Published in final edited form as:
Am Heart J. 2010 September ; 160(3): 464–470. doi:10.1016/j.ahj.2010.06.012.

Serum Magnesium and Risk of Sudden Cardiac Death in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—We hypothesized that serum magnesium (Mg) is associated with increased risk of sudden cardiac death (SCD).

Methods—The Atherosclerosis Risk in Communities (ARIC) Study assessed risk factors and levels of serum Mg in a cohort of 45–64 year olds in 1987–1989 (n = 14,232). After an average of 12 years of follow-up we observed 264 cases of SCD, as determined by physician review of all suspected cases. We used proportional hazards regression to evaluate the association of serum Mg with risk of SCD.

Results—Individuals in the highest quartile of serum Mg were at significantly lower risk of SCD in all models. This association persisted after adjustment for potential confounding variables, with an almost 40% reduced risk of SCD (HR=0.62, 95% CI=0.42–0.93) in quartile 4 vs. 1 of serum Mg observed in the fully-adjusted model.

Conclusions—This study suggests that low levels of serum Mg may be an important predictor of SCD, and warrants further research into the effectiveness of Mg supplementation for those considered to be at high risk for SCD.

Keywords

sudden cardiac death; magnesium; cohort study

Introduction

Sudden cardiac death (SCD) is a major public health problem comprising more than half of all cardiovascular disease (CVD) deaths in the USA. [1] Even with estimates of coronary heart

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disease (CHD) mortality declining by more than 50% from 1950 to 1999, the relative proportion of SCD of all CVD deaths in the USA simultaneously increased during this time. [1, 2] Secular trends in Olmsted County, Minnesota from 1979 to 2003 have shown much larger declines in in-hospital death rates, with declines in out-of-hospital death rates occurring much more slowly. [3] Major risk factors for SCD include hypertension, diabetes, smoking, family history of myocardial infarction, and obesity, but the majority of SCDs occur in those with no prior history of CVD.[4]

Magnesium (Mg), a micronutrient and common cation in the human body, is a natural calcium antagonist and modulates vasomotor tone, blood pressure, and peripheral blood flow. Though virtually all Mg is stored in cells, low levels of serum Mg are usually predictive of low levels of total body Mg as well.[5] Previous epidemiological studies have reported that serum and dietary Mg are associated inversely with CVD risk factors such as hypertension,[6,7] type 2 diabetes mellitus, [8] the metabolic syndrome, [9] in addition to CHD.[10,11] Additional evidence from ecologic, clinical, and autopsy studies has shown higher Mg to be potentially protective against SCD,[12,13] but no prospective studies have reported the association of Mg levels with incidence of SCD in the general population. In addition to its role in the regulation of blood pressure and maintenance of vascular smooth muscle tone, Mg deficiencies are known to cause ventricular arrhythmias, the most common precursors to SCD. [12,14] Serum Mg levels are modified by intake of dietary Mg, calcium (Ca) and potassium (K), in addition to alcohol intake and physical exercise. [15,16]

Previous studies in the Atherosclerosis Risk in Communities (ARIC) cohort have shown that serum Mg levels are associated inversely with incidence of hypertension, [9] CHD,[10,11] and diabetes. [8] In three of these studies,[8–10] there were no associations between dietary Mg as measured from a food frequency questionnaire and these outcomes. The current study was conducted to assess the relative contribution of serum Mg and dietary Mg intake to the incidence of SCD.

Research Design and Methods

Study Population

The ARIC Study [17] is a multicenter prospective cohort study investigating the etiology of atherosclerotic disease in a middle-aged biracial population. One aspect of the study includes a 1987–89 baseline examination and follow-up of population-based cohorts of 45–64 year olds from Forsyth County, NC; Jackson, MS (African-Americans only); the northwest suburbs of Minneapolis, MN; and Washington County, MD.

The ARIC Study protocol was approved by the institutional review board of each participating university. After obtaining written informed consent, participants underwent a baseline clinical examination (visit 1). Approximately 46% of those eligible in Jackson and 65% in the other three communities completed visit 1, yielding a total of 15,792 participants. Participants were re-examined in 1990–92 (94% return rate), 1993–95 (86%), and 1996–98 (80%). Response to annual telephone interviews has been 93% of cohort survivors.

Risk Factor Measurements

Most SCD risk factors examined in this analysis were ascertained at the baseline examination. Participants were asked to fast for twelve hours prior to the clinic exam. Blood was drawn from an antecubital vein of seated participants into vacuum tubes containing ethylenediaminetetraacetic acid (for measurement of lipids) or a serum separator gel (Mg, K, and glucose). Aliquots were stored at −70°C and were shipped to central laboratories for analyses. The measurement of serum Mg was performed at visits 1 and 2 and was based on the

procedure of Gindler and Heth using the metallochromic dye, Calmagite (1-(1-hydroxy-4-methyl-2-phenylazo)-2-napthol-4sulfonic acid). Serum K was measured on a Coulter DACOS analyzer (Coulter Instruments, Hialeah, FL) using a direct ion-selective electrode. The laboratory coefficient of variation for Mg, based on split samples sent 1 week apart blindly to the laboratory, was 3%, [17] and repeated testing of 40 individuals over several weeks yielded a reliability coefficient of 0.69 for Mg and 0.66 for K. [18] The correlation coefficient of serum Mg measured at visit 1 versus visit 2 was 0.46. Serum glucose was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method. Prevalent diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, a self-reported physician diagnosis, or current treatment for diabetes. Prevalent hypertension was defined as resting systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current hypertension treatment.

Questionnaires assessed education, smoking status, number of cigarettes smoked per day and duration of smoking (pack years computed), and usual alcohol consumption (grams per week computed). Level of sports physical activity was assessed by the Baecke Questionnaire. [19] Usual dietary intake over the last year was collected using an adapted version of Willett's 61-item food frequency questionnaire. [20] Dietary Mg intake was computed by multiplying the Mg content of each food item by the frequency of its daily consumption and summing over all items. All medications used in the two weeks before each clinic visit were recorded from bottles brought by the participant.

Participants underwent a standard supine digitally recorded 12-lead electrocardiogram at rest, ≥1 hour after smoking or caffeine ingestion. Computer analysis at the ARIC ECG Reading Center included measurement of the voltage and duration of the ECG waves and ECG classification according to the Minnesota Code. [21,22] In those free of Minnesota codes for conduction defects (right or left bundle branch block, or intraventricular conduction defect), the QT interval duration was computed and corrected by Bazett's formula [23,24]: QTcorrected = QT/√ (heart rate standard/heart rate). The standard heart rate used was 60 beats/min.

Follow-up and Sudden Cardiac Death Definition

All participants were contacted annually by phone and all hospitalizations and deaths in the previous year were identified. Hospitalizations related to potential myocardial infarctions (MI) or coronary deaths were abstracted by trained nurses. For deaths, we obtained death certificates. If the death occurred out-of-hospital, we also sought next of kin interviews and physician, coroner, and autopsy information about the death. Events were classified as definite, probable, possible, or no MI, and if fatal, as definite fatal MI, definite fatal CHD, possible fatal CHD, or non-CHD death. Incident CHD was defined for analysis as definite or probable MI or definite fatal CHD.

To classify sudden cardiac death (SCD), all events classified as having fatal CHD (definite fatal MI, definite fatal CHD, or possible fatal CHD, in- and out-of-hospital) were reviewed again and adjudicated by a committee of physicians, funded through the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center. SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. After review of data available, cases were classified as either definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable. For this analysis, SCD was defined as the first two categories above. Reviewers were blinded to serum Mg status.

Data Analysis and Statistical Methods

We hypothesized that serum Mg is inversely associated with incidence of SCD. From the original ARIC cohort (n = 15,792), we excluded participants in very small minority groups

(*n* = 103), those missing baseline serum Mg measurements (*n* = 149), those not fasting at least 8 hours for the baseline examination (*n* = 550), and those missing covariates (*n* = 758). This left 14,232 in the cohort at risk.

Analyses were conducted using SAS software (v. 9.1; SAS Institute, Inc., Cary, NC). To explore possible confounding factors of associations between Mg and SCD, means or prevalences of risk factors were computed by quartile of serum Mg using ANOVA. An individual's quartile rank was based on up to two serum Mg measurements (visits 1 and 2). Those individuals who were censored before or did not attend visit 2 were ranked using their single visit 1 serum Mg measurement. Those individuals who attended visit 2 and were censored after that visit were ranked using the mean value of their two measurements.

Person-years at risk were calculated from the date of baseline clinical examination until the date of sudden cardiac death, other death, loss to follow-up, or 31 May 2001, whichever occurred first. Crude SCD rates (per 1000 person-years) were calculated for quartiles of serum Mg. Adjusted hazard ratios (HRs) for the association of serum Mg with SCD were calculated by using Cox proportional hazards regression. Model 1 included adjustment for baseline age, sex, race and ARIC field center. Adjustment for continuous measures of HDL-c, LDL-c, triglycerides, serum K, heart rate-adjusted QT-interval, physical activity score, weekly alcohol intake, and pack years of smoking in addition to baseline smoking status (yes, no), and education level (< high school, ≥high school) were added to Model 2. The final model included adjustment for diabetes, hypertension, and use of diuretics (yes, no), modeled as time-varying covariates with the status at the last visit before death or censoring compared to that of all other participants still at risk. The test for linear trend in HRs modeled each quartile group as equally-spaced categories. The proportional hazards assumption of the Cox model was found not to be violated by testing an interaction between quartiles of serum Mg and time.

We also analyzed the association of SCD with dietary Mg. All diet models were adjusted for total energy intake, and the final model included dietary covariates highly correlated with Mg: K, Ca, dietary fiber, protein, caffeine (all measured continuously), and polyunsaturated to saturated fat ratio.

The ARIC Study is supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022, and the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Results

The cohort at risk for SCD included 7,887 women and 6,345 men aged 45–64 years at baseline. Serum Mg levels measured at visits 1 and 2 ranged from 0.4 to 3.1 mEq/L and appeared to be normally distributed, with 98% of individuals from 1.2 to 2.0 mEq/L. As table 1 shows, LDL-c and HDL-c, heart rate-adjusted QT interval, serum K, physical activity, education, and dietary Mg intake were all associated positively with levels of serum Mg. Fasting triglycerides, pack-years of smoking, systolic blood pressure, hypertension, diabetes, use of diuretics, female sex, being African-American, and education were associated inversely with serum Mg. There were no differences in the percentage of current or former smokers, mean weekly alcohol intake, or daily total energy intake by quartile of serum Mg.

Through May 31, 2001, 264 individuals were classified as having died from either definite (n=217) or possible (n=47) SCD. There were 46 events in Forsyth County, 93 in Jackson, 48 in Minneapolis, and 77 in Washington County. Table 2 shows that the age-, race-, sex-, and field center-adjusted risk of SCD was inversely associated with serum Mg (p for linear trend

<0.0001). Compared to the lowest quartile of Mg, the risk of SCD was 55% lower (HR=0.45, 95% C.I., 0.31–0.67) in the highest Mg quartile and 47% lower in the second highest quartile (HR=0.53, 95% C.I., 0.38–0.74). This strong association persisted after adjustment for potentially confounding variables, including baseline measures of fasting lipids, heart rate adjusted-QT interval, serum K, physical activity score, smoking status and pack years, regular alcohol intake, and education level (Model 2) (p for linear trend = 0.0006), but point estimates of the association were attenuated modestly (HR = 0.55 for quartile 4 vs. 1, 95% C.I. = 0.37–0.83; and HR = 0.62 for quartile 3 vs. 1, 95% C.I. = 0.44–0.88). Apart from lower Mg, only greater age, male sex, being African-American, not being at the Forsyth County field center, lower HDL, higher LDL, greater pack-years of smoking, and less education were associated with greater risk of SCD in Model 2.

After further adjustment for prevalent diabetes, prevalent hypertension, and use of diuretics (Model 3), each associated with greater risk of SCD, the serum Mg association was attenuated slightly (p for linear trend = 0.006), with both quartiles 4 (HR = 0.62, 95% C.I. = 0.42–0.93) and 3 (HR = 0.70, 95% C.I. = 0.49–0.99) at significantly reduced risk of SCD when compared to the lowest quartile of serum Mg. Restriction of this analysis to only definite cases of SCD (n=217) attenuated these results, with quartile 4 (HR = 0.72, 95% C.I. = 0.46–1.11) no longer associated with a reduced risk of SCD (data not shown).

In order to assess the specificity of this association, we restricted the definition of SCD in three ways: cases that were 1) unwitnessed, 2) determined to have taken place outside of the hospital, or 3) determined to not be associated with MI by the physician reviewers (Table 2 bottom). The risk of unwitnessed SCD in the fully-adjusted model was marginally lower than for all SCD cases for quartile 4 compared to quartile 1 (HR = 0.49, 95% C.I. = 0.25–0.99), but the linear trend was no longer significant (p = 0.07). Restricting the SCD cases to out-of-hospital events did not change the overall association. The serum Mg association with SCD was somewhat stronger for cases not associated with MI, with quartile 4 (HR = 0.51, 95% C.I. = 0.32–0.83) at one-half the risk of death as the lowest quartile, greatly excluding the null.

To explore potential effect modification by prevalent CHD, we redid the analysis several different ways. Additional analyses which excluded prevalent CHD cases at baseline and censored individuals at the time of an incident non-fatal event (definite or possible MI, ECG-detected silent MI between examinations, coronary revascularization), reducing the number of cases by about half, showed similar, albeit weaker, results with wide confidence intervals including the null. Alternatively, adjusting for incident CHD occurrence before SCD by modeling it as a time-dependent covariate attenuated the association, with quartile 4 (HR = 0.69, 95% C.I. = 0.46–1.04), no longer significantly associated with a reduced risk of SCD. There was no evidence of effect modification by prevalent or incident CHD on the association of serum Mg with SCD. None of the two-way interactions of sex, race, heart rate-adjusted QT interval, serum K, and diuretic use with serum Mg was statistically significant at p<0.05.

Figure 1 illustrates the pattern of risk in those individuals who had serum Mg measured at both clinic examinations (n=13,010 at risk, 194 cases). For this figure, the cohort was dichotomized at the median value of both measurements of serum Mg, thereby comparing the upper two quartiles vs. lower two. Compared to those with Mg < median at both visits, individuals with serum Mg above the median at only one visit were not at a different risk of SCD. However, the risk of SCD was 42% lower in those individuals with serum Mg above the median at both visits (HR = 0.58, 95% C.I. = 0.37–0.89).

We also compared this association to that of serum Mg with CHD deaths not classified as definite or possible SCD. Over the same time period, 868 individuals were classified as having died from CHD, but not SCD. In all three models, the association was present, but attenuated

compared with the association of Mg level with SCD (Model 3 HR = 0.69, 95% C.I. = 0.56–0.84). Similar analyses were performed with dietary Mg as the exposure of interest. There was no evidence of an association between dietary Mg intake and risk of SCD in any of the models described above (data not shown).

Discussion

The main finding from this analysis was a significantly reduced risk of SCD in the highest quartile compared to the lowest quartile of serum Mg in a prospective cohort with over 173,000 person years of follow-up. This association persisted after adjustment for the major predictors of SCD and potential confounders (or mediators) of the Mg – SCD relationship, including hypertension, diabetes, serum K, heart-rate adjusted QT interval, and use of diuretics. The association was monotonic with a declining risk of SCD with each quartile of higher serum Mg. This association did not differ by race, sex, prevalent CHD, use of diuretics, serum K level, or heart-rate adjusted QT interval. Despite these strong findings for serum Mg, we observed no association between dietary Mg and risk of SCD. This is not surprising given previous reports from this cohort showing no association of dietary Mg with either incident hypertension or CHD, despite associations of these outcomes with serum Mg. [9,10]

The reliability coefficient for serum Mg was moderate at 0.69, [18] but we were still able to detect a strong association between low serum Mg and risk of SCD. Individuals who maintained serum Mg levels above the median value at two visits 3 years apart had the lowest risk of SCD. Nevertheless, a limitation of our study was an inability to assess levels of serum Mg just prior to an event. It could be that a sudden drop in Mg is important. However, measurement just before SCD is not possible in a prospective study. Serial measurements of serum Mg over many years would improve our ability to understand the impact of short-term transient changes in serum Mg on the risk of SCD.

The final model included adjustment for important predictors of SCD that may or may not be on the causal pathway of the Mg/SCD association. Hypertension is a known risk factor for SCD, [4,25,26] and a previous analysis in this population showed a modest association of low serum Mg with incident hypertension.[7] It is unclear to what degree depleted Mg affects risk of SCD through its influence on blood pressure and risk of hypertension, but it seems unlikely that this is a major pathway given that adjustment had little impact on risk estimates.

Prescription of diuretics for hypertension presents an unusual circumstance whereby the medication use clearly reduces blood pressure at the same time it leads to excessive Mg loss through urinary excretion. [12,27] Previous case-control studies have shown an increased odds of SCD in patients taking non-potassium-sparing diuretics. [28,29] Recent large clinical trials have not clearly shown diuretics to affect risk of death and cardiovascular events differently from beta blockers and ACE inhibitors. [30,31]

Low serum Mg is often observed in conjunction with low serum K, and low levels of both micronutrients have been implicated in ECG changes, including a shortening of the QT interval. [32,33] In addition, serum Mg deficiency has been shown to lead to ventricular arrhythmias, the most common precursor to SCD. [12] In the multivariable-adjusted models, there was no association of serum K or heart rate-adjusted QT interval with SCD. At least one study has shown that Mg may serve to block the short-term increase in intracellular calcium during myocardial ischemia, another precursor to arrhythmia. [15,34] The addition of these variables to the models had little influence on the HRs of SCD by quartile of serum Mg, suggesting an independent pathway whereby Mg influences risk of SCD.

Several studies have shown that serum Mg deficiency is frequently detected in patients who have survived an MI. [13] Mg therapy during and after an MI has been shown to reduce the

occurrence of ventricular arrhythmias, [13,14] and improve survival, in some, but not all studies. [14,15,36_39] In addition, autopsy studies have shown Mg in myocardial tissue of SCD cases is lower than in those dying of other causes. [13] Whether these lower levels of Mg are a cause or result of SCD remain unknown. Low levels of serum Mg in the normal range, such as in this study, may predispose individuals to serum Mg deficiency that could be detected with serial measurements. Additional prospective studies with more frequent measurements of serum Mg would help address this question. Despite the positive results on the prevention of secondary events with Mg therapy, no clinical trials on the efficacy of Mg supplementation on the primary prevention of SCD have been conducted.

In summary, this analysis is the first to demonstrate a significantly higher risk of SCD in individuals in the lowest quartile of the normal physiologic range of serum Mg compared to those in the highest quartile. This association is independent of other risk factors for SCD with only marginal attenuation of the association after full adjustment for all known potential predictors. There is a similar, albeit weaker, increased risk of non-sudden CHD death in individuals with low levels of serum Mg. The association reported here is moderately strong, and potentially modifiable. It becomes stronger in SCD cases that are unrelated to MI. A better understanding of the causal mechanism will require more detailed studies of temporal changes in serum Mg levels just before SCD and related events. Replication of these findings in other populations and additional research into the causal mechanism is warranted. If the association is consistent and replicated across other studies, it may warrant the initiation of clinical trials to evaluate the impact of targeted Mg supplementation in individuals at higher risk for SCD.

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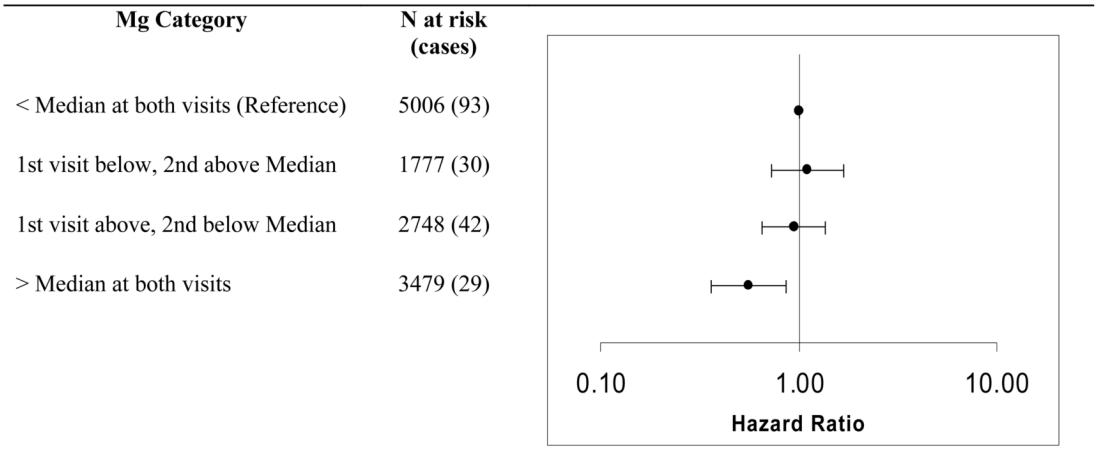

Figure 1. Adjusted* hazard ratios (95% CI) of definite or possible Sudden Cardiac Death by categories of serum Magnesium at two ARIC visits

* Adjusted for age, race, sex, field center, HDL, LDL, TG, BMI, serum K, heart rate-adjusted QT interval, physical activity, current smoking, pack years, ETOH intake, education, prevalent diabetes, hypertension, and diuretics use

Table 1

Age-, race-, sex-, and field center-adjusted means or percentages of potential Sudden Cardiac Death risk factors by serum Magnesium quartiles

Variable	Serum Magnesium (meq/L) ≤1.5 (n=3105)	1.55–1.6 (n=3835)	1.65–1.7 (n=4146)	≥1.75 (n=3146)	p-value for difference*
Age (yrs)	54.4	54.0	54.1	54.3	0.008
Female (%)	58.2	56.5	53.4	54.1	<0.0001
African-American (%)	27.3	24.0	23.7	23.1	<0.0001
LDL-cholesterol (mg/dL)	133.1	137.4	139.5	140.4	<0.0001
HDL-cholesterol (mg/dL)	50.9	51.8	52.2	52.6	<0.0001
Triglycerides (mg/dL)	138.0	126.0	119.4	117.1	<0.0001
Serum K (mmol/L)	4.3	4.4	4.5	4.5	<0.0001
Heart rate-adjusted QT Interval (mseconds)	391	394	396	396	0.0003
Current smoking (%)	26.7	25.8	24.3	25.0	0.13
Former smoking (%)	33.5	31.8	32.1	31.4	0.26
Smoking (pack yrs)	354.9	324.2	301.8	300.0	<0.0001
Alcohol intake (g/wk)	44.3	40.9	42.3	42.2	0.49
Baecke Sports Index	2.40	2.45	2.46	2.45	0.006
Diabetes (%)	19.5	9.8	7.3	5.2	<0.0001
Systolic BP (mm Hg)	123.4	120.8	120.0	119.6	<0.0001
Hypertension (%)	43.8	33.6	29.7	28.8	<0.0001
HS graduate (%)	73.4	78.3	79.0	77.8	<0.0001
Baseline Diuretics use (%)	25.0	17.8	17.1	14.6	<0.0001
Dietary Mg (mg/day)	251	254	253	260	0.0008
Total Energy Intake (kcal)	1621	1628	1609	1638	0.22

*F-test from ANOVA

Table 2

Crude incidence rate and adjusted hazard ratios (95% CI) of definite or possible Sudden Cardiac Death by baseline serum Magnesium quartiles in the ARIC Study (1987 to 2001)

	Serum Magnesium (meq/L)				
	≤1.5	**1.55–1.60**	**1.65–1.70**	**≥1.75**	**p for linear trend** *
Cases	89	80	58	38	
Person Years	*36807*	*46557*	*51181*	*38729*	
Crude Incidence Rate (per 1000 Person Yrs)	2.41	1.72	1.13	0.98	
Model 1 *(adjusted for age, race, sex, field center)*	1.00	0.79 (0.58,1.08)	0.53 (0.38,0.74)	0.45 (0.31,0.67)	<0.0001
Model 2 *(also adjusted for HDL, LDL, TG, serum K, heart rate-adjusted QT interval, physical activity, current smoking, pack years, ETOH intake, education)*	1.00	0.88 (0.65,1.21)	0.62 (0.44,0.88)	0.55 (0.37,0.83)	0.0006
Model 3*(also adjusted for prevalent diabetes, hypertension, diuretics use)*	1.00	0.97 (0.71,1.33)	0.70 (0.49,0.99)	0.62 (0.42,0.93)	0.006
Restricted SCD definitions					
Cases	38	39	29	11	
Unwitnessed events	1.00	1.20 (0.75,1.92)	0.95 (0.57,1.60)	0.49 (0.25,0.99)	0.07
Cases	81	75	54	33	
Out-of-hospital events	1.00	1.02 (0.73,1.41)	0.75 (0.52,1.08)	0.61 (0.40,0.94)	0.01
Cases	74	59	52	26	
Unrelated to MI	1.00	0.87 (0.61,1.25)	0.78 (0.53,1.13)	0.51 (0.32,0.83)	0.007

* Linear trend in quartile number