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Associations of calcium and dairy products with all-cause and cause-specific mortality in the REasons for Geographic and Racial Differences in Stroke (REGARDS) prospective cohort study[i]

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Abstract

Associations of calcium and dairy product intakes with cardiovascular disease risk and cancer mortality are controversial.

We investigated associations of calcium and dairy product intakes with mortality in the prospective REasons for Geographic and Racial Differences in Stroke study (n=30,239). Of 2,966 total deaths, 32.3% were from CVD and 28.8% from cancer.

For those in the upper relative to the lowest quintile of intakes, from Cox proportional hazards regression models, the multivariable-adjusted hazard ratios (HRs) for all-cause mortality were 1.13 (95% confidence intervals [CI] 0.95–1.35; *P*-trend 0.004) for whole milk, and 0.75 (CI 0.61–0.93; *P*-trend 0.001) for non-fat milk; for CVD mortality the corresponding HRs were 0.80 (CI 0.55–1.16; *P*-trend 0.80) and 0.72 (CI 0.49–1.05; *P*-trend 0.06); and for cancer mortality they were 1.56 (CI 1.17–2.08; *P*-trend 0.006) and 0.89 (CI 0.62–1.28; *P*-trend 0.86). Calcium (total, dietary, supplemental) and total dairy products intakes were not associated with all-cause, cardiovascular, or cancer mortality.

These results suggest that whole milk consumption may be directly associated with cancer mortality; non-fat milk consumption may be inversely associated with all-cause and cardiovascular- and cancer-specific mortality; and calcium intake independent of milk products intakes may not be associated with mortality.

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Keywords

Calcium; dairy; milk; mortality; prospective cohort study

INTRODUCTION

Calcium is an essential nutrient required for many processes, including bone health, cardiac and vascular smooth muscle function, nerve transmission, and enzyme secretion. Calcium concentrations are tightly maintained in the body and sources are both dietary and supplemental. Dietary Reference Intakes in adults over age 50 is 1,000 mg/d for males and 1,200 mg/d for females until the age of 70, at which point the overall recommendation for both sexes is 1,200 mg/d [1]. Dairy products are one of the leading sources of dietary calcium in the average American diet, and the recently released 2015 Dietary Guidelines recommends consumption of 3 cup-equivalents per day of fat-free and low-fat dairy products for adults [2].

Recent reviews and meta-analyses reported inverse associations between calcium and dairy products with risk for colorectal cancer and metabolic syndrome [3–5], which suggests that higher intakes, within reasonable limits, may reduce the risk of cardiovascular disease and cancer mortality. Heart disease and cancer are the two leading causes of mortality in the United States and worldwide [6, 7], and calcium supplements are commonly recommended, especially among women and the elderly. However, recent reports have raised concern of a potential increase in risk for myocardial infarction and related deaths among older postmenopausal women taking calcium supplements [8, 9]. Observational studies also reported higher risk of prostate cancer associated with intakes of dietary and dairy calcium and dairy products but not with supplemental or non-dairy calcium [10], suggesting components of dairy products other than calcium, such as insulin-like growth factor 1 (IGF-1), may contribute to risk.

In general, there are no clear patterns of association from numerous clinical trials and observational studies of calcium and dairy products with cardiovascular disease mortality, and few studies reported associations with cancer mortality. Thus, the purpose of this analysis was to investigate associations of total, dietary, and supplemental calcium and milk products with risk of all-cause, cardiovascular disease-specific, and cancer-specific mortality in the prospective REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

MATERIALS AND METHODS

Study Population

The REGARDS study is a national prospective cohort study designed to recruit equal numbers of black and white men and women. Details on the study population and objectives were described previously [11, 12]. Briefly, between January 2003 and October 2007, participants aged 45 years and older were recruited from the continental United States with an oversampling of blacks and persons residing in the “Stroke Belt,” a region of high stroke mortality defined at the design of this study to encompass Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee. Potential participants were first contacted via mail and then telephone by trained interviewers to determine eligibility. Exclusion criteria included race other than black or white, active treatment for cancer, medical conditions that would prevent long-term participation, cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. The study was approved by the Institutional Review Boards at all participating institutions. Verbal and written informed consent were obtained from all participants.

Computer-assisted telephone interviews, in-home visits, and self-administered questionnaires left with participants to complete after the in-home visit were used to collect data. Medical history, medication use, smoking status, alcohol use, demographics, and physical activity (times per week) were collected via telephone interview, while blood and urine samples, anthropometrics, and additional risk factor data were collected during in-home visits. Self-administered questionnaires included the Block 98 Food Frequency Questionnaire (FFQ) and a family history questionnaire.

Dietary Assessment

Dietary intake was assessed using a self-administered Block FFQ (developed by NutritionQuest, Berkeley, California), which contains over 150 multiple-choice questions based on 107 food items and was validated for most nutrients and in different populations [13, 14]. Participants were provided with pictures to assist in identifying portion sizes, and frequency choices varied from never/few times per year to every day. Relevant questions that were used to create variables of interest for this analysis included those to assess intakes of calcium supplements and multivitamins, dairy products (milk, cream, fermented dairy products, ice cream, butter, cheeses), and other non-dairy, calcium-containing foods (e.g., fortified orange juice). Available milk choices were whole, reduced fat (2%), low-fat (1%), and non-fat (skim).

Outcome Assessment

Participants and their proxies were contacted via telephone at 6-month intervals to ascertain hospitalizations and deaths, for which medical records were also obtained. For reported deaths, interviews with next of kin or proxy were conducted to collect information relevant to the death. Deaths were confirmed through death certificates and National Death Index data. Two adjudicators independently reviewed reported deaths, using baseline participant clinical characteristics, proxy interviews, death certificates, and if available, medical records for hospitalizations occurring within 30 days of the death to determine the cause of the participant’s death. The Social Security and National Death Indices were searched for participants who were reported as lost to follow-up. For our analyses, all-cause and cause-specific (cardiovascular and cancer) mortalities were the primary outcomes. Cardiovascular disease (CVD) mortality included deaths from coronary heart disease, myocardial infarction, stroke, heart failure, other cardiac, and other cardiovascular causes. Deaths from specific types of cancers were not collected.

Statistical Analyses

The focus of our analyses was on calcium (from dairy and other sources), milk (as a prominent source of calcium) with and without fat, and the non-fat/non-calcium component of milk, in an attempt to clarify which components of milk, individually or combined, may or may not affect risk for dying of the two major overall causes of death in the US. Other specific dairy products were not a focus of our analyses either because they were consumed by relatively few study participants, contain no or minimal amounts of calcium (e.g., butter), or contain potentially confounding added components (e.g., ice cream, yogurt). Thus, given our hypotheses, we focused on the "cleanest" dairy exposures (types of milk), and only analyzed the other types of dairy products as part of a total dairy products variable.

Since dietary data obtained from food frequency questionnaires are semi-quantitative and primarily used to rank participants relative to one another in relation to their intakes of foods and nutrients [13], sex-specific quintiles of calcium and dairy product intakes were used in this analysis, with the lowest categories used as reference. For supplemental calcium and whole, low-fat, and non-fat milks, the reference category was no consumption and quartiles of consumption were used as the remaining 4 categories. For our analyses, low-fat (1%) and reduced fat (2%) milks were combined as low-fat milk. The characteristics of the study population at baseline were summarized according to quintiles of total calcium and total dairy intakes, and chi-square tests for categorical variables and analysis of variance for continuous variables were used to test differences across exposure quintiles.

Total follow-up time was calculated as the time between the first interview date and the date of death, last follow-up date, or December 31, 2012, whichever came first. Because dietary calcium intake was highly correlated with milk intake, residuals from the linear regression models of non-fat milk with dietary calcium were determined to examine the association of non-fat milk adjusted for dietary calcium. This method was patterned after the energy adjustment residual method [15] with the dependent variable being non-fat milk and the independent variable being dietary calcium; the intent was that the calcium-adjusted residuals would represent a possible indirect indicator of the non-calcium, non-fat components of milk (such as IGF-1). The same procedure was followed for whole and low-fat milk. All calcium-adjusted residuals were categorized into sex-specific quintiles for Cox proportional hazards models in which dietary calcium was included because of its expected independent associations with mortality.

Cox proportional hazards models were used to calculate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of quintiles of calcium and dairy product intakes with all-cause and cause-specific mortalities. Age was used as the time variable in all models. Potential confounders were selected on the basis of biological plausibility, previous literature, and whether inclusion of the variable changed the adjusted HR for the primary exposure variable by ≥ 10%. Potential confounding variables considered included age (continuous), sex (male/female), race (black/white), region (Belt, Buckle, Non-belt), body mass index (BMI; kg/m^2; continuous), smoking status (never, past, current), alcohol intake (none, moderate, heavy), physical activity (none, 1–3 times/week, 4+ times/week), nonsteroidal anti-inflammatory drug (NSAID) and aspirin use (yes/no), hormone replacement therapy use in females (yes/no), college education or higher (yes/no), annual income categories (refused, < $20,000, $20,000-$34,000, $35,000-$74,000; ≥ $75,000), total energy intake (kcal), fruit and vegetable servings/day, processed and red meat servings/day, whole grain servings/day, nut servings/day, vitamin D (IU/day), dietary fiber (g/day), and a dietary oxidative balance score (OBS). The dietary OBS was calculated using a previously described equal weight method [16] and is comprised of anti- (carotene, lutein, lycopene, vitamin C and E, omega-3 fatty acids, flavonoids) and pro-oxidant (dietary iron, omega-6 fatty acids, saturated fat) nutrients. The fully adjusted model included age, sex, race, region, body mass index, smoking status, alcohol intake, physical activity, NSAID and aspirin use, hormone replacement therapy use, education, annual income, the dietary OBS, and total energy, total fruit and vegetable, and processed and red meat intakes. Proportional hazards assumptions were tested using Log-Log survival curves, Schoenfeld residuals, and extended Cox models for each exposure and potential covariate. Trends across quintiles of calcium and dairy product intakes were assessed by including quintile- and sex-specific median values as a continuous variable in regression models.

To assess potential effect modification for all-cause and cause-specific mortalities, stratified analyses were conducted by sex, race, region, BMI (sex-specific medians: males < / ≥ 27.8 kg/m^2, females < / ≥ 28.5 kg/m^2), NSAID and aspirin use, smoking status, alcohol intake, physical activity (none, 1–3 times/week, ≥ 4 times/week), total energy intake (sex-specific medians: males < / ≥ 1,744 kcal/day, females </ ≥ 1,460 kcal/day), total fat intake (sex-specific medians: males < / ≥ 71.5 g/day, females </ ≥ 59.5 g/day), and supplemental calcium use (yes / no).

Sensitivity analyses were also conducted. Models were further adjusted for baseline comorbidities (self-reported history of cardiovascular disease, diabetes, or cancer). We also excluded deaths that occurred within 1 or 2 years of enrollment to assess the potential influence of pre-morbid health conditions. Additionally, we excluded participants based on age limits of 75, 80, and 90 years of age. Participants who were at the age limit or older at baseline were excluded, and for those who reached the limit during follow-up, follow-up time was calculated as the period between baseline and the point at which the age limit was reached. Finally, supplemental calcium users who reported taking supplements for less than 1 year were categorized as non-supplemental calcium users.

A two-sided P value of < 0.05 or a 95% confidence interval that did not contain 1.00 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Of the original 30,239 participants enrolled in the REGARDS study, we excluded 8,812 who did not complete ≥ 15% of the FFQ questions or reported implausible energy intakes (< 800 or > 5,000 kcal/day for men and < 500 or > 4,500 kcal/day for women) leaving a final sample size of 21,427 for the analytic cohort. The overall median baseline total calcium intake was 839.8 mg/day, with intakes higher than the median more common among whites (67%) than among blacks (33%). Mean dietary and supplemental calcium, as well as total dairy product intakes were higher among whites ($P < 0.0001$ for all variables).

Characteristics at baseline are summarized by total calcium and by total dairy product quintiles (Table 1). Those in the highest quintiles of total calcium and dairy intake, on average, were older and had a lower BMI, and were more likely to currently smoke, have a college education or higher, participate in physical activity at least once a week, and regularly take aspirin or NSAIDs. Women in the highest quintiles were also more likely to take hormone replacement therapy. Those with the highest intakes of total calcium were less likely to have a history of diabetes and more likely have a higher annual household income. Additionally, those in the highest quintiles of total calcium and dairy intake had higher mean intakes of total energy, dietary fiber, supplemental calcium, total vitamin D, total meat, and fruits and vegetables.

Upon comparison of the highest to the lowest quintiles of intake (Table 2), in the unadjusted models total calcium was associated with a statistically significant 26% lower risk for all-cause mortality; however, in the multivariable-adjusted models, total calcium was not associated with risk for all-cause or cancer mortality, but there was an estimated non-statistically significant 9% lower risk for CVD mortality. When we built these models forward, addition of smoking status, education, and total fruit and vegetable intake tended to attenuate the estimated associations, whereas total energy intake tended to strengthen them; however, removal of no single covariate from the full models substantially affected any of the risk estimates. Dietary and supplemental calcium were not associated with all-cause, CVD, or cancer mortality.

Total dairy products were not associated with all-cause or cause-specific mortality (Table 2). However, as noted in Table 3, for those in the upper relative to the lowest categories of intakes, whole milk was associated with an estimated 13% higher risk of all-cause mortality (point estimate not statistically significant, but P-trend = 0.004), 20% lower risk for CVD mortality (not statistically significant), and statistically significant 56% higher risk for all cancer mortality. Low-fat milk was associated with an estimated 8% higher risk for all-cause mortality and 20% higher risk for CVD mortality, but was associated with 11% lower risk for cancer mortality (all associations not statistically significant). On the other hand, non-fat milk was statistically significantly associated with an estimated 25% lower risk for all-cause mortality, non-statistically significant 28% lower risk for CVD mortality, and non-statistically significant 11% lower risk for cancer mortality.

As shown in Table 4, for those in the upper relative to the lowest quintiles, residuals of total whole and low-fat milks were associated with an estimated borderline statistically significant 11% higher risk of all-cause mortality, 17% higher risk of CVD mortality (not statistically significant), and 16% higher risk of cancer mortality (not statistically significant). However, non-fat milk residuals were associated with borderline statistically significant 19% lower risk for all-cause mortality, non-statistically significant 29% lower risk for CVD mortality, and non-statistically significant 11% higher risk of cancer mortality.

Because previous evidence suggested that supplemental calcium use, especially without concomitant supplemental vitamin D, in postmenopausal women may increase risk for myocardial infarction and related deaths [8, 9], we conducted an additional analysis of calcium supplement use among pre- and postmenopausal females. However, we found no evidence of higher risk for all-cause or cause-specific mortality among postmenopausal women who took calcium supplements, with or without vitamin D (data not shown).

Analyses stratified by race and other participant characteristics were repeated for all exposures, but there were no strong or consistent patterns to suggest effect modification (Supplemental Tables 1 – 11). In sensitivity analyses, further adjustment for comorbidities at baseline, exclusion of deaths that occurred within 1 or 2 years after enrollment, re-classification of supplemental calcium use for less than 1 year as no supplemental calcium use, and exclusions and follow-up time adjustments based on age limits of 75, 80, and 90 years of age did not materially change any of the associations (data not shown).

DISCUSSION

The results from this study suggest that whole milk may be associated with higher risk of cancer mortality, while non-fat milk may be associated with lower risk for all-cause and cardiovascular- and cancer-specific mortality. We found no evidence that total, dietary, or supplemental calcium were associated with all-cause or cardiovascular- or cancer-specific mortality, thus suggesting that calcium intake independent of milk product intake may not be associated with mortality. Our results also raise the possibility that the non-fat/non-calcium components of milk (which include IGF-1) may be associated with modestly higher risk for cancer mortality.

Calcium and dairy products may plausibly affect risk for CVD and cancer by various mechanisms. Calcium binds bile acids and free fatty acids in the gut, decreasing fat absorption, potentially lowering cholesterol, and reducing damage to gut epithelial cells, which decreases the risk for colorectal cancer [17, 18]. Calcium is also essential for normal cardiac and vascular smooth muscle function and is needed for platelet activation and coagulation [19, 20], but high levels may also increase coronary artery calcification, especially among those with reduced renal function [21]. The mechanisms of action of milk products are expected to be similar, although other nutrients with different potential mechanisms are present. Clinical trials of calcium supplementation, with or without vitamin D, reported favorable changes in blood lipids but no appreciable effects on blood pressure [22, 23], while trials of dairy products reported no changes in blood lipid profiles or blood pressure with non-fat milk consumption [24, 25].

The most recent meta-analysis of a nested case-control study and prospective cohort studies reported inconsistent associations of calcium with mortality. Total calcium was associated with higher risk of all-cause, CVD, and cancer mortality, while dietary calcium was associated with lower risks [26]. Supplemental calcium was associated with higher risk of cancer mortality but lower risk of CVD and all-cause mortality (statistically significant). An additional meta-analysis of 8 prospective cohort studies with a weighted mean follow-up time of 13.4 years reported 13% higher risk of CVD mortality associated with higher baseline levels of serum calcium [27].

Associations of dairy products with cardiovascular disease and mortality are also inconsistent. In the most recent meta-analysis, there was no association of milk intake with risk of all-cause mortality per 200 mL daily increase [28], though significant heterogeneity was noted ($P = 0.001$). Milk intake was only statistically significantly associated with lower risk of CVD. Since the publication of this meta-analysis, 2 additional studies were published, including a cross-sectional analysis of overweight or obese adults finding that total dairy products, reduced fat milk, and dairy calcium were inversely associated with BMI, percent body fat, and waist circumference, while whole milk and dairy fat were positively associated [29]. A population-based cohort study of total dairy product intake found no associations with risk of coronary heart disease or stroke [30].The fat content of dairy products was hypothesized to increase CVD risk, but the most recent review of high-fat dairy product consumption and cardiovascular outcomes reported inconsistent associations with total high-fat dairy products and whole milk [31]. In our study, low-fat milk was associated with higher risk, while whole and non-fat milks were associated with lower risk (all associations non-statistically significant). Whole and low-fat milk residuals, adjusted for dietary calcium were associated with higher risk, suggesting that milk fat intake may be directly associated with CVD mortality. However, chance or uncontrolled confounding as explanations for our findings cannot be ruled out.

In our analyses, whole milk was statistically significantly associated with higher risk of cancer mortality, but low- and non-fat milk intakes were inversely associated with cancer mortality. However, the pattern of modest positive associations of whole/low-fat and non-fat milk residuals we observed suggest the possibility that non-calcium components of milk may be associated with modestly higher risk of cancer mortality. Our findings for these residuals, which may be an indirect measure of other milk components, such as IGF-1, are consistent with previous studies that reported positive associations of IGF-1 levels with risk for breast, prostate, and colorectal cancers. In the most recent meta-analysis, IGF-1 was associated with 93% higher risk of pre-menopausal breast cancer, 83% higher risk of prostate cancer, and 58% higher risk of colorectal cancer, all statistically significant [32]. The most recent meta-analysis of calcium, milk products, and risk for prostate cancer reported positive associations of dietary and dairy calcium, total milk products, and total milk with risk for prostate cancer [10]. Supplemental and non-dairy calcium were not associated with prostate cancer risk, supporting the hypothesis that the positive association with prostate cancer risk may be due to a non-calcium component of milk products. IGF-1 may plausibly increase risk for cancers since many tumor cells both produce IGF-1 and overexpress the IGF-1 receptor, potentially leading to increased cell survival and tumor growth [33]. However, it will be important to further investigate specific cancer mortalities because although IGF-1 was previously associated with higher risk of cancers and dietary calcium was associated with higher risk of prostate cancer, total calcium was previously associated with lower risk of all-cause and colorectal cancer-specific mortality [34]. Therefore, the association of calcium, dairy products, and the IGF-1 component of milk with cancer mortality may vary by cancer type.

Our results do not suggest an association of supplemental calcium intake among postmenopausal women with CVD mortality. Previous studies reported that supplemental calcium was inversely associated with CVD mortality in postmenopausal women [35, 36], but recent trials and observational studies suggested conflicting associations [8, 9]. The most recent meta-analysis of postmenopausal women from 18 randomized controlled trials reported no effect of calcium supplementation, with or without vitamin D, on risk for coronary heart disease, all-cause mortality, or other cardiovascular disease outcomes [37].

Our study had several limitations. Data on specific cancers were unavailable. Self-reported FFQs also may not accurately capture all sources of each nutrient; however, the Block 98 is a standardized and validated FFQ, and categories of calcium and dairy product intakes were used in this analysis, rather than absolute values. No data were collected to distinguish between conventionally- and organically-produced milk, which may be important to collect in future studies since higher IGF-1 concentrations were reported in conventionally-produced than in organic milk due to the use of bovine somatotropin hormone [38]. Although our estimated milk residuals were fully adjusted for dietary calcium, further research is needed on the use of residuals to estimate the non-calcium component of milk, in general, and IGF-1 exposure from milk, in particular. Finally, covariate information and dietary data were available only at baseline. However, although dietary patterns may change, many other covariates, such as race, sex, and region, are unlikely to change over time.

Strengths of our study include the use of a novel approach in estimating fat-containing and non-fat milk residuals to investigate the non-calcium and non-fat components of milk products, the prospective design, and a study population that included sufficient numbers of black and white men and women to allow analyses stratified by race and sex. Finally, all causes of death were adjudicated by clinicians using death certificates, medical records, and interviews with proxies and family members.

In summary, taken together with previous literature, our results suggest that whole milk may be associated with higher risk of cancer mortality, while non-fat milk may be associated with lower risk for all-cause and cardiovascular- and cancer-specific mortality. We found no evidence that total, dietary, or supplemental calcium were associated with all-cause or cardiovascular- or cancer-specific mortality, thus suggesting that calcium intake independent of milk product intake may not be associated with mortality. Our results also raise the possibility that the non-fat/non-calcium components of milk (which include IGF-1), may be associated with modestly higher risk for cancer mortality. Further study of the fat and non-calcium/non-fat components of milk and dairy products are needed to clarify our findings. Finally, our results, taken together with previous literature, suggest that current dietary recommendations for the consumption dairy products as part of a balanced diet that may reduce the risk of chronic diseases [39] may be dependent on the fat and IGF-1 composition of these products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

BMI	body mass index
CVD	cardiovascular disease
FFQ	food frequency questionnaire
HR	hazard ratio
IGF-1	insulin-like growth factor 1
KCAL	kilocalorie
NSAID	non-steroidal anti-inflammatory drug
REGARDS	REasons for Geographic and Racial Differences in Stroke
95% CI	95% confidence interval

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Table 1.

Selected characteristics of REGARDS participants at baseline by quintiles of total calcium and total dairy product intakes[a]

	Total Calcium Quintiles				Total Dairy Products Quintiles			
	1 (*n* = 4,284)	3 (*n* = 4,285)	5 (*n* = 4,285)	*P*[b]	1 (*n* = 3,439)	3 (*n* = 4,256)	5 (*n* = 4,438)	*P*[b]
Demographics								
Age, years	63.8 ± 9.1	64.6 ± 9.6	66.6 ± 9.2	<0.0001	64.4 ± 8.8	64.6 ± 9.2	65.4 ± 9.7	<0.0001
Male, %	44.1	44.1	44.1	1.00	58.4	42.0	41.8	<0.0001
White, %	49.6	66.5	81.6	<0.0001	47.5	68.5	80.8	<0.0001
Region, Stroke Belt,[c] %	31.1	31.2	32.8	<0.0001	33.7	34.3	33.7	<0.0001
Medical history,[d] %								
Heart disease	17.3	17.2	16.5	0.05	18.8	16.1	17.6	0.0002
Diabetes	23.7	20.3	15.3	<0.0001	20.8	19.1	19.8	0.39
Cancer	7.6	8.6	11.6	<0.0001	9.1	8.0	10.6	<0.0001
College graduate or higher, %	28.5	38.5	44.9	<0.0001	32.2	38.1	40.9	<0.0001
Annual income $35,000+, %	43.0	49.0	50.8	<0.0001	43.1	50.5	48.6	<0.0001
Lifestyle Factors								
Current smokers, %	41.7	46.1	49.2	<0.0001	39.1	44.9	48.7	<0.0001
Moderate alcohol consumption (0–14 M, 0–7 F drinks/week), %	30.3	36.0	38.4	<0.0001	33.4	35.9	36.0	<0.0001
Body mass index, kg/m^2	30.0 ± 6.5	29.3 ± 6.4	28.1 ± 5.9	<0.0001	29.2 ± 5.9	29.3 ± 6.3	28.8 ± 6.3	<0.0001
Physical activity, ≥ 1 times/week, %	25.8	29.1	35.8	<0.0001	27.2	29.4	33.0	<0.0001
NSAID or aspirin use, %	47.2	51.1	57.8	<0.0001	49.1	53.8	53.9	<0.0001
HRT, % females	49.8	57.7	67.0	<0.0001	22.7	34.8	35.7	<0.0001
Dietary Intakes								
Total energy, kcal/day	1,211 ± 401	1,853 ± 682	2,043 ± 779	<0.0001	1,440 ± 629	1,692 ± 679	2,049 ± 753	<0.0001
Total fat, % total energy	37.4 ± 8.5	37.6 ± 7.7	36.3 ± 7.5	<0.0001	37.2 ± 8.7	38.0 ± 7.6	35.9 ± 7.6	<0.0001
Saturated fat, g/day	14.2 ± 6.1	22.8 ± 10.7	24.2 ± 12.1	<0.0001	15.9 ± 8.5	20.6 ± 10.0	25.4 ± 12.3	<0.0001
Dietary fiber, g/day	10.3 ± 4.7	17.0 ± 7.7	20.8 ± 0.1	<0.0001	13.4 ± 7.9	15.9 ± 8.0	19.0 ± 9.4	<0.0001
Total calcium, mg/day	343 ± 90	887 ± 163	1,896 ± 351	<0.0001	602 ± 436	928 ± 480	1,534 ± 570	<0.0001
Dietary calcium	316 ± 90	719 ± 210	999 ± 425	<0.0001	351 ± 174	581 ± 180	1,133 ± 333	<0.0001
Supplemental calcium	27.4 ± 52.5	168 ± 245	897 ± 386	<0.0001	252 ± 398	347 ± 448	401 ± 472	<0.0001
Total vitamin D, IU/day	153 ± 155	332 ± 203	495 ± 224	<0.0001	219 ± 194	297 ± 195	482 ± 245	<0.0001
Total meat, servings/day	1.5 ± 0.8	2.1 ± 1.3	2.2 ± 1.3	<0.0001	1.8 ± 1.2	2.0 ± 1.2	2.1 ± 1.3	<0.0001
Total fruit and vegetable, servings/day	1.9 ± 1.3	3.2 ± 2.1	3.8 ± 2.7	<0.0001	2.4± 2.1	3.0 ± 2.1	3.4 ± 2.4	<0.0001
Total dairy, servings/d	2.3 ± 1.8	8.1 ± 4.8	13.0 ± 8.6	<0.0001	0.9 ± 0.7	5.5 ± 0.9	17.8 ± 5.9	<0.0001
Whole milk, servings/week	0.3 ± 0.8	0.7 ± 2.4	0.9 ± 3.9	<0.0001	0.1 ± 0.2	0.5 ± 1.3	1.6 ± 4.9	<0.0001
Reduced/low-fat milk, servings/week	1.2 ± 2.3	4.6 ± 7.5	6.0 ± 11.7	<0.0001	0.3 ± 0.6	3.0 ± 3.8	8.9 ± 13.8	<0.0001
Skim milk, servings/week	0.1 ± 0.6	1.2 ± 3.3	3.2 ± 6.4	<0.0001	0.03 ± 0.2	0.6 ± 1.4	4.3 ± 7.2	<0.0001

Abbreviations: HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

[a]Continuous variables are presented as means ± standard deviations; categorical variables are presented as percentages.

[b]*P* values from Chi-square test for categorical variables and analysis of variance for continuous variables.

[c]Stroke Belt defined as Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee; otherwise, live in other continental US states.

[d]Medical history of heart disease including self-reported myocardial infarction, coronary bypass grafting, cardiac bypass, angioplasty, stenting, or evidence of myocardial infarction via electrocardiogram; self-reported diabetes; history of any type of cancer.

Table 2.

Associations of calcium and total dairy intakes with all-cause and cause-specific mortality, REGARDS

	Quintiles[a,b,c,d]					
Total Calcium	**1 (*n* = 4,284)**	**2 (*n* = 4,287)**	**3 (*n* = 4,285)**	**4 (*n* = 4,286)**	**5 (*n* = 4,285)**	***P*-trend[e]**
All-cause						
Number of deaths	648	585	578	527	628	
Unadjusted HR (95% CI)	1.00	0.86 (0.77, 0.96)	0.79 (0.71, 0.89)	0.71 (0.63, 0.79)	0.74 (0.66, 0.82)	0.0001
Fully adjusted HR (95% CI)[f]	1.00	0.94 (0.84, 1.06)	0.96 (0.85, 1.08)	0.89 (0.79, 1.02)	1.04 (0.91, 1.18)	0.86
CVD[g]						
Number of deaths	224	179	193	172	189	
Unadjusted HR (95% CI)	1.00	0.76 (0.63, 0.93)	0.76 (0.63, 0.92)	0.67 (0.55, 0.81)	0.63 (0.52, 0.77)	0.002
Fully adjusted HR (95% CI)[f]	1.00	0.85 (0.70, 1.05)	0.93 (0.76, 1.15)	0.87 (0.69, 1.08)	0.91 (0.73, 1.15)	0.41
Cancer						
Number of deaths	184	180	160	157	173	
Unadjusted HR (95% CI)	1.00	0.94 (0.76, 1.15)	0.79 (0.64, 0.98)	0.74 (0.60, 0.91)	0.74 (0.60, 0.91)	0.02
Fully adjusted HR (95% CI)[f]	1.00	1.00 (0.81, 1.23)	0.91 (0.72, 1.14)	0.88 (0.69, 1.12)	0.97 (0.76, 1.23)	0.66
Dietary Calcium	(n = 4,282)	(n = 4,285)	(n = 4,289)	(n = 4,286)	(n = 4,285)	
All-causes						
Number of deaths	635	588	571	591	581	
Unadjusted HR (95% CI)	1.00	0.91 (0.81, 1.02)	0.85 (0.76, 0.95)	0.85 (0.76, 0.95)	0.80 (0.72, 0.90)	0.58
Fully adjusted HR (95% CI)[f]	1.00	0.98 (0.88, 1.10)	0.95 (0.84, 1.07)	1.00 (0.88, 1.14)	0.98 (0.85, 1.13)	0.97
CVD[g]						
Number of deaths	219	192	170	187	189	
Unadjusted HR (95% CI)	1.00	0.87 (0.71, 1.05)	0.74 (0.60, 0.90)	0.78 (0.64, 0.95)	0.76 (0.62, 0.92)	0.93
Fully adjusted HR (95% CI)[f]	1.00	0.97 (0.79, 1.18)	0.86 (0.69, 1.06)	0.97 (0.78, 1.22)	0.99 (0.77, 1.28)	0.87
Cancer						
Number of deaths	174	181	179	156	164	
Unadjusted HR (95% CI)	1.00	1.01 (0.82, 1.24)	0.97 (0.79, 1.20)	0.83 (0.67, 1.03)	0.85 (0.69, 1.05)	0.94
Fully adjusted HR (95% CI)[f]	1.00	1.05 (0.85, 1.30)	1.03 (0.82, 1.29)	0.92 (0.72, 1.17)	0.94 (0.71, 1.23)	0.44
Supplemental Calcium[h]	(n = 8,114)	(n = 3,360)	(n = 4,208)	(n = 1,999)	(n = 3,746)	
All-causes						
Number of deaths	1,230	411	582	226	517	
Unadjusted HR (95% CI)	1.00	0.80 (0.72, 0.90)	0.82 (0.74, 0.90)	0.64 (0.56, 0.74)	0.72 (0.65, 0.80)	<0.0001
Fully adjusted HR (95% CI)[f]	1.00	1.00 (0.89, 1.12)	0.94 (0.85, 1.04)	0.92 (0.79, 1.07)	1.05 (0.94, 1.17)	0.96
CVD[g]						
Number of deaths	399	134	195	76	153	
Unadjusted HR (95% CI)	1.00	0.81 (0.66, 0.98)	0.85 (0.72, 1.01)	0.67 (0.52, 0.85)	0.65 (0.54, 0.79)	0.001
Fully adjusted HR (95% CI)[f]	1.00	1.05 (0.86, 1.29)	0.95 (0.80, 1.14)	0.97 (0.75, 1.26)	0.95 (0.78, 1.16)	0.32

Total Calcium	**Quintiles**[a,b,c,d] **1 (*n* = 4,284)**	**2 (*n* = 4,287)**	**3 (*n* = 4,285)**	**4 (*n* = 4,286)**	**5 (*n* = 4,285)**	***P*-trend**[e]
Cancer						
Number of deaths	371	114	163	62	144	
Unadjusted HR (95% CI)	1.00	0.74 (0.60, 0.91)	0.76 (0.63, 0.91)	0.59 (0.45, 0.77)	0.67 (0.55, 0.81)	0.002
Fully adjusted HR (95% CI)[f]	1.00	0.91 (0.73, 1.13)	0.85 (0.70, 1.03)	0.84 (0.63, 1.10)	0.95 (0.78, 1.17)	0.48
Total Dairy Products	(n = 3,715)	(n = 4,592)	(n = 4,256)	(n = 4,219)	(n = 4,645)	
All-causes						
Number of deaths	512	648	572	563	671	
Unadjusted HR (95% CI)	1.00	0.95 (0.85, 1.07)	0.91 (0.81, 1.02)	0.81 (0.72, 0.92)	0.87 (0.77, 0.97)	0.09
Fully adjusted HR (95% CI)[i]	1.00	0.97 (0.86, 1.09)	1.01 (0.90, 1.15)	0.93 (0.82, 1.06)	1.05 (0.93, 1.19)	0.39
CVD[g]						
Number of deaths	171	201	200	181	204	
Unadjusted HR (95% CI)	1.00	0.88 (0.72, 1.08)	0.95 (0.77, 1.17)	0.78 (0.63, 0.96)	0.78 (0.64, 0.96)	0.92
Fully adjusted HR (95% CI)[i]	1.00	0.90 (0.73, 1.11)	1.11 (0.90, 1.37)	0.93 (0.74, 1.16)	1.03 (0.82, 1.29)	0.75
Cancer						
Number of deaths	145	193	171	155	190	
Unadjusted HR (95% CI)	1.00	1.00 (0.80, 1.24)	0.96 (0.77, 1.20)	0.81 (0.64, 1.01)	0.89 (0.72, 1.11)	0.64
Fully adjusted HR (95% CI)[i]	1.00	1.01 (0.81, 1.25)	1.03 (0.82, 1.30)	0.90 (0.71, 1.14)	1.02 (0.80, 1.29)	0.85

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval.

[a] The median (range) intakes (mg/d) of total calcium in the quintiles for men were 371 (77.9 – 475), 567 (475 - <658), 757 (658 - <879), 1,044 (879 - <1,313), 1,677 (1,313 – 3,800), and for women they were 345 (85.8 – 477), 607 (477 - <758), 975 (758 - <1,259), 1,471 (1,259 – 1,661), 1,917 (1,661 – 3,823), respectively.

[b] The median (range) intakes (mg/d) of dietary calcium in the quintiles for men were 316 (77.9 – 402), 476 (402 - <552), 627 (552 - <711), 815 (711 - <945), 1,160 (945 – 2,884), and for women they were 255 (76.9 – 337), 411 (337 - <483), 559 (483 - <644), 745 (644 - <882), 1,100 (882 – 2,693), respectively.

[c] The median (range) intakes (mg/d) of supplemental calcium in the categories for men were 0 (0), 37.2 (>0 - <93.0), 130 (93.0 - <286), 323 (286 - <752), 1,130 (752 – 1,130), and for women they were 0 (0), 130 (>0 - <286), 379 (286 - <845), 1,000 (845 - <1,093), 1,130 (1,093 – 1,130), respectively.

[d] The median (range) intakes (g/d) of total dairy products in the quintiles for men were 22.2 (0 - <46.8), 79.8 (46.8 - <116), 154 (116 - <206), 268 (206 - <350), 511 (350 – 1,468), and for women they were 17.0 (0 - <37.1), 31.4 (37.1 - <93.8), 133 (93.8 - <177), 242 (177 - <319), 484 (319 – 1,368), respectively.

[e] *P*-trend calculated using sex-specific medians of each quantile.

[f] Adjusted for age, sex, race, region, body mass index, smoking, alcohol, physical activity, non-steroidal anti-inflammatory drug and aspirin use, hormone replacement therapy use (females), education, annual income, total energy intake, fruit and vegetable intake, processed and red meat intake, dietary oxidative balance score.

[g] Cardiovascular disease mortality includes deaths due to myocardial infarction, stroke, heart failure, sudden death, other cardiac causes, and other cardiovascular non-cardiac causes.

[h] Supplemental calcium analyzed as 5 categories of intake with no intake as the reference category.

[i]Adjusted for age, sex, race, region, body mass index, smoking, alcohol, physical activity, non-steroidal anti-inflammatory drug and aspirin use, hormone replacement therapy use (females), education, annual income, supplemental calcium, total energy intake, fruit and vegetable intake, processed and red meat intake, dietary oxidative balance score.

Table 3

Associations of milk intakes with all-cause and cause-specific mortality, REGARDS

	Categories[a,b,c,d]					
	1 (*n* = 18,429)	**2 (*n* = 738)**	**3 (*n* = 760)**	**4 (*n* = 748)**	**5 (*n* = 752)**	P_{trend}[e]
Whole Milk						
All-causes						
No. of deaths	2,429	136	125	136	140	
Unadjusted HR (95% CI)	1.00	1.78 (1.50, 2.12)	1.44 (1.21, 1.73)	1.48 (1.25, 1.76)	1.40 (1.18, 1.66)	<0.001
Fully adjusted HR (95% CI)[f]	1.00	1.25 (1.05, 1.50)	1.05 (0.87, 1.26)	1.05 (0.88, 1.25)	1.13 (0.95, 1.35)	0.004
CVD[g]						
No. of deaths	806	40	34	45	32	
Unadjusted HR (95% CI)	1.00	1.56 (1.15, 2.17)	1.19 (0.85, 1.68)	1.48 (1.10, 2.00)	0.95 (0.67, 1.36)	0.38
Fully adjusted HR (95% CI)[f]	1.00	1.09 (0.78, 1.52)	0.84 (0.59, 1.20)	1.09 (0.80, 1.48)	0.80 (0.55, 1.16)	0.80
Cancer						
No. of deaths	689	35	41	34	55	
Unadjusted HR (95% CI)	1.00	1.61 (1.14, 2.26)	1.62 (1.18, 2.23)	1.29 (0.91, 1.82)	2.00 (1.52, 2.63)	<0.001
Fully adjusted HR (95% CI)[f]	1.00	1.14 (0.81, 1.62)	1.20 (0.87, 1.65)	0.87 (0.62, 1.24)	1.56 (1.17, 2.08)	0.006
Low-Fat Milk	(*n* = 9,114)	(*n* = 3,074)	(*n* = 3,087)	(*n* = 3,074)	(*n* = 3,078)	
All-causes						
No. of deaths	1,236	387	414	434	495	
Unadjusted HR (95% CI)	1.00	1.10 (0.98, 1.23)	0.94 (0.84, 1.05)	0.98 (0.88, 1.09)	1.01 (0.91, 1.12)	0.002
Fully adjusted HR (95% CI)[f]	1.00	1.02 (0.91, 1.14)	0.95 (0.85, 1.06)	1.00 (0.90, 1.12)	1.08 (0.97, 1.12)	0.65
CVD[g]						
No. of deaths	369	140	139	147	162	
Unadjusted HR (95% CI)	1.00	1.35 (1.12, 1.65)	1.04 (0.86, 1.27)	1.11 (0.91, 1.34)	1.09 (0.91, 1.31)	0.004
Fully adjusted HR (95% CI)[f]	1.00	1.24 (1.02, 1.51)	1.04 (0.85, 1.26)	1.14 (0.94, 1.38)	1.20 (0.99, 1.45)	0.12
Cancer						
No. of deaths	372	108	123	135	116	
Unadjusted HR (95% CI)	1.00	0.98 (0.79, 1.22)	0.95 (0.77, 1.16)	1.02 (0.84, 1.25)	0.82 (0.66, 1.01)	0.93
Fully adjusted HR (95% CI)[f]	1.00	0.95 (0.76, 1.18)	0.99 (0.81, 1.22)	1.07 (0.88, 1.31)	0.89 (0.72, 1.10)	0.33
Non-Fat Milk	(*n* = 17,749)	(*n* = 917)	(*n* = 920)	(*n* = 906)	(*n* = 935)	
All-causes						
No. of deaths	2,575	98	92	110	91	
Unadjusted HR (95% CI)	1.00	0.78 (0.64, 0.96)	0.60 (0.49, 0.74)	0.74 (0.61, 0.90)	0.56 (0.46, 0.69)	<0.001
Fully adjusted HR (95% CI)[f]	1.00	0.93 (0.76, 1.14)	0.76 (0.61, 0.94)	1.01 (0.83, 1.22)	0.75 (0.61, 0.93)	0.001
CVD[g]						
No. of deaths	829	36	26	38	28	
Unadjusted HR (95% CI)	1.00	0.91 (0.65, 1.27)	0.53 (0.36, 0.78)	0.80 (0.58, 1.10)	0.53 (0.37, 0.78)	0.01

	Categories[a,b,c,d]					
	1 (*n* = 18,429)	**2 (*n* = 738)**	**3 (*n* = 760)**	**4 (*n* = 748)**	**5 (*n* = 752)**	P_{trend}[e]
Fully adjusted HR (95% CI)[f]	1.00	1.02 (0.73, 1.43)	0.65 (0.44, 0.97)	1.05 (0.75, 1.46)	0.72 (0.49, 1.05)	0.06
Cancer						
No. of deaths	735	22	26	40	31	
Unadjusted HR (95% CI)	1.00	0.60 (0.39, 0.91)	0.60 (0.41, 0.89)	0.93 (0.68, 1.28)	0.68 (0.47, 0.97)	0.22
Fully adjusted HR (95% CI)[f]	1.00	0.73 (0.47, 1.11)	0.75 (0.50, 1.12)	1.25 (0.90, 1.73)	0.89 (0.62, 1.28)	0.86

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval.

[a]Five categories of milk intake with no intake as reference category.

[b]The median (range) intakes (g/d) of whole milk in the categories for men were 0 (0), 10.9 (>0 - <34.8), 74.2 (34.8 - <112), 171 (112 - <246), 382 (246 – 1,216), and for women they were 0 (0), 10.4 (>0 - <20.9), 41.9 (20.9 - < 78.0), 119 (78.0 - <186), 325 (186 – 1,288), respectively.

[c]The median (range) intakes (g/d) of low-fat milk in the categories for men were 0 (0), 11.9 (>0 - <39.4), 78.5 (39.4 - <121), 177 (121 - <249), 382 (249 – 1,310), and for women they were 0 (0), 8.1 (>0 - <23.7), 56.9 (23.7 - < 97.3), 144 (97.3 - <230), 348 (230 – 1,351), respectively.

[d]The median (range) intakes (g/d) of non-fat milk in the categories for men were 0 (0), 56.6 (>0 - <109), 162 (109 - <239), 291 (239 - <383), 552 (383 – 1,220), and for women they were 0 (0), 38.9 (>0 - <105), 146 (105 - < 208), 271 (208 - <382), 534 (382 – 1,175), respectively.

[e]*P*-trend calculated using sex-specific medians of each quantile.

[f]Adjusted for age, sex, race, region, body mass index, smoking, alcohol, physical activity, non-steroidal anti-inflammatory drug and aspirin use, hormone replacement therapy use (females), education, annual income, supplemental calcium, total energy intake, fruit and vegetable intake, processed and red meat intake, dietary oxidative balance score.

[g]Cardiovascular disease mortality includes deaths due to myocardial infarction, stroke, heart failure, sudden death, other cardiac causes, and other cardiovascular non-cardiac causes.

Table 4.

Associations of whole/low-fat and non-fat milk residuals with all-cause and cause-specific mortality, REGARDS

	Quintiles					
	1	**2**	**3**	**4**	**5**	***P*-trend**[a]
Whole/Low-Fat Milk Residuals	(*n* = 6,116)	(*n* = 3,827)	(*n* = 3,828)	(*n* = 3,828)	(*n* = 3,828)	
All-causes						
Number of deaths	699	523	508	580	656	
Unadjusted HR (95% CI)	1.00	1.38 (1.23, 1.55)	1.25 (1.12, 1.41)	1.33 (1.19, 1.49)	1.32 (1.18, 1.46)	<0.0001
Fully adjusted HR (95% CI)[b]	1.00	1.16 (1.02, 1.31)	1.03 (0.92, 1.16)	1.11 (0.99, 1.24)	1.11 (0.99, 1.25)	0.03
CVD[c]						
Number of deaths	218	179	147	204	209	
Unadjusted HR (95% CI)	1.00	1.53 (1.25, 1.86)	1.17 (0.95, 1.44)	1.49 (1.23, 1.80)	1.33 (1.10, 1.61)	<0.0001
Fully adjusted HR (95% CI)[b]	1.00	1.34 (1.08, 1.65)	0.98 (0.79, 1.21)	1.23 (1.01, 1.50)	1.17 (0.95, 1.43)	0.10
Cancer						
Number of deaths	207	152	149	160	186	
Unadjusted HR (95% CI)	1.00	1.34 (1.09, 1.66)	1.24 (1.00, 1.53)	1.26 (1.03, 1.55)	1.32 (1.09, 1.61)	0.0004
Fully adjusted HR (95% CI)[b]	1.00	1.13 (0.90, 1.42)	1.03 (0.83, 1.27)	1.09 (0.88, 1.34)	1.16 (0.94, 1.44)	0.33
Non-fat Milk Residuals	(*n* = 17,749)	(*n* = 918)	(*n* = 920)	(*n* = 920)	(*n* = 920)	
All-causes						
Number of deaths	2,575	93	88	103	107	
Unadjusted HR (95% CI)	1.00	0.68 (0.55, 0.83)	0.66 (0.53, 0.81)	0.67 (0.55, 0.82)	0.65 (0.54, 0.79)	<0.0001
Fully adjusted HR (95% CI)[b]	1.00	0.86 (0.70, 1.07)	0.83 (0.67, 1.04)	0.86 (0.70, 1.05)	0.81 (0.66, 1.00)	0.0001
CVD[c]						
Number of deaths	829	27	27	43	31	
Unadjusted HR (95% CI)	1.00	0.61 (0.42, 0.89)	0.63 (0.43, 0.93)	0.88 (0.64, 1.19)	0.58 (0.41, 0.84)	0.02
Fully adjusted HR (95% CI)[b]	1.00	0.75 (0.50, 1.11)	0.79 (0.54, 1.17)	1.07 (0.78, 1.46)	0.71 (0.49, 1.03)	0.09
Cancer						
Number of deaths	735	23	24	32	40	
Unadjusted HR (95% CI)	1.00	0.58 (0.39, 0.88)	0.61 (0.40, 0.91)	0.74 (0.52, 1.05)	0.86 (0.63, 1.18)	0.19
Fully adjusted HR (95% CI)[b]	1.00	0.74 (0.48, 1.13)	0.74 (0.49, 1.13)	0.96 (0.67, 1.38)	1.11 (0.79, 1.55)	0.99

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval.

[a] *P*-trend calculated using sex-specific medians of each quintile.

[b] Adjusted for age, sex, race, region, body mass index, smoking, alcohol, physical activity, non-steroidal anti-inflammatory drug and aspirin use, hormone replacement therapy use (females), education, annual income, dietary calcium, total energy intake, fruit and vegetable intake, processed and red meat intake, dietary oxidative balance score.

[c] Cardiovascular disease mortality includes deaths due to myocardial infarction, stroke, heart failure, sudden death, other cardiac causes, and other cardiovascular non-cardiac causes.