

Vitamin D supplementation as a protective factor for mortality, morbidity, and limb amputation

Ariel Israel^{1,2}, Abraham Weizman³, Sarah Israel⁴, Shai Ashkenazi⁵, Shlomo Vinker¹, Eli Magen⁶, Eugene Merzon^{1,5}

- 1 - Leumit Research Institute, Leumit Health Services; Tel-Aviv, Israel
- 2 - School of Public Health, Faculty of Medical & Health Sciences, Tel Aviv University; Tel-Aviv, Israel
- 3 - Sagol School of Neurosciences, Faculty of Medical & Health Sciences, Tel-Aviv University; Tel-Aviv, Israel
- 4 - Department of Infectious Diseases, Hadassah-Hebrew University Medical Center; Jerusalem Israel
- 5 - Adelson School of Medicine, Ariel University; Ariel, Israel
- 6 - Ashdod University Medical Center, Ben Gurion University of the Negev; Beer Sheva, Israel

Background

Vitamin D deficiency is widespread and has been linked to adverse health outcomes, but its causal role remains debated.

Methods

We analyzed data from two large healthcare networks — Leumit Health Services (LHS) in Israel and the US-based TriNetX network — using matched cohort designs to compare individuals with severe vitamin D deficiency (<10 ng/mL) to those with sufficient levels (>30 ng/mL). Vitamin D showed strong seasonal variation, and deficiency was associated with increased risks of mortality, cardiovascular events, dialysis, and leg/foot amputation in both cohorts. To assess causality, we modeled serum vitamin D levels based on monthly pharmacy-dispensed supplementation and performed time-dependent Cox regressions adjusting for baseline deficiency.

Results

We identified a dose-dependent reduction in risk with supplementation associated, independent of baseline levels, with substantial absolute risk reductions. These findings support vitamin D deficiency as a modifiable risk factor and provide a rationale for targeted clinical trials in severely deficient populations.

Figure 2: Kaplan-Meier survival and cumulative incidence curves in LHS and TrinetX

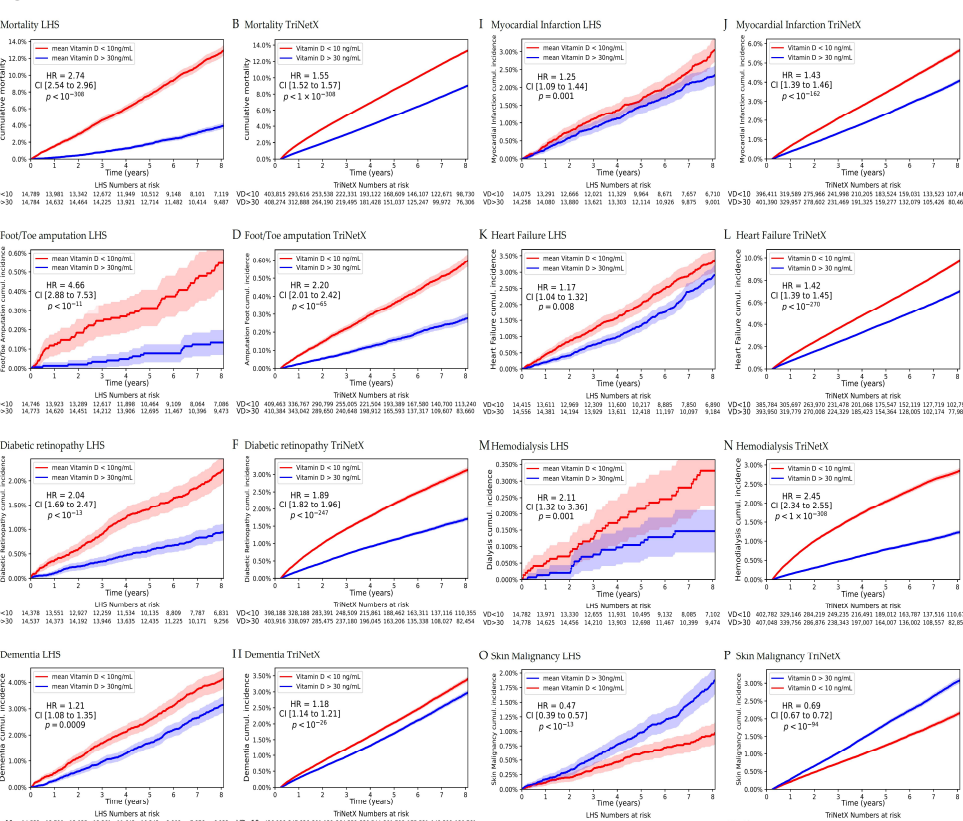


Figure 1: Seasonal Variation and Population Distribution of Serum 25(OH)D Levels in LHS

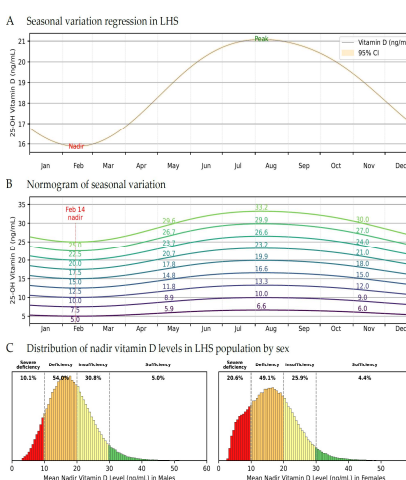


Figure 3: Independent Associations of Baseline Vitamin D Status and Supplementation with Major Health Outcomes in LHS

