

Circulating ceramides and cardiovascular outcomes in a real-world setting, using Mayo Clinic electronic medical records

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Background

- Ceramides are bioactive sphingolipids implicated in lipid metabolism, inflammation, and cardiovascular (CV) disease.¹
- Longitudinal research cohorts have shown that elevated ceramides are associated with CV risk.²
- A composite ceramide risk score (0-12), based on plasma levels of Cer(16:0), Cer(18:0), and Cer(24:1) relative to population quartiles, has been developed and is used for risk stratification at the Mayo Clinic.^{3,4}
- It is unknown whether this risk score is associated with CV risk and mortality in real-world, clinical settings.
- We evaluated associations between ceramide risk scores, low-density lipoprotein cholesterol (LDL-C), and CVD using electronic health records.

Table 1. Demographic and clinical characteristics at baseline. Values are mean (sd) or n (%).

Characteristic	Low (0-2) N=2,898	Moderate (3-6) N=2,454	Increased (7-9) N=889	Highest (10-12) N=242
Age (years)	57.3 (13.6)	57.5 (13.9)	57.2 (13.5)	58.6 (13.6)
Female	904 (31.2)	927 (37.8)	416 (46.8)	119 (49.2)
LDL-C (mg/dL)	104 (43.8)	128 (57.2)	158 (64.4)	170 (125)
Statin use	882 (30.4)	689 (28.1)	238 (26.8)	78 (32.2)
Hyperlipidemia	2,066 (71.3)	1,857 (75.7)	717 (80.7)	192 (79.3)
Erectile dysfunction	701 (24.2)	561 (22.9)	177 (19.9)	50 (20.7)
Ordering Provider				
Cardiology	1,411 (48.7)	1,100 (44.8)	327 (36.8)	105 (43.4)
Internal/Family Medicine	921 (31.8)	909 (37.0)	381 (42.9)	86 (35.5)
Urology	247 (8.5)	161 (6.6)	45 (5.1)	18 (7.4)

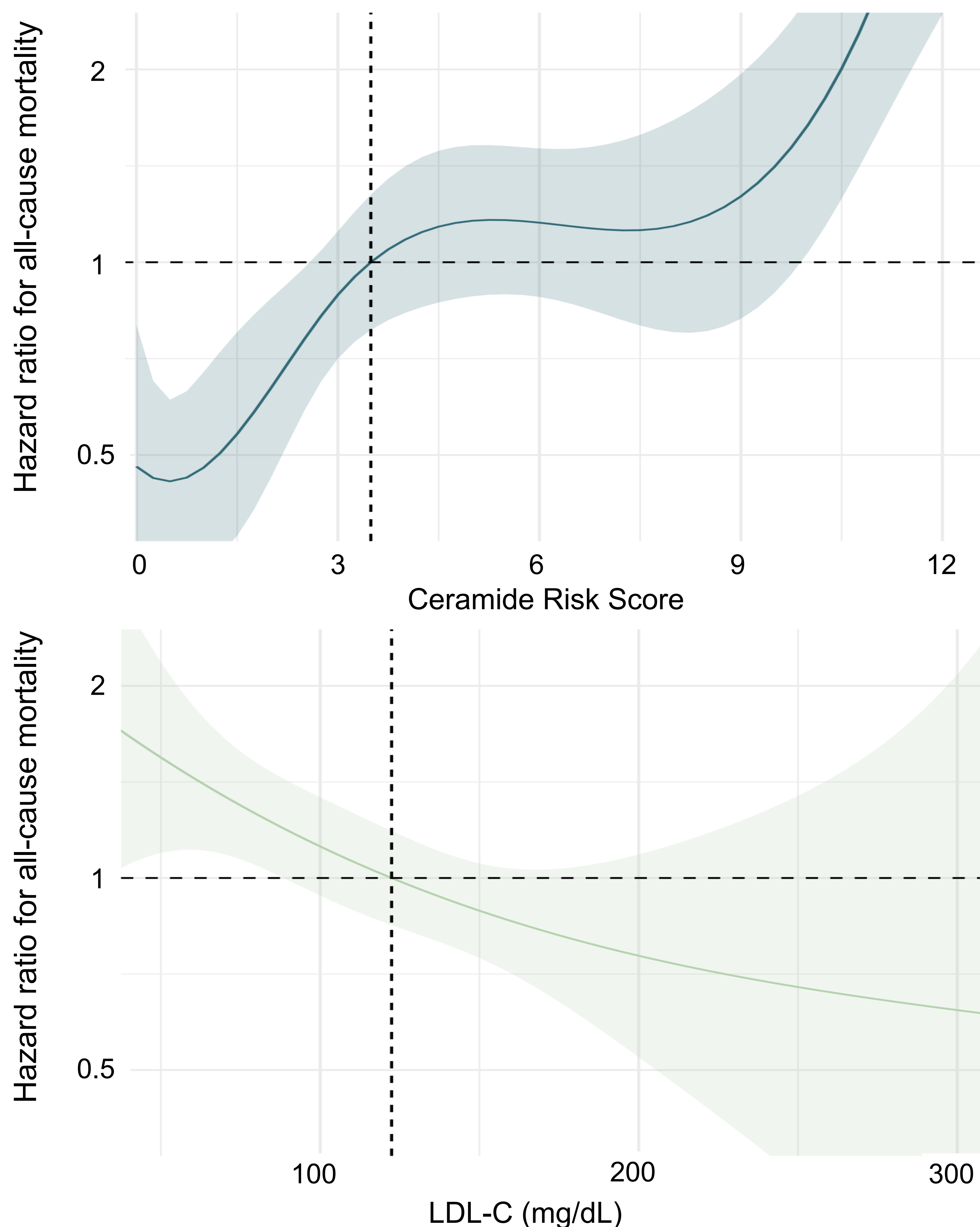
Methods

- We included adults with a ceramide risk score measurement from 2016-2024, indexing on the first available measurement (n=6,483).
- Risk scores were categorized to clinically-meaningful risk groups: low (0-2), moderate (3-6), increased (7-9) and highest (10-12) risk.
- We used ICD-codes to identify incident CV outcomes: major adverse cardiovascular events (all-cause mortality, myocardial infarction, stroke, and revascularization), atrial fibrillation, and heart failure
- Cox proportional hazard models were used to model time to CV outcome or mortality (with up to 9 years of follow-up), adjusted for covariates selected using a 2% change-in-estimate criterion.
- We assessed for interaction between ceramide risk score and LDL-C.

Table 2. Percent of patients with an incident prescription for a lipid-lowering agent in the year after baseline.

Incident Rx	Low (0-2)	Moderate (3-6)	Increased (7-9)	Highest (10-12)
Statins	32.84	38.13	48.2	46.4
PCSK9 Inhibitors	4.31	7.04	7.03	11.72
Ezetimibe	7	9.72	10.98	15.38

Figure 1. Nonlinear associations* between ceramide risk scores or LDL-C and hazard ratios for all-cause mortality. HRs are estimated relative to the hazard at the mean value of the running variable (depicted at vertical dashed line).

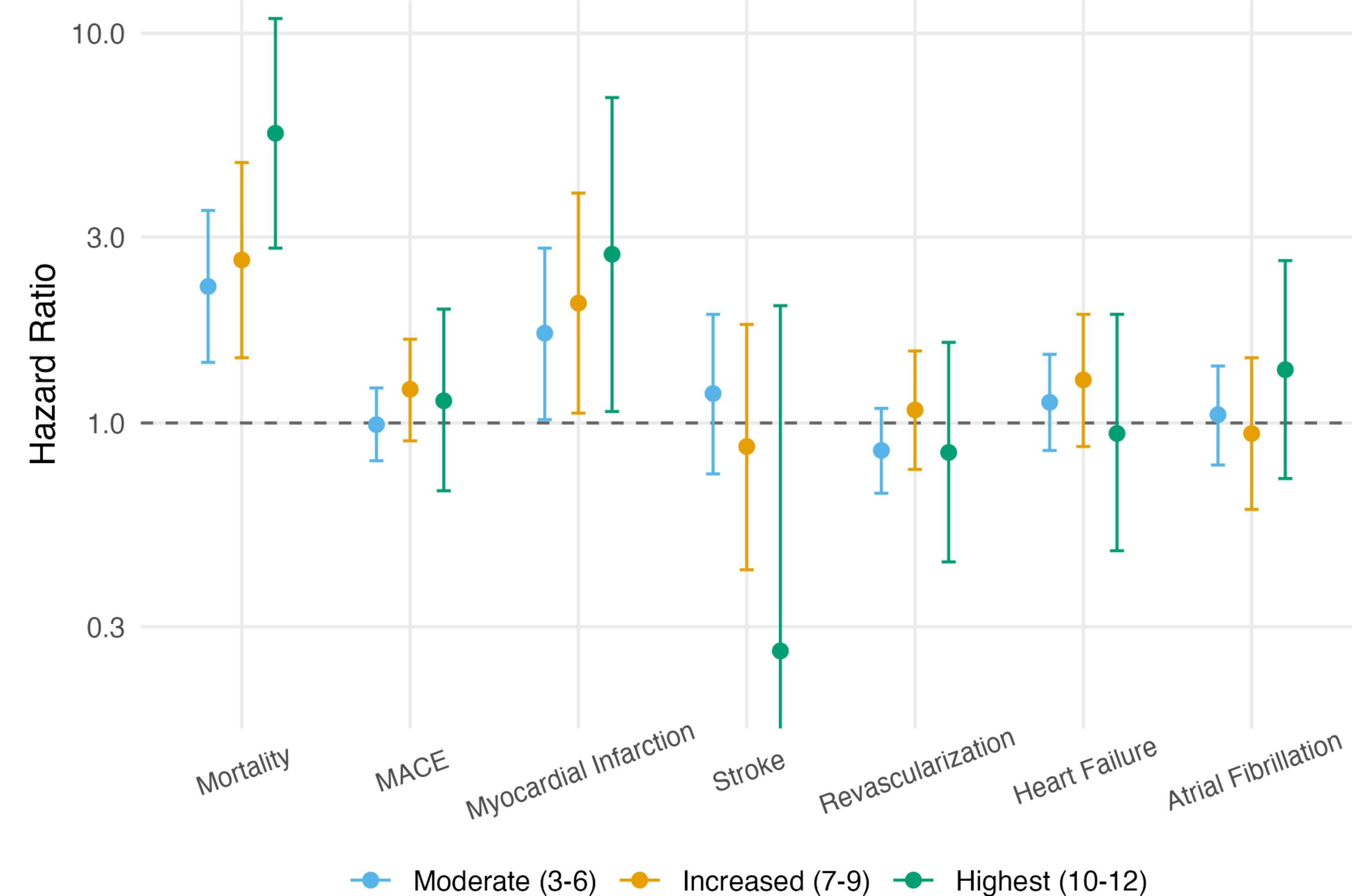


*Non-linear relationships fit using cubic b-splines with knots at the 25th, 50th, and 75th percentile of ceramide risk score or LDL-C.

Results

- The mean ceramide risk score was 3.5, with 3.7% in the highest risk group.
- The cohort had a high baseline comorbidity burden (**Table 1**).
- Patients in the highest ceramide risk group had a higher risk of all-cause mortality compared with the lowest risk group (HR = 5.5, 95% CI: 2.8-10.9), independent of and with a larger effect size than LDL-C (**Figure 1**).
- Ceramide risk scores were not associated with CV outcomes, though some confidence intervals were wide. (**Figure 2**)
- Statistically significant interaction between ceramides and LDL-C was observed for heart failure, but not for other outcomes.
- Individuals in the highest, increased, and moderate risk groups were more likely to receive lipid-lowering prescriptions compared to the low risk group (**Table 2**).

Figure 2. Adjusted* hazard ratios for the association between ceramide risk scores, CV outcomes, and mortality using the low risk group (0-2) as the reference.



*Models were adjusted for age, sex, race, coronary artery disease, and LDL-C.

Discussion

- In this real-world clinical cohort, higher ceramide risk scores were associated with increased all-cause mortality independent of LDL-C.
- Limited power due to rare CV events, along with the inability to account for clinical interventions initiated after ceramide measurements, may explain why our results deviate from published work on the relationship between ceramides and CVD.
- Future work with larger sample sizes should investigate whether lipid-lowering therapies mediate the relationship between ceramides and CVD.

References

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