Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Hellenic Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Hellenic Journal of Cardiology

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

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Extremely reduced COVID-19 mortality in a "Blue Zone": an observational cohort study

The Coronavirus disease 2019 (COVID-19) pandemic has, as of July 21st 2022, claimed the lives of more than 6.3 M people, following almost 565M infections (lumped mortality rate of 1.11%)[1] and has caused enormous disruptions in global health and healthcare. However, it is now evident that not all populations around the world are affected by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the same degree. Beyond differences in healthcare systems, these discrepancies have been associated with[2] the success of preventive measures, environmental and socio-demographic features (including comorbidities), and inter-population variations in biological functions.

As an example of the latter point, in 2011, the island of Ikaria, in the eastern Aegean Sea, Greece, has been recognized as one of the places on Earth with significantly extended longevity, thus joining the "*Blue Zones*"[3]. Notably, the mean population age of the island was similar to that of Greece as a whole (41.9 years per the 2011 census), attributable to past outflowing migration of (now) middle-aged inhabitants, whereas elders (then middle-aged) remained in the island and younger generations are active in the tourism and services sectors. Consequently, there is limited representation of the 40-70 years age cluster in the island, leading to this apparent paradox.

To examine COVID-19 mortality in such a "Blue Zone", from February 26th, 2020 (when the first case was confirmed in Greece) to January 31st, 2022, daily numbers of all laboratory-confirmed COVID-19 infections, as well related deaths, in Ikaria island (total population: 8,423 people) and the entire country (total population 10.72M people), were provided by the National Public Health Organization (NPHO), which is responsible for COVID-19 surveillance in Greece (permission #7/11-02-2022). No individual data were provided.

In total, 1,033 laboratory confirmed COVID-19 cases were reported in Ikaria during the pandemic (12.5% of the total population, though some may constitute reinfections). Overall, daily COVID-19 incidence in the island was significantly lower as compared to the incidence observed for the entire Greek population (0.17 vs. 0.26 cases per 1,000 Greek inhabitants ($p = 0.01$) (Fig. 1A). However, over certain periods, COVID-19 incidence in Ikaria exceed that observed for the total Greek population. Of note, time frame of available data (February 26th, 2020, to January 31st, 2022) provides that both the full impact of Delta mutation and the current dominance of Omicron variant have been considered, including their effect on mortality.

Regarding mortality, only 3 nonagenarians Ikariots (i.e., 0.4 per 1,000 inhabitants, 2.9 per 1,000 infected cases) died due to COVID-19. These rates are significantly lower when compared to the Greek population, where 23,500 deaths due to COVID-19 have been confirmed by January 31st, 2022, out of 1,940,723 reported infections (mortality 2.19 per 1,000 inhabitants, 12.1 per 1,000 infected cases. $p < 0.001$, Fig. 1B).

Notably, 70.5% of the Greek population has been fully vaccinated, versus 77% of Ikariots (both figures as of 03/08/2022 – obviously vaccination rates were lower during data acquisition).

Although the design of the present study does not allow for etiologic or environmental associations, it is evident that COVID-19 pandemic affected Ikaria Island, a known "Blue Zone", to a much lower degree than the entire Greek population. Several plausible explanations can be offered.

- Various clinical and biological[4] characteristics of Ikariots, including improved endothelial function (so crucial in the course of COVID-19), simultaneously associated with longevity[5]. Ikaria itself may play a role in this peculiarity[6].
- Previous analyses, based on the Ikaria Study data, have already revealed the significant benefits in terms of quality of life and longevity that Ikariot people share, mainly due to their unique lifestyle-related behaviors[7] and idiosyncrasy ("… the poorest, yet happiest, island in the Aegean Sea.")[8]. Their dietary habits could in theory be associated with gut microbiome patterns linked to healthy aging[9]. Close-knit communities assure proper care of family members, including the elderly, ensuring adequate symptom relief measures and monitoring for signs of deterioration.
- A plain natural selection effect cannot be excluded, since Ikaria has always been an island with scarce resources, poor infrastructure, and subject to a tumultuous history (abode of pirates, place of exile). Consequently, those of weak constitution would certainly be at a disadvantage in terms of survival.

To summarize:

- COVID-19 incidence in Ikaria is roughly similar to that in the rest of Greece; in fact, successive pandemic waves are present with the same pattern in both areas, yet mortality appears significantly lower in the former, potentially due to local features.
- Furthermore, these favorable findings are not attributable to better access to advanced healthcare facilities, given that the island does not have a tertiary hospital (and neither would it be entitled to one, based on demographics). Small regional health

Peer review under responsibility of Hellenic Society of Cardiology.

https://doi.org/10.1016/j.hjc.2022.09.004

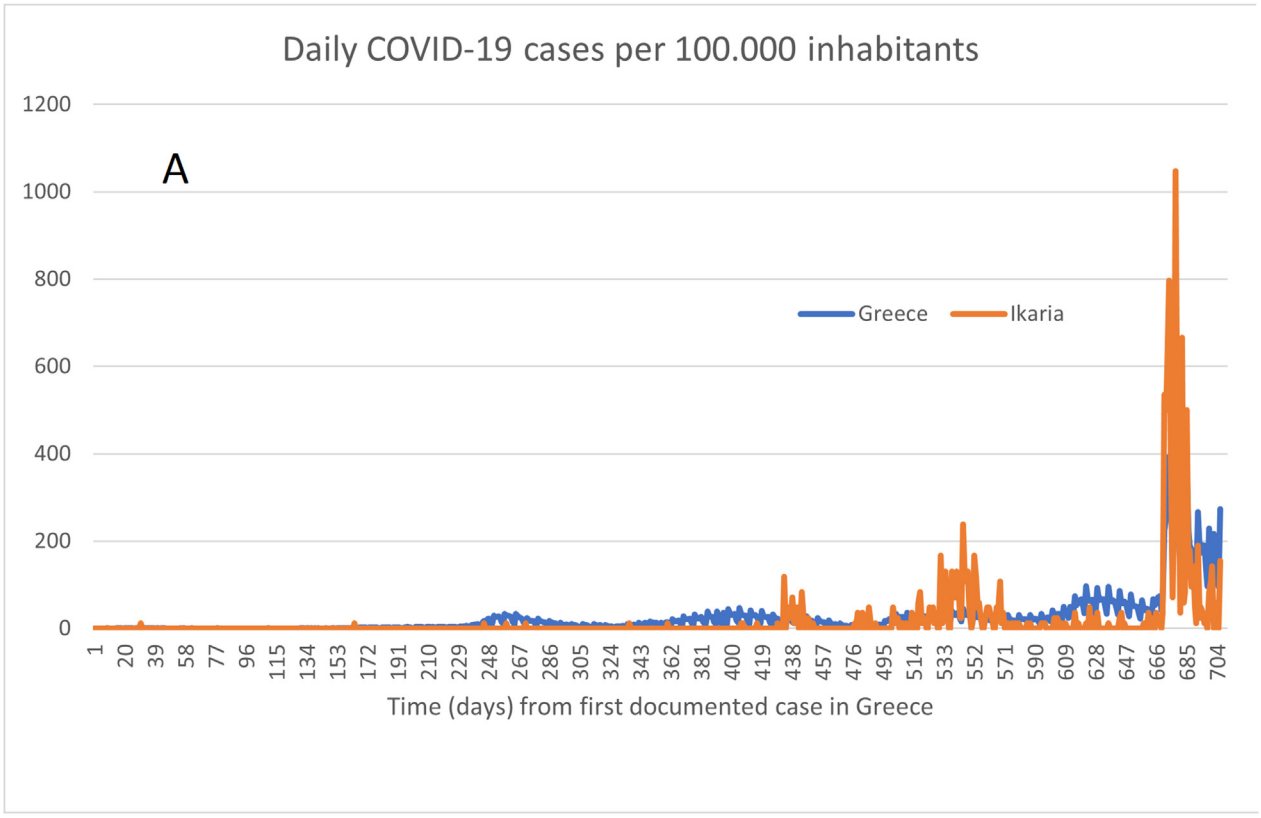

Figure 1. Time series of laboratory confirmed COVID-19 cases (A) and deaths (B) per 1.000 of population, in Greece and Ikaria Island, from February 26th, 2020 to January 31st, 2022.

centers and a secondary-level hospital are the only healthcare system units.

Limitations of current study include the following:

- Possible under-reporting of cases to avoid stigmatization in such a closed community.
- The lack of a tertiary level hospital may have led to missed diagnoses due to a lack of organized testing facilities – although

Please cite this article as: C. Stefanadis, C. Chrysohoou, D. Tsiachris *et al.*, Extremely reduced COVID-19 mortality in a "Blue Zone": an observational cohort study, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2022.09.004

the risks that SARS-CoV-2 infection carries for the elderly increases the chances of testing being performed at home and further help sought to combat the disease.

- Although in theory relevant data from similar (regarding size, population size and age, health infrastructure, and distance from mainland) would complement reported findings, the unique cultural and, to some extent, biological aspects of Ikaria, combined with distance from mainland Greece not being analogous to *connectivity*, make such comparisons less appropriate.

All the above suggest a possible interpretation of our observational data that would include Ikariot features associated with the island's classification as a "Blue Zone", mainly improved baseline endothelial function, providing a further stimulus for intensifying research in the field of COVID-19-related endotheliitis treatment as a means to combat the pandemic. As a further clinical implication, it is conceivable that measures of endothelial function could be prognosticators of COVID-19 morbidity/mortality.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Conflict of interest

Authors report no relationships that could be construed as a conflict of interest.

Declaration

All authors had access to raw data and actively participated in manuscript preparation, accepting responsibility for all findings presented herein.

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18 September 2022
Available online xxx