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Antinuclear Antibodies Are Associated With All-Cause Mortality and Cardiovascular Outcomes in the General Population

Individuals with systemic autoimmune disease exhibit a heightened risk for cardiovascular disease (CVD) (1). Antinuclear autoantibodies (ANA) have been reported in approximately 25% of the general population (2); yet, only a small fraction of those individuals will develop autoimmune disease. The significance of this "benign autoimmunity" is unknown, and the role of ANA as a cardiovascular risk factor in the general population has not been clearly defined. We examined the associations among ANA and all-cause mortality and cardiovascular events in the DHS (Dallas Heart Study), a multiethnic, population-based, cohort study (2,3).

The study population included 2,803 participants who were free of CVD, had no self-reported autoimmune disease with use of an immunosuppressive medication, and had complete follow-up for events through December 2010. Plasma ANA were measured at baseline using an enzyme-linked immunosorbent assay (Inova, San Diego, California) and reported as enzyme-linked immunosorbent assay units (EU) (2). HEp2-cell indirect immunofluorescence (IF) is used more commonly in clinical practice; however, we have previously reported a high correlation of ANA EU with immunofluorescence titers ($r = 0.8$; $p = 0.02$) (2).

Mortality data were queried from the National Death Index through 2010. Atherosclerotic cardiovascular disease (ASCVD) events were adjudicated, and included cardiovascular death, myocardial infarction, coronary revascularization, and stroke (3). Associations of log-transformed ANA with all-cause mortality, cardiovascular death, and ASCVD were assessed by Cox proportional hazards regression, adjusting for: 1) age, race/ethnicity, and sex; and 2) model 1 plus hypertension, diabetes, smoking, body mass index, estimated glomerular filtration rate, statin use, total cholesterol, triglycerides, and high-density lipoprotein cholesterol. Sensitivity analyses excluded participants with an ANA >65 EU ($n = 150$).

Participants with higher ANA were more likely to be female and African-American ($p < 0.0001$ for each). Higher ANA were seen in participants with hypertension ($p = 0.02$) and in nonsmokers ($p < 0.0001$). We did not find differences in ANA on the basis of age, diabetes, hypercholesterolemia, and metabolic syndrome.

Over a median 9.4-year follow-up, 158 total deaths, 54 cardiovascular deaths, and 157 ASCVD events were recorded. After adjusting for age, sex, and race/ethnicity, higher ANA were associated with all-cause mortality (hazard ratio [HR] per 1 SD of log [ANA]: 1.27; 95% confidence interval [CI]: 1.10 to 1.46; $p = 0.0008$), cardiovascular death (HR: 1.42; 95% CI: 1.13 to 1.77; $p = 0.002$), and ASCVD (HR: 1.17; 95% CI: 1.01 to 1.35; $p = 0.04$) (**Table 1**). ANA remained independently associated with all-cause mortality, cardiovascular death, and ASCVD after adjustment for CVD risk factors. The associations of ANA with all-cause and cardiovascular death remained significant after excluding participants with ANA >65 EU (immunofluorescence titer of 1:160).

The major finding of this study is that higher ANA are independently associated with all-cause mortality, cardiovascular death, and ASCVD in an ethnically diverse, community-based population. Importantly, these associations are evident at ANA levels below those traditionally considered to be indicative of autoimmune disease.

A limited number of studies have investigated associations of low-level autoimmunity with CVD (4,5). Liang et al. (5) found that ANA positivity was associated with cardiovascular events and mortality after adjusting for cardiovascular risk factors and autoimmune disease. However, ANA were measured for clinical purposes, resulting in a prevalence of autoimmune disease that was 10-fold higher than in the

TABLE 1 ANA Associations With Mortality Outcomes and Cardiovascular Events

	Events (n)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality	158	1.29 (1.13–1.48)	1.27 (1.10–1.46)	1.26 (1.10–1.46)
p Value		0.0002	0.0008	0.002
Cardiovascular death	54	1.45 (1.17–1.79)	1.42 (1.13–1.77)	1.37 (1.10–1.73)
p Value		0.0006	0.002	0.01
ASCVD	157	1.16 (1.01–1.35)	1.17 (1.01–1.35)	1.18 (1.01–1.37)
p Value		0.04	0.04	0.04
Sensitivity Analysis in Participants With ANA <65 EU				
All-cause mortality	145	1.31 (1.07–1.61)	1.28 (1.03–1.58)	1.25 (1.002–1.56)
p Value		0.01	0.02	0.047
Cardiovascular death	50	1.69 (1.19–2.40)	1.62 (1.13–2.30)	1.49 (1.02–2.17)
p Value		0.003	0.009	0.04
ASCVD	148	1.22 (0.99–1.50)	1.23 (1.0–1.51)	1.22 (0.98–1.51)
p Value		0.058	0.054	0.07

N = 2,803. Hazard ratios (HRs) and 95% confidence intervals (CIs) for 1 SD increase in log (ANA).
ANA = antinuclear autoantibodies; ASCVD = atherosclerotic cardiovascular disease; EU = enzyme-linked immunosorbent assay unit(s).

general population. In contrast, our study represents a population-based assessment of the implications of low-level ANA.

The DHS is an observational cohort; thus, we cannot determine whether the association between ANA and adverse events is causal. These findings raise the possibility that the presence of ANA signals immunological events that are affecting vascular health, although the exact role requires further study.

Several study limitations are noteworthy. Baseline ANA were performed; thus, we cannot account for variability in ANA or autoimmunity over time. Exclusion of participants with autoimmune disease was on the basis of self-report, rather than physician evaluation.

In conclusion, increasing ANA are independently associated with all-cause mortality, cardiovascular death, and ASCVD in a representative multiethnic population-based cohort. ANA may identify individuals at increased risk of death and ASCVD independent of traditional risk factors or clinical autoimmune disease, a finding that potentially affects a substantial percent of the population.

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Light and Moderate Joggers Do Not Have Lower Mortality Rates Than Strenuous Joggers

The recently published paper by Schnohr et al. (1) on jogging and long-term mortality concluded that there was a U-shaped association between all-cause mortality and dose of jogging, and that low-intensity