

Article

The Cholesterol Paradox in Long-Livers from a Sardinia Longevity Hot Spot (Blue Zone)

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Abstract: **Background/Objectives:** Hypercholesterolemia is commonly viewed as a risk factor for coronary heart disease; however, several studies have reported an inverse relationship between cholesterol levels and cardiovascular mortality, particularly in older adults. This “cholesterol paradox” challenges the conventional understanding of lipid metabolism. Despite often being dismissed as a result of reverse causality, the precise causes of this paradox remain poorly understood. This study aimed to investigate the potential existence of the cholesterol paradox in a long-lived population from central Sardinia, Italy. **Methods:** We recruited 168 baseline nonagenarians (81 males, 87 females) from the longevity Blue Zone area in 2018 and followed them until December 2024. The lipid profile was determined for all participants according to current guidelines, and its impact on survival was analyzed with Kaplan–Meier curves and Cox proportional hazards regression models. **Results:** The median total cholesterol was 199.5 (range 89–314) mg/dL in males and 202.5 (range 89–324) mg/dL in females. Survival time was significantly longer in participants with LDL cholesterol (LDL-C) above 130 mg/dL compared to that in nonagenarians with LDL-C lower than 130 mg/dL (3.82 ± 1.88 years vs. 2.79 ± 1.56 years, $p < 0.0001$). Cox regression analysis revealed a significant reduction in the hazard ratio (HR) for mortality in participants with mild hypercholesterolemia (LDL-C ≥ 130 mg/dL) compared to that in those with normal cholesterol (OR 0.600, 95%CI 0.405–0.891). **Conclusions:** In the long-lived population examined, the cholesterol paradox was unlikely to be a reflection of reverse causality. Our results challenge the common view that longevity is invariably associated with low cholesterol levels. Furthermore, moderate hypercholesterolemia does not preclude the oldest adult from attaining advanced ages, contrary to common belief.

Keywords: cholesterol paradox; blue zone; longevity; Sardinia; elderly

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1. Introduction

Cardiovascular disease, the leading cause of mortality in high-resource countries, is often attributed to several risk factors, (including sex, family history, hypertension, cigarette smoking, obesity, and dyslipidemia [1]), which independently increase the probability of atherosclerosis development. The notion that high blood cholesterol is one of the primary factors for cardiovascular risk owes much to the work of Alexander Ignatowski, Nikolai Anichkov, and Semen Chalotov in the first two decades of the last century, when

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