

Article

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

Alessandra Errigo ¹, Maria Pina Dore ^{1,2}, Michele Portoghese ³ and Giovanni Mario Pes ^{1,4,*}

- ¹ Dipartimento di Medicina, Chirurgia e Farmacia, University of Sassari, Clinica Medica, Viale San Pietro 8, 07100 Sassari, Italy; a.errigo@studenti.uniss.it (A.E.); mpdore@uniss.it (M.P.D.)
- ² Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA
- ³ Cardiovascular Surgery Unit, AOU Sassari, Via Enrico de Nicola 14, 07100 Sassari, Italy; michele.portoghese@ausassari.it
- ⁴ Sardinia Blue Zone Longevity Observatory, 08040 Ogliastra, Italy
- * Correspondence: gpes@uniss.it; Tel.: +39-347-4539532

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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Table of Contents Long Livers 17

1. Understanding the eBook Long Livers 17
 - The Rise of Digital Reading Long Livers 17
 - Advantages of eBooks Over Traditional Books
2. Identifying Long Livers 17
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Long Livers 17
 - User-Friendly Interface
4. Exploring eBook Recommendations from Long Livers 17
 - Personalized Recommendations
 - Long Livers 17 User Reviews and Ratings
 - Long Livers 17 and Bestseller Lists
5. Accessing Long Livers 17 Free and Paid eBooks
 - Long Livers 17 Public Domain eBooks

- Long Livers 17 eBook Subscription Services
- Long Livers 17 Budget-Friendly Options
- 6. Navigating Long Livers 17 eBook Formats
 - ePub, PDF, MOBI, and More
 - Long Livers 17 Compatibility with Devices
 - Long Livers 17 Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Long Livers 17
 - Highlighting and Note-Taking Long Livers 17
 - Interactive Elements Long Livers 17
- 8. Staying Engaged with Long Livers 17
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Long Livers 17
- 9. Balancing eBooks and Physical Books Long Livers 17
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Long Livers 17
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Long Livers 17
 - Setting Reading Goals Long Livers 17
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Long Livers 17
 - Fact-Checking eBook Content of Long Livers 17
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks

14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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