |  |  |  |  |  |
| Use    |         |       |       |       |       |       |       |       |       |
| Never user | 1895  | 128489 | 1 (Ref) | 967   | 81419 | 1 (Ref) | 928   | 47070 | 1 (Ref) |
| Ever user | 794   | 42652  | 1.02 (0.93-1.12) | 378   | 25325 | 0.94 (0.82-1.08) | 416   | 17327 | 1.10 (0.96-1.26) |
| Duration of use |  |  |  |  |  |  |  |  |  |
| Never user | 1895  | 128489 | 1 (Ref) | 967   | 81419 | 1 (Ref) | 928   | 47070 | 1 (Ref) |
| <10 years | 487   | 25291  | 1.14 (1.01-1.28) | 245   | 15730 | 1.02 (0.87-1.20) | 242   | 9561  | 1.27 (1.07-1.50) |
| ≥10 years | 307   | 17361  | 0.90 (0.80-1.02) | 133   | 9595  | 0.84 (0.70-1.02) | 174   | 7766  | 0.97 (0.81-1.15) |
| \(P_{\text{trend}}\) |  | 0.11   | 0.08   |  |  |  |  |  | 0.62   |
| Age of first use |  |  |  |  |  |  |  |  |  |
| Never user | 1895  | 132923 | 1 (Ref) | 967   | 83716 | 1 (Ref) | 928   | 49206 | 1 (Ref) |
| <60 years of age | 189  | 12005  | 0.93 (0.80-1.09) | 79    | 6119  | 0.90 (0.71-1.14) | 110   | 5886  | 0.97 (0.78-1.19) |
| ≥60 years of age | 587   | 30569  | 0.73 (0.66-0.81) | 290   | 18917 | 0.68 (0.59-0.79) | 297   | 11651 | 0.77 (0.67-0.90) |
| \(P_{\text{trend}}\) | <0.001 | <0.001 |  |  |  |  |  |  |  |
| Obesity-associated cancer mortalityc |  |  |  |  |  |  |  |  |  |
| Use    |         |       |       |       |       |       |       |       |       |
| Never user | 446   | 141863 | 1 (Ref) | 206   | 88695 | 1 (Ref) | 240   | 53168 | 1 (Ref) |
| Ever user | 201   | 50802  | 0.78 (0.64-0.94) | 83    | 29046 | 0.70 (0.53-0.93) | 118   | 21756 | 0.83 (0.64-1.07) |
| Duration of use |  |  |  |  |  |  |  |  |  |
| Never user | 446   | 141863 | 1 (Ref) | 206   | 88695 | 1 (Ref) | 240   | 53168 | 1 (Ref) |
| <10 years | 128   | 30338  | 0.82 (0.65-1.03) | 56    | 18147 | 0.74 (0.53-1.04) | 72    | 12191 | 0.87 (0.63-1.18) |
| Age of first use | 0.73 (0.56-0.94) | 0.64 (0.42-0.96) | 0.79 (0.56-1.10) |
|-----------------|------------------|------------------|------------------|
| \( P_{\text{trend}} \) | 0.02 | 0.03 | 0.17 |

### Age of first use

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|------------------|-----------------|
| Never user | 446 | 141864 | 27 | 10899 | 46 | 9565 |
| <60 years of age | 34 | 13242 | 16 | 6614 | 18 | 6628 |
| ≥60 years of age | 163 | 36125 | 65 | 21570 | 98 | 14555 |

### Duration of use

| Use | Never user | <10 years | ≥10 years |
|-----|------------|-----------|-----------|
| Never user | 471 | 46367 | 0.99 (0.88-1.12) | 294 | 25932 |
| <10 years | 292 | 27618 | 1.09 (0.93-1.26) | 193 | 16125 |
| ≥10 years | 1116 | 133589 | 0.90 (0.76-1.06) | 101 | 9806 |

### Age of first use

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|------------------|-----------------|
| Never user | 433 | 141863 | 193 | 88695 | 193 | 88696 |
| <60 years of age | 124 | 30338 | 52 | 18147 | 52 | 18147 |
| ≥60 years of age | 72 | 20464 | 26 | 10899 | 26 | 10899 |

### Duration of use

| Use | Never user | <10 years | ≥10 years |
|-----|------------|-----------|-----------|
| Never user | 433 | 141863 | 193 | 88695 | 193 | 88696 |
| <10 years | 124 | 30338 | 52 | 18147 | 52 | 18147 |
| ≥10 years | 72 | 20464 | 26 | 10899 | 26 | 10899 |

### Age of first use

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|------------------|-----------------|
| Never user | 433 | 141863 | 193 | 88695 | 193 | 88696 |
| <60 years of age | 32 | 13242 | 14 | 6614 | 14 | 6614 |
| ≥60 years of age | 160 | 36125 | 62 | 21570 | 62 | 21570 |

### Smoking-associated cancer mortality

| Use | Never user | <10 years | ≥10 years |
|-----|------------|-----------|-----------|
| Never user | 433 | 141863 | 193 | 88695 | 193 | 88696 |
| <10 years | 124 | 30338 | 52 | 18147 | 52 | 18147 |
| ≥10 years | 72 | 20464 | 26 | 10899 | 26 | 10899 |

### Smoking-associated cancer incidence

| Use | Never user | <10 years | ≥10 years |
|-----|------------|-----------|-----------|
| Never user | 433 | 141863 | 193 | 88695 | 193 | 88696 |
| <10 years | 124 | 30338 | 52 | 18147 | 52 | 18147 |
| ≥10 years | 72 | 20464 | 26 | 10899 | 26 | 10899 |
| Duration of use       | Ever user | Duration of use | Ever user | Duration of use | Ever user | Duration of use | Ever user | Duration of use | Ever user |
|-----------------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
|                       | 322       | 48148           | 1.00      | (0.86-1.17)     | 149       | 27697           | 0.96      | (0.77-1.20)     | 173       | 20451          | 1.02      | (0.83-1.27)    |
| Never user            | 704       | 137094          | 1 (Ref)   | 339             | 86021     | 1 (Ref)         | 365       | 51073           | 1 (Ref)   |
| <10 years             | 193       | 28816           | 1.05      | (0.87-1.27)     | 97        | 17320           | 1.02      | (0.78-1.33)     | 96        | 11496          | 1.06      | (0.81-1.38)    |
| ≥10 years             | 129       | 19332           | 0.95      | (0.78-1.16)     | 52        | 10377           | 0.89      | (0.66-1.20)     | 77        | 8955           | 0.99      | (0.76-1.29)    |
|                       |           |                 |           |                 |           |                 |           |                 |           |
|                       |           |                 | P_{trend} | 0.61            |           |                 | 0.45      |                 |           |
|                       |           |                 |           |                 |           |                 |           |                 |           |
| Age of first use      |           |                 |           |                 |           |                 |           |                 |           |
| Never user            | 704       | 138266          | 1 (Ref)   | 339             | 86582     | 1 (Ref)         | 365       | 51684           | 1 (Ref)   |
| <60 years of age      | 72        | 12783           | 0.94      | (0.73-1.21)     | 29        | 6407            | 0.96      | (0.65-1.42)     | 43        | 6376           | 0.94      | (0.67-1.31)    |
| ≥60 years of age      | 240       | 34427           | 0.75      | (0.64-0.89)     | 114       | 20635           | 0.72      | (0.57-0.91)     | 126       | 13792          | 0.77      | (0.61-0.98)    |
|                       |           |                 | P_{trend} | 0.001           |           |                 | 0.007     |                 |           |
|                       |           |                 |           |                 |           |                 |           |                 |           |

\(^{a}\)All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. CI = confidence interval; HR = hazard ratio; Ref = reference.

\(^{b}\)The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

\(^{c}\)Obesity-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

\(^{d}\)Smoking-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, kidney and other urinary cancer.
Supplementary Table 4. Association of lipid-lowering medications with total, obesity-associated, and smoking-associated cancer mortality and incidence among never smokers in ARIC (1990-2015)

| Model<sup>a</sup> | Overall | Women | Men |
|-------------------|---------|-------|-----|
|                   | Cases   | Person-time | HR (95% CI) | Cases   | Person-time | HR (95% CI) | Cases   | Person-time | HR (95% CI) |
| Total cancer mortality Use |         |         |       |         |         |       |         |         |         |       |
| Never user        | 305     | 84376  | 1 (Ref) | 195     | 60366  | 1 (Ref) | 110     | 24010  | 1 (Ref) |
| Ever user         | 141     | 27012  | 0.81 (0.64-1.01) | 88      | 18960  | 0.80 (0.60-1.06) | 53      | 8051   | 0.80 (0.55-1.16) |
| Duration of use   |         |         |       |         |         |       |         |         |         |       |
| Never user        | 305     | 84376  | 1 (Ref) | 195     | 60366  | 1 (Ref) | 110     | 24010  | 1 (Ref) |
| <10 years         | 97      | 16693  | 0.85 (0.65-1.10) | 59      | 11856  | 0.81 (0.58-1.14) | 38      | 4837   | 0.89 (0.58-1.37) |
| ≥10 years         | 44      | 10319  | 0.74 (0.53-1.02) | 29      | 7104   | 0.78 (0.52-1.16) | 15      | 3214   | 0.67 (0.38-1.16) |
| &lt;sup&gt;b&lt;/sup&gt;|         |         |       |         |         |       |         |         |         |       |
| P<sub>trend</sub> |         |         |       |         |         |       |         |         |         |       |
| Age of first use  |         |         |       |         |         |       |         |         |         |       |
| Never user        | 305     | 84376  | 1 (Ref) | 195     | 60366  | 1 (Ref) | 110     | 24010  | 1 (Ref) |
| <60 years of age  | 25      | 6441   | 0.99 (0.65-1.51) | 19      | 4261   | 1.24 (0.76-2.03) | 6       | 2180   | 0.61 (0.26-1.42) |
| ≥60 years of age  | 113     | 19808  | 0.79 (0.62-1.01) | 67      | 14170  | 0.71 (0.52-0.97) | 46      | 5638   | 0.94 (0.63-1.40) |
| &lt;sup&gt;b&lt;/sup&gt;|         |         |       |         |         |       |         |         |         |       |
| P<sub>trend</sub> |         |         |       |         |         |       |         |         |         |       |
| Total cancer incidence Use |         |         |       |         |         |       |         |         |         |       |
| Never user        | 939     | 76693  | 1 (Ref) | 578     | 55490  | 1 (Ref) | 361     | 21203  | 1 (Ref) |
| Ever user         | 353     | 23055  | 1.01 (0.88-1.17) | 219     | 16597  | 1.00 (0.83-1.19) | 134     | 6458   | 1.05 (0.84-1.31) |
| Duration of use   |         |         |       |         |         |       |         |         |         |       |
| Never user        | 939     | 76693  | 1 (Ref) | 578     | 55490  | 1 (Ref) | 361     | 21203  | 1 (Ref) |
| <10 years         | 224     | 14087  | 1.12 (0.95-1.33) | 145     | 10273  | 1.12 (0.90-1.38) | 79      | 3815   | 1.14 (0.85-1.52) |
| ≥10 years         | 129     | 8968   | 0.90 (0.74-1.09) | 74      | 6325   | 0.85 (0.66-1.10) | 55      | 2643   | 0.97 (0.72-1.30) |
| &lt;sup&gt;b&lt;/sup&gt;|         |         |       |         |         |       |         |         |         |       |
| P<sub>trend</sub> |         |         |       |         |         |       |         |         |         |       |
| Age of first use  |         |         |       |         |         |       |         |         |         |       |
| Never user        | 939     | 79148  | 1 (Ref) | 578     | 57003  | 1 (Ref) | 361     | 22145  | 1 (Ref) |
| <60 years of age  | 76      | 5936   | 0.88 (0.69-1.12) | 47      | 3941   | 0.96 (0.71-1.30) | 29      | 1995   | 0.78 (0.52-1.14) |
| ≥60 years of age  | 268     | 17010  | 0.71 (0.61-0.82) | 167     | 12483  | 0.70 (0.57-0.84) | 101     | 4527   | 0.73 (0.57-0.94) |
| &lt;sup&gt;b&lt;/sup&gt;|         |         |       |         |         |       |         |         |         |       |
| P<sub>trend</sub> |         |         |       |         |         |       |         |         |         |       |
| Obesity-associated cancers mortality<sup>c</sup> Use |         |         |       |         |         |       |         |         |         |       |
| Never user        | 136     | 84376  | 1 (Ref) | 88      | 60366  | 1 (Ref) | 48      | 24010  | 1 (Ref) |
| Ever user         | 53      | 27012  | 0.62 (0.43-0.88) | 30      | 18960  | 0.54 (0.34-0.85) | 23      | 8051   | 0.75 (0.43-1.32) |
| Duration of use   |         |         |       |         |         |       |         |         |         |       |
| Never user        | 136     | 84376  | 1 (Ref) | 88      | 60366  | 1 (Ref) | 48      | 24010  | 1 (Ref) |
## Obesity

| Age of first use | Use     | Duration of use | Age of first use | Use     |
|------------------|---------|-----------------|------------------|---------|
| <10 years        | 39      | 16693           | 0.69 (0.46-1.04) | 23      | 11856 | 0.63 (0.38-1.06) |
| ≥10 years        | 14      | 10319           | 0.49 (0.28-0.86) | 7       | 7104  | 0.38 (0.17-0.83) |
| **P** _trend<sup>b</sup> | 0.01    | 0.01            | 0.01             | 0.01    |

### Obesity-associated cancer incidences<sup>c</sup>

| Use | Duration of use | Age of first use | Use |
|-----|-----------------|------------------|-----|
| Never user | 136 | 84377 | 1 (Ref) | 88 | 60366 | 1 (Ref) |
| <60 years of age | 9 | 6441 | 0.78 (0.39-1.57) | 6 | 4261 | 0.95 (0.40-2.24) |
| ≥60 years of age | 42 | 19080 | 0.60 (0.41-0.88) | 22 | 14170 | 0.45 (0.27-0.75) |
| **P** _trend<sup>b</sup> | 0.009 | 0.002 |

### Smoking-associated cancer mortality<sup>d</sup>

| Use | Duration of use | Age of first use | Use |
|-----|-----------------|------------------|-----|
| Never user | 129 | 84376 | 1 (Ref) | 81 | 60366 | 1 (Ref) |
| <10 years | 35 | 16693 | 0.64 (0.42-0.97) | 19 | 11856 | 0.54 (0.31-0.95) |
| ≥10 years | 14 | 10319 | 0.51 (0.29-0.89) | 7 | 7104 | 0.40 (0.18-0.89) |
| **P** _trend<sup>b</sup> | 0.02 | 0.02 |

### Smoking-associated cancer incidence<sup>d</sup>

| Use | Duration of use | Age of first use | Use |
|-----|-----------------|------------------|-----|
| Never user | 129 | 84376 | 1 (Ref) | 81 | 60366 | 1 (Ref) |
| <60 years of age | 8 | 6441 | 0.73 (0.35-1.52) | 19 | 11856 | 0.54 (0.31-0.95) |
| ≥60 years of age | 39 | 19080 | 0.58 (0.39-0.86) | 22 | 14170 | 0.45 (0.27-0.75) |
| **P** _trend<sup>b</sup> | 0.007 |

### Notes

- All comparisons are statistically significant (p < 0.05).
- The table presents the number of cases and controls, along with the odds ratios and 95% confidence intervals.
| Duration of use | Never user | 272 | 81859 | 1 (Ref) | 168 | 58644 | 1 (Ref) | 104 | 23215 | 1 (Ref) |
|----------------|------------|-----|--------|---------|-----|--------|---------|-----|--------|---------|
| <10 years      | 63         | 15957 | 0.88 (0.64-1.21) | 41 | 11394 | 0.88 (0.59-1.31) | 22 | 4564 | 0.87 (0.51-1.48) |
| ≥10 years      | 41         | 9871  | 0.89 (0.63-1.25) | 22 | 6835  | 0.78 (0.49-1.24) | 19 | 3036  | 1.05 (0.63-1.74) |
| **P_{trend}**<sup>b</sup> | 0.50 | 0.29 | 0.86 |

| Age of first use | Never user | 272 | 82398 | 1 (Ref) | 168 | 58974 | 1 (Ref) | 104 | 23969 | 1 (Ref) |
|------------------|------------|-----|--------|---------|-----|--------|---------|-----|--------|---------|
| <60 years of age | 22         | 6285 | 0.82 (0.52-1.28) | 13 | 4145  | 0.85 (0.48-1.53) | 9  | 2140  | 0.76 (0.38-1.54) |
| ≥60 years of age | 76         | 18947 | 0.62 (0.47-0.82) | 46 | 13642 | 0.57 (0.40-0.82) | 30 | 5305  | 0.71 (0.45-1.12) |
| **P_{trend}**<sup>b</sup> | <0.001 | 0.002 | 0.13 |

<sup>a</sup>All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. CI = confidence interval; HR = hazard ratio; Ref = reference.

<sup>b</sup>The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

<sup>c</sup>Obesity-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

<sup>d</sup>Smoking-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, kidney and other urinary cancer.
Supplementary Table 5. Association of lipid-lowering medication use with total, obesity-associated, and smoking-associated cancer mortality and incidence among participants with normal total cholesterol among non-users and normal total cholesterol among users prior to initiating lipid-lowering medication use in ARIC (1990-2015)

| Modela | Overall | Women | Men |
|--------|---------|-------|-----|
|        | Cases   | Person-time | HR (95% CI) | Cases   | Person-time | HR (95% CI) | Cases   | Person-time | HR (95% CI) |
| Total cancer mortality Use | | | | | | | | |
| Never user | 562 | 99809 | 1 (Ref) | 210 | 52332 | 1 (Ref) | 352 | 47477 | 1 (Ref) |
| Ever user | 144 | 17422 | 0.76 (0.62-0.94) | 51 | 7449 | 0.90 (0.63-1.26) | 93 | 9973 | 0.68 (0.52-0.88) |
| Duration of use | | | | | | | | |
| Never user | 562 | 99809 | 1 (Ref) | 210 | 52332 | 1 (Ref) | 352 | 47477 | 1 (Ref) |
| <10 years | 121 | 14422 | 0.75 (0.60-0.93) | 39 | 6441 | 0.75 (0.51-1.10) | 82 | 7981 | 0.72 (0.54-0.95) |
| ≥10 years | 23 | 3000 | 0.83 (0.54-1.27) | 12 | 1008 | 1.84 (1.01-3.34) | 11 | 1992 | 0.51 (0.28-0.94) |
| | | | \(P_{\text{trend}}\) | | | | | | |
| Never user | 562 | 99809 | 0.12 | 210 | 52332 | 0.20 | 352 | 47477 | 0.008 |
| <60 years of age | 11 | 1982 | 0.99 (0.54-1.82) | 8 | 764 | 2.80 (1.34-5.85) | — | — | — |
| ≥60 years of age | 132 | 15154 | 0.75 (0.60-0.93) | 43 | 6589 | 0.80 (0.56-1.16) | — | — | — |
| | | | \(P_{\text{trend}}\) | | | | | | |
| Total cancer incidence Use | | | | | | | | |
| Never user | 1323 | 88911 | 1 (Ref) | 508 | 47659 | 1 (Ref) | 815 | 41252 | 1 (Ref) |
| Ever user | 295 | 13943 | 1.03 (0.89-1.20) | 101 | 6301 | 1.01 (0.79-1.29) | 194 | 7642 | 1.05 (0.87-1.26) |
| Duration of use | | | | | | | | |
| Never user | 1323 | 88911 | 1 (Ref) | 508 | 47659 | 1 (Ref) | 815 | 41252 | 1 (Ref) |
| <10 years | 248 | 11514 | 1.05 (0.89-1.23) | 83 | 5405 | 0.95 (0.72-1.24) | 165 | 6108 | 1.11 (0.91-1.36) |
| ≥10 years | 47 | 2429 | 0.97 (0.72-1.30) | 18 | 895 | 1.36 (0.84-2.19) | 29 | 1534 | 0.84 (0.58-1.23) |
| | | | \(P_{\text{trend}}\) | | | | | | |
| Never user | 1323 | 93974 | 0.97 | 508 | 49724 | 1 (Ref) | 815 | 44250 | 1 (Ref) |
| <60 years of age | 30 | 1708 | 1.14 (0.79-1.65) | 13 | 688 | 1.53 (0.87-2.69) | 17 | 1020 | 0.94 (0.58-1.54) |
| ≥60 years of age | 261 | 13079 | 0.73 (0.63-0.85) | 88 | 5965 | 0.71 (0.55-0.91) | 173 | 7114 | 0.75 (0.62-0.90) |
| | | | \(P_{\text{trend}}\) | | | | | | |
| Obesity-associated cancer mortalityc Use | | | | | | | | |
| Never user | 348 | 99809 | 1 (Ref) | 120 | 52332 | 1 (Ref) | 228 | 47477 | 1 (Ref) |
| Ever user | 81 | 17422 | 0.72 (0.55-0.95) | 20 | 7449 | 0.61 (0.36-1.02) | 61 | 9973 | 0.76 (0.54-1.05) |
| Duration of use | Never user | 348 99809 | 1 (Ref) | 410 48318 | 1 (Ref) | 369 45278 | 1 (Ref) | 228 47477 | 1 (Ref) |
|----------------|------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| <10 years      | 68         | 14422     | 0.72 (0.53-0.96) | 66      | 5612   | 0.91 (0.67-1.23) | 74      | 7447    | 0.91 (0.68-1.24) |
| ≥10 years      | 13         | 3000      | 0.76 (0.43-1.34) | 14      | 915     | 1.24 (0.72-2.14) | 12      | 1820    | 0.66 (0.36-1.18) |
| **P**\text{trend} |            | 0.13      |         |          |         |            | 0.007   |          |          |
| Age of first use | Never user | -         | -       | -        | -       | -         | -       | -        | -       |
| <60 years of age | -         | -         | -       | -        | -       | -         | -       | -        | -       |
| ≥60 years of age | -         | -         | -       | -        | -       | -         | -       | -        | -       |
| **P**\text{trend} |            | 0.16      |         |          |         |            | 0.016   |          |          |

**Obesity-associated cancer incidence**

| Use | Never user | 779 93596 | 1 (Ref) | 410 48318 | 1 (Ref) | 369 45278 | 1 (Ref) | 228 47477 | 1 (Ref) |
|-----|------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Ever user | 166       | 15794    | 0.91 (0.75-1.10) | 80      | 6527   | 0.96 (0.73-1.27) | 86      | 9267    | 0.86 (0.65-1.13) |
| **P**\text{trend} |            | 0.34      |         |          |         |            | 0.007   |          |          |

**Age of first use**

| Never user | 779 96230 | 1 (Ref) | 410 50057 | 1 (Ref) | 369 45278 | 1 (Ref) | 228 47477 | 1 (Ref) |
| <60 years of age | 15       | 1836     | 0.87 (0.51-1.46) | 11      | 697     | 1.46 (0.79-2.71) | -       | -       | -       |
| ≥60 years of age | 150      | 14198    | 0.70 (0.58-0.85) | 69      | 6081   | 0.66 (0.50-0.88) | -       | -       | -       |
| **P**\text{trend} |            | <0.001   |         |          |         |          | 0.007   |          |          |

**Smoking-associated cancer mortality**

| Use | Never user | 339 99809 | 1 (Ref) | 111 52332 | 1 (Ref) | 228 47477 | 1 (Ref) | 61 9973 | 0.76 (0.54-1.05) |
|-----|------------|-----------|---------|-----------|---------|-----------|---------|---------|-----------|
| Ever user | 81       | 17422    | 0.74 (0.56-0.97) | 20      | 7449   | 0.64 (0.38-1.08) | 61      | 9973    | 0.76 (0.54-1.05) |

Duration of use

| Never user | 339 99809 | 1 (Ref) | - | - | - | 228 47477 | 1 (Ref) |
| <10 years | 68 | 14422 | 0.73 (0.54-0.98) | - | - | - | 53 | 7981 | 0.79 (0.56-1.13) |
| ≥10 years | 13 | 3000 | 0.78 (0.44-1.36) | - | - | - | 8 | 1992 | 0.61 (0.30-1.25) |
| **P**\text{trend} |            | 0.16      |         |          |         |            | 0.016   |          |          |

Age of first use

| Never user | - | - | - | - | - | - | - | - |
| <60 years of age | - | - | - | - | - | - | - | - |
| ≥60 years of age | - | - | - | - | - | - | - | - |
| **P**\text{trend} |            | 0.16      |         |          |         |            | 0.016   |          |          |

**Smoking-associated cancer incidence**

Use

Duration of use

| Never user | 348 99809 | 1 (Ref) | - | - | - | 228 47477 | 1 (Ref) |
| <10 years | 68 | 14422 | 0.72 (0.53-0.96) | - | - | - | 53 | 7981 | 0.79 (0.56-1.13) |
| ≥10 years | 13 | 3000 | 0.76 (0.43-1.34) | - | - | - | 8 | 1992 | 0.61 (0.30-1.25) |
| **P**\text{trend} |            | 0.13      |         |          |         |            | 0.007   |          |          |

Age of first use

| Never user | - | - | - | - | - | - | - | - |
| <60 years of age | - | - | - | - | - | - | - | - |
| ≥60 years of age | - | - | - | - | - | - | - | - |
| **P**\text{trend} |            | 0.16      |         |          |         |            | 0.016   |          |          |
|                                     | Never user | Ever user | 1 (Ref) | 177 | 50757 | 1 (Ref) | 365 | 45318 | 1 (Ref) |
|-------------------------------------|------------|-----------|---------|-----|-------|---------|-----|-------|---------|
| Duration of use                     |            |           |         |     |       |         |     |       |         |
| Never user                          | 542        | 96075     | 1       | 177 | 50757 | 1       | 365 | 45318 | 1       |
| <10 years                           | 102        | 13558     | 0.85    | 29  | 6104  | 0.75    | 73  | 7454  | 0.91    |
| ≥10 years                           | 20         | 2807      | 0.83    | 8   | 974   | 1.38    | 12  | 1832  | 0.66    |
| $P_{\text{trend}}^{b}$             |            |           |         |     | 0.27  |         |     |       | 0.14    |
| Age of first use                    |            |           |         |     |       |         |     |       |         |
| Never user                          | 542        | 97489     | 1       | 177 | 51279 | 1       |     |       |         |
| <60 years of age                    | 9          | 1883      | 0.71    | 6   | 732   | 1.86    |     |       |         |
| ≥60 years of age                    | 112        | 14504     | 0.70    | 31  | 6382  | 0.61    |     |       |         |
| $P_{\text{trend}}^{b}$             |            |           |         |     | 0.002 |         |     |       | 0.03    |

$^{a}$All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. CI = confidence interval; HR = hazard ratio; Ref = reference.

$^{b}$The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

$^{c}$Obesity-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, post-menopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

$^{d}$Smoking-associated cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, kidney and other urinary cancer.
### Supplementary Table 6. Association of lipid-lowering medications with site-specific cancer mortality and incidence in ARIC (1990-2015)

| Modela | Overall | | | Women | | | Men | |
|--------|---------|------------------|------------------|------------------|------------------|------------------|
|        | Cases   | Person-time      | HR (95% CI)      | Cases   | Person-time      | HR (95% CI)      | Cases   | Person-time      | HR (95% CI)      |
| Bladder cancer mortality | | | | | | | | | |
| Use     |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user | 22      | 200548           | 1 (Ref)          |        |                  |                  | 15     | 85009            | 1 (Ref)          |
| Ever user | 15      | 66925            | 0.98 (0.46-2.11) |        |                  |                  | 12     | 30581            | 1.43 (0.57-3.53) |
| Duration of use |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user | 22      | 200548           | 1 (Ref)          |        |                  |                  | 15     | 85009            | 1 (Ref)          |
| <10 years | 9       | 41106            | 0.89 (0.37-2.17) |        |                  |                  | 6      | 18180            | 1.05 (0.35-3.18) |
| ≥10 years | 6       | 25818            | 1.14 (0.43-2.97) |        |                  |                  | 6      | 12401            | 1.95 (0.69-5.51) |
| $P_{\text{trend}}$ |         |                  |                  | 0.77   |                  |                  | 0.19   |                  |                  |
| Age of first use |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user |        |                  |                  |        |                  |                  |        |                  |                  |
| <60 years of age |        |                  |                  |        |                  |                  |        |                  |                  |
| ≥60 years of age |        |                  |                  |        |                  |                  |        |                  |                  |
| $P_{\text{trend}}$ |         |                  |                  | 0.62   |                  |                  | 0.35   |                  |                  |
| Bladder cancer incidence | | | | | | | | | |
| Use     |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user | 113     | 197505           | 1 (Ref)          | 32     | 113893           | 1 (Ref)          | 81     | 83612            | 1 (Ref)          |
| Ever user | 68      | 65435            | 1.23 (0.87-1.75) | 14     | 35791            | 0.76 (0.38-1.54) | 54     | 29644            | 1.48 (0.99-2.23) |
| Duration of use |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user | 113     | 197505           | 1 (Ref)          | 32     | 113893           | 1 (Ref)          | 81     | 83612            | 1 (Ref)          |
| <10 years | 42      | 40223            | 1.32 (0.86-2.02) | 14     | 35791            | 0.76 (0.38-1.54) | 33     | 17651            | 1.67 (1.02-2.73) |
| ≥10 years | 26      | 25211            | 1.14 (0.72-1.78) |        |                  |                  | 21     | 11993            | 1.32 (0.79-2.20) |
| $P_{\text{trend}}$ |         |                  |                  | 0.62   |                  |                  | 0.35   |                  |                  |
| Age of first use |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user | 113     | 197761           | 1 (Ref)          |        |                  |                  | 81     | 83799            | 1 (Ref)          |
| <60 years of age | 15      | 16550            | 1.08 (0.61-1.90) |        |                  |                  | 13     | 8481             | 1.29 (0.69-2.41) |
| ≥60 years of age | 52      | 47273            | 0.86 (0.59-1.25) |        |                  |                  | 41     | 20581            | 0.99 (0.64-1.53) |
| $P_{\text{trend}}$ |         |                  |                  | 0.46   |                  |                  | 0.99   |                  |                  |
| Breast cancer mortality | | | | | | | | | |
| Use     |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user |        |                  |                  | 78     | 115540           | 1 (Ref)          |        |                  |                  |
| Ever user |        |                  |                  | 35     | 36306            | 0.93 (0.59-1.47) |        |                  |                  |
| Duration of use |         |                  |                  |        |                  |                  |        |                  |                  |
| Never user |        |                  |                  | 78     | 115540           | 1 (Ref)          |        |                  |                  |
| Age of first use | Never user | <60 years of age | ≥60 years of age | \( P_{\text{trend}} \) |
|------------------|-----------|-----------------|-----------------|-----------------|
| <10 years        | 28        | 10              | 7               | 0.20            |
| ≥10 years        | 7         | 10              | 25              | 0.57            |
| \( P_{\text{trend}} \) |           |                 |                 |                 |

### Breast cancer incidence

| Use | Never user | Ever user | \( P_{\text{trend}} \) |
|-----|------------|-----------|-----------------|
| Never user | 427       | 129       | 0.11            |
| Ever user   | 427       | 129       | 0.11            |

### Colorectal cancer mortality

| Use | Never user | Ever user | \( P_{\text{trend}} \) |
|-----|------------|-----------|-----------------|
| Never user | 427       | 129       | 0.11            |
| Ever user   | 427       | 129       | 0.11            |

### Colorectal cancer incidence

| Use | Never user | Ever user | \( P_{\text{trend}} \) |
|-----|------------|-----------|-----------------|
| Never user | 22905     | 13400     | 0.20            |
| Ever user   | 22905     | 13400     | 0.20            |
### Lung Cancer Mortality

|                   | Never user | 196897 | 1 (Ref) | 139 | 113470 | 1 (Ref) | 140 | 83428 | 1 (Ref) |
|-------------------|------------|--------|---------|-----|--------|---------|-----|-------|---------|
| Duration of use   | Never user | 279    |         |     |        |         |     |       |         |
|                   | <10 years  | 43     | 40181   | 0.65 | (0.45-0.93) | 22    | 22370 | 0.63 | (0.38-1.04) | 21    | 17810 | 0.64 | (0.38-1.08) |
|                   | ≥10 years  | 34     | 25311   | 0.75 | (0.52-1.08) | 17    | 13190 | 0.79 | (0.47-1.31) | 17    | 12121 | 0.72 | (0.43-1.21) |
| \( P_{\text{trend}} \) |            |        |         |     |        |         |     |       |         |
|                   | Never user | 279    | 197540  | 1 (Ref) | 139 | 113778 | 1 (Ref) | 140 | 83761 | 1 (Ref) |
| Age of first use  | <60 years of age | 15 | 16703 | 0.59 | (0.35-1.00) | 7 | 8116 | 0.60 | (0.28-1.30) | 8 | 8587 | 0.58 | (0.28-1.20) |
|                   | ≥60 years of age | 57 | 47178 | 0.47 | (0.35-0.64) | 29 | 26465 | 0.46 | (0.30-0.70) | 28 | 20713 | 0.49 | (0.31-0.76) |
| \( P_{\text{trend}} \) |            |        |         |     |        |         |     |       |         |

### Lung Cancer Incidence

|                   | Never user | 200548 | 1 (Ref) | 119 | 115539 | 1 (Ref) | 221 | 85009 | 1 (Ref) |
|-------------------|------------|--------|---------|-----|--------|---------|-----|-------|---------|
| Duration of use   | Never user | 340    |         |     |        |         |     |       |         |
|                   | <10 years  | 88     | 41106   | 0.89 | (0.67-1.17) | 36    | 22926 | 0.97 | (0.63-1.48) | 52    | 18180 | 0.79 | (0.55-1.13) |
|                   | ≥10 years  | 57     | 25818   | 0.94 | (0.70-1.27) | 26    | 13418 | 1.15 | (0.74-1.79) | 31    | 12401 | 0.78 | (0.52-1.15) |
| \( P_{\text{trend}} \) |            |        |         |     |        |         |     |       |         |

### Prostate Cancer Mortality

|                   | Never user | 197511 | 1 (Ref) | 141 | 113832 | 1 (Ref) | 245 | 83678 | 1 (Ref) |
|-------------------|------------|--------|---------|-----|--------|---------|-----|-------|---------|
| Duration of use   | Never user | 386    | 197511  | 1 (Ref) | 141 | 113832 | 1 (Ref) | 245 | 83678 | 1 (Ref) |
|                   | <10 years  | 105    | 40323   | 1.15 | (0.89-1.49) | 53    | 22479 | 1.30 | (0.90-1.89) | 52    | 17844 | 0.97 | (0.68-1.40) |
|                   | ≥10 years  | 61     | 25248   | 0.99 | (0.75-1.32) | 30    | 13114 | 1.19 | (0.79-1.80) | 31    | 12135 | 0.81 | (0.55-1.20) |
| \( P_{\text{trend}} \) |            |        |         |     |        |         |     |       |         |

### Prostate Cancer Incidence

|                   | Never user | 197923 | 1 (Ref) | 141 | 113987 | 1 (Ref) | 245 | 86314 | 1 (Ref) |
|-------------------|------------|--------|---------|-----|--------|---------|-----|-------|---------|
| Age of first use  | <60 years of age | 38 | 16582 | 1.16 | (0.82-1.64) | 18 | 8026 | 1.45 | (0.86-2.43) | 308 | 105435 | 0.91 | (0.56-1.47) |
|                   | ≥60 years of age | 127 | 47406 | 0.90 | (0.71-1.13) | 65 | 26593 | 1.04 | (0.75-1.46) | 266 | 93179 | 0.73 | (0.53-1.01) |
| \( P_{\text{trend}} \) |            |        |         |     |        |         |     |       |         |
|                                | Never user | — | — | — | — | — | 65 | 85009 | 1 (Ref) |
|--------------------------------|------------|---|---|---|---|---|-----|--------|---------|
|                                | Ever user  | — | — | — | — | — | 30 | 30581 | 0.75 (0.45-1.22) |
| Duration of use                |            |   |   |   |   |   |     |        |         |
|                                | Never user | — | — | — | — | — | 65 | 85009 | 1 (Ref) |
|                                | <10 years  | — | — | — | — | — | 21 | 18180 | 0.77 (0.44-1.36) |
|                                | ≥10 years  | — | — | — | — | — | 9  | 12401 | 0.70 (0.34-1.45) |
|                                |            |   |   |   |   |   |     |        | 0.33    |
|                                |            |   |   |   |   |   |     |        |         |
| Age of first use               |            |   |   |   |   |   |     |        |         |
|                                | Never user | — | — | — | — | — | 596| 79258 | 1 (Ref) |
|                                | <60 years  | — | — | — | — | — | 49 | 8142  | 0.83 (0.62-1.13) |
|                                | ≥60 years  | — | — | — | — | — | 139| 18685 | 0.68 (0.55-0.83) |
|                                |            |   |   |   |   |   |     |        | 0.001   |
|                                |            |   |   |   |   |   |     |        |         |

*All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. Models for bladder cancer, breast cancer, colorectal cancer, lung cancer and prostate cancer additionally adjusted for family history of site-specific cancer (not including total cancer, smoking-associated cancers, and obesity-associated cancer). Breast cancer models did not include a term for sex and are additionally adjusted for hormone replacement therapy use. Models for colorectal cancer, and lung cancer are additionally adjusted for joint terms for sex and HRT use (female nonuser, female user [reference is men]). Models for colorectal cancer are additionally adjusted for processed meat and red meat consumption. Models for prostate cancer did not include a term for sex and are adjusted for smoking status and time since quitting smoking (current/former that quit <10 years, former that quit ≥10 years, [reference is never]). CI = confidence interval; HR = hazard ratio; Ref = reference.

**The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.**
Supplementary Table 7. Association of lipid-lowering medications with site-specific cancer mortality and incidence by race in ARIC (1990-2015)

| Modela | Black | White |
|--------|-------|-------|
|        | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) |
| Bladder cancer mortality |       |       |       |       |       |       |
| Use     |       |       |       |       |       |       |
| Never user | 18   | 147821 | 1 (Ref) |       |       |       |
| Ever user | 12   | 53441  | 0.91 (0.39-2.11) |       |       |       |
| Duration of use |       |       |       |       |       |       |
| Never user | 18   | 147821 | 1 (Ref) |       |       |       |
| <10 years | 6    | 31721  | 0.70 (0.25-1.97) |       |       |       |
| ≥10 years | 6    | 21720  | 1.22 (0.45-3.28) |       |       |       |
| P trendb |       |       | 0.62    |       |       |       |
| Age of first use |       |       |       |       |       |       |
| Never user |       |       |       |       |       |       |
| <60 years of age |       |       |       |       |       |       |
| ≥60 years of age |       |       |       |       |       |       |
| P trendb |       |       | 0.62    |       |       |       |
| Bladder cancer incidence |       |       |       |       |       |       |
| Use     |       |       |       |       |       |       |
| Never user | 14   | 52187  | 1 (Ref) | 99   | 145318 | 1 (Ref) |
| Ever user | 7    | 13309  | 1.10 (0.37-3.25) | 61   | 52126  | 1.25 (0.86-1.82) |
| Duration of use |       |       |       |       |       |       |
| Never user |       |       |       | 99   | 145318 | 1 (Ref) |
| <10 years |       |       |       | 36   | 30916  | 1.31 (0.83-2.07) |
| ≥10 years |       |       |       | 25   | 21209  | 1.19 (0.75-1.90) |
| P trendb |       |       | 0.51    |       |       |       |
| Age of first use |       |       |       |       |       |       |
| Never user |       |       |       | 99   | 145550 | 1 (Ref) |
| <60 years of age |       |       |       | 14   | 13638  | 1.12 (0.62-2.02) |
| ≥60 years of age |       |       |       | 46   | 37109  | 0.86 (0.58-1.29) |
| P trendb |       |       | 0.50    |       |       |       |
| Breast cancer mortality |       |       |       |       |       |       |
| Use     |       |       |       |       |       |       |
| Never user | 32   | 33865  | 1 (Ref) | 46   | 81675  | 1 (Ref) |
| Ever user | 10   | 8934   | 0.78 (0.35-1.75) | 25   | 27372  | 1.05 (0.60-1.83) |
| Duration of use |       |       |       |       |       |       |
| Never user |       |       |       |       |       |       |
| <10 years |       |       |       |       |       |       |
| Age of first use       | Never user | <60 years of age | ≥60 years of age |
|------------------------|------------|------------------|------------------|
| ≥10 years              |            |                  |                  |
|                        |            |                  |                  |
|                        |            |                  |                  |
| _P trend^b_            |            |                  |                  |

**Age of first use**

| Use         | Never user | <60 years of age | ≥60 years of age |
|-------------|------------|------------------|------------------|
| Never user  |            |                  |                  |
|            |            |                  |                  |
|            |            |                  |                  |
| _P trend^b_ |            |                  |                  |

**Breast cancer incidence**

| Use         | Never user | <60 years of age | ≥60 years of age |
|-------------|------------|------------------|------------------|
| Never user  |            |                  |                  |
|            |            |                  |                  |
|            |            |                  |                  |
| _P trend^b_ |            |                  |                  |

**Colorectal cancer mortality**

| Use         | Never user | <60 years of age | ≥60 years of age |
|-------------|------------|------------------|------------------|
| Never user  |            |                  |                  |
|            |            |                  |                  |
|            |            |                  |                  |
| _P trend^b_ |            |                  |                  |

**Colorectal cancer incidence**

| Use         | Never user | <60 years of age | ≥60 years of age |
| Age of first use | Never user | <60 years of age | ≥60 years of age |
|-----------------|------------|-----------------|-----------------|
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |

Lung cancer mortality

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|-----------------|-----------------|
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |

Age of first use

| Never user | <60 years of age | ≥60 years of age |
|------------|-----------------|-----------------|
| Age of first use | Never user | <60 years of age | ≥60 years of age |
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |

Lung cancer incidence

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|-----------------|-----------------|
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |

Age of first use

| Never user | <60 years of age | ≥60 years of age |
|------------|-----------------|-----------------|
| Age of first use | Never user | <60 years of age | ≥60 years of age |
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |

Prostate cancer mortality

| Use | Never user | <60 years of age | ≥60 years of age |
|-----|------------|-----------------|-----------------|
| Age of first use | Never user | <60 years of age | ≥60 years of age |
| Duration of use | Never user | <10 years | 190 | 145386 | 1 (Ref) |
|                 |            | ≥10 years | 32 | 31025 | 0.72 (0.47-1.10) |
|                 |            |           | 251 | 147821 | 0.92 (0.72-1.17) |
| Ever user | — | — | — | 25 | 26004 | 0.82 (0.46-1.47) |
| Duration of use | — | — | — | 36 | 66029 | 1 (Ref) |
| <10 years | — | — | — | 16 | 15084 | 0.80 (0.41-1.58) |
| ≥10 years | — | — | — | 9 | 10921 | 0.85 (0.40-1.83) |
| ₚₜₑₚ₞ | 0.71 |
| Age of first use | — | — | — | — | — | — |
| <60 years of age | — | — | — | — | — | — |
| ≥60 years of age | — | — | — | — | — | — |
| ₚₜₑₚ₞ | — | — |
| Prostate cancer incidence | — | — | — | — | — | — |
| Use | — | — | — | — | — | — |
| Never user | 198 | 17121 | 1 (Ref) | 398 | 62137 | 1 (Ref) |
| Ever user | 49 | 3677 | 1.18 (0.82-1.69) | 143 | 23379 | 1.03 (0.83-1.28) |
| Duration of use | — | — | — | — | — | — |
| Never user | 198 | 17121 | 1 (Ref) | 398 | 62137 | 1 (Ref) |
| <10 years | 33 | 2485 | 1.38 (0.88-2.16) | 80 | 13470 | 1.15 (0.87-1.52) |
| ≥10 years | 16 | 1192 | 0.96 (0.57-1.63) | 63 | 9909 | 0.93 (0.71-1.23) |
| ₚₜₑₚ₞ | 0.62 |
| Age of first use | — | — | — | — | — | — |
| Never user | 198 | 17748 | 1 (Ref) | 398 | 63335 | 1 (Ref) |
| <60 years of age | 13 | 1203 | 0.86 (0.48-1.54) | 36 | 6940 | 0.84 (0.59-1.20) |
| ≥60 years of age | 36 | 2499 | 0.80 (0.53-1.19) | 103 | 16186 | 0.64 (0.50-0.81) |
| ₚₜₑₚ₞ | 0.25 |

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All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and packyears, drinking status, and family history of any cancer. Models for bladder cancer, breast cancer, colorectal cancer, lung cancer and prostate cancer additionally adjusted for family history of site-specific cancer (not including total cancer, smoking-associated cancers, and obesity-associated cancer). Breast cancer models did not include a term for sex and are additionally adjusted for hormone replacement therapy use. Models for colorectal cancer, and lung cancer are additionally adjusted for joint terms for sex and HRT use (female nonuser, female user [reference is men]). Models for colorectal cancer are additionally adjusted for processed meat and red meat consumption. Models for prostate cancer did not include a term for sex and are adjusted for smoking status and time since quitting smoking (current/former that quit <10 years, former that quit ≥10 years, [reference is never]). CI = confidence interval; HR = hazard ratio; Ref = reference.

The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.
**Supplementary Table 8. Association of lipid-lowering medications with colorectal cancer mortality and incidence among participants that ever had a sigmoidoscopy or colonoscopy at visit 3 in ARIC (1992-2015)**

| Modela | Colorectal Cancer Mortality | Colorectal Cancer Incidence |
|--------|-----------------------------|----------------------------|
|        | Cases | Person-time | HR (95% CI) | Cases | Person-time | HR (95% CI) |
| Use    |       |             |             |       |             |             |
| Never user | 28   | 50206       | 1 (Ref)     | 62   | 48703       | 1 (Ref)     |
| Ever user | 9    | 23917       | 0.43 (0.19-0.95) | 21   | 23314       | 0.62 (0.36-1.06) |
| Duration of use |       |             |             |       |             |             |
| Never user |     |             |             | 62   | 48703       | 1 (Ref)     |
| <10 years |     |             |             | 14   | 13374       | 0.69 (0.36-1.35) |
| ≥10 years |     |             |             | 7    | 9940        | 0.52 (0.23-1.15) |
| Ptrendb  |     |             | 0.10        |       |             |             |
| Age of first use |       |             |             |       |             |             |
| Never user |     |             |             | 62   | 49137       | 1 (Ref)     |
| <60 years of age |     |             |             | 6    | 5673        | 0.84 (0.35-1.99) |
| ≥60 years of age |     |             |             | 15   | 17071       | 0.45 (0.25-0.82) |
| Ptrendb  |     |             | 0.01        |       |             |             |

a All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, smoking status and packyears, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, joint terms for sex and HRT use (female nonuser, female user [reference is men]), drinking status, processed meat and red meat consumption, family history of any cancer, and family history of colorectal cancer. CI = confidence interval; HR = hazard ratio; Ref = reference.

b The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.