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Estudio prospectivo sobre el consumo regular de leche y el riesgo de mortalidad por todas las causas y causas específicas en adultos de EE. UU.: hallazgos del NHANES 2003-2008

Fei Zhao[1], Liyan Zhu[1], Ye Lu[1], Hongwei Xia[2], Shengchao Zhang[2], Ping Zhang[3]

[1]Department of Nursing; [2]Department of Thoracic Surgery; [3]Department of Medical Affairs. Qingpu Branch of Zhongshan Hospital Affiliated to Fudan University. Shanghai, People's Republic of China

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Correspondence: Shengchao Zhang. Department of Thoracic Surgery. Qingpu Branch of Zhongshan Hospital, Affiliated to Fudan University. 1158 Park East Road. Shanghai 201700, People's Republic of China
e-mail: zhang.shengchao@qphospital.com

Data availability statement: the datasets used in this investigation are accessible in the National Health and Nutrition Examination Survey (NHANES) at https://www.cdc.gov/nchs/nhanes.

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the present manuscript.

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ABSTRACT

Background: scholars have studied the influences of milk consumption on health. This prospective cohort study evaluated the association between regular milk consumption (RMD) and mortality, including all-cause, cardiovascular disease (CVD), and cancer-specific mortality, in Americans who were aged 20 years and older.

Methods: it was attempted to analyze data from the 2003 to 2008 National Health and Nutrition Examination Survey (NHANES), including 8,653 participants with an average follow-up of 160.59 months (standard deviation = 0.96). Regular milk consumption (RMD) was defined as drinking milk at least five times per week. Cox proportional hazards regression models were thereafter utilized for analysis.

Results: a significant association was noticeable particularly between RMD and higher rates of all-cause mortality (hazard ratio (HR) = 1.27; 95 % confidence interval (CI): 1.03-1.56; p = 0.03) and cancer mortality (HR = 1.53; 95 % CI: 1.01-2.32; p = 0.04), rather than with CVD mortality (HR = 1.03; 95 % CI: 0.73-1.44; p = 0.84). The association between RMD and all-cause mortality was notably observed across various subgroups in sensitivity and subgroup

analyses.

Conclusions: these outcomes unveiled the importance of exercising caution with milk consumption, which could be emphasized in public health recommendations.

Keywords: Regular milk drinking. Mortality. NHANES. Cardiovascular disease. Cancer.

RESUMEN

Antecedentes: se ha estudiado ampliamente la influencia del consumo de leche en la salud. Este estudio de cohortes prospectivo evaluó la asociación entre el consumo regular de leche (CRL) y la mortalidad, incluyendo la mortalidad por todas las causas, por enfermedades cardiovasculares (ECV) y por cáncer, en adultos estadounidenses de 20 años o más.

Métodos: se analizaron datos de la Encuesta Nacional de Examen de Salud y Nutrición (NHANES) de 2003 a 2008, con 8653 participantes y un seguimiento medio de 160,59 meses (desviación estándar = 0,96). El consumo regular de leche (CRL) se definió como ingerir leche al menos cinco veces por semana. Para el análisis se emplearon modelos de regresión de riesgos proporcionales de Cox.

Resultados: se observó una asociación significativa entre el CRL y una mayor tasa de mortalidad por todas las causas (razón de riesgos (HR) = 1,27; intervalo de confianza (IC) del 95 %: 1,03-1,56; p = 0,03) y de mortalidad por cáncer (HR = 1,53; IC 95 %: 1,01-2,32; p = 0,04), mientras que no se encontró una asociación significativa con la

mortalidad por ECV (HR = 1,03; IC 95 %: 0,73-1,44; p = 0,84). La relación entre el CRL y la mortalidad por todas las causas se observó de manera consistente en diversos subgrupos en los análisis de sensibilidad y subgrupos.

Conclusiones: estos hallazgos destacan la importancia de ejercer precaución en el consumo de leche, lo que podría considerarse en las recomendaciones de salud pública.

Palabras clave: Consumo de leche. Mortalidad. NHANES. Enfermedad cardiovascular. Cáncer.

INTRODUCTION

Milk contains a variety of micronutrients, macronutrients, and growth-promoting compounds that may contribute to humans' nutritional needs (1). However, the link of drinking milk with health-associated outcomes is a topic of significant debate. While some studies suggested that drinking milk may have beneficial effects on bone health and lessen the incidence of certain disorders (2-8), others reported potential adverse associations with various health outcomes, including cardiovascular diseases (CVDs) and cancer (9-12).

The identification of such links particularly in a diverse and nationally representative sample was accomplished via the National Health and Nutrition Examination Survey (NHANES). The National Center for Health Statistics (NCHS) implemented the NHANES once data on the

nutritional and health conditions of non-institutionalized civilian Americans became available. Accordingly, it is feasible to examine dietary habits and their influences on health outcomes particularly during prolonged follow-up (13,14).

Previous studies on the impact of milk consumption on mortality have yielded controversial results. The link of drinking milk with the diminished possibility of death was documented (15,16), whereas its function in elevating the risk of mortality was concluded by multiple scholars (17,18). These conflicting outcomes highlight the need for further reliable studies and advanced statistical methods to identify potential confounders.

The present investigation attempted to test the link of regular milk drinking (RMD) with mortality, involving CVDs, cancer, and all-cause mortality. Adult participants' follow-up, particularly recruited from the NHANES during 2003 to 2008, was conducted until December 31, 2019. The possible influence of RMD on mortality was figured out through defining RMD as drinking milk at least five times per week. The potential prolonged health-linked functions of RMD were summarized via adjusting for demographic, health-based, and lifestyle factors. The outcomes may be advantageous particularly for the future nutritional guidelines, as well as expanding individual dietary choices.

MATERIALS AND METHODS

Research population

In the present investigation, a subset of NHANES participants from the 2003-2008 survey cycles was selected, comprising 30,619 cases. Cases under 20 years, along with those lacking follow-up data or

having incomplete information on RMD and covariates, were excluded. The analysis included 8,653 cases with an average follow-up period of 160.59 (standard deviation = 0.96) months (Fig. 1). The information used in this analysis was obtained from a de-identified public source, ensuring confidentiality and privacy protection for study participants. The National Center for Health Statistics Research Ethics Review Board authorized the NHANES, and the written informed consent form was signed by each participant.

Exposure assessment

RMD was defined as drinking any type of milk at least five times per week. This definition was applied using the NHANES dietary behavior questionnaire variable dbq229, which recorded milk consumption habits for participants who were aged 20 years and older.

Participants reported their lifelong milk consumption habits by selecting one of three options: consistent regular milk drinking, never having been a regular milk drinker, or variable milk consumption patterns. These responses were categorized into three groups: RMD, for consistent milk consumption of at least five times per week; non-RMD, for no history of regular milk drinking; and sometimes RMD, for variable milk consumption patterns. To ensure data quality, participants with missing or unresponsive data were excluded, enhancing the dataset's integrity for subsequent analyses.

Covariates

Covariate data were gathered using questionnaires distributed during the household interview and the Mobile Examination Center (MEC) visit. Several influential factors have been identified in the investigation in three primary categories:

1) Demographic information: age, gender (male, female), race/ethnicity (Mexican American, non-Hispanic Black, non-Hispanic White, other races), poverty income ratio (PIR; ≤ 1, > 1-≤ 3, or > 3), and educational level (below high school, high school, or above high school).
2) Health status: health status was assessed based on body mass index (BMI; < 25, ≥ 25-< 30, or ≥ 30 kg/m²), history of diabetes (categorized as yes, no, or borderline), hypertension (yes or no), CVD (yes or no), chronic obstructive pulmonary disease (COPD; yes or no), chronic kidney disease (yes or no), and cancer (yes or no). Information was collected through self-reported physician diagnoses, medication use, and/or laboratory-measured biochemical markers.
3) Lifestyle factors: smoking status (never, former, or current), alcohol drinking (never, former, light/moderate, or heavy), and physical activity (low, medium, or high) were evaluated. The classification methods for alcohol drinking and physical activity were based on prior research (19,20).

Mortality estimation

The related mortality data for all participants were gathered from the National Death Index (NDI) until December 31, 2019. The leading causes of death were determined by the ICD-10. The present research concentrated on three important mortality outcomes: CVD mortality (codes I00-I9, I11, I13, and I20-I51), cancer mortality (codes C00-C97), and all-cause mortality.

Statistical analysis

To investigate participants' baseline features, categorical data were

analyzed using the Chi-square test to discern any significant differences among various groups. To explore the link of RMD with mortality outcomes, it was attempted to employ Cox proportional hazards regression models. The analysis accounted for the complex survey design and weighting of the NHANES dataset. Four distinct models were developed for each relationship analysis:

- Model 1: adjusted for age.
- Model 2: Model 1 + gender, race/ethnicity, PIR, educational level, BMI.
- Model 3: Model 2 + smoking status, alcohol drinking, physical activity.
- Model 4: Model 3 + diabetes, hypertension, CVD, COPD, chronic kidney disease, cancer.

Sensitivity analysis was conducted by excluding participants categorized as sometimes-RMD. Cox regression analysis was performed to compare all-cause mortality between RMD and non-RMD cases. However, CVD or cancer mortality comparisons were not included in the sensitivity and subgroup analyses. Subgroup analysis was performed to assess potential effect modification by various factors. All variables, except the grouping variable, were adjusted in the models. Interaction terms between RMD and each factor were included in the Cox models. Factors considered for subgroup analysis included age, gender, race/ethnicity, PIR, educational level, BMI, smoking status, alcohol use, physical activity, diabetes, hypertension, CVD, COPD, chronic kidney disease, and cancer. Statistical analysis was conducted using R 4.0.1 software, and statistical significance was defined as $p < 0.05$.

RESULTS

Baseline characteristics

This analysis comprised 8,653 cases. By the end of the survey day on December 31, 2019, 1,464 cases were deceased (mean follow-up: 160.59 (SD = 0.96) months), involving 374 (25.5 %) CVD cases and 355 (24.2 %) cancer cases.

The baseline data for RDM participants are accessible in table I. RDM participants were predominantly male, non-Hispanic white, and well-educated. The lack of significant differences in BMI, smoking status, alcohol drinking, physical activity, diabetes, hypertension, CVD, COPD, chronic kidney disease, and cancer was noteworthy ($p > 0.05$).

RMD and mortality

In general, RMD was linked to an elevated risk of all-cause and cancer mortality, rather than CVD mortality (Table II). In the model with all variables adjusted, the multivariable-adjusted HRs (95 % CIs) in the three categories of RMD were 1.00 (reference), 1.26 (0.96, 1.65), and 1.27 (1.03, 1.56) for all-cause mortality, 1.00 (reference), 1.30 (0.90, 1.90), and 1.03 (0.73, 1.44) for CVD mortality, and 1.00 (reference), 1.47 (0.96, 2.26), and 1.53 (1.06, 2.21) for cancer mortality, respectively.

Sensitivity and stratified analyses

In sensitivity analysis excluding sometimes-RMD patients ($n = 3057$), the link of RMD with the escalated risk of all-cause mortality was confirmed (Fig. 2). Positive associations persisted after stratifying by gender (female or male), age (20-39, 40-59, or ≥ 60 years), ethnicity/race (non-Hispanic white or other), PIR, educational level, BMI, smoking status, alcohol drinking, physical activity, diabetes, hypertension, CVD, COPD, chronic kidney disease, and cancer.

Notably, the linkages became unremarkable at certain levels. Of note, aside from the variable hypertension (yes or no), there were no significant interactions between RMD and the stratification factors.

DISCUSSION

The present investigation, using data from NHANES 2003-2008 with follow-up until December 31, 2019, revealed the link of RMD with a remarkably escalated risk of all-cause and cancer mortality, rather than with CVD mortality. These associations persisted even after adjusting for a broad range of demographic, health status, and lifestyle factors. Sensitivity and subgroup analyses further confirmed these findings, suggesting the link of RMD with the escalated all-cause mortality risk.

The link of milk consumption with mortality has been examined in prior studies with varied results (15-18). Some research has linked milk consumption with lower mortality rates, whereas others have suggested an elevated risk. These inconsistencies might be attributed to differences in study populations, methods of measuring milk consumption, and adjustment for potential confounders. Our study contributes to this body of knowledge by providing evidence from a nationally representative sample of American adults and employing statistical methods to account for various confounding factors.

Our results align with those of some previous studies, suggesting potential adverse health effects of high milk consumption. For instance, studies have reported that high milk intake increases the risk of developing cancer (18,21,22). A dose-response meta-analysis found that milk consumption exceeding 450 g/day was associated with a 30% increased risk of breast cancer (23). Additionally, a meta-analysis of 17 studies involving 32,690 cases (milk intake range: 0-

840 g/day) identified a nonlinear dose-response relationship between total milk consumption and prostate cancer risk. Specifically, at lower intake levels (≤ 300 g/day), prostate cancer risk increased by 2 % per 200 g/day increment in milk consumption. However, this association plateaued at higher intake levels, as milk consumption beyond 400 g/day was no longer significantly associated with increased risk (24). These associations may be mediated by molecular mechanisms related to milk components, particularly insulin-like growth factor-1 (IGF-1). Milk consumption has been shown to elevate IGF-1 levels, which are linked to an increased risk of breast and prostate cancers (25). IGF-1 promotes cancer cell proliferation and plays a critical role in malignant transformation, as its inhibition can prevent oncogene-induced tumorigenesis. Recombinant bovine growth hormone (rBGH), commonly administered to dairy cows to boost milk production, further elevates IGF-1 concentrations in milk. Importantly, IGF-1 is not eliminated during pasteurization, raising concerns that it may persist through digestion in the gastrointestinal tract and exert biological effects in humans (26).

In contrast, the present study found no noticeable link of RMD with CVD mortality. However, it was frequently suggested that drinking milk could diminish the probability of CVD and death (15,16). Calcium, magnesium, and potassium in milk may have a counterbalancing impact, lowering CVD risk (25). However, additional research is essential to comprehend the complex interplay of these nutrients with other dietary factors.

The findings of the present study underwent sensitivity and subgroup analyses, exhibiting consistent associations across various demographic and health-related strata. Noticeably, the absence of significant interactions between RMD and most stratum variables,

except for hypertension, was confirmed. This suggests the link of RMD with mortality that might be modified by the presence of hypertension, highlighting the need for more targeted research in this subgroup.

The present investigation has outstanding advantages, including the utilization of a sample that is large and representative nationally and extensive correction for a variety of possible confounders. The use of NHANES data, with its rigorous data collection methods and linkage to the NDI, provides high-quality information for our analysis. However, deficiencies of this investigation should be pointed out. This study's observational nature limits making causal assumptions. Although various factors were controlled, residual confounding cannot be completely eliminated. Furthermore, milk intake was self-reported, which might result in memory bias. Milk drinkers are classified based on their self-reported behaviors across their lifetime, resulting in possible misclassification bias. A significant limitation is the lack of detailed data on the type of milk consumed, particularly regarding fat content. Different types of milk and their fat composition might have distinct health effects, potentially influencing our results.

Future research should aim to explore the mechanisms underlying the observed associations, particularly concentrating on the biological pathways linking milk consumption with cancer mortality. Longitudinal studies with detailed dietary assessments and biomarkers of milk intake will provide more novel insights. Furthermore, future research that distinguishes between milk types and fat content could provide more precise insights into the health impacts of milk consumption.

CONCLUSIONS

In conclusion, this prospective cohort study found the link of RMD with

a remarkably escalated risk of all-cause and cancer mortality in a nationally representative sample of American adults. These findings highlight the importance of considering the potential long-term health influences of regular milk consumption in dietary guidelines and public health recommendations. Future research should aim to elucidate the underlying mechanisms and explore the differential effects of various types of milk on health outcomes.

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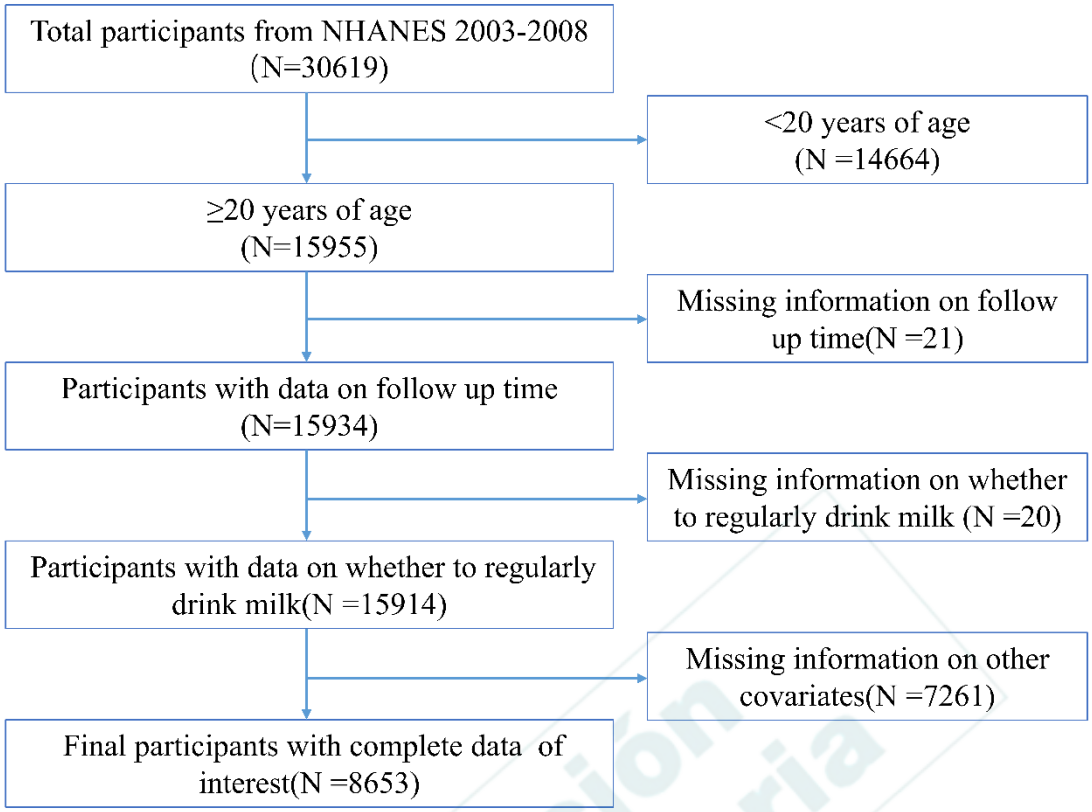

Figure 1. Flowchart of the study population selection process.

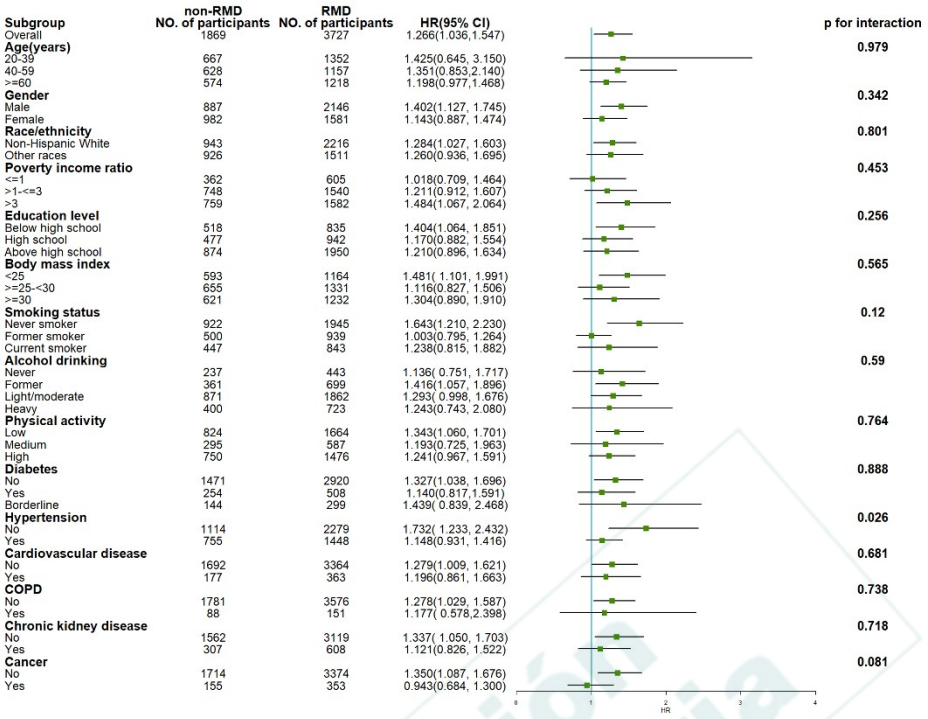

Figure 2. Forest plots summarizing hazard ratios of RMD in subgroup analyses (RMD: regular milk drinking).

Table I. Baseline characteristics of study participants by regular milk drinking status in NHANES 2003-2008

Characteristic	**Non-RMD**	**Sometimes-RMD**	**RMD**	***p* value**
	(*n* = 1869)	**(*n* = 3057)**	**(*n* = 3727)**	
Age(years), n (%)				*0.005*
20-39	667 (38.4)	1060 (38.2)	1352 (39.8)	
40-59	628 (41.8)	1115 (44.0)	1157 (38.7)	
≥60	574 (19.8)	882 (17.7)	1218 (21.5)	
Gender, n (%)				*< 0.0001*
Male	887 (42.2)	1649 (51.9)	2146 (55.9)	
Female	982 (57.8)	1408 (48.1)	1581 (44.1)	
Race/ethnicity, n (%)				*< 0.0001*
Mexican American	337 (7.4)	544 (7.0)	581 (6.2)	
Non-Hispanic Black	406 (11.)	598 (9.5)	627 (8.2)	
Non-Hispanic White	943 (71.6)	1588 (73.4)	2216 (79.2)	
Other races	183 (9.8)	327 (10.1)	303 (6.4)	
Poverty income ratio, n (%)				*0.001*
≤ 1	362 (13.0)	470 (9.8)	605 (10.9)	
> 1-≤ 3	748 (33.1)	1189 (31.9)	1540 (35.1)	
> 3	759 (53.8)	1398 (58.3)	1582 (54)	
Education level, n (%)				*< 0.0001*
Below high school	518 (18.0)	656 (13.0)	835 (14.22)	
High school	477 (26.3)	690 (22.2)	942 (25.6)	
Above high school	874 (55.74)	1711 (64.81)	1950 (60.27)	
Body mass index, n (%)				*0.78*
< 25	593 (34.1)	897 (32.2)	1164 (33.1)	
≥ 25-< 30	655 (34.5)	1095 (35)	1331 (35.11)	
≥ 30	621 (31.4)	1065 (32.8)	1232 (31.8)	
Smoking status, n (%)				*0.12*
Never smoker	922 (48.4)	1515 (50.3)	1945 (52.2)	
Former smoker	500 (26)	848 (26.8)	939 (244)	
Current smoker	447 (25.7)	694 (22.9)	843 (23.8)	
Alcohol drinking, n (%)				*0.43*
Never	237 (9.8)	323 (8.9)	443 (9.8)	

Former	361 (16.9)	574 (14.9)	699 (15.3)	
Light/moderate	871 (51.0)	1529 (54.5)	1862 (53.9)	
Heavy	400 (22.2)	631 (21.7)	723 (21.0)	
Physical activity, n (%)				*0.6*
Low	824 (44.4)	1406 (47.2)	1664 (46.2)	
Medium	295 (17)	500 (16.9)	587 (16.2)	
High	750 (38.6)	1151 (35.9)	1476 (37.6)	
Diabetes, n (%)				*0.8*
No	1471 (83.8)	2401 (83.7)	2920 (82.7)	
Yes	254 (9.3)	416 (9.5)	508 (10.2)	
Borderline	144 (6.9)	240 (6.9)	299 (7.1)	
Hypertension, n (%)				*0.65*
No	1114 (65)	1839 (64.7)	2279 (65.8)	
Yes	755 (35.1)	1218 (35.3)	1448 (34.2)	
Cardiovascular disease, n (%)				*0.68*
No	1692 (93.5)	2774 (93.2)	3364 (92.9)	
Yes	177 (6.5)	283 (6.8)	363 (7.1)	
COPD, n (%)				*0.14*
No	1781 (95.5)	2918 (96)	3576 (96.5)	
Yes	88 (4.5)	139 (4.0)	151 (3.5)	
Chronic kidney disease, n (%)				*0.22*
No	1562 (87.3)	2582 (88.8)	3119 (88.3)	
Yes	307 (12.8)	475 (11.2)	608 (11.8)	
Cancer, n (%)				*0.87*
No	1714 (92.1)	2796 (91.9)	3374 (91.7)	
Yes	155 (7.9)	261 (8.1)	353 (8.3)	

NHANES: National Health and Nutrition Examination Survey; %: weighted percentage; RMD: regular milk drinking.

Table II. Hazard ratios for all-cause, cardiovascular, and cancer mortality associated with regular milk drinking among participants in NHANES 2003-2008

	non-RMD	**sometimes-RMD**	**RMD**	***p* for trend**
All-cause mortality				
Deaths, No. (%)	284 (9.93)	478 (10.69)	702 (12.59)	0.004
Unadjusted	1 [Reference)	1.07 (0.88,1.32)	1.26 (1.07,1.48)	0.004
Model 1	1 [Reference)	1.16 (0.94, 1.43)	1.22 (1.05, 1.43)	0.01
Model 2	1 [Reference)	1.23 (0.99, 1.54)	1.22 (1.05, 1.43)	0.02
Model 3	1 [Reference)	1.25 (0.99, 1.58)	1.24 (1.04, 1.47)	0.02
Model 4	1 [Reference)	1.26 (0.96, 1.65)	1.27 (1.03, 1.56)	0.03
CVD mortality				
Deaths, No. (%)	74 (2.58)	134 (2.81)	166 (2.70)	0.88
Unadjusted	1 [Reference)	1.08 (0.76,1.55)	1.04 (0.72,1.49)	0.92
Model 1	1 [Reference)	1.19 (0.85, 1.67)	1.00 (0.72, 1.39)	0.77
Model 2	1 [Reference)	1.26 (0.91, 1.75)	0.99 (0.70, 1.40)	0.66
Model 3	1 [Reference)	1.28 (0.92, 1.79)	1.01 (0.72, 1.43)	0.76
Model 4	1 [Reference)	1.30 (0.90, 1.90)	1.03 (0.73, 1.44)	0.78
Cancer mortality				
Deaths, No. (%)	62 (2.08)	113 (2.81)	180 (3.35)	0.02
Unadjusted	1 [Reference)	1.35 (0.92,1.98)	1.61 (1.08,2.39)	0.02
Model 1	1 [Reference)	1.43 (0.98, 2.10)	1.58 (1.08, 2.29)	0.02
Model 2	1 [Reference)	1.46 (0.98,	1.49 (1.02,	0.06

		2.18)	2.18)	
Model 3	1 [Reference)	1.47 (0.98, 2.21)	1.50 (1.00, 2.24)	0.08
Model 4	1 [Reference)	1.47 (0.96, 2.26)	1.53 (1.01, 2.32)	0.06

The data are given as hazard ratios with 95 % confidence intervals. Model 1: adjusted for age. Model 2: Model 1 + gender, race/ethnicity, poverty income ratio, education level, body mass index. Model 3: Model 2 + smoking status, alcohol drinking, physical activity. Model 4: Model 3 + diabetes, hypertension, CVD, COPD, chronic kidney disease, cancer. %: weighted percentage; NHANES: National Health and Nutrition Examination Survey; CVD: cardiovascular disease; RMD: regular milk drinking.